Pharmaceutical Process Scale-Up

edited by

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To my wife Sonia,
my children Hanna, Daniela, Ilan, and Emanuel,
and to the memory of my parents.

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Preface

Pharmaceutical Process Scale-Up deals with a subject both fascinating and vitally important for the pharmaceutical industry—the procedures of transferring the results of R&D obtained on laboratory scale to the pilot plant and finally to production scale. The primary objective of the text is to provide insight into the practical aspects of process scale-up. As a source of information on batch enlargement techniques, it will be of practical interest to formulators, process engineers, validation specialists and quality assurance personnel, as well as production managers. The book also provides interesting reading for those involved in technology transfer and product globalization.

Since engineering support and maintenance are crucial for proper scale-up of any process, Chapter 10 discusses plant design and machinery maintenance issues. Regulatory aspects of scale-up and postapproval changes are addressed throughout the book but more specifically in Chapter 11. A diligent attempt was made to keep all references to FDA regulations as complete and current as possible. Although some theory and history of process scale-up are discussed, knowledge of physics or engineering is not required of the reader since all theoretical considerations are fully explained.

Michael Levin

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Introduction

Scale-up is generally defined as the process of increasing the batch size. Scale-up of a process can also be viewed as a procedure for applying the same process to different output volumes. There is a subtle difference between these two definitions: batch size enlargement does not always translate into a size increase of the processing volume.

In mixing applications, scale-up is indeed concerned with increasing the linear dimensions from the laboratory to the plant size. On the other hand, processes exist (e.g., tableting) for which "scale-up" simply means enlarging the output by increasing the speed. To complete the picture, one should point out special procedures (especially in biotechnology) in which an increase of the scale is counterproductive and "scale-down" is required to improve the quality of the product.

In moving from R&D to production scale, it is sometimes essential to have an intermediate batch scale. This is achieved at the so-called pilot scale, which is defined as the manufacturing of drug product by a procedure fully representative of and simulating that used for full manufacturing scale. This scale also makes possible the production of enough product for clinical testing and samples for marketing. However, inserting an intermediate step between R&D and production scales does not in itself guarantee a smooth transition. A well-defined process may generate a perfect product in both the laboratory and the pilot plant and then fail quality assurance tests in production.

Imagine that you have successfully scaled up a mixing or a granulating process from a 10-liter batch to a 75-liter and then to a 300-liter batch. What exactly happened? You may say, "I got lucky." Apart from luck, there had to be some

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physical similarity in the processing of the batches. Once you understand what makes these processes similar, you can eliminate many scale-up problems.

A rational approach to scale-up has been used in physical sciences, viz. fluid dynamics and chemical engineering, for quite some time. This approach is based on process similarities between different scales and employs dimensional analysis that was developed a century ago and has since gained wide recognition in many industries, especially in chemical engineering [1].

Dimensional analysis is a method for producing dimensionless numbers that completely characterize the process. The analysis can be applied even when the equations governing the process are not known. According to the theory of models, two processes may be considered completely similar if they take place in similar geometrical space and if all the dimensionless numbers necessary to describe the process have the same numerical value [2]. The scale-up procedure, then, is simple: express the process using a complete set of dimensionless numbers, and try to match them at different scales. This dimensionless space in which the measurements are presented or measured will make the process scale invariant.

Dimensionless numbers, such as Reynolds and Froude numbers, are frequently used to describe mixing processes. Chemical engineers are routinely concerned with problems of water-air or fluid mixing in vessels equipped with turbine stirrers in which scale-up factors can be up to 1:70 [3]. This approach has been applied to pharmaceutical granulation since the early work of Hans Leuenberger in 1982 [4].

One way to eliminate potential scale-up problems is to develop formulations that are very robust with respect to processing conditions. A comprehensive database of excipients detailing their material properties may be indispensable for this purpose. However, in practical terms, this cannot be achieved without some means of testing in a production environment, and, since the initial drug substance is usually available only in small quantities, some form of simulation is required on a small scale.

In tableting applications, the process scale-up involves different speeds of production in what is essentially the same unit volume (die cavity in which the compaction takes place). Thus, one of the conditions of the theory of models (similar geometric space) is met. However, there are still kinematic and dynamic parameters that need to be investigated and matched for any process transfer. One of the main practical questions facing tablet formulators during development and scale-up is whether a particular formulation will sustain the required high rate of compression force application in a production press without lamination or capping. Usually, such questions are never answered with sufficient credibility, especially when only a small amount of material is available and any trial-and-error approach may result in costly mistakes along the scale-up path.

As tablet formulations are moved from small-scale research presses to high-speed machines, potential scale-up problems can be eliminated by simulation of production conditions in the formulation development lab. In any process transfer

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from one tablet press to another, one may aim to preserve mechanical properties of a tablet (density and, by extension, energy used to obtain it) as well as its bioavailability (e.g., dissolution that may be affected by porosity). A scientifically sound approach would be to use the results of the dimensional analysis to model a particular production environment. Studies done on a class of equipment generally known as compaction simulators or tablet press replicators can be designed to facilitate the scale-up of tableting process by matching several major factors, such as compression force and rate of its application (punch velocity and displacement), in their dimensionless equivalent form.

Any significant change in a process of making a pharmaceutical dosage form is a regulatory concern. Scale-Up and Postapproval Changes (SUPAC) are of special interest to the FDA, as is evidenced by a growing number of regulatory documents released in the past several years by the Center for Drug Evaluation and Research (CDER), including Immediate Release Solid Oral Dosage Forms (SUPAC-IR), Modified Release Solid Oral Dosage Forms (SUPAC-MR), and Semisolid Dosage Forms (SUPAC-SS). Additional SUPAC guidance documents being developed include: Transdermal Delivery Systems (SUPAC-TDS), Bulk Actives (BACPAC), and Sterile Aqueous Solutions (PAC-SAS). Collaboration between the FDA, the pharmaceutical industry, and academia in this and other areas has recently been launched under the framework of the Product Quality Research Institute (PQRI).

Scale-up problems may require postapproval changes that affect formulation composition, site, and manufacturing process or equipment (from the regulatory standpoint, scale-up and scale-down are treated with the same degree of scrutiny). In a typical drug development cycle, once a set of clinical studies has been completed or an NDA/ANDA has been approved, it becomes very difficult to change the product or the process to accommodate specific production needs. Such needs may include changes in batch size and manufacturing equipment or process.

Postapproval changes in the size of a batch from the pilot scale to larger or smaller production scales call for submission of additional information in the application, with a specific requirement that the new batches are to be produced using similar test equipment and in full compliance with CGMPs and the existing SOPs. Manufacturing changes may require new stability, dissolution, and in vivo bioequivalence testing. This is especially true for Level 2 equipment changes (change in equipment to a different design and different operating principles) and the process changes of Level 2 (process changes, e.g., in mixing times and operating speeds within application/validation ranges) and Level 3 (change in the type of process used in the manufacture of the product, such as from wet granulation to direct compression of dry powder).

Any such testing and accompanying documentation are subject to FDA approval and can be very costly. In 1977, the FDA's Office of Planning and Evaluation (OPE) studied the impact on industry of the SUPAC guidance, including its effects on cost. The findings indicated that the guidance resulted in substantial

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savings because it permitted, among other things, shorter waiting times for site transfers and more rapid implementation of process and equipment changes, as well as increases in batch size and reduction of quality control costs.

In early development stages of a new drug substance, relatively little information is available regarding its polymorphic forms, solubility, and other aspects. As the final formulation is developed, changes to the manufacturing process may change the purity profile or physical characteristics of the drug substance and thus cause batch failures and other problems with the finished dosage form.

FDA inspectors are instructed to look for any differences between the process filed in the application and the process used to manufacture the bio/clinical batch. Furthermore, one of the main requirements of a manufacturing process is that it will yield a product that is equivalent to the substance on which the biostudy or pivotal clinical study was conducted. Validation of the process development and scale-up should include sufficient documentation so that a link between the bio/clinical batches and the commercial process can be established. If the process is different after scale-up, the company has to demonstrate that the product produced by a modified process will be equivalent, using data such as granulation studies, finished product test results, and dissolution profiles.

Many of the FDA's postapproval, premarketing inspections result in citations because validation (and consistency) of the full-scale batches could not be established owing to problems with product dissolution, content uniformity, and potency. Validation reports on batch scale-ups may also reflect selective reporting of data. Of practical importance are the issues associated with a technology transfer in a global market. Equipment standardization inevitably will cause a variety of engineering and process optimization concerns that can be classified as SUPAC.

This book presents the significant aspects of pharmaceutical scale-up to illustrate potential concerns, theoretical considerations, and practical solutions based on the experience of the contributing authors. A prudent reader may use this handbook as a reference and an initial resource for further study of the scale-up issues.

Michael Levin

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1

Dimensional Analysis and Scale-Up in Theory and Industrial Application

Marko Zlokarnik
Graz, Austria

I. INTRODUCTION

A chemical engineer is generally concerned with the industrial implementation of processes in which chemical or microbiological conversion of material takes place in conjunction with the transfer of mass, heat, and momentum. These processes are scale dependent; that is, they behave differently on a small scale (in laboratories or pilot plants) and on a large scale (in production). They include heterogeneous chemical reactions and most unit operations. Understandably, chemical engineers have always wanted to find ways of simulating these processes in models to gain insights that will assist them in designing new industrial plants. Occasionally, they are faced with the same problem for another reason: An industrial facility already exists but will not function properly, if at all, and suitable measurements have to be carried out to discover the cause of the difficulties and provide a solution.

Irrespective of whether the model involved represents a "scale-up" or a "scale-down," certain important questions always apply:

1. How small can the model be? Is one model sufficient, or should tests be carried out in models of different sizes?
2. When must or when can physical properties differ? When must the measurements be carried out on the model with the original system of materials?
3. Which rules govern the adaptation of the process parameters in the model measurements to those of the full-scale plant?
4. Is it possible to achieve complete similarity between the processes in the model and those in its full-scale counterpart? If not, how should one proceed?

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These questions touch on the fundamentals of the theory of models, which are based on dimensional analysis. Although they have been used in the field of fluid dynamics and heat transfer for more than a century—cars, aircraft, vessels, and heat exchangers were scaled up according to these principles—these methods have gained only a modest acceptance in chemical engineering. University graduates are usually not skilled enough to deal with such problems at all. On the other hand, there is no motivation for this type of research at universities, since, as a rule, they are not confronted with scale-up tasks and are not equipped with the necessary apparatus on the bench scale. All this gives a totally wrong impression that these methods are, at most, of marginal importance in practical chemical engineering, for otherwise would they have been taught and dealt with in greater depth.

II. DIMENSIONAL ANALYSIS

A. The Fundamental Principle

Dimensional analysis is based upon the recognition that a mathematical formulation of a physicotechnological problem can be of general validity only when the process equation is *dimensionally homogenous,* which means that it must be valid in any system of dimensions.

B. What Is a Dimension?

A dimension is a purely qualitative description of a perception of a physical entity or a natural appearance. A length can be experienced as a height, a depth, a breadth. A mass presents itself as a light or heavy body, time as a short moment or a long period. The dimension of a length is length (L), the dimension of a mass is mass (M), etc.

C. What Is a Physical Quantity?

Unlike a dimension, a physical quantity represents a quantitative description of a physical quality (e.g., a mass of 5 kg). It consists of a measuring unit and a numerical value. The measuring unit of length can be a meter, a foot, a cubit, a yardstick, a nautical mile, a light year, etc. The measuring units of energy are, e.g., joules, cal, eV. (It is therefore necessary to establish the measuring units in an appropriate measuring system.)

D. Basic and Derived Quantities, Dimensional Constants

A distinction is being made between *basic* and *secondary* quantities, the latter often being referred to as *derived* quantities. Basic quantities are based on standards and are quantified by comparison with them. Secondary units are derived from the

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primary ones according to physical laws, e.g., velocity = length/time. (The borderline separating both types of quantities is largely arbitrary: 50 years ago a measuring system was used in which force was a primary dimension instead of mass!)

All secondary units must be coherent with the basic units (Table 1); e.g., the measuring unit of velocity must not be miles/hr or km/hr but meters/sec!

If a secondary unit has been established by a physical law, it can happen that it contradicts another one. *Example:* According to the Newton's second law of motion, the force F is expressed as a product of mass m and acceleration a: $F = ma$, having the measuring unit of $[\mathrm{kg \cdot m/sec^2} \equiv \mathrm{N}]$. According to the Newton's law of gravitation, force is defined by $F \propto m_1 m_2 / r^2$, thus leading to a completely different measuring unit $[\mathrm{kg^2/m^2}]$. To remedy this, the gravitational constant $\boldsymbol{G}$—a dimensional constant—had to be introduced to ensure the dimensional homogeneity of the latter equation: $F = \boldsymbol{G} m_1 m_2 / r^2$. Another example affects the universal gas constant $\boldsymbol{R}$, the introduction of which ensures that in the perfect gas equation of state $pV = n\boldsymbol{R}T$, the secondary unit for work $W = pV$ $[\mathrm{ML^2T^{-2}}]$ is not offended.

Another class of derived quantities is represented by the coefficients in diverse physical equations, e.g., transfer equations. They are established by the respective equations and determined via measurement of their constituents, e.g., heat and mass transfer coefficients.

E. Dimensional Systems

A dimensional system consists of all the primary and secondary dimensions and corresponding measuring units. The currently used International System of Dimensions (Système International d'unités, SI) is based on seven basic dimensions. They are presented in Table 1 together with their corresponding basic units. For some of them a few explanatory remarks may be necessary.

Temperature expresses the thermal level of a system and not its energetic contents. (A fivefold mass of a matter has the fivefold thermal energy at the same temperature!) The thermal energy of a system can indeed be converted into me-

Table 1 Base Quantities, Their Dimensions, and Their Units According to SI

Base quantity	Base dimension	Base unit
Length	L	m (meter)
Mass	M	kg (kilogram)
Time	T	sec (second)
Thermodynamic temperature	Θ	K (Kelvin)
Amount of substance	N	mol (mole)
Electric current	I	A (ampere)
Luminous intensity	I_v	cd (candela)

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Table 2 Often-Used Physical Quantities and Their Dimensions According to the Currently Used SI in Mechanical and Thermal Problems

Physical quantity	Dimension
Angular velocity	T^{-1}
Shear rate, frequency	
Mass transfer coefficient $k_L a$	
Velocity	$L\,T^{-1}$
Acceleration	$L\,T^{-2}$
Kinematic viscosity	$L^2\,T^{-1}$
Diffusion coefficient	
Thermal diffusivity	
Density	$M\,L^{-3}$
Surface tension	$M\,T^{-2}$
Dynamic viscosity	$M\,L^{-1}\,T^{-1}$
Momentum	$M\,L\,T^{-1}$
Force	$M\,L\,T^{-2}$
Pressure, stress	$M\,L^{-1}\,T^{-2}$
Angular momentum	$M\,L^2\,T^{-1}$
Energy, work, torque	$M\,L^2\,T^{-2}$
Power	$M\,L^2\,T^{-3}$
Heat capacity	$L^2\,T^{-2}\,\Theta^{-1}$
Thermal conductivity	$M\,L\,T^{-3}\,\Theta^{-1}$
Heat transfer coefficient	$M\,T^{-3}\,\Theta^{-1}$

chanical energy (base unit, joule). Moles are the amount of matter and must not be confused with the quantity of mass. The molecules react as individual entities regardless of their mass: One mole of hydrogen (2 g/mol) reacts with one mole of chlorine (71 g/mol) to produce two moles of hydrochloric acid, HCl. Table 2 shows the most important secondary dimensions. Table 3 refers to some very frequently used secondary units that have been named after famous researchers.

Table 3 Important Secondary Measuring Units in Mechanics, Named After Famous Researchers

Secondary quantity	Dimension	Measuring unit	Abbreviation for:
Force	$M\,L\,T^{-2}$	kg m sec^{-2} (N)	Newton
Pressure	$M\,L^{-1}\,T^{-2}$	kg m^{-1} sec^{-2} (Pa)	Pascal
Energy	$M\,L^2\,T^{-2}$	kg m^2 sec^{-2} (J)	Joule
Power	$M\,L^2\,T^{-3}$	kg m^2 sec^{-3} (W)	Watt

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F. Dimensional Homogeneity of a Physical Content

The aim of dimensional analysis is to check whether or not the physical content under examination can be formulated in a dimensionally homogeneous manner. The procedure necessary to accomplish this consists of two parts:

1. First, all physical parameters necessary to describe the problem are listed. This so-called "relevance list" of the problem consists of the quantity in question and of all the parameters that influence it. In each case only *one* target quantity must be considered; it is the only dependent variable. On the other hand, all the influencing parameters must be primarily independent of each other.
2. In the second step the dimensional homogeneity of the physical content is checked by transferring it into a dimensionless form. *Note:* A physical content that can be transformed into dimensionless expressions is dimensionally homogeneous!

The information given to this point will be made clear by the following amusing but instructive example.

Example 1: What Is the Correlation Between the Baking Time and the Weight of a Christmas Turkey? We first recall the physical situation. To facilitate this we draw a sketch (Sketch 1). At high oven temperatures the heat is transferred from the heating elements to the meat surface by both radiation and heat convection. From there it is transferred solely by the unsteady-state heat conduction that surely represents the rate-limiting step of the whole heating process.

Physical quantity	Symbol	Dimension
Baking time	θ	T
Surface of meat	A	L^2
Thermal diffusivity	a	$L^2\,T^{-1}$
Temperature on the surface	T_0	Θ
Temperature distribution	T	Θ

The higher the thermal conductivity λ of the body, the faster the heat spreads out. The higher its volume-related heat capacity ρC_p, the slower the heat transfer. Therefore, the unsteady-state heat conduction is characterized by only one material property, the thermal diffusivity $a = \lambda/\rho C_p$ of the body.

Baking is an endothermal process. The meat is cooked when a certain temperature distribution (T) is reached. It's about the time θ necessary to achieve this temperature range.

After these considerations we are able to precisely construct the relevance list:

$$\{\theta, A, a, T_0, T\} \tag{1}$$

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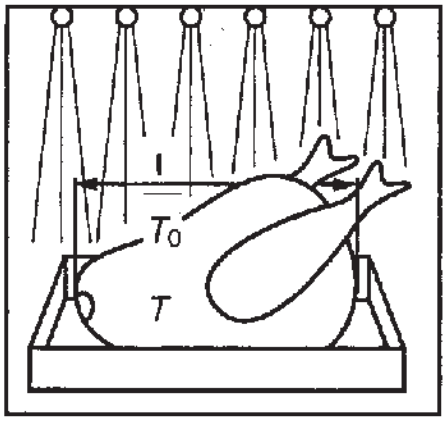

Sketch 1

The base dimension of temperature Θ appears in only two parameters. They can therefore produce only one dimensionless quantity:

$$\Pi_1 \equiv T/T_0 \qquad \text{or} \qquad (T_0 - T)/T_0 \tag{2}$$

The three residual quantities form one additional dimensionless number:

$$\Pi_2 \equiv a\theta/A \equiv \text{Fo} \tag{3}$$

In the theory of heat transfer, Π_2 is known as the Fourier number. Therefore, the baking procedure can be presented in a two-dimensional frame:

$$T/T_0 = f\,(\text{Fo}) \tag{4}$$

Here, five dimensional quantities [Eq. (1)] produce two dimensionless numbers [Eq. (4)]. This had to be expected because the dimensions in question are made up of three basic dimensions: $5 - 3 = 2$ (see pi theorem).

We can now easily answer the question concerning the correlation between the baking time and the weight of the Christmas turkey, without explicitly knowing the function f that connects both numbers, Eq. (4). To achieve the same temperature distribution T/T_0 or $(T_0 - T)/T_0$ in different-size bodies, the dimensionless quantity $a\theta/A \equiv \text{Fo}$ must have the same (= idem) value. Due to the fact that the thermal diffusivity a remains unaltered in meat of the same kind (a = idem), this demand leads to

$$T/T_0 = \text{idem} \rightarrow \text{Fo} \equiv a\theta/A = \text{idem} \rightarrow \theta/A = \text{idem} \rightarrow \theta \propto A \tag{5}$$

This statement is obviously useless as a scale-up rule because meat is bought according to weight and not surface. We can remedy this simply: In bodies, the following correlation between mass m, surface A, and volume V exists:

$$m = \rho V \propto \rho L^3 \propto \rho A^{\frac{3}{2}} \qquad (A \propto L^2) \tag{6}$$

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Table 4 Important Named Dimensionless Numbers

Name	Symbol	Group	Remarks
A. Mechanical unit operations			
Reynolds	Re	vl/ν	$\nu \equiv \mu/\rho$
Froude	Fr	$v^2/(lg)$	
	Fr*	$v^2\rho/(lg\Delta\rho)$	$\equiv$ Fr$(\rho/\Delta\rho)$
Galilei	Ga	gl^3/ν^2	$\equiv$ Re^2/Fr
Archmedes	Ar	$g\Delta\rho\ 1^3/\nu^2\rho$	$\equiv$ Ga $(\Delta\rho/\rho)$
Euler	Eu	$\Delta p/(\rho v^2)$	
Newton	Ne	$F/(\rho v^2 l^2)$	force
		$P/(\rho v^3 l^2)$	power
Weber	We	$\rho v^2 l/\sigma$	
Ohnesorg	Oh	$\mu/(\rho\sigma l)^{\frac{1}{2}}$	$\equiv$ We$^{\frac{1}{2}}$/Re
Mach	Ma	v/v_s	v_s = velocity of sound
Knudsen	Kn	λ_m/l	λ_m = molecular free path length
B. Thermal unit operations (heat transfer)			
Nusselt	Nu	hl/λ	
Prandtl	Pr	ν/a	$a \equiv \lambda/(\rho C_p)$
Grashof	Gr	$\beta\Delta T g l^3/\nu^2$	$\equiv \beta\Delta$TGa
Fourier	Fo	at/l^2	
Péclet	Pe	vl/a	$\equiv$ RePr
Rayleigh	Ra	$\beta\Delta T g l^3/(a\nu)$	$\equiv$ GrPr
Stanton	St	$h/(v\rho C_p)$	$\equiv$ Nu/(RePr)
C. Thermal unit operations (mass transfer)			
Sherwood	Sh	kl/D	k = mass transfer coefficient
Schmidt	Sc	ν/D	
Bodenstein	Bo	vl/D_{ax}	D_{ax} = axial dispersion coefficient
Lewis	Le	a/D	$\equiv$ Sc/Pr
Stanton	St	k/v	$\equiv$ Sh/(Re Sc)
D. Chemical reaction engineering			
Arrhenius	Arr	$E/(RT)$	E = activation energy
Hatta	Hat_1	$(k_1 D)^{\frac{1}{2}}/k_L$	1st-order reaction
	Hat_2	$(k_2 c_2 D)^{\frac{1}{2}}/k_L$	2nd-order reaction
Damköhler	Da	$\dfrac{cH_R}{\rho C_p T_0}$	Genuine; see Ref. 5
	Da_I	$k_1\tau$	τ = residence time
	Da_{II}	$k_1 l^2/D$	$\equiv$ Da_I Bo
	Da_{III}	$k_1\tau\left(\dfrac{cH_R}{C_p\rho T_0}\right)$	$\equiv$ $Da_I\left(\dfrac{cH_R}{\rho C_p T_0}\right)$
	Da_{IV}	$\dfrac{k_1 cH_R l^2}{\lambda T_0}$	$\equiv$ Da_I Re Pr $\left(\dfrac{cH_R}{\rho C_p T_0}\right)$

Therefore, from $\rho = \text{idem}$ it follows that

$$A \propto m^{\frac{2}{3}}$$

and by this

$$\theta \propto A \propto m^{\frac{2}{3}} \rightarrow \theta_2/\theta_1 \propto (m_2/m_1)^{\frac{2}{3}} \tag{7}$$

This is the scale-up rule for baking or cooking time in the case of meat of the same kind (*a,* $\rho = \text{idem}$). It states that by doubling the mass of meat, the cooking time will increase by $2^{\frac{2}{3}} = 1.58$.

G. B. West [1] refers to (inferior) cookbooks that simply say something like "20 minutes per pound," implying a linear relationship with weight. However, superior cookbooks exist such as the *Better Homes and Gardens Cookbook* (Des Moines Meredith Corp., 1962), that recognize the nonlinear nature of this relationship. The graphical representation of measurements in this book confirms the relationship

$$\theta \propto m^{0.6} \tag{8}$$

which is very close to the theoretical evaluation giving $\theta \propto m^{\frac{2}{3}} = m^{0.67}$.

The elegant solution of this first example should not tempt the reader to believe that dimensional analysis can be used to solve every problem. To treat this example by dimensional analysis, the physics of unsteady-state heat conduction had to be understood. Bridgman's [2] comment on this situation is particularly appropriate: "The problem cannot be solved by the philosopher in his armchair, but the knowledge involved was gathered only by someone at some time soiling his hands with direct contact." This transparent and easy example clearly shows how dimensional analysis deals with specific problems and what conclusions it allows. It should now be easier to understand Lord Rayleigh's sarcastic comment with which he began his short essay on "The Principle of Similitude" [3]: "I have often been impressed by the scanty attention paid even by original workers in physics to the great principle of similitude. It happens not infrequently that results in the form of 'laws' are put forward as novelties on the basis of elaborate experiments, which might have been predicted a priori after a few minutes' consideration."

From the foregoing example we also learn that a transformation of a physical dependency from a dimensional into a dimensionless form is automatically accompanied by an essential *compression* of the statement: The set of the dimensionless numbers is smaller than the set of the quantities contained in them, but it describes the problem equally comprehensively. In our example the dependency between five dimensional parameters is reduced to a dependency between only two dimensionless numbers! This is the proof of the so-called pi theorem (pi after Π, the sign used for products).

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G. The Pi Theorem

> Every physical relationship between n physical quantities can be reduced to a relationship between $m = n - r$ mutually independent dimensionless groups, whereby r stands for the rank of the dimensional matrix, made up of the physical quantities in question and generally equal to the number of the basic quantities contained in them.

(The pi theorem is often associated with the name of E. Buckingham [4], because he introduced this term in 1914. But the proof of it had already been accomplished in the course of a mathematical analysis of partial differential equations by A. Federmann in 1911; see Ref. 5.)

III. THE DETERMINATION OF A PI SET BY MATRIX CALCULATION

A. The Establishment of a Relevance List of a Problem

As a rule, more than two dimensionless numbers will be necessary to describe a physicotechnological problem, and therefore they cannot be derived by the method just described. In this case the easy and transparent matrix calculation introduced by J. Pawlowski [6] is increasingly used. It will be demonstrated by the following example. It treats an important problem in industrial chemistry and biotechnology, because the contact between gas and liquid in mixing vessels occurs very frequently in mixing operations.

Example 2: The Determination of the Pi Set for the Stirrer Power in the Contact Between Gas and Liquid. We examine the power consumption of a turbine stirrer (so-called Rushton turbine; see inset in Fig. 1) installed in a baffled vessel and supplied by gas from below (see Sketch 2). We facilitate the procedure by systematically listing the target quantity and all the parameters influencing it:

1. Target quantity: mixing power P
2. Influencing parameters
   a. Geometrical: stirrer diameter d
   b. Physical properties:
      Fluid density ρ
      Kinematic viscosity ν
   c. Process related:
      Stirrer speed n
      Gas throughput q
      Gravitational acceleration g

The relevance list is:

$$\{P; d; \rho, \nu; n, q, g\} \tag{9}$$

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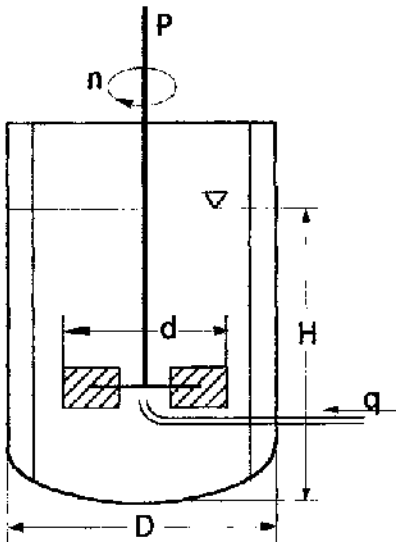

Sketch 2

We interrupt the procedure to ask some important questions concerning: (1) the determination of the characteristic geometric parameter, (2) the setting of all relevant material properties, and (3) the taking into account the gravitational acceleration.

1. *Determination of the characteristic geometric parameter:* It is obvious that we could name all the geometric parameters indicated in Sketch 2. They were all the geometric parameters of the stirrer and of the vessel, especially its diameter D and the liquid height H. In case of complex geometry such a procedure would necessarily deflect us from the problem. It is therefore advisable to introduce only one characteristic geometric parameter, knowing that all the others can be transformed into dimensionless geometric numbers by division with this one. As the characteristic geometric parameter in the Example 2, the stirrer diameter was introduced. This is reasonable. One can imagine how the mixing power would react to an increase in the vessel diameter *D:* It is obvious that from a certain D on, it would have no influence, but a small change of the stirrer diameter d would always have an impact!

2. *Setting of all relevant material properties:* In the preceding relevance list, only the density and the viscosity of the liquid were introduced. The material properties of the gas are of no importance as compared with the physical properties of the liquid. It was also ascertained by measurements that the interfacial tension σ does not effect the stirrer power. Furthermore, measurements [7] revealed that the coalescence behavior of the material system is not affected if aqueous glycerol or cane syrup mixtures are used to increase viscosity in model experiments.

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3. *The importance of the gravitational constant:* Due to the extreme density difference between gas and liquid (ca. 1:1.000), it must be expected that the gravitational acceleration g will exert a big influence. One should actually write $g\Delta\rho$, but—since $\Delta\rho = \rho_L - \rho_G \approx \rho_L$—the dimensionless number would contain $g\Delta\rho/\rho_L \approx g\rho_L/\rho_L = g$.

We now proceed to solve Example 2.

B. Constructing and Solving the Dimensional Matrix

In transforming the relevance list—Eq. (9)—of the preceding seven physical quantities into a dimensional matrix, the following should be kept in mind in order to minimize the calculations required.

1. The dimensional matrix consists of a square core matrix and a residual matrix.
2. The rows of the matrix are formed of base dimensions, contained in the dimensions of the quantities, and they will determine the rank r of the matrix. The columns of the matrix represent the physical quantities or parameters.
3. Quantities of the square core matrix may eventually appear in all of the dimensionless numbers as "fillers," whereas each element of the residual matrix will appear in only one dimensionless number. For this reason the residual matrix should be loaded with essential variables like the target quantity and the most important physical properties and process-related parameters.
4. By the—extremely easy!—matrix rearrangement (linear transformations), the core matrix is transformed into a matrix of unity. The main diagonal consists only of ones and the remaining elements are all zero. One should therefore arrange the quantities in the core matrix in a way to facilitate this procedure.
5. After the generation of the matrix of unity, the dimensionless numbers are created as follows: Each element of the residual matrix forms the numerator of a fraction, while its denominator consists of the fillers from the matrix of unity with the exponents indicated in the residual matrix.

Let us return to Example 2. The dimensional matrix reads:

	ρ	d	n	P	v	q	g
Mass M	1	0	0	1	0	0	0
Length L	−3	1	0	2	2	3	1
Time T	0	0	−1	−3	−1	−1	−2
	core matrix			residual matrix			

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Only one linear transformation is necessary to transform -3 in L-row/ρ-column into zero. The subsequent multiplication of the T-row by -1 transfers -1 to 1:

	ρ	d	n	P	ν	q	g
M	**1**	0	0	1	0	0	0
3M + L	0	**1**	0	5	2	3	1
−T	0	0	**1**	3	1	1	2
	unity matrix			residual matrix			

The residual matrix contains four parameters, so four numbers result:

$$\frac{P}{\rho^1 n^3 d^5} = \frac{P}{\rho n^3 d^5} \equiv \mathrm{Ne} \qquad \text{(Newton number)}$$

$$\frac{\nu}{\rho^0 n^1 d^2} = \frac{\nu}{n d^2} \equiv \mathrm{Re}^{-1} \qquad \text{(Reynolds number)}$$

$$\frac{q}{d^3 n} \equiv \mathrm{Q} \qquad \text{(Gas throughput number)}$$

$$\frac{g}{d n^2} \equiv \mathrm{Fr}^{-1} \qquad \text{(Froude number)}$$

The interdependence of seven dimensional quantities of the relevance list, Eq. (9), reduces to a set of only $7 - 3 = 4$ dimensionless numbers:

$$\{\mathrm{Ne}, \mathrm{Re}, \mathrm{Q}, \mathrm{Fr}\} \qquad \text{or} \qquad f(\mathrm{Ne}, \mathrm{Re}, \mathrm{Q}, \mathrm{Fr}) = 0 \tag{10}$$

thus again confirming the pi theorem.

C. Determination of the Process Characteristics

The functional dependency, Eq. (10), is the maximum that dimensional analysis can offer here. It cannot provide any information about the form of the function f. This can be accomplished solely by experiments.

The first question we must ask is: Are laboratory tests, performed in one single piece of laboratory apparatus—i.e., on one single scale—capable of providing binding information on the decisive process number? The answer here is affirmative. We can change Fr by means of the rotational speed of the stirrer, Q by means of the gas throughput, and Re by means of the liquid viscosity independent of each other.

The results of these model experiments are described in detail in Ref. 7. For our consideration, it is sufficient to present only the main result here. This states that, in the industrially interesting range ($\mathrm{Re} \geqslant 10^4$ and $\mathrm{Fr} \geqslant 0.65$), the power

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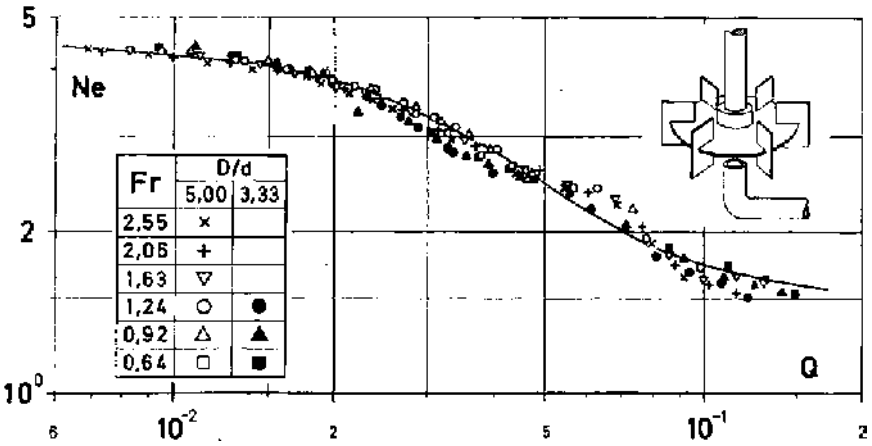

Figure 1 Power characteristics of a turbine stirrer (Rushton turbine) in the range Re $\geqslant$ 10^4 and Fr $\geqslant$ 0.65 for two *D*/*d* values. Material system: water/air. (From Ref. 7.)

number Ne is dependent only on the gas throughput number Q; see Figure 1. By raising the gas throughput number Q and thus enhancing gas hold-up in the liquid, liquid density diminishes and the Newton number Ne decreases to only one-third of its value in a nongassed liquid.

Knowledge of this power characteristic, the analytical expression for which is

$$\mathrm{Ne} = 1.5 + (0.5\mathrm{Q}^{0.075} + 1600\mathrm{Q}^{2.6})^{-1} \qquad (\mathrm{Q} \leqslant 0.15) \tag{11}$$

can be used to reliably design a stirrer drive for the performance of material conversions in the gas/liquid system (e.g., oxidations with O_2 or air, fermentations) as long as the physical, geometric, and process-related boundary conditions (Re, Fr, and Q) comply with those of the model measurement.

IV. FUNDAMENTALS OF THE THEORY OF MODELS AND OF SCALE-UP

A. Theory of Models

The results in Figure 1 have been obtained by changing the rotational speed of the stirrer and the gas throughput, whereas the liquid properties and the characteristic length (stirrer diameter d) remained constant. But these results could have also been obtained by changing the stirrer diameter. It does not matter by which means a relevant number (here Q) is changed because it is dimensionless and therefore independent of scale ("scale-invariant"). This fact presents the ba-

sis for a reliable scale-up:

> Two processes may be considered completely similar if they take place in similar geometrical space and if all the dimensionless numbers necessary to describe them have the same numerical value (Π_i = identical or idem).

Clearly, the scale-up of a desired process condition from a model to industrial scale can be accomplished reliably only if the problem was formulated and dealt with according to dimensional analysis!

B. Model Experiments and Scale-Up

In the foregoing example the process characteristics (here power characteristics) presenting a comprehensive description of the process were evaluated. This often expensive and time-consuming method is certainly not necessary if one only has to scale-up a given process condition from the model to the industrial plant (or vice versa). With the last example, and assuming that the Ne(Q) characteristic like that in Figure 1 is not explicitly known, the task is to predict the power consumption of a Rushton turbine of $d = 0.8$ m, installed in a baffled vessel of $D = 4$ m ($D/d = 5$) and rotating with $n = 200\ \text{min}^{-1}$. The air throughput is $q = 500\ \text{m}^3/\text{hr}$ and the material system is water/air.

One only needs to know—and this is *essential*—that the hydrodynamics in this case are governed *solely* by the gas throughput number and that the process is described by an unknown dependency Ne(Q). Then one can calculate the Q number of the industrial plant:

$$\text{Q} \equiv q/nd^3 = 8.14 \times 10^{-2}$$

What will the power consumption of the turbine be?

Let us assume that we have a geometrically similar laboratory device of $D = 0.4$ m ($V = 0.050\ \text{m}^3$) with the turbine stirrer of $d = 0.08$ m and that the rotational speed of the stirrer is $n = 750\ \text{min}^{-1}$. What must the gas throughput be to obtain Q = idem in the laboratory device? The answer is

$$q/nd^3 = 8.14 \times 10^{-2} \rightarrow \text{q} = 1.88\ \text{m}^3/\text{hr}$$

Under these conditions the stirrer power must be measured and the power number $\text{Ne} \equiv P/(\rho n^3 d^5)$ calculated. We find Ne = 1.75. Due to the fact that Q = idem results in Ne = idem, the power consumption P_T of the industrial stirrer can be obtained:

$$\text{Ne} = \text{idem} \rightarrow \text{Ne}_\text{T} = \text{Ne}_\text{M} \rightarrow \left(\frac{P}{\rho n^3 d^5}\right)_T = \left(\frac{P}{\rho n^3 d^5}\right)_M \tag{12}$$

From Ne = 1.75 found in laboratory measurement, the power P of the industrial turbine stirrer of $d = 0.8$ m and a rotational speed of $n = 200\ \text{min}^{-1}$ is calculated

as follows:

$$P = \mathrm{Ne}\rho n^3 d^5 = 1.75 \times 1 \times 10^3 \times (200/60)^3 \times 0.8^5 = 21{,}200\ W \cong 21\ kW$$

This results in 21/50 kW/m^3 = 0.42 kW/m^3, which is a fair volume-related power input for many conversions in the gas/liquid system.

We realize that in scale-up, comprehensive knowledge of the functional dependency $f(\Pi_i) = 0$—like that in Figure 1—is not necessary. All we need is to know which pi space describes the process.

V. FURTHER PROCEDURES TO ESTABLISH A RELEVANCE LIST

A. Consideration of the Acceleration Due to Gravity *g*

If a natural or universal physical constant has an impact on the process, it has to be incorporated into the relevance list, whether it will be altered or not. In this context the greatest mistakes are made with regard to the gravitational constant *g*. Lord Rayleigh [3] complained bitterly, saying: "I refer to the manner in which gravity is treated. When the question under consideration depends essentially upon gravity, the symbol of gravity (g) makes no appearance, but when gravity does not enter the question at all, g obtrudes itself conspicuously." This is all the more surprising in view of the fact that the relevance of this quantity is easy enough to recognize if one asks the following question: Would the process function differently if it took place on the moon instead of on Earth? If the answer to this question is affirmative, g is a relevant variable.

The gravitational acceleration g can be effective solely in connection with density as gravity $g\rho$. When inertial forces play a role, the density ρ has to be listed additionally. Thus it follows that:

1. In cases involving the ballistic movement of bodies, the formation of vortices in stirring, the bow wave of a ship, the movement of a pendulum, and oher processes affected by the Earth's gravity, the relevance list comprises $g\rho$ *and* ρ.
2. Creeping flow in a gravitational field is governed by the gravity $g\rho$ alone.
3. In heterogeneous physical systems with density differences (sedimentation or buoyancy), the gravity difference $g\Delta\rho$ *and* ρ play a decisive role.

In the second example we already treated a problem where the gravitational constant is of prime importance, due to extreme difference in densities in the gas/liquid system, provided that the Froude number is low: Fr < 0.65.

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B. Introduction of Intermediate Quantities

Many engineering problems involve several parameters that impede the elaboration of the pi space. Fortunately, in some cases a closer look at a problem (or previous experience) facilitates reduction of the number of physical quantities in the relevance list. This is the case when some relevant variables affect the process by way of a so-called "intermediate" quantity. Assuming that this intermediate variable can be measured experimentally, it should be included in the problem relevance list if this facilitates the removal of more than one variable from the list.

The fluid velocity v in pipes—or the superficial gas velocity v_G in mixing vessels or in bubble columns—presents a well-known intermediate quantity. Its introduction into the relevance list removes two others (throughput q and diameter D), because $v \propto q/D^2$ and $v_G \propto q_G/D^2$, respectively.

The impact, which the introduction of intermediate quantities can have on the relevance list, will be demonstrated in the following by one elegant example.
Example 3: Mixing-Time Characteristics for Liquid Mixtures with Differences in Density and Viscosity. The mixing time θ necessary to achieve a molecular homogeneity of a liquid mixture—normally measured by decolorization methods—depends, in material systems *without* differences in density and viscosity, on only four parameters: stirrer diameter d, density ρ, kinematic viscosity ν, rotational speed n:

$$\{\theta; d; \rho, \nu; n\} \tag{13}$$

From this, the mixing-time characteristics are

$$n\theta = f(\mathrm{Re}) \qquad \mathrm{Re} \equiv nd^2/\nu \tag{14}$$

See Example 5.2 later and Figure 10.

In material systems *with* differences in density and viscosity, the relevance list, Eq. (13), enlarges by the physical properties of the second mixing component, by the volume ratio of both phases $\varphi = V_2/V_1$, and, due to the density differences, inevitably by the gravity difference $g\Delta\rho$ to nine parameters:

$$\{\theta; d; \rho_1, \nu_1, \rho_2, \nu_2, \varphi; g\Delta\rho, n\} \tag{15}$$

This results in a mixing-time characteristics incorporating six numbers:

$$n\theta = f(\mathrm{Re}, \mathrm{Ar}, \rho_2/\rho_1, \nu_2/\nu_1, \varphi) \tag{16}$$

$\mathrm{Re} \equiv nd^2/\nu_1$ − Reynolds number,

$Ar \equiv g\Delta\rho\, d^3/(\rho_1\nu_1^2)$ − Archimedes number

Meticulous observation of this mixing process (the slow disappearance of the Schlieren patterns as result of the disappearance of density differences) reveals that macromixing is quickly accomplished compared to the micromixing. This time-consuming process already takes place in a material system that can be fully

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described by the physical properties of the mixture:

$$\nu^* = f(\nu_1, \nu_2, \varphi) \qquad \text{and} \qquad \rho^* = f(\rho_1, \rho_2, \varphi) \tag{17}$$

By introducing these intermediate quantities ν^* and ρ^*, the nine-parameter relevance list, Eq. (15), reduces by three parameters to a six-parametric one:

$$\{\theta; d; \rho^*, \nu^*; g\Delta\rho, n\} \tag{18}$$

and gives a mixing characteristics of only three numbers:

$$n\theta = f(\text{Re}, \text{Ar}) \tag{19}$$

(In this case, Re and Ar have to be formed by ρ^* and ν^*!)

The process characteristics of a cross-beam stirrer was established in this pi space by evaluation of corresponding measurements in two different-size mixing vessels ($D = 0.3$ and 0.6 m) using different liquid mixtures ($\Delta\rho/\rho^* = 0.01 - 0.29$ and $\nu_2/\nu_1 = 1 - 5300$). It reads [8]:

$$\sqrt{n\theta} = 51.6\,\text{Re}^{-1}(\text{Ar}^{1/3} + 3) \qquad \text{Re} = 10^1 - 10^5; \text{Ar} = 10^2 - 10^{11} \tag{20}$$

This example clearly shows the big advantages achieved by the introduction of intermediate quantities. This will also be made clear by upcoming Example 4.

C. Material Systems of Unknown Physical Properties

With the foams, sludges, and slimes often encountered in biotechnology, we are confronted with the problem of not being able to list the physical properties because they are still unknown and therefore cannot be quantified. This situation often leads to the opinion that dimensional analysis would fail in such cases.

It is obvious that this conclusion is wrong: Dimensional analysis is a *method* based on logical and mathematical fundamentals [2,6]. If relevant parameters cannot be listed because they are unknown, one cannot blame the method! The only solution is to perform the model measurements with the same material system and to change the model scales.

Example 4: Scale-Up of a Mechanical Foam Breaker. The question is posed about the mode of performing and evaluating model measurements with a given type of mechanical foam breaker (foam centrifuge; see sketch in Fig. 2) to obtain reliable information on dimensioning and scale-up of these devices. Preliminary experiments have shown that for each foam emergence—proportional to the gas throughput q_G—for each foam breaker of diameter d, a minimum rotational speed $n_{\min}$ exists that is necessary to control it. The dynamic properties of the foam (e.g., density and viscosity, elasticity of the foam lamella) cannot be fully named or measured. We will have to content ourselves with listing them wholesale as material properties S_i. In our model experiments we will of course be able to replace S_i by the known type of surfactant (foamer) and its concentration c_f [ppm].

In discerning the process parameters we realize that the gravitational acceleration g has no impact on the foam breaking *within* the foam centrifuge: The centrifugal acceleration n^2d exceeds the gravitational one (g) by far! However, we have to recognize that the water content of the foam entering the centrifuge depends very much on the gravitational acceleration: On the moon the water drainage would be by far less effective! In contrast to the dimensional analysis presented in Ref. 9, we are well advised to add g to the relevance list:

$$\{n_{\min};\ d;\ \text{type of foamer},\ c_f,\ q_G,\ g\} \tag{21}$$

For the sake of simplicity, in the following $n_{\min}$ will be replaced by n and q_G by q. For each type of foamer we obtain the following pi space:

$$\left\{\frac{nd^3}{q},\ \frac{n^2d}{g},\ c_f\right\} \quad \text{or, abbreviated,} \qquad \{\mathrm{Q}^{-1},\ \mathrm{Fr},\ c_f\} \tag{22}$$

To prove this pi space, measurements in different-size model equipment are necessary to produce reliable process characteristics. For a particular foamer (Mersolat H of Bayer AG, Germany) the results are given in Figure 2. They fully confirm the pi space [Eq. (22)].

The straight line in Figure 2 corresponds to the analytic expression

$$\mathrm{Q}^{-1} = \mathrm{Fr}^{-0.4} {c_f}^{0.32} \tag{23}$$

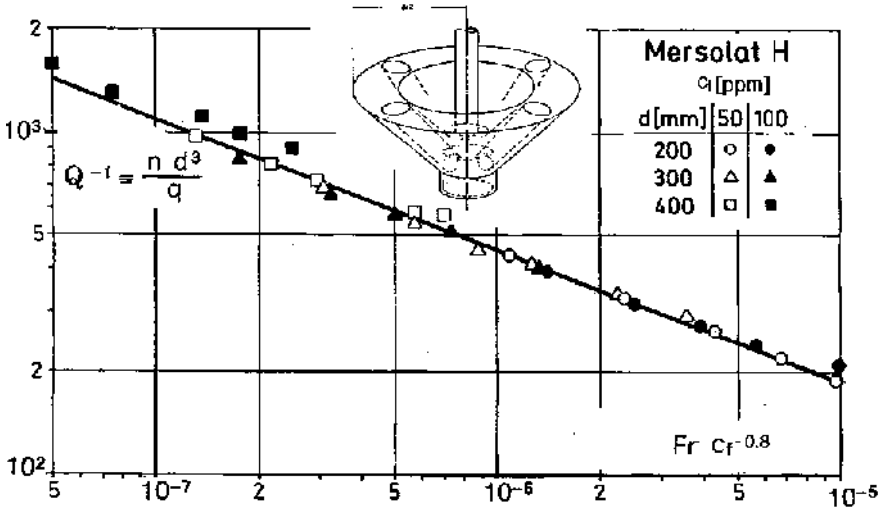

Figure 2 Process characteristics of the foam centrifuge (sketch) for a particular foamer (Mersolat H of Bayer AG, Germany). (From Ref. 9.)

which reduces to

$$nd = \text{const}\, q^{0.2} f(c_f) \tag{24}$$

Here, the foam breaker will be scaled up according to its tip speed $u = \pi nd$ in model experiments, which will also depend moderately on the foam yield (q).

In all other foamers examined [9], the correspondence $\mathrm{Q}^{-1} \propto \mathrm{Fr}^{-0.45}$ was found. If the correlation

$$Q^{-1} \propto Fr^{-0.5} f(c_f) \tag{25}$$

proves to be true, then it can be reduced to

$$n^2 d/g = \text{const}(c_f) \tag{26}$$

In this case the centrifugal acceleration ($n^2 d$) would present the scale-up criterion and would depend only on the foamer concentration and not on foam yield (q).

D. Short Summary of the Essentials of Dimensional Analysis and Scale-Up

The advantages made possible by correct and timely use of dimensional analysis are as follows.

1. *Reduction of the number of parameters required to define the problem.* The pi theorem states that a physical problem can always be described in dimensionless terms. This has the advantage that the number of dimensionless groups that fully describe it is much smaller than the number of dimensional physical quantities. It is generally equal to the number of physical quantities minus the number of base units contained in them.
2. *Reliable scale-up of the desired operating conditions from the model to the full-scale plant.* According to the theory of models, two processes may be considered similar to one another if they take place under geometrically similar conditions and all dimensionless numbers which describe the process have the same numerical value.
3. *A deeper insight into the physical nature of the process.* By presenting experimental data in a dimensionless form, one distinct physical state can be isolated from another (e.g., turbulent or laminar flow region) and the effect of individual physical variables can be identified.
4. *Flexibility in the choice of parameters and their reliable extrapolation within the range covered by the dimensionless numbers.* These advantages become clear if one considers the well-known Reynolds number, $\mathrm{Re} = vL/\nu$, which can be varied by altering the characteristic velocity v or a characteristic length L or the kinematic viscosity ν. By choosing

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appropriate model fluids, the viscosity can very easily be altered by several orders of magnitude. Once the effect of the Reynolds number is known, extrapolation of both v and L is allowed within the examined range of Re.

E. Area of Applicability of the Dimensional Analysis

The application of dimensional analysis is indeed heavily dependent on the available knowledge. The following five steps (see Fig. 3) can be outlined as:

1. The physics of the basic phenomenon is unknown—Dimensional analysis cannot be applied.
2. Enough is known about the physics of the basic phenomenon to compile a first, tentative relevance list—The resultant pi set is unreliable.
3. All the relevant physical variables describing the problem are known—The application of dimensional analysis is unproblematic.
4. The problem can be expressed in terms of a mathematical equation—A

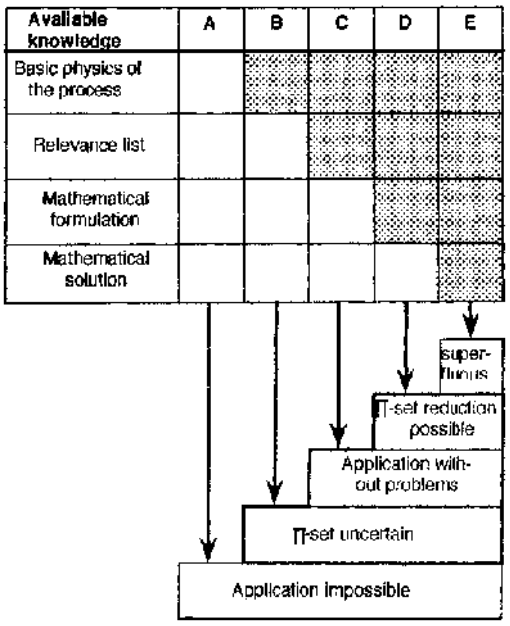

Figure 3 Graphical representation of the four levels of knowledge and their impact on the treatment of the problem by dimensional analysis. (From J. Pawlowski, personal communication, 1984.)

closer insight into the pi relationship is feasible and may facilitate a reduction of the set of dimensionless numbers.

5. A mathematical solution of the problem exists—The application of dimensional analysis is superfluous.

It must, of course, be said that approaching a problem from the point of view of dimensional analysis also remains useful even if all the variables relevant to the problem are not yet known: The timely application of dimensional analysis may often lead to the discovery of forgotten variables or the exclusion of artifacts.

F. Experimental Methods for Scale-Up

In Section I, a number of questions were posed that are often asked in connection with model experiments.

How small can a model be? The size of a model depends on the scale factor L_T/L_M and on the experimental precision of measurement. Where $L_T/L_M = 10$, a $\pm 10\%$ margin of error may already be excessive. A larger scale for the model will therefore have to be chosen to reduce the error.

Is one model scale sufficient, or should tests be carried out in models of different sizes? One model scale is sufficient if the relevant numerical values of the dimensionless numbers necessary to describe the problem (the so-called "process point" in the pi space describing the operational condition of the technical plant) can be adjusted by choosing the appropriate process parameters or physical properties of the model material system. If this is not possible, the process characteristics must be determined in models of different sizes, or the process point must be extrapolated from experiments in technical plants of different sizes.

When must model experiments be carried out exclusively with the original material system? Where the material model system is unavailable (e.g., in the case of non-Newtonian fluids) or where the relevant physical properties are unknown (e.g., foams, sludges, slimes), the model experiments must be carried out with the original material system. In this case measurements must be performed in models of various sizes (cf. Example 4).

G. Partial Similarity

The theory of models requires that in the scale-up from a model (index $_M$) to the industrial scale (index $_T$) not only the geometric similarity be ensured but also all dimensionless numbers describing the problem retain the same numerical values ($\Pi_i = \text{idem}$). This means, e.g., that in scale-up of boats or ships the dimensionless numbers governing the hydrodynamics here

$$\text{Fr} \equiv \frac{v^2}{Lg} \qquad \text{and} \qquad \text{Re} \equiv \frac{vL}{v}$$

must retain their numerical values: $Fr_T = Fr_M$ and $Re_T = Re_M$. It can easily be shown that this requirement cannot be fulfilled here!

Due to the fact that the gravitational acceleration g cannot be varied on Earth, the Froude number Fr of the model can be adjusted to that of the full-scale vessel only by its velocity v_M. Subsequently, Re = idem can be achieved only by adjusting the viscosity of the model fluid. In the case where the model size is only 10% of the full size (scale factor $L_T/L_M = 10$), Fr = idem is achieved in the model at $v_M = 0.32 v_T$. To fulfill Re = idem, for the kinematic viscosity of the model fluid v_M it follows:

$$\frac{\nu_M}{\nu_T} = \frac{v_M}{v_T}\frac{L_M}{L_T} = 0.32 \times 0.1 = 0.032$$

No liquid exists whose viscosity would be only 3% of that of water!

We have to realize that sometimes requirements concerning physical properties of model materials exist that cannot be implemented. In such cases only a partial similarity can be realized. For this, essentially only two procedures are available (for details see Refs. 5 and 10). One consists of a well-planned experimental strategy, in which the process is divided into parts that are then investigated separately under conditions of complete similarity. This approach was first applied by William Froude (1810–1879) in his efforts to scale up the drag resistance of the ship's hull.

The second approach consists in deliberately abandoning certain similarity criteria and checking the effect on the entire process. This technique was used by Gerhard Damköhler (1908–1944) in his trials to treat a chemical reaction in a catalytic fixed-bed reactor by means of dimensional analysis. Here the problem of a simultaneous mass and heat transfer arises—they are two processes that obey completely different fundamental principles!

It is seldom realized that many "rules of thumb" utilized for scale-up of different types of equipment are represented by quantities that fulfill only a partial similarity. As examples, only the volume-related mixing power P/V—widely used for scaling-up mixing vessels—and the superficial velocity v, which is normally used for scale-up of bubble columns, should be mentioned here.

The volume-related mixing power P/V presents an adequate scale-up criterion only in liquid/liquid dispersion processes and can be deduced from the pertinent process characteristics $d_p/d \propto We^{-0.6}$ (d_p is the particle or droplet diameter; We is the Weber number). In the most common mixing operation, the homogenization of miscible liquids, where a macro- and back-mixing is required, this criterion fails completely [10]!

Similarly, the superficial velocity v or v_G of the gas throughput as an intensity quantity is a reliable scale-up criterion only in mass transfer in gas/liquid systems in bubble columns. In mixing operations in bubble columns, requiring that

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the whole liquid content be back-mixed (e.g., in homogenization), this criterion completely loses its validity [10].

We have to draw the following conclusion: A particular scale-up criterion that is valid in a given type of apparatus for a particular process is not necessarily applicable to other processes occurring in the same device.

VI. TREATMENT OF VARIABLE PHYSICAL PROPERTIES BY DIMENSIONAL ANALYSIS

It is generally assumed that the physical properties of the material system remain unaltered in the course of the process. Process equations, e.g., the heat characteristics of a mixing vessel or a smooth straight pipe

$$\mathrm{Nu} = f(\mathrm{Re}, \mathrm{Pr}) \tag{27}$$

are valid for any material system with Newtonian viscosity and for any constant process temperature, i.e., for any *constant* physical property.

However, constancy of physical properties cannot be assumed in every physical process. A temperature field may well generate a viscosity field or even a density field in the material system treated. In non-Newtonian (pseudoplastic or viscoelastic) liquids, a shear rate can also produce a viscosity field.

In carrying out a scale-up, the industrial process has to be similar to the laboratory process in every relation. Besides the geometric and process-related similarity, it is self-evident that the fluid dynamics of the material system also has to behave similarly. This requirement normally represents no problems when Newtonian fluid are treated. But it can cause problems, when—e.g., in some biotechnological processes—material systems are involved that exhibit non-Newtonian viscosity behavior. Then the shear stress exerted by the stirrer causes a viscosity field.

Although most physical properties (e.g., viscosity, density, heat conductivity and capacity, surface tension) must be regarded as variable, it is particularly the value of viscosity that can be varied by many orders of magnitude under certain process conditions [5,11]. In the following, dimensional analysis will be applied, via examples, to describe the temperature dependency of the density und viscosity of non-Newtonian fluids as influenced by the shear stress.

A. Dimensionless Representation of the Material Function

Similar behavior of a certain physical property common to different material systems can only be visualized by dimensionless representation of the material function of that property (here the density ρ). It is furthermore desirable to formulate

this function as uniformly as possible. This can be achieved by the "standard representation" [6] of the material function in which a standardized transformation of the material function $\rho(T)$ is defined in such a way that the expression produced,

$$\rho/\rho_0 = \phi\{-\beta_0(T - T_0)\} \tag{28}$$

meets the requirement

$$\phi(0) = \phi'(0) = 1$$

where $\beta_0 \equiv \left(\frac{1}{\rho_0}\frac{\delta\rho}{\delta T}\right)_{T0}$ − temperature coefficient of the density and $\rho_0 \equiv \rho(T_0)$. T_0 is any reference temperature.

Figure 4A shows the dependency $\rho(T)$ for four different liquids, and Figure 4B depicts the standard representation of this behavior. This confirms that propene, toluene, and CCl_4 behave similarly with regard to $\rho(T)$, whereas water behaves differently. This implies that water cannot be used in model experiments if one of the other three liquids will be employed in the industrial plant.

B. Pi Set for Temperature-Dependent Physical Properties

The type of dimensionless representation of the material function affects the (extended) pi set within which the process relationship is formulated (for more information see Ref. 5). When the standard representation is used, the relevance list must include the reference density ρ_0 instead of ρ and incorporate two additional parameters β_0, T_0. This leads to two additional dimensionless numbers in the process characteristics. With regard to the heat transfer characteristics of a mixing vessel or a smooth straight pipe, Eq. (27), it now follows that

$$Nu = f(Re_0, Pr_0, \beta_0\Delta T, \Delta T/T_0) \tag{29}$$

where the subscript zero in Re and Pr denotes that these two dimensionless numbers are to be formed with ρ_0 (which is the numerical value of ρ at T_0).

If we consider that the standard transformation of the material function can be expressed invariantly with regard to the reference temperature T_0 (Fig. 4b), then the relevance list is extended by only one additional parameter, β_0. This, in turn, leads to only one additional dimensionless number. For the foregoing problem it now follows that

$$Nu = f(Re_0, Pr_0, \beta_0\Delta T) \tag{30}$$

C. Non-Newtonian Liquids

The main characteristics of Newtonian liquids is that simple shear flow (e.g., Couette flow) generates shear stress τ that is proportional to the shear rate $\dot{\gamma} \equiv dv/dy$

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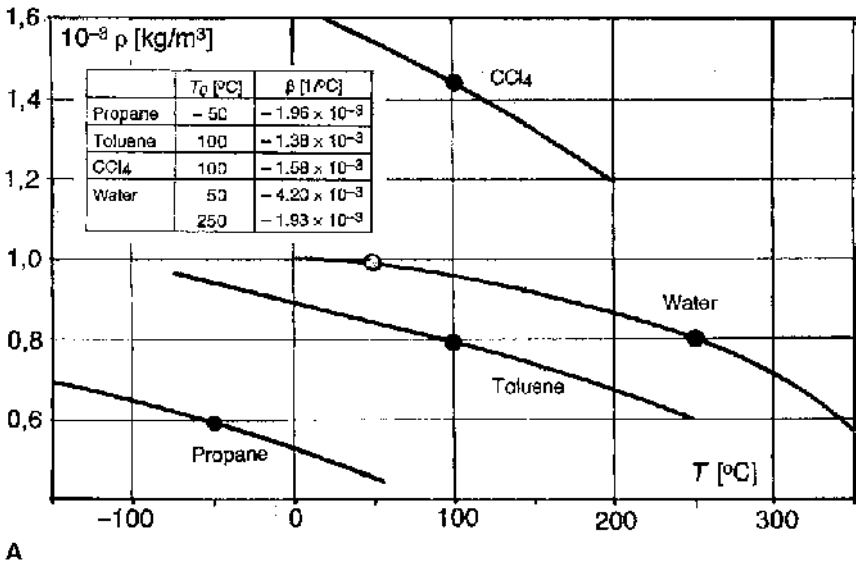
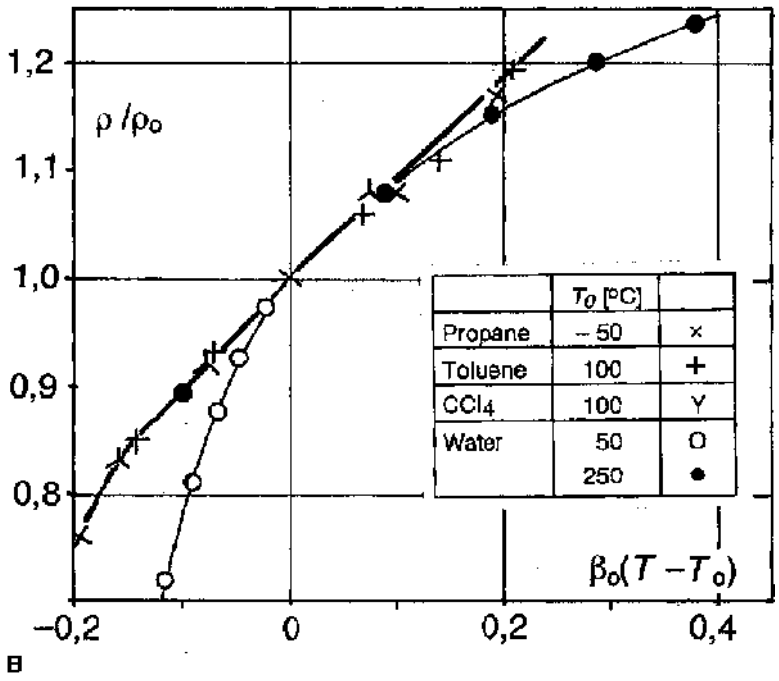


A



B

Figure 4 (A) Temperature dependency of the density, ρ(T), for four different liquids. (B) The standard representation of the behavior ρ(T) for the same liquids.

[sec^{-1}]. The proportionality constant, the dynamic viscosity μ, is the only material constant in Newton's law of motion:

$$\tau = \mu\dot{\gamma} \tag{31}$$

μ depends only on temperature.

In the case of non-Newtonian liquids, μ depends on $\dot{\gamma}$ as well. These liquids can be classified into various categories of materials depending on their flow behavior: $\mu(\dot{\gamma})$ = flow curve and $\mu(\tau)$ = viscosity curve.

D. Pseudoplastic Fluids

An extensive class of non-Newtonian fluids is formed by pseudoplastic fluids whose flow curves obey the so-called "power law":

$$\tau = K\dot{\gamma}^{m} \rightarrow \mu_{\text{eff}} = K\dot{\gamma}^{(m-1)} \tag{32}$$

These liquids are known as Ostwald–de Waele fluids. Figure 5 depicts a typical course of such a flow curve. Figure 6 shows a dimensionless standardized material function of two pseudoplastic fluids often used in biotechnology. It proves that they behave similarly with respect to viscosity behavior under shear stress.

E. Viscoelastic Liquids

Almost every biological solution of low viscosity [but also viscous biopolymers like xanthane and dilute solutions of long-chain polymers, e.g., carboxymethylcellulose (CMC), polyacrylamide (PAA), and polyacrylnitrile (PAN)] displays

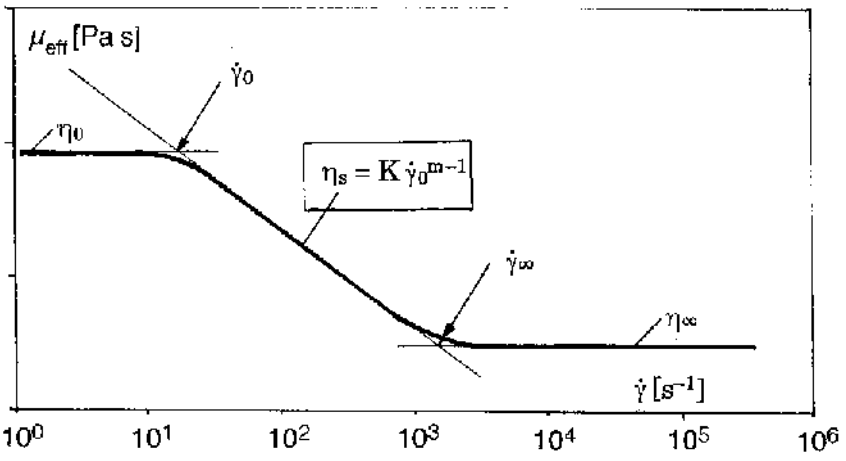


Figure 5 Typical flow behavior of pseudoplastic fluids.

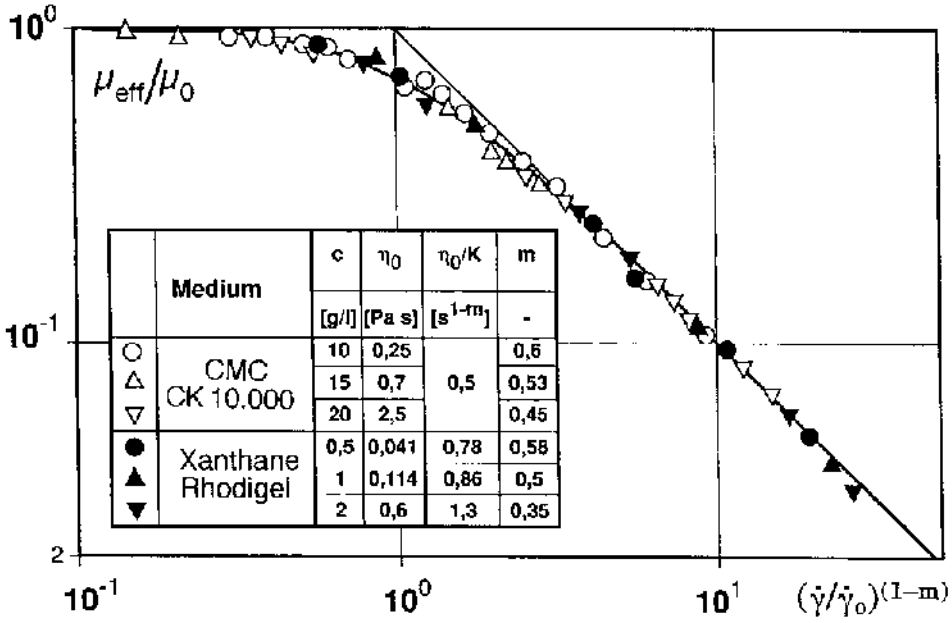


Figure 6 Dimensionless standardized material function of some pseudoplastic fluids used as model substances in biotechnological research. (From Ref. 2.)

not only viscous but also viscoelastic flow behavior. These liquids are capable of storing a part of the deformation energy elastically and reversibly. They evade mechanical stress by contracting like rubber bands. This behavior causes a secondary flow that often runs contrary to the flow produced by mass forces (e.g., the liquid "climbs" the shaft of a stirrer, the so-called "Weissenberg effect").

Elastic behavior of liquids is characterized mainly by the ratio of first differences in normal stress, N_1, to the shear stress, τ. This ratio, the Weissenberg number $\mathrm{Wi} = N_1/\tau$, is usually represented as a function of the rate of shear $\dot{\gamma}$. Figure 7 depicts flow curves of some viscoelastic fluids, and Figure 8 presents a dimensionless standardized material function of these fluids. It again verifies that they behave similarly with respect to viscoelastic behavior under shear stress.

F. Pi Set for Non-Newtonian Fluids

The transition from a Newtonian to a non-Newtonian fluid results in the following consequences regarding the extension of the pi set.

1. All pi numbers of the Newtonian case also appear in the non-Newtonian case, whereby μ is exchanged by a quantity H with the dimension of viscosity (mostly μ_0).

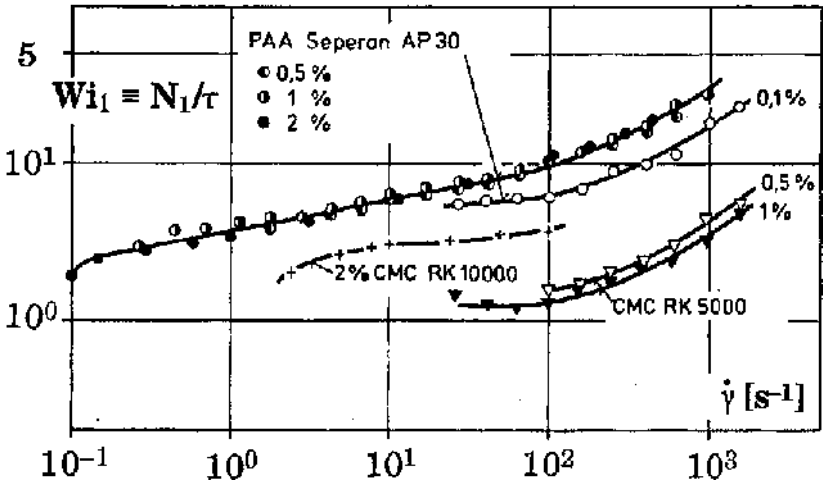


Figure 7 Flow curves of viscoelastic fluids often used in the biotechnological research (PAA, CMC). (From Ref. 12.)

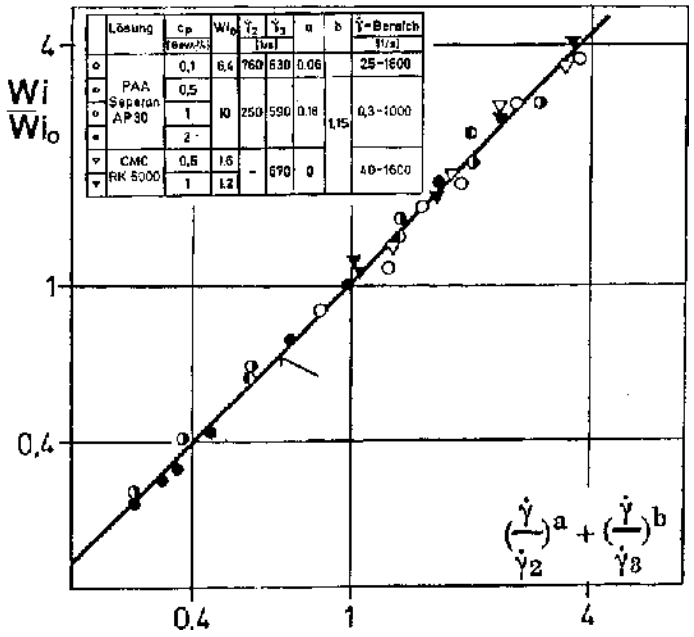


Figure 8 Dimensionless standardized material function of the fluids in Figure 7, verifying the similar viscoelastic behavior under shear stress. (From Ref. 12.)

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2. An additional pi number appears that contains a quantity Θ with the dimension of time (mostly $1/\dot{\gamma}_0$).
3. The pure material numbers are extended by Π_{rheol}.

The table below illustrates this using the example chosen at the beginning of this chapter, namely the heat transfer characteristics of a mixing vessel or a smooth straight pipe, Eq. (27). It shows the complete set of pi numbers for a temperature independent (a) and temperature dependent (b) viscosity of a Newtonian and a non-Newtonian fluid.

(33)

	Newtonian fluid	non-Newtonian fluid
a	Nu, Re, Pr	Nu, Re_H, Pr_H, $\nu\Theta/\text{L}$, Π_{rheol}
b	Nu, Re_0, Pr_0, $\gamma_0\,\Delta T$	Nu, $\text{Re}_{H\text{o}}$, $\text{Pr}_{H\text{o}}$, $\upsilon\Theta_0/L$, $\gamma_{H\text{o}}\Delta T$, γ_Θ/γ_H, Π_{rheol}

In (b), the pi numbers μ_w/μ and $\gamma_{\text{Ho}}\Delta\text{T}$ as well as γ_Θ/γ_H, have to be added ($\gamma_\Theta \equiv \partial\ln\Theta/\partial T$). Besides this, completely other phenomena can occur (e.g., creeping of a viscoelastic liquid on a rotating stirrer shaft opposite to gravity—the so-called Weissenberg effect) that require additional parameters (in this case g) to be incorporated into the relevance list.

VII. DETERMINATION OF OPTIMUM PROCESS CONDITIONS BY COMBINING PROCESS CHARACTERISTICS

The next example shows how a meaningful combination of appropriate process characteristics makes it possible to gain the information necessary for the optimization of the process in question.

Example 5: Optimum Conditions for the Homogenization of Liquid Mixtures. The homogenization of miscible liquids is one of most frequent mixing operations. It can be executed properly if the power characteristics and the mixing-time characteristics of the stirrer in question are known. If these characteristics are known for a series of common stirrer types under favorable installation conditions, one can go on to consider optimum operating conditions by asking the following question: Which type of stirrer operates within the requested mixing time θ with the lowest power consumption P and hence the minimum mixing work ($P\theta$ = min) in a given material system and a given vessel (vessel diameter D)?

Example 5.1: Power Characteristics of a Stirrer. The relevance list for this task consists of the target quantity (mixing power P) and the following parameters: stirrer diameter d, density ρ and kinematic viscosity ν of the liquid, and stirrer

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speed n:

$$\{P; d; \rho, \nu; n\} \tag{34}$$

By choosing the dimensional matrix

	ρ	d	n	P	ν
Mass M	1	0	0	1	0
Length L	−3	1	0	2	2
Time T	0	0	−1	−3	−1
		core matrix		residual matrix	

only one linear transformation is necessary to obtain the unity matrix:

	ρ	d	n	P	ν
M	**1**	0	0	1	0
3M + L	0	**1**	0	5	2
−T	0	0	**1**	3	1
		unity matrix		residual matrix	

The residual matrix consists of only two parameters, so only two pi numbers result:

$$\Pi_1 \equiv \frac{P}{\rho^1 n^3 d^5} = \frac{P}{\rho n^3 d^5} \equiv \text{Ne (Newton number)}$$

$$\Pi_2 \equiv \frac{\nu}{\rho^0 n^1 d^2} = \frac{\nu}{n d^2} \equiv \text{Re}^{-1} \text{ (Reynolds number)}$$

The process characteristics

$$\text{Ne} = f(\text{Re}) \tag{35}$$

for three well-known, slowly rotating stirrers (leaf, frame, and cross-beam stirrers) is presented in Fig. 9.

1. In the range Re < 20, the proportionality Ne $\propto$ Re^{-1} is found, thus resulting in the expression NeRe $\equiv P/(\mu n^2 d^3) = \text{const}$. Density is irrelevant here—we are dealing with the *laminar* flow region.
2. In the range Re > 50 (vessel with baffles) or Re $> 5 \times 10^4$ (unbaffled vessel), the Newton number Ne $\equiv P/(\rho n^3 d^5)$ remains constant. In this case, viscosity is irrelevant—we are dealing with a *turbulent* flow region.

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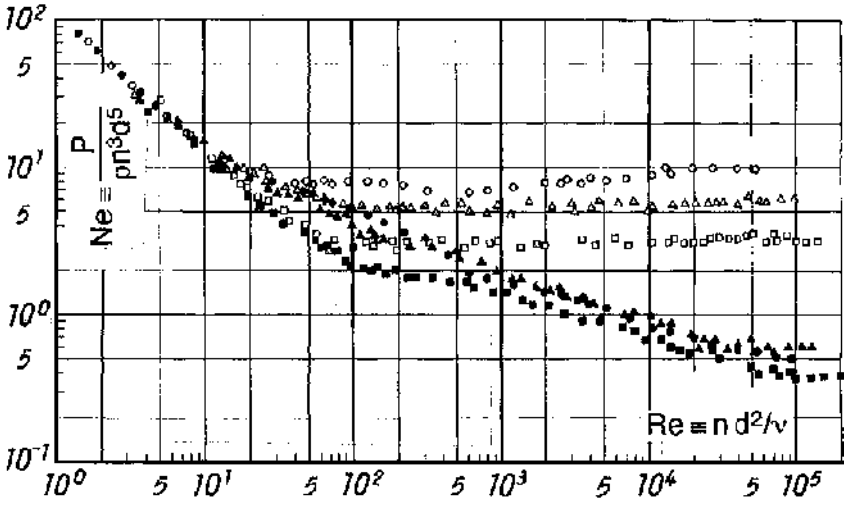

Figure 9 Power characteristics for three slowly rotating stirrers (leaf, frame, cross-beam stirrers) installed in a vessel with and without baffles. Stirrer geometry and the installation conditions are given in Figure 10. (From Ref. 13.)

3. Understandably, the baffles do not influence the power characteristics within the laminar flow region, where viscosity forces prevent rotation of the liquid. However, their influence is extremely strong at $\mathrm{Re} > 5 \times 10^4$. Here, the installation of baffles under otherwise unchanged operating conditions increases the power consumption of the stirrer by a factor of 20!
4. The power characteristics of these three stirrers do not differ much from each other. This is understandable because their mixing patterns are very similar.

Example 5.2: Mixing-Time Characteristics of a Stirrer. Mixing time θ is the time necessary to completely homogenize an admixture with the liquid contents of the vessel. It can easily be determined visually by a decolorization reaction (neutralization, redox reaction in the presence of a color indicator). The relevance list of this task consists of the target quantity (mixing time θ) and of the same parameters as in the case of mixing power—on condition that (contrary to Example 3) both liquids have similar physical properties):

$$\{\theta; d; \rho, \nu; n\} \tag{36}$$

This relevance list yields the two parametric mixing-time characteristics

$$n\theta = f(\mathrm{Re}) \tag{37}$$

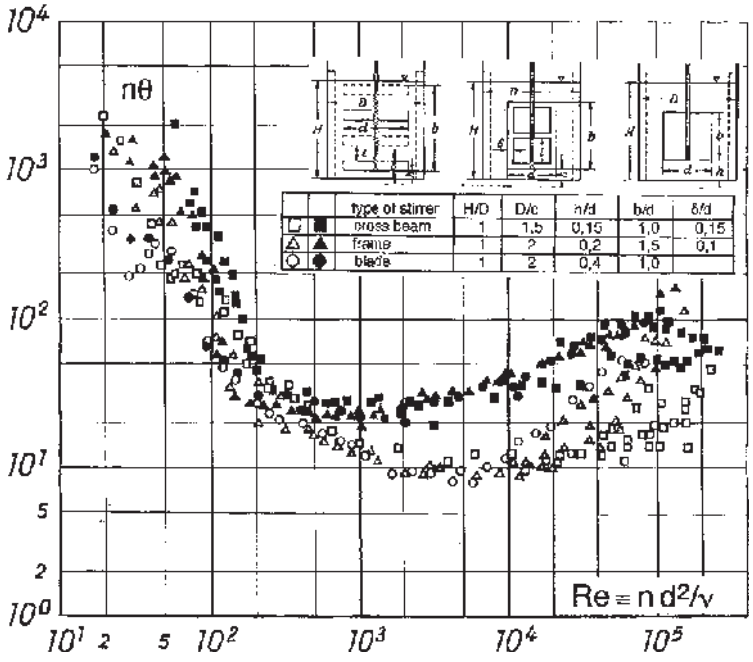

Figure 10 Mixing-time characteristics for three slowly rotating stirrers (leaf, frame, cross-beam stirrers) in a vessel with and without baffles. To correlate the data in order to emphasize the similarity, $n\theta$ values of the cross-beam stirrer were multiplied by 0.7 and of the leaf stirrer by 1.25. Full signs: unbaffled vessel. (From Ref. 13.)

For the three stirrer types treated in this example, the mixing-time characteristics are presented in Fig. 10.

One should not be mistaken by the course of the $n\theta(\mathrm{Re})$ curves: The mixing time does not increase with higher Re numbers, it simply diminishes more slowly until at $\mathrm{Re} \approx 10^6$ the minimum achievable mixing time is reached:

$$n\theta \propto \mathrm{Re} \rightarrow \theta \propto d^2/\nu \qquad (\mathrm{Re} \geqslant 10^6) \tag{38}$$

From Eq. (38) we learn that the minimum achievable mixing time corresponds to the square of the stirrer diameter: Bigger volumes require longer mixing times.

A. Minimum Mixing Work ($P\theta$ = min) for Homogenization

To gain the information on minimum mixing work ($P\theta$ = min) necessary for a homogenization, the mixing-time characteristics as well as the power characteristics have to be combined in a suitable manner. Both of them contain the rotational speed n and the stirrer diameter d, knowledge of which would unnecessarily con-

strict the statement. Therefore the ratio D/d, tank diameter/stirrer diameter, which is known for frequently used stirrer types, also has to be incorporated.

From the pi frame

$$\{\text{Ne}, n\theta, \text{Re}, D/d\} \tag{39}$$

the following two dimensionless numbers can now be formed:

$$\Pi_1 \equiv \text{Ne Re } D/d = \frac{PD}{\rho\nu^3} = \frac{PD\rho^2}{\mu^3} \tag{40}$$

$$\Pi_2 \equiv n\theta \, \text{Re}^{-1} \, (D/d)^2 = \frac{\theta\nu}{D^2} = \frac{\theta\mu}{D^2\rho} \tag{41}$$

These numbers could have been extracted in advance from the following relevance list:

$$\{P, \theta; D; \nu, \rho\} \tag{42}$$

which results in the following dimensional matrix:

	ρ	d	n	P	ν
M	1	0	0	1	0
L	−3	1	0	2	2
T	0	0	−1	−3	−1
M	**1**	0	0	1	0
L + 3M	0	**1**	0	5	2
−T	0	0	**1**	3	1

Figure 11 shows this relationship $\Pi_1 = f(\Pi_2)$ for those stirrer types that exhibit the lowest Π_1 values within a specific range of Π_2, i.e., the stirrers requiring the least power in this range. It represents the working sheet for the determination of optimum working conditions on the homogenization of liquid mixtures in mixing vessels.

This graph is extremely easy to use. The physical properties of the material system, the diameter of the vessel (D), and the desired mixing time (θ) are all known, and this is enough to generate the dimensionless number Π_2.

1. From the numerical value of Π_2 the stirrer type and baffling conditions can be read off the abscissa. The diameter of the stirrer and the installation conditions can be determined from data on stirrer geometry in the sketch.

The curve $\Pi_1 = f(\Pi_2)$ in Figure 11 then provides the following information.

2. The numerical value of Π_1 can be read off at the intersection of the Π_2 value with the curve. The power consumption P can then be calculated from this.

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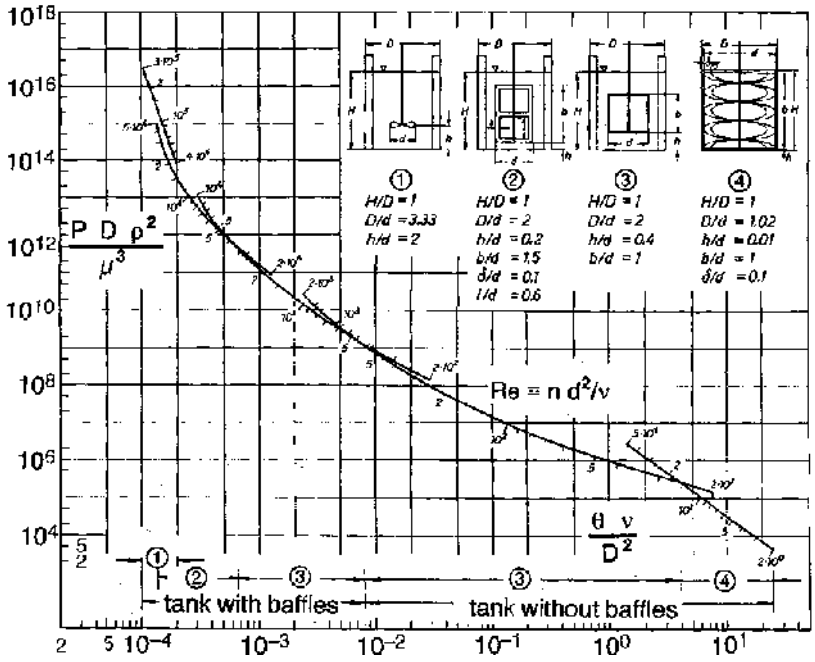

Figure 11 Working sheet for the determination of optimum working conditions in the homogenization of liquid mixtures in mixing vessels. (From Ref. 13.)

3. The numerical value of Re can be read off the Re scale at the same intersection. This, in turn, makes it possible to determine the rotational speed of the stirrer.

For further examples of this optimization technique see Refs. 5 and 11.

VIII. DIMENSIONAL ANALYSIS AND SCALE-UP OF MILLS FOR EMULSIFICATION AND FOR GRINDING

In this section, two unit operations will be discussed that are often encountered in the pharmaceutical industry.

Example 6: Emulsification of Nonmiscible Liquids. Liquid/liquid emulsions consist of two (or more) nonmiscible liquids. Classic examples of oil in water (O/W) emulsions are milk, mayonnaise, lotions, creams, water-soluble paints, and photo emulsions. As appliances serve dispersion and colloid mills, as well as high-pressure homogenizers. All of them utilize a high-energy input to produce the finest droplets of the disperse (mostly oil) phase. The aim of this oper-

ation is the narrowest possible droplet size distribution. It is normally characterized by the "Sauter mean diameter" d_{32} [14] or by the median d_{50} of the size distribution. d_{32} or d_{50}, respectively, therefore has to be regarded as the target quantity of this operation.

The characteristic length of the dispersion chamber, e.g., the slot width between rotor and stator in dispersion mills or the nozzle diameter in high-pressure homogenizers (utilizing high-speed fluid shear), will be denoted as d.

As material parameters, the densities and the viscosities of both phases as well as the interfacial tension σ must be listed. We incorporate the material parameters of the disperse phase ρ_d and μ_d in the relevance list and note separately the material numbers ρ/ρ_d and μ/μ_d. Additional material parameters are the (dimensionless) volume ratio of both phases φ and the mass portion c_i of the emulsifier (surfactant) (e.g., given in ppm).

The process parameters have to be formulated as intensive quantities. In appliances where liquid throughput q and power input P are separated from each other as two freely adjustable process parameters, the volume-related power input P/V and the period of its duration ($\tau = V/q$) must be considered:

$$(P/V)\,\tau = E/V\,[M\,L^{-1}\,T^{-2}] \tag{43}$$

In appliances with only one degree of freedom (e.g., high-pressure homogenizers), the power is being introduced by the liquid throughput. Here, the relevant intensively formulated power P is therefore power per liquid throughput, P/q. In nozzles, $P \propto \Delta p\, q$, which results in

$$P/q = (\Delta p\, q)/q = \Delta p[M\,L^{-1}\,T^{-2}] \tag{44}$$

Therefore, the volume-related energy input E/V and the throughput-related power input P/q ($\triangleq \Delta p$) represent homologous quantities of the same dimension. For the sake of simplicity Δp will be introduced in the relevance list.

Now, this six-parameter relevance list of the dimensional parameters (the dimensionless parameters ρ/ρ_d, μ/μ_d, φ, c_i are excluded) reads

$$\{d_{32};\, d;\, \rho_d,\, \mu_d,\, \sigma;\, \Delta p\} \tag{45}$$

The corresponding dimensional matrix

	ρ_d	d	σ	Δp	μ_d	d_{32}
M	1	0	1	1	1	0
L	−3	1	0	−1	−1	0
T	0	0	−2	−2	−1	0
M + T/2	**1**	0	0	0	1	0
3M + L + 3T/2	0	**1**	0	3	2	1
−T/2	0	0	**1**	1	1	2

delivers the remaining three dimensionless numbers:

$$\Pi_1 \equiv \frac{\Delta p\, d}{\sigma} \qquad \equiv \text{Eu We} \qquad \equiv \text{La (Laplace number)}$$

$$\Pi_2 \equiv \frac{\mu_d}{(\rho_d\, d\, \sigma)^{\frac{1}{2}}} \qquad \equiv \frac{\text{We}^{\frac{1}{2}}}{\text{Re}} \qquad \equiv \text{Oh (Ohnesorge number)}$$

$$\Pi_3 \equiv d_{32}/d$$

The complete pi set is given as

$$\{d_{32}/d,\ \text{La},\ \text{Oh},\ \rho/\rho_d,\ \mu/\mu_d,\ \varphi,\ c_i\} \tag{46}$$

Assuming a quasi-uniform power distribution in the throughput or in the volume, a characteristic length of the dispersion space becomes irrelevant. In the relevance list, Eq. (45), the parameter d must be cancelled. The target number $\Pi_3 \equiv d_{32}/d$ has to be dropped and the dimensionless numbers La* and Oh* have to be built by d_{32} instead of d. At given and constant material conditions (ρ/ρ_d, μ/μ_d, φ, c_i = const) the process characteristics will be represented in the following pi space:

$$\text{Oh}^{*-2} = f(\text{La}^*\text{Oh}^{*2}) \qquad \rightarrow \qquad d_{32}\left(\frac{\rho_d\,\sigma}{\mu_d^{\,2}}\right) = f\left\{\Delta p\left(\frac{\mu_d^{\,2}}{\rho_d\,\sigma^2}\right)\right\} \tag{47}$$

This dependency has been confirmed on two colloid mills in the scale 1:2.2 [15]; see Fig. 12. For a material system of vegetable oil/water and $\varphi = 0.5$, the following correlation is found:

$$d_{32} = 4.64 \times 10^5 \Delta p^{-\frac{2}{3}} \qquad d_{32}[\mu\text{m}]; \quad \Delta p[\text{M}/(\text{L}\,\text{T}^2)] \tag{48}$$

Similar results have been presented for other two-parameter appliances [16].

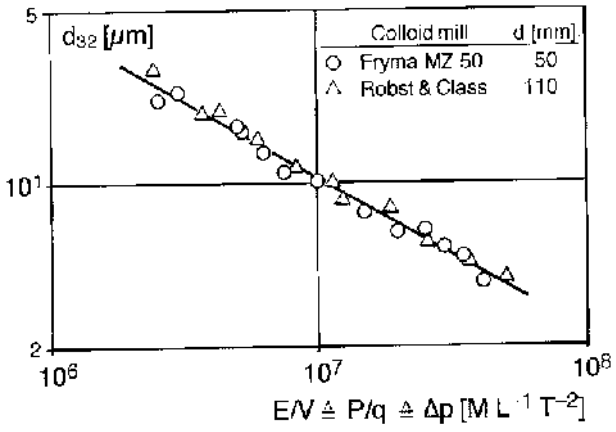

Figure 12 The relationship $d_{32} = f(\Delta p)$ for two colloid mills of different size. Material system: vegetable oil/water and $\varphi = 0.5$. (From Ref. 15.)

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It should be pointed out that the dimensional representations in the form of Eq. (48) as $d_{32} = f(\Delta p)$ present a serious disadvantage as compared to the dimensionless one: Eq. (48) is valid only for the investigated material system and tells nothing about the influence of the physical parameters!

Example 7: Fine Grinding of Solids in Stirred-Ball Mills. The fine grinding of solids in mills of different shape and mode of operation is used to produce finest particles with a narrow particle size distribution. Therefore—as in the previous example—the target quantity is the median value d_{50} of the particle size distribution.

The characteristic length of a given mill type is *d.* The physical properties are given by the particle density ρ_p, the specific energy of the fissure area β, and the tensile strength σ_Z of the material. Should there be additional material parameters of relevance, they can easily be converted to material numbers by the aforementioned ones.

As process parameter, the mass-related energy input $E/\rho V$ must be taken into account. The relevance list reads

$$\{d_{50}; d; \rho_p, \beta, \sigma_Z; E/\rho V\} \tag{49}$$

	ρ_p	d	β	$E/\rho V$	σ_Z	d_{50}
M	1	0	1	0	1	0
L	−3	1	0	2	−1	1
T	0	0	−2	−2	−2	0
M + T/2	**1**	0	0	−1	0	0
3M + L + 3T/2	0	**1**	0	−1	−1	1
−T/2	0	0	**1**	1	1	0

From this dimensional matrix the following pi set arises:

$$\{d_{50}/d, (E/\rho V)\rho d/\beta, \sigma_Z d/\beta\} \tag{50}$$

Assuming a quasi-uniform energy input in the mill chamber, its characteristic diameter *d* will be irrelevant. Then the pi set is reduced to

$$\{(E/\rho V)\rho d_{50}/\beta, \sigma_Z d_{50}/\beta\} \quad \rightarrow \quad d_{50}(\sigma_Z/\beta) = f\{(E/\rho V)(\rho/\sigma_Z)\} \tag{51}$$

In the case of unknown physical properties, σ_Z and β, Eq. (51) is reduced to $d_{50} = f(E/\rho V)$, which is then used for the scale-up of a given type of mill and a given grinding material.

For fine-grinding of, e.g., limestone for paper and pottery manufacturing, bead mills are widely used. The beads of steel, glass, or ceramic have a diameter of 0.2–0.3 mm and occupy up to 90% of the total mill volume ($\phi \leq 0.9$). They are

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kept in motion by perforated stirrer discs while the liquid/solid suspension is pumped through the mill chamber. Mill types frequently in use are stirred disc mill, centrifugal fluidized-bed mill, ring gap mill.

H. Karbstein et al. [17] pursued the question of the smallest size of the laboratory bead mill that would still deliver reliable data for scale-up. In different-size rigs ($V = 0.25$–25 liters) a sludge consisting of limestone ($d_{50} = 16$ μm) and 10% aqueous Luviscol solution (mass portion of solids $\varphi = 0.2$) was treated. It was found that the minimum size of the mill chamber should be $V = 1$ liter. A further, unexpected but dramatic result was that the validity of the process characteristics

$$d_{50} \propto (E/\rho V)^{-0.43} \qquad E/\rho V \leqslant 10^4 \tag{52}$$

expires at $E/\rho V \cong 10^4$ and the finest particle diameter cannot fall below $d_{50} \cong 1$ μm.

These facts and the scattering of the results made a systematic investigation of the grinding process necessary [18]. The grinding process in bead mills is determined by the frequency and the intensity of the collision between beads and grinding medium. According to this assumption, the grinding result will remain constant if both these quantities are kept constant. The intensity of the collision is essentially given by the kinetic energy of the beads:

$$E_{\text{kin}} \propto m_M u^2 \propto \mathrm{V_M}\, \rho_{\mathrm{M}}\, \mathrm{u}^2 \propto \mathrm{d_M^3}\, \rho_{\mathrm{M}}\, \mathrm{u}^2 \tag{53}$$

($\mathrm{d_M}$, ρ_{M} = diameter and density of the mill beads, u = tip velocity of the stirrer). On the other hand, the frequency depends on the size of the mill chamber and therefore on the overall mass-related energy input. To achieve the same grinding result in different-size bead mills, E_{kin} as well as $E/\rho V$ have to be kept idem. The input of the mechanical energy can be measured from the torque and the rotational speed of the perforated discs, and the kinetic energy can be calculated from Eq. (53).

The preceding assumption was examined with the same material system and the same grinding media (beads). Three different-size bead mills were used (V [liters] = 0.73; 5.54; 12.9). Figure 13 shows the results. To achieve a satisfactory correlation, the size of the mill chamber d will have to be introduced in the relevance list. A further finding is that under the same conditions a smaller mill delivers a coarser product. This had already been found in the previously cited paper [17].

As to the course of the function $d_{50} = f(E_{\text{kin}})$ at $E/\rho V = 10^3$ kJ/kg = const, the following explanation is given in Ref. 18. With E_{kin} increasing, the particle size first diminishes but later increases. This is plausible if the introduced specific energy is viewed as a product of the frequency and the intensity of the collision. At $E/\rho V$ = const and increasing the intensity of the collision, the frequency has to diminish, resulting in a coarser product.

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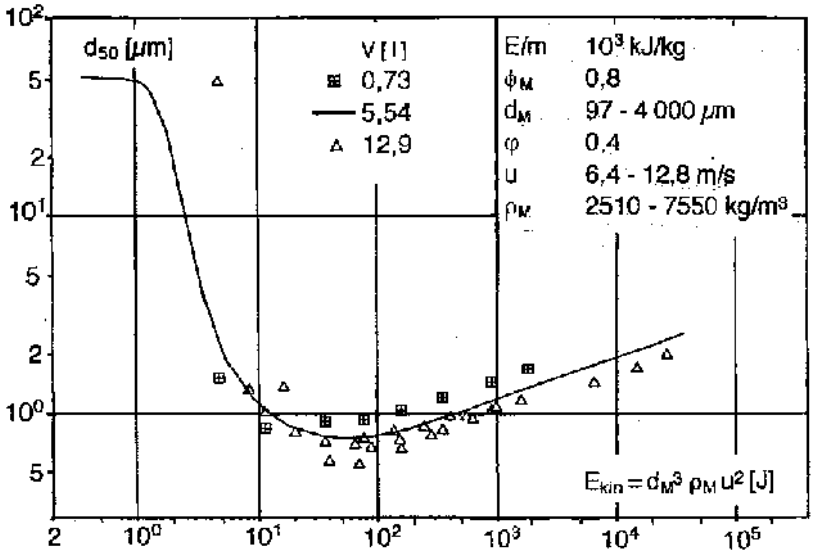

Figure 13 The relationship $d_{50} = f(E_{\text{kin}})$ for three colloid mills of the same type but different size. Identical material system and constant $E/\rho V = 10^3$ kJ/kg. (From Ref. 18.)

IX. NOMENCLATURE

a	thermal diffusivity ($\equiv\lambda/\rho C_p$)
A	surface
c_f	concentration of foamer and flocculant, resp.
C_p	heat capacity at constant pressure
d	stirrer diameter
d_p	particle or droplet diameter
D	vessel diameter
$\boldsymbol{D}$	diffusivity
F	force
g	gravitational accleration
G	gravitational constant
l, L	characteristic length
m	mass
M	dimension of mass
n	rotational speed
$p, \Delta p$	pressure, pressure difference
P	power
q	volumetric throughput

$\boldsymbol{R}$	universal gas constant
t	(running) time
T	dimension of time
v	velocity
v_s	velocity of sound
V	liquid volume

A. Greek Characters

β	temperature coefficient of density; specific energy of the fissure area in grinding
ϕ	degree of filling
γ	temperature coefficient of dynamic viscosity
$\dot{\gamma}$	shear rate
ν	kinematic viscosity
μ	dynamic viscosity; scale-up factor ($\mu = l_T/l_M$)
φ	volume or mass portion
λ	termal conductivity
Π	dimensionless product
ρ, $\Delta\rho$	density, density difference
σ	(interfacial) surface tension
σ_Z	tensile strength
θ	period of time
T, ΔT	temperature, temperature difference
Θ	dimension of temperature
τ	residence time; shear stress

B. Subscripts

G	gas
L	liquid
S	solid
M	model, laboratory scale
T	technological, industrial scale

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2
Parenteral Drug Scale-Up

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I. INTRODUCTION

The term *parenteral* is applied to preparations administered by injection through one or more layers of skin tissue. The word, derived from the Greek words *para* and *etheron,* meaning "outside of the intestine," is used for those dosage forms administered by routes other than the oral route. Because the administration of injectables, by definition, requires circumventing the highly protective barriers of the human body, the skin, and the mucous membranes, the dosage form must achieve an exceptional purity. This is generally accomplished by strict adherence to good manufacturing practices.

The basic principles employed in the preparation of parenteral products do not vary from those widely used in other sterile and nonsterile liquid preparations. However, it is imperative that all calculations be accurate and precise. Therefore, the issue of parenteral solution scale-up essentially becomes a liquid scale-up task, which requires a high degree of accuracy. A practical yet scientifically sound means of performing this scale-up analysis of liquid parenteral systems is presented in this chapter. The approach is based on the scale-of-agitation method. For single-phase liquid systems, the primary scale-up criterion is equal liquid motion when comparing pilot-size batches to a larger, production-size batches.

One of the most important processes involved in the scale-up of liquid parenteral preparations is mixing [1]. For liquids, mixing can be defined as a transport process that occurs simultaneously in three different scales, during which one substance (*solute*) achieves a uniform concentration in another substance (*solvent*). On a large, visible scale, mixing occurs by *bulk diffusion,* in which the elements are blended by the pumping action of the mixer's impeller. On the microscopic scale, elements that are in proximity are blended by eddy currents, and they

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create drag, where local velocity and shear-stress differences act on the fluid. On the smallest scale, final blending occurs via molecular diffusion, whose rate is unaffected by the mechanical mixing action. Therefore, large-scale mixing depends primarily on flow within the vessel, whereas small-scale mixing is dependent mostly on shear. This approach focuses on large-scale mixing using three viable approaches, specifically concentrating on the scale-of-agitation method.

II. GEOMETRIC SIMILARITY

There are several methods to achieve appropriate scale-up of mixing. The first involves geometric similarity. This technique employs proportional scale-up of geometric parameters of the vessel. The scaled-up parameters may include such geometric ratios as D/T, where D is the diameter of the impeller and T is the diameter of the tank, and Z/T, where Z is the height of the liquid in the vessel. Similar ratios are compared for both small-scale equipment (D_1T_1) and the larger-scale equipment (D_2T_2). For example,

$$R = D_1T_1 = D_2T_2 \tag{1}$$

where R is the geometric scaling factor.

After R has been determined, other required parameters, such as the rotational speed of the larger equipment, can then be calculated by power law relationships. In the preceding example, the required rotational speed, N, can be calculated as

$$N_2 = N_1\left(\frac{1}{R}\right)^n \tag{2}$$

Rotational speeds may be expressed either in terms of rpm or in terms of $\sec^{-1}$. The power law exponent, n, has a definite physical significance. The value of n and its corresponding significance are determined either empirically or through theoretical means. Table 1 lists the most common values assigned to n.

The scale-up can be completed by using predicted values of N_2 to determine the horsepower requirements of the large-scale system. In most designs, D/T will be in the following range:

$$0.15 \leq \frac{D}{T} \leq 0.6 \tag{3}$$

and Z/T will be in the range

$$0.3 \leq \frac{Z}{T} \leq 1.5 \tag{4}$$

These values, in conjunction with N and the horsepower requirements, completely define the major parameters of the systems.

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Table 1 Common Values Assigned to the Power Law Exponent, n, When Comparing Large- to Small-Scale Equipment

n	Physical interpretation
0	Equal blend time
$\frac{1}{2}$	Equal surface motion
$\frac{2}{3}$	Equal mass transfer rates
$\frac{3}{4}$	Equal solids supension
1	Equal liquid motion (equal average fluid velocity)

III. DIMENSIONLESS NUMBERS METHOD

The second method for achieving appropriate scale-up of mixing uses dimensionless numbers to predict scale-up parameters. The use of dimensionless numbers simplifies design calculations by reducing the number of variables to consider. The dimensionless-number approach has been used with good success in heat transfer calculations and to some extent in gas dispersion (mass transfer) for mixer scale-up. Usually, the primary independent variable in a dimensionless-number correlation is the Reynolds number:

$$N_{\mathrm{Re}} = \frac{D^2 \rho N}{\mu} \tag{5}$$

where

N = shaft speed (sec^{-1})
D = propeller blade diameter (cm)
ρ = density of solution dispersion ($\mathrm{g/cm}^3$)
μ = viscosity of solution dispersion (g/[cm/sec]).

Other dimensionless numbers are used widely for various scale-up applications. One example is the Froude number:

$$N_{\mathrm{Fr}} = \frac{DN^2}{g} \tag{6}$$

where g is acceleration due to gravity in $\mathrm{cm/sec}^{-1}$. The Froude number compares inertial forces to gravitational forces inside the system.

Another example is the power number, which is a function of the Reynolds number and the Froude number:

$$N_P = \frac{P g_c}{\rho N^3 D^5} \tag{7}$$

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where P is power and g_c is a gravitational conversion factor. This number relates density, viscosity, rotational speed, and the diameter of the impeller. The power number correlation has been used successfully for impeller geometric scale-up. Approximately half a dozen other dimensionless numbers are involved in the various aspects of mixing, heat and mass transfer, etc.

Both of the preceding methods belong to a traditional fluid mechanical approach known as *dimensional analysis* [2]. Unfortunately, these methods cannot always achieve results in certain manufacturing environments. Therefore, a third method is introduced, which can be applied easily to the various research and production situations. This method actually is a combination of the first two methods.

IV. SCALE-OF-AGITATION APPROACH

The basis of the scale-of-agitation approach is a geometric scale-up with the power law exponent, $n = 1$ (see Table 1). This provides for equal fluid velocities in both large- and small-scale equipment. Furthermore, several dimensionless groups are used to relate the fluid properties to the physical properties of the equipment being considered. In particular, bulk-fluid velocity comparisons are made around the largest blade in the system. This method is best suited to turbulent flow agitation in which tanks are assumed to be vertical cylinders.

Although good success may be achieved in applying this technique to marine-type propeller systems, the original development was based on low-rpm, axial, or radial impeller arrangements. Because the most intensive mixing occurs in the volume immediately around the impeller, this discussion focuses on this particular region of mixing. Table 2 describes the nomenclature used to develop the theory behind the approach.

The analysis proceeds as follows. First, determine the D/T ratio of the tank, based on the largest impeller, in which the original (usually R&D) batches had

Table 2 Nomenclature

Q	Effective pumping capacity or volumetric pumping flow, in cm^3/sec
N	Shaft speed, in sec^{-1}
N_{Re}	Impeller Reynolds number, dimensionless
N_Q	Pumping number, dimensionless
D	Diameter of the largest mixer blade, in cm
ρ	Density of the fluid, in g/cm^3
μ	Viscosity of the fluid, in g/[cm/sec]
v_b	Bulk fluid velocity, in cm
T	Diameter of the tank, in cm
A	Cross-sectional area of the tank, in cm^2

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been compounded. It is also necessary to know the rotational speed and the horsepower of the mixer used.

The only two product physical properties needed are density and viscosity. Generally, parenterals, like most solution-type products, will follow Newtonian fluid behavior and may also be considered incompressible. Therefore, point densities and viscosities can be used satisfactorily.

The next step in the analysis is to calculate the impeller Reynolds number achieved during this original compounding using Eq. (5). The impeller Reynolds number must be greater than 2000 to proceed with the analysis [3]. Mixing achieved in the initial R&D processing must be in the turbulent range. If the impeller Reynolds number is less than 2000, then mixing in the pilot tank was either inadequate or represented some other special case, such as moderately viscous fluids. In these situations, another D/T ratio curve must be used.

Proceeding further, obtain the value of the terminal pumping number in the R&D pilot process by using the following formula:

$$N_Q = 1.1283 - 1.07118\left(\frac{D}{T}\right) \tag{8}$$

Equation (8) is an empirical relationship obtained by the linear regression between D/T and the terminal pumping numbers [4]. It is important to note that a family of curves exists for each D/T ratio when N_Q (pumping number) is plotted against the impeller Reynolds number [5]. In the turbulent range ($N_{\mathrm{Re}} > 2000$), the N_Q curves flatten out and thus are independent of the Reynolds number. The terminal pumping number, $N_{Q/\mathrm{Re}>2000}$, plotted against the D/T ratio results in Eq. (8). The cross-sectional area of the pilot-size tank is determined by using Eq. (9):

$$A = \frac{\pi T^2}{4}\ \mathrm{cm}^2 \tag{9}$$

Then the value of the effective pumping capacity for the pilot-size mixer is calculated using Eq. (10):

$$Q = N_Q N D^3\ \mathrm{cm}^3/\mathrm{sec} \tag{10}$$

Finally, by inserting the values derived in Eqs. (9) and (10) into Eq. (11), the value for bulk-fluid velocity around the largest impeller of the system is obtained:

$$v_b = \frac{Q}{A}\ \mathrm{cm/sec} \tag{11}$$

The bulk-fluid velocity can be inserted into Table 3 to determine the level of agitation achieved in the original R&D pilot batch. The larger-size production tank and mixer are then designed so that the scale of agitation produced in the larger vessel matches that required for the pilot-size batches. The scale-of-agitation approach was first developed in the mid-1970s by engineers at Chemineer,

Table 3 Process Requirements: The Set Degree of Agitation for Blending and Motion

Scale of agitation	Bulk-fluid velocity (cm/sec)	Description of mixing
1	3	Agitation levels 1 and 2 are characteristic of applications requiring minimum fluid velocities to achieve the product result
2	6	Agitators capable of level 2 will: a. Blend miscible fluids to uniformity if specific gravity differences are less than 0.1 and if the viscosity of the most viscous is less than 100 times that of the other b. Establish complete fluid-batch control c. Produce a flat but moving fluid-batch surface
3	9	Agitation levels 3–6 are characteristic of fluid velocities in most chemical (including pharmaceutical) industries agitated batches
4	12	Same as 3
5	15	Same as 3 and 4
6	18	Agitators capable of level 6 will: a. Blend miscible fluids to uniformity if specific gravity differences are less than 0.6 and if the viscosity of the most viscous is less than 10,000 times that of the other b. Suspend trace solids ($<2\%$) with settling rates of 2–4 ft/min c. Produce surface rippling at lower viscosities
7	21	Agitation levels 7–10 are characteristic of applications requiring high fluid velocities for process result, such as mixing of the high-viscosity suspension preparations
8	24	Same as 7
9	27	Same as 7 and 8
10	30	Agitators capable of level 10 will: a. Blend miscible fluids to uniformity if specific gravity differences are less than 1.0 and if the viscosity of the most viscous is less than 100,000 times that of the other b. Suspend trace solids ($<2\%$) with settling rates of 4–6 ft/min c. Provide surging surface at low viscosities

Inc. [6]. Table 3 summarizes the scale-of-agitation parameters and gives a qualitative description of the type of mixing associated with the various levels. According to this approach, mixing is a similar process if the calculated bulk-fluid velocities for the production-size vessels lie within ± 1 unit level of the scale of agitation required from an analysis of the R&D pilot batches. It is quite easy to match the required scale of agitation by simply adjusting the rpm when working

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with variable-speed equipment. Thus, a given tank equipped with a variable-speed mixer will generally be capable of several agitation levels.

V. SCALE-OF-AGITATION APPROACH EXAMPLE

To illustrate the actual application of the scale-of-agitation approach to scale-up, the method was applied to the scale-up of typical injectables solution from a 378 liter pilot batch to a 3780 liter production-size batch. The example product is a Newtonian fluid with density of 1.018 g/cm^3 and a viscosity of 0.0588 g/(cm/sec)(5.88 cps). The tank used in the manufacturing of the pilot batch had the following parameters:

T = diameter of the tank = 74.6 cm

A = cross-sectional area = 4371 cm^2

The agitation was accomplished with a turbine-type mixer, and the largest axial impeller was 40.64 cm. The pilot batch was mixed at 90 rpm (1.5 sec^{-1}). From the initial known data the D/T ratio was determined:

$$\frac{D_{378L}}{T_{378L}} = \frac{40.64 \text{ cm}}{74.60 \text{ cm}} = 0.54 \tag{12}$$

Then the value of the impeller Reynolds number was obtained by plugging known values into Eq. (5):

$$N_{\text{Re}(3785L)} = \frac{D_{378L}^2 \rho N_{378L}}{\mu} = \frac{(40.64 \text{ cm})^2 (1.018 \text{ g/cm}^3)(1.5 \text{ sec}^{-1})}{0.0588 \text{ g/(cm/sec)}} = 44449 \tag{13}$$

Because the value of the Reynolds number is greater than 2000, Eq. (8) is used to obtain the pumping number. The pumping number is inserted into Eq. (10) to obtain the effective pumping capacity:

$$Q_{378L} = (N_{Q(378L)})(N_{378L})(D_{378L}^3) = (0.55)(1.5 \text{ sec}^{-1})(40.64 \text{ cm})^3 = 55375 \text{ cm}^3/\text{sec} \tag{14}$$

Knowing the effective pumping capacity of agitation and the cross-sectional area of the pilot-batch tank, bulk-fluid velocity is obtained by using Eq. (11):

$$v_{b(378L)} = \frac{Q_{378L}}{A_{378L}} = \frac{55{,}375 \text{ cm}^3/\text{sec}}{4371 \text{ cm}^2} = 12.6 \text{ cm/sec} \tag{15}$$

Inserting this bulk-fluid velocity into Table 3, one can calculate the level of agitation used in the pilot batch of indictable solution as 4, which is described as

characteristic of fluid velocities in most chemical process industries' agitated batches.

Now the appropriate shaft speed for scaled-up production equipment can be calculated. The tank used for production batches has a capacity of 3780 L. It is equipped with a turbine-type agitator, which has a shaft speed range of 20–58 rpm. The diameter of this tank is 167 cm. The diameter of the largest axial impeller is 87 cm. Given the diameter of the production tank, the cross-sectional area can be determined as

$$A_{3780\text{L}} = \frac{\pi T_{3780\text{L}}^2}{4} = \frac{\pi(167\text{ cm})^2}{4} = 21{,}904\text{ cm}^2 \tag{16}$$

The next step is solving Eq. (10) for effective pumping capacity in the larger vessel:

$$Q_{3780\text{L}} = (v_{b(378\text{L})})(A_{3780\text{L}}) = (12.6\text{ cm/sec})(21{,}904\text{ cm}^2) = 275{,}990\text{ cm}^3\text{/sec} \tag{17}$$

Earlier, the analysis established that the mixing of this product occurs in the turbulent flow regime because the Reynolds number obtained far exceeds the minimally required 2000. Therefore, the pumping number can be calculated for the 3780-L tank by using Eq. (8) to obtain

$$N_{Q(3780\text{L})} = 1.1283 - \left[(1.07118)\left(\frac{87\text{ cm}}{167\text{ cm}}\right)\right] = 0.57 \tag{18}$$

Finally, Eq. (10) is rearranged to solve for the appropriate shaft speed to be used in a 3780-L batch:

$$N_{3780\text{L}} = \frac{Q_{3780\text{L}}}{N_{Q(3780\text{L})} D_{3780\text{L}}^3} = \frac{275{,}990\text{ cm}^3\text{/sec}}{(0.57)(87\text{ cm})^3} = 0.73\text{ sec}^{-1} = 44\text{ rpm} \tag{19}$$

The shaft speed value obtained is well within the rpm range of the 3780-L tank agitator. To determine the rpm range for production batches, start with level-3 agitation at the low rpm end and level-5 agitation at the high rpm end. Table 3 provides bulk velocities for levels 3 and 5. In turn, these are used to calculate the respective pumping capacities, defined via Eq. (11). The low and high speeds are then calculated, as described earlier, by rearranging Eq. (10).

This method can easily be used to show the logic behind the scale-up from original R&D batches to production-scale batches. Although scale-of agitation analysis has its limitations, especially in the mixing of suspension, non-Newtonian fluids and gas dispersions, similar analysis could be applied to these systems, provided that pertinent system variables were used. These variables may include superficial gas velocity, dimensionless aeration numbers for gas systems, and terminal settling velocity for suspensions.

VI. LATEST REVISIONS OF THE APPROACH

As was discussed earlier, the scale-of-agitation approach has been successfully used in the scale-up of various liquid systems, including parenteral drugs. However, in the late 1990s, it was revised slightly to ensure even more accurate results [7]. We have already determined that the mixing in the agitated tank must be in the turbulent state in order for Eq. (8) to work properly. Therefore, an assumption is made that the full turbulence is achieved at N_{Re} above 2000. However, one should be aware that this assumption may result in an error of 12% in the N_Q calculation. One may come to the conclusion that some inadequacies may be encountered in the areas of mixing close to $N_{\mathrm{Re}} = 2000$. This later revision of the approach thrived on the fact that because this scale-up process was based on the use of existing equipment, it may not be possible to build in as much of a safety factor as possible when engineering a new facility. Therefore, it would be important to determine N_Q very accurately. Trying to achieve an even more accurate N_Q determination, the relationship between the D/T ratio on the N_{Re} vs. N_Q grid was reexamined. Upon replotting Figure 1 using linear coordinates, the following trend was observed (see Fig. 2). The curves rise sharply at first, which somewhat resembles the dissolution profile for a solid dosage form. Lagenbucher's equation for dissolution profile curves is:

$$Y = 1 - \exp\left[\frac{-(X)^{\mathrm{a}}}{b}\right] \tag{20}$$

Similarly, an equation for curves in Figure 2 may be expressed as follows:

$$N_Q = 1 - \exp\left[\frac{-(N_{\mathrm{Re}})^{a}}{b}\right] \tag{21}$$

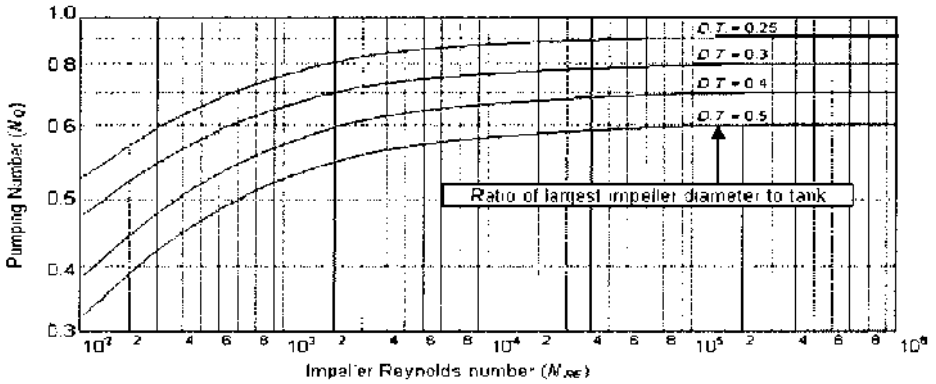

Figure 1 Pumping number versus impeller Reynolds number for turbine- and marine-type propeller agitators.

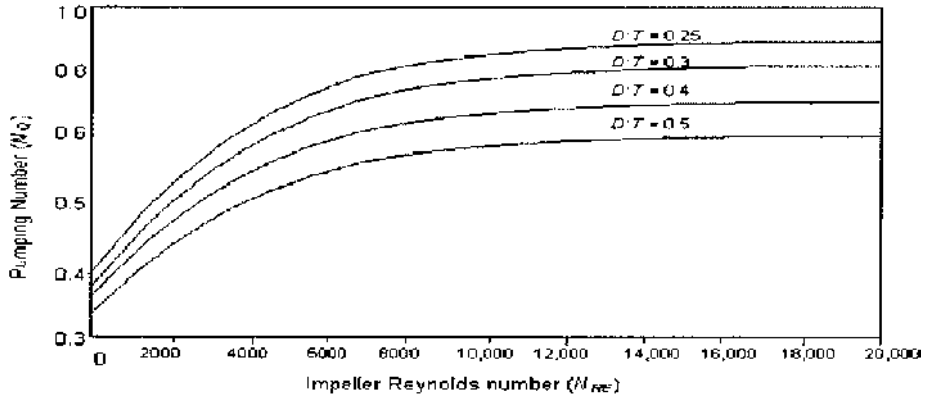

Figure 2 Pumping number versus impeller Reynolds number for turbine- and marine-type propeller agitators on linear coordinates.

where a and b are constants. Further, the equation for constant a was determined by

$$a = -0.272\left(\frac{D}{T}\right) + 0.39 \tag{22}$$

The constant b was found to be independent of the D/T ratio and had a value of 7.7.

However, Eq. (21) covered applications only where N_{Re} were below 1000. Another equation [8] to determine N_Q in the systems where N_{Re} is higher than 1000 is

$$N_Q = \frac{AN_{\mathrm{Re}}}{N_{\mathrm{Re}} + B} \tag{23}$$

where both A and B are functions of the D/T ratio and were determined to be

$$A = -1.08\left(\frac{D}{T}\right) + 1.12 \tag{24}$$

$$B = 578 - 1912\left(\frac{D}{T}\right) + 1980\left(\frac{D}{T}\right)^2 \tag{25}$$

These equations yield an approximate 5% maximum error, as compared to an approximate 10% error in Eq. (8).

However, it is also necessary to mention that the strength of the analysis is in its ability to mathematically transfer the mixing environment from the bench scale to the maximum compounding vessel, as close to the original pilot batch as possible. In our experience, the maximum rpm ranges empirically achieved dur-

ing compounding equal 6–20 rpm, which are well within the maximum 10% error that one may encounter via Eq. 8 in the marginal cases, where N_{Re} is close to 2000. Therefore, it is safe to conclude that the method outlined in Eq. (8) through (11) is the most efficient for finding mixing parameters of the scaled-up system. Yet Eq. (25) and (23) show the way for a closer N_Q determination, which may be more useful for the systems with higher viscosities and thus with lower N_{Re}.

VII. SCALE-OF-AGITATION APPROACH FOR SUSPENSIONS

In order to reduce the problem of adequately dispersing the insoluble drug during the formulation of sterile aqueous suspensions, the micronized material, i.e., material with a particle size of 10–30 μm, is used. Uniform distribution of the drug is required to ensure an adequate dose at the concentration per unit volume indicated on the label. Improper formulation or scale-up can result in caking of the insoluble material at the bottom of the container, making it difficult to disperse, to take up in a syringe, and thus to administer. To avoid caking, various flocculating agents are added to the product. Proper scale-up, however, is essential for adequate mixing conditions, which affect the caking process. During scale-up of a suspension product, along with the parameters, already discussed, the settling rate should be considered. The presence of a two-phase, solid–liquid system classifies an agitation problem as a solid–suspension one. In such problems, the suspension of solid particles having a settling velocity greater than 0.5 ft/min (0.25 cm/sec) within a continuous liquid phase is the purpose of the proper agitation and scale-up. The estimated terminal settling velocity, u_t, of spherical particles of a 10- to 30μ size in low-viscosity 1- to 300-cps suspensions is empirically determined as 1. For ease of analysis, the particle shape is assumed to be a sphere, since most of the studies for settling velocities are conducted on spherical beads. A different particle geometry (cylinders, disks, crushed solids, many crystalline forms) would not compromise the integrity of the analysis, due to the usage of micronized materials. First, one must determine the design settling velocity u_d, which is a product of the terminal settling velocity u_t and a correction factor f_w, from Table 4.

$$u_d = u_t f_w \tag{26}$$

Upon determination of the design settling velocity, one must choose the scale of agitation required, using Table 5 [9], which serves as a suspension products equivalent of Table 3. The chosen scale of agitation is than plugged into the chart of Figure 3 to find the value of constant ϕ. Rearranging Eq. (27) for constant ϕ, we get

$$\phi = \frac{N^{3.75} D^{2.81}}{u_d} \tag{27}$$

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Table 4 % Solids vs. Correct Factor f_w in Suspensions

Solids, %	Factor, f_w
2	0.8
5	0.84
10	0.91
15	1.0
20	1.10
25	1.20
30	1.30
35	1.42
40	1.55

Table 5 Process Requirements Set the Degree of Agitation for Solids Suspension

Scale of agitation	Description of mixing
1–2	Agitation levels 1 and 2 are characteristic of applications requiring minimal solids-suspension levels to achieve the process result. Agitators capable of scale levels of 1 and 2 will: a. Produce motion of all of the solids of the design settling velocity in the vessel b. Permit moving fillets of solids on the tank bottom, which are periodically suspended.
3–5	Agitation levels 3–5 are characteristic of most chemical process industry solids-suspension applications and are typically used for dissolving solids. Agitators capable of scale levels of 3–5 will: a. Suspend all the solids of design settling velocity completely off the vessel bottom b. Provide slurry uniformity to at least 1/3 of fluid-batch height c. Be suitable for slurry drawoff at low exit-nozzle elevations
6–8	Agitation levels 6–8 characterize applications where the solids-suspension levels approach uniformity. Agitators capable of scale levels of 6–8 will: a. Provide concentration uniformity of solids to 95% of the fluid-batch height. b. Be suitable for slurry drawoff up to 80% of fluid-batch height
9–10	Agitation levels 9 and 10 characterize applications where the solid–suspension uniformity is the maximum practical. Agitators capable of scale levels of 9 and 10 will: a. Provide slurry uniformity of solids to 98% of the fluid-batch height b. Be suitable for slurry drawoff by means of overflow

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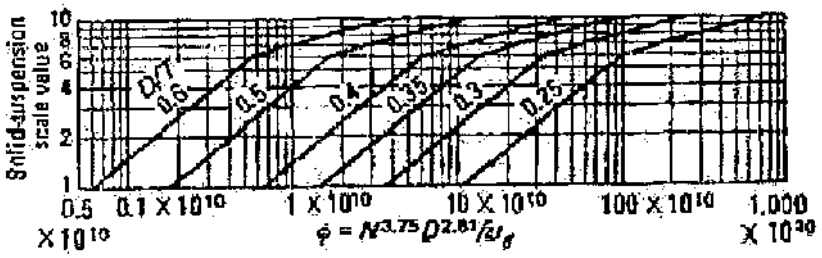

Figure 3 Solid-suspension scale value vs. ϕ

Plugging this into Eq. (28) for mixer speed we easily find the agitation rpm:

$$N = \sqrt[\frac{1}{3.75}]{\frac{\phi u_d}{D^{2.81}}} \tag{28}$$

VIII. CONCLUSIONS

The foregoing scale-up approach for liquid parenteral solutions provides a precise transfer of the compounding mixing equipment environment to the production scale. Due to the unsurpassed importance of proper agitation during the preparation of injectables, the lion's share of this chapter was devoted to the scale-up of agitating equipment. Other pieces of equipment used during the manufacture of parenteral drugs, such as sterilization equipment, filtration systems, various pumps, and packaging equipment, are geometrically scalable and are easily selected from the wide variety available.

One must also stress the importance of quality considerations during compounding and full adherence to current Good Manufacturing Practices while producing parenteral products. Personnel responsible for the process design and scale-up of the equipment must ensure proper documentation of the scale-up with tractability of all the preparatory work from the pilot batch(es) to the manufacture of the marketed products. Spreadsheet programs are useful for documenting equipment parameters and for the subsequent calculations required for proper scale-up.

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3
Nonparenteral Liquids and Semisolids

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I. INTRODUCTION

A manufacturer's decision to scale up (or scale down) a process is ultimately rooted in the economics of the production process, i.e., in the cost of materiél, personnel, and equipment associated with the process and its control. While process scale-up often reduces the unit cost of production and is therefore economically advantageous per se, there are additional economic advantages conferred on the manufacturer by scaling up a process. Thus, process scale-up may allow for faster entry of a manufacturer into the marketplace or improved product distribution or response to market demands and correspondingly greater market-share retention.[1] Given the potential advantages of process scale-up in the pharmaceutical industry, one would expect the scale-up task to be the focus of major efforts on the part of pharmaceutical manufacturers. However, the paucity of published studies or data on scale-up—particularly for nonparenteral liquids and semisolids—suggests otherwise. On the other hand, one could argue that the paucity of published studies or data is nothing more than a reflection of the need to maintain a competitive advantage through secrecy.

One could also argue that this deficiency in the literature attests to the complexity of the unit operations involved in pharmaceutical processing. If pharma-

[1] On the other hand, the manufacturer may determine that the advantages of process scale-up are compromised by the increased cost of production on a larger scale and/or the potential loss of interest or investment income. R. G. Griskey [1] addresses the economics of scale-up in some detail in his chapter on engineering economics and process design, but his examples are taken from the chemical industry. For a more extensive discussion of process economics, see Holland and Wilkinson [2].

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ceutical technologists view scale-up as little more than a ratio problem, whereby

$$\text{scale-up ratio} = \frac{\text{large-scale production rate}}{\text{small-scale production rate}} \quad (1)$$

then the successful resolution of a scale-up problem will remain an empirical, trial-and-error task, rather than a scientific one. In 1998, in a monograph on the scale-up of disperse systems, Block [3] noted that due to the complexity of the manufacturing process that involves more than one type of unit operation[2] (e.g., mixing, transferring), process scale-up from the bench or pilot plant level to commercial production is not a simple extrapolation:

> The successful linkage of one unit operation to another defines the functionality of the overall manufacturing process. Each unit operation per se may be scalable, in accordance with a specific ratio, but the composite manufacturing process may not be, as the effective scale-up ratios may be different from one unit operation to another. Unexpected problems in scale-up are often a reflection of the dichotomy between *unit operation* scale-up and *process* scale-up. Furthermore, commercial production introduces problems that are not a major issue on a small scale: e.g., storage and materials handling may become problematic only when large quantities are involved; heat generated in the course of pilot plant or production scale processing may overwhelm the system's capacity for dissipation to an extent not anticipated based on prior laboratory-scale experience [3].

Furthermore, unit operations may function in a rate-limiting manner as the scale of operation increases. When Astarita [4] decried the fact, in the mid-1980s, that "there is no scale-up algorithm which permits us to rigorously predict the behavior of a large-scale process based upon the behavior of a small-scale process," it was presumably as a consequence of all of these problematic aspects of scale-up.

A clue to the resolution of the scale-up problem for liquids and semisolids resides in the recognition that their processing invariably involves the unit operation of mixing. Closer examination of this core unit operation reveals that flow conditions and viscosities during processing can vary by several orders of magnitude, depending upon the scale of scrutiny employed, i.e., whether on a *microscopic* (e.g., molecular) or a *macroscopic* (e.g., bulk) scale. Therefore, the key to effective processing scale-up is the appreciation and understanding of microscale and macroscale transport phenomena, i.e., diffusion and bulk flow, respectively. Transport by diffusion involves the flow of a property (e.g., mass, heat, momentum, electromagnetic energy) from a region of high concentration to a region of

[2] The term *unit* **operations**, coined by Arthur D. Little in 1915, is generally used to refer to distinct *physical* changes or unit actions (e.g., pulverizing, mixing, drying), while unit operations involving *chemical* changes are sometimes referred to as *unit* **processes**. The physical changes comprising unit operations involve primarily contact, transfer of a physical property, and separation between phases or streams.

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low concentration as a result of the microscopic motion of electrons, atoms, molecules, etc. Bulk flow, whether convection or advection, however, involves the flow of a property as a result of macroscopic or bulk motion induced artificially (e.g., by mechanical agitation) or naturally (e.g., by density variations) [5].

II. TRANSPORT PHENOMENA IN LIQUIDS AND SEMISOLIDS AND THEIR RELATIONSHIP TO UNIT OPERATIONS AND SCALE-UP

Over the last four decades or so, transport phenomena research has benefitted from the substantial efforts made to replace empiricism by fundamental knowledge based on computer simulations and theoretical modeling of transport phenomena. These efforts were spurred on by the publication in 1960 by Bird, Stewart, and Lightfoot [6] of their quintessential monograph on the interrelationships among three fundamental types of transport phenomena: mass transport, energy transport, and momentum transport. All transport phenomena follow the same pattern in accordance with the generalized diffusion equation, or GDE. The unidimensional *flux,* or overall transport rate per unit area in one direction, is expressed as a system property multiplied by a gradient [5]:

$$\left.\frac{\partial \Gamma}{\partial t}\right|_x = \delta\left(\frac{\partial^2 \Gamma}{\partial x^2}\right) = \delta\left(\left(\frac{\partial \Gamma}{\partial x}\right)\right) = \delta\left(\frac{\partial E}{\partial x}\right) \tag{2}$$

The letter Γ represents the concentration of a property Q (e.g., mass, heat, electrical energy) per unit volume, i.e., $\Gamma = Q/V$, t is time, x is the distance measured in the direction of transport, δ is the generalized diffusion coefficient, and E is the gradient or driving force for transport.

Mass and heat transfer can be described in terms of their respective concentrations Q/V. While the concentration of mass, m, can be specified directly, the concentration of heat is given by

$$\frac{mC_pT}{V} = \rho C_pT \tag{3}$$

where C_p is the specific heat capacity and T is temperature. Thus, the specification of ρC_pT in any form of the generalized diffusion equation will result in the elimination of ρC_p, assuming it to be a constant, thereby allowing the use of temperature as a measure of heat concentration [5]. In an analogous manner, momentum transfer can be specified in terms of the concentration of momentum u when its substantial derivative is used instead of its partial derivative with respect to time:

$$\frac{Du}{Dt} = \nu\nabla^2 u \tag{4}$$

where ν is the kinematic viscosity. If pressure and gravitational effects are introduced, one arrives at the Navier–Stokes relationships that govern Newtonian fluid dynamics.

When the flux of Γ is evaluated three-dimensionally, it can be represented by [5]:

$$\frac{d\Gamma}{dt} = \frac{\partial\Gamma}{\partial t} + \frac{\partial\Gamma}{\partial x}\frac{dx}{\partial t} + \frac{\partial\Gamma}{\partial y}\frac{dy}{\partial t} + \frac{\partial\Gamma}{\partial z}\frac{dz}{\partial t} \tag{5}$$

At the simplest level, as Griskey [1] notes, Fick's law of diffusion for mass transfer and Fourier's law of heat conduction characterize mass and heat transfer, respectively, as vectors; i.e., they have magnitude and direction in the three coordinates *x, y,* and *z*. Momentum or flow, however, is a tensor, which is defined by nine components rather than three. Hence, its more complex characterization at the simplest level, in accordance with Newton's law,

$$\tau_{yx} = -\eta\left(\frac{dv_x}{dy}\right) \tag{6}$$

where τ_{yx} is the shear stress in the *x*-direction, dv_x/dy is the rate of shear, and η is the coefficient of Newtonian viscosity. The solution of Eq. (2), the generalized diffusion equation,

$$\Gamma = f(t,x,y,z) \tag{7}$$

will take the form of a parabolic partial differential equation [5]. However, the more complex the phenomenon—e.g., with convective transport a part of the model—the more difficult it is to achieve an analytic solution to the GDE. Numerical solutions, however, where the differential equation is transformed to an algebraic one, may be somewhat more readily achieved.

A. Transport Phenomena and Their Relationship to Mixing as a Unit Operation[3]

As noted earlier, virtually all liquid and semisolid products involve the unit of operation of mixing.[4] In fact, in many instances, it is the primary unit operation.

[3] Reprinted in part, with revisions and updates, by courtesy of Marcel Dekker, Inc., from L. H. Block, "Scale-up of disperse systems: theoretical and practical aspects," in *Pharmaceutical Dosage Forms: Disperse Systems* (H. A. Lieberman, M. M. Rieger, and G. S. Banker, eds.), 2nd ed., vol. 3, Marcel Dekker, New York, 1998, pp. 366–378.

[4] *Mixing,* or *blending,* refers to the random distribution of two or more initially separate phases into and through one another, while *agitation* refers only to the induced motion of a material in some sort of container. Agitation does not necessarily result in an intermingling of two or more separate components of a system to form a more or less uniform product. Some authors reserve the term *blending* for the intermingling of miscible phases, while *mixing* is employed for materials that may or may not be miscible.

Even its indirect effects, e.g., on heat transfer, may be the basis for its inclusion in a process. Yet mechanistic and quantitative descriptions of the mixing process remain incomplete [7–9]. Nonetheless, enough fundamental and empirical data are available to allow some reasonable predictions to be made.

The diversity of dynamic mixing devices is unsettling: Their dynamic, or moving, component's blades may be impellers in the form of propellers, turbines, paddles, helical ribbons, Z-blades, or screws. In addition, one can vary the number of impellers, the number of blades per impeller, the pitch of the impeller blades, and the location of the impeller and thereby affect mixer performance to an appreciable extent. Furthermore, while dispersators or rotor/stator configurations may be used rather than impellers to effect mixing, mixing may also be accomplished by jet mixing or static mixing devices. The bewildering array of mixing equipment choices alone would appear to make the likelihood of effective scale-up an impossibility. However, as diverse as mixing equipment may be, evaluations of the rate and extent of mixing and of flow regimes[5] make it possible to find a common basis for comparison.

In low-viscosity systems, miscible liquid blending is achieved through the transport of unmixed material, via flow currents (i.e., bulk or convective flow), to a mixing zone (i.e., a region of high shear or intensive mixing). In other words, mass transport during mixing depends on *streamline* or *laminar* flow, involving well-defined paths, and *turbulent* flow, involving innumerable, variously sized, eddies or swirling motions. Most of the highly turbulent mixing takes place in the region of the impeller, fluid motion elsewhere serving primarily to bring fresh fluid into this region. Thus, the characterization of mixing processes is often based on the flow regimes encountered in mixing equipment. Reynolds' classic research on flow in pipes demonstrated that flow changes from laminar to irregular, or turbulent, once a critical value of a dimensionless ratio of variables has been exceeded [10,11]. This ratio, universally referred to as the Reynolds number, N_{Re}, is defined by Eqs. (8a) and (8b),

$$N_{\mathrm{Re}} = \frac{L\nu\rho}{\eta} \tag{8a}$$

$$N_{\mathrm{Re}} = \frac{D^2 N\rho}{\eta} \tag{8b}$$

where ρ is density, ν is velocity, L is a characteristic length, and η is the Newtonian viscosity; Eq. (8b) is referred to as the *impeller* Reynolds number, since D is the impeller diameter and N is the rotational speed of the impeller. N_{Re} represents the ratio of the inertia forces to the viscous forces in a flow. High values of N_{Re}

[5] The term *flow regime* is used to characterize the hydraulic conditions (i.e., volume, velocity, and direction of flow) within a vessel.

correspond to flow dominated by motion, while low values of N_{Re} correspond to flow dominated by viscosity. Thus, the transition from laminar to turbulent flow is governed by the density and viscosity of the fluid, its average velocity, and the dimensions of the region in which flow occurs (e.g., the diameter of the pipe or conduit, the diameter of a settling particle). For a straight circular pipe, laminar flow occurs when $N_{Re} < 2{,}100$; turbulent flow is evident when $N_{Re} > 4{,}000$. For $2{,}100 \leqslant N_{Re} \leqslant\alpha\, 4{,}000$, flow is in transition from a laminar to a turbulent regime. Other factors, such as surface roughness, shape, and cross-sectional area of the affected region, have a substantial effect on the critical value of N_{Re}. Thus, for particle sedimentation, the critical value of N_{Re} is 1; for some mechanical mixing processes, N_{Re} is 10–20 [12]. The erratic, relatively unpredictable nature of turbulent eddy flow is further influenced, in part, by the size distribution of the eddies, which are dependent on the size of the apparatus and the amount of energy introduced into the system [10]. These factors are indirectly addressed by N_{Re}. Further insight into the nature of N_{Re} can be gained by viewing it as inversely proportional to eddy advection time, i.e., the time required for eddies or vortices to form.

In turbulent flow, eddies move rapidly, with an appreciable component of their velocity in the direction perpendicular to a reference point, e.g., a surface past which the fluid is flowing [13]. Because of the rapid eddy motion, mass transfer in the turbulent region is much more rapid than that resulting from molecular diffusion in the laminar region, with the result that the concentration gradients existing in the turbulent region will be smaller than those in the laminar region [13]. Thus mixing is much more efficient under turbulent flow conditions. Nonetheless, the technologist should bear in mind potentially compromising aspects of turbulent flow, e.g., increased vortex formation [14] and a concomitant incorporation of air, increased shear and a corresponding shift in the particle size distribution of the disperse phase.

Although continuous-flow mixing operations are employed to a limited extent in the pharmaceutical industry, the processing of liquids and semisolids most often involves batch processing in some kind of tank or vessel. Thus, in the general treatment of mixing that follows, the focus will be on batch operations[6] in which mixing is accomplished primarily by the use of dynamic mechanical mixers with impellers, although jet mixing [17,18] and static mixing devices [19]—long used in the chemical process industries—are gaining advocates in the pharmaceutical and cosmetic industries.

Mixers share a common functionality with pumps. The power imparted by the mixer, via the impeller, to the system is akin to a pumping effect and is characterized in terms of the shear and flow produced:

[6] The reader interested in continuous-flow mixing operations is directed to references that deal specifically with that aspect of mixing, such as the monographs by Oldshue [15] and Tatterson [16].

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$$\left.\begin{array}{l} P \,\alpha\, Q\rho H \\ \text{or} \\ H \,\alpha\, \dfrac{P}{Q\rho} \end{array}\right\} \tag{9}$$

where P is the power imparted by the impeller, Q is the flow rate (or pumping capacity) of material through the mixing device, ρ is the density of the material, and H is the velocity head, or shear. Thus, for a given P, there is an inverse relationship between shear and volume throughput.

The power input in mechanical agitation is calculated using the *power number, N_P*,

$$N_P = \frac{Pg_c}{\rho N^3 D^5} \tag{10}$$

where g_c is the force conversion factor

$$g_c = \frac{kg{\cdot}m{\cdot}\sec^{-2}}{newton} = \frac{g{\cdot}cm{\cdot}\sec^{-2}}{dyne}$$

N is the impeller rotational speed ($\sec^{-1}$), and D is the diameter of the impeller. For a given impeller/mixing tank configuration, one can define a specific relationship between the Reynolds number [Eq. (8)][7] and the power number [Eq. (10)] in which three zones (corresponding to the laminar, transitional, and turbulent regimes) are generally discernible. Tatterson [20] notes that for mechanical agitation in laminar flow, most *laminar* power correlations reduce to $N_P N_{\mathrm{Re}} = B$, where B is a complex function of the geometry of the system,[8] and that this is equivalent to $P \,\alpha\, \eta \cdot N^2 D^3$; "if power correlations do not reduce to this form for laminar mixing, then they are wrong and should not be used." Turbulent correlations are much simpler: for systems employing baffles,[9] $N_P = B$; this is equivalent to $P \,\alpha\, \rho \cdot N^3 D^5$. Based on this function, slight changes in D can result in substantial changes in power.

Valuable insights into the mixing operation can be gained from a consideration of system behavior as a function of the Reynolds number, N_{Re} [21]. This is shown schematically in Figure 1 in which various dimensionless parameters (dimensionless velocity, ν/ND; pumping number, Q/ND^3; power number, $N_P = Pg_c/\rho N^3 D^5$; and dimensionless mixing time, $t_m N$) are represented as a log-log function of N_{Re}. Although density, viscosity, mixing vessel diameter, and impeller rotational speed are often viewed by formulators as independent variables, their

[7] Here, the Reynolds number for mixing is defined in SI-derived units as $N_{\mathrm{Re}} = (1.667 \times 10^{-5}\, ND^2\rho)/\eta$, where D, impeller diameter, is in millimeters, η is in Pa·sec, N is impeller speed, in r.p.m., and ρ is density.

[8] An average value of B is 300, but B can vary between 20 and 4000 [20].

[9] Baffles are obstructions placed in mixing tanks to redirect flow and minimize vortex formation.

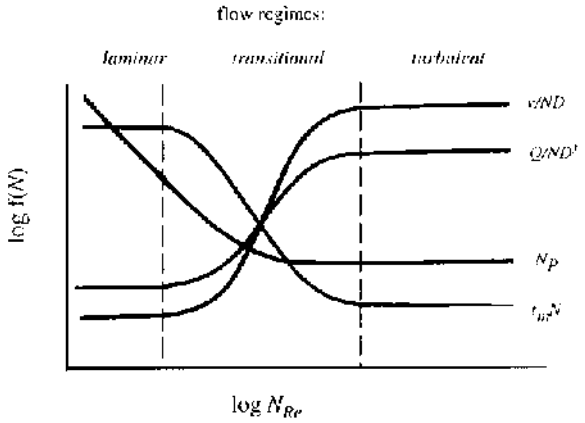

Figure 1 Various dimensionless parameters (dimensionless velocity, $v^* = v/ND$; pumping number, $N_Q = Q/ND^3$; power number, $N_P = Pg_c\backslash\rho N^3D^5$; and dimensionless mixing time, $t^* = t_mN$) as a function of the Reynolds number for the analysis of turbine-agitator systems. (Adapted from Ref. 21.)

interdependency, when incorporated in the dimensionless Reynolds number, is quite evident. Thus, the schematic relationships embodied in Figure 1 are not surprising.[10]

Mixing time is the time required to produce a mixture of predetermined quality; the rate of mixing is the rate at which mixing proceeds toward the final state. For a given formulation and equipment configuration, mixing time, t_m, will depend upon material properties and operation variables. For geometrically similar systems, if the geometrical dimensions of the system are transformed to ratios, mixing time can be expressed in terms of a dimensionless number, i.e., the dimensionless mixing time, θ_m or t_mN:

$$t_mN = \theta_m = f(N_{\mathrm{Re}}, N_{\mathrm{Fr}}) \Rightarrow f(N_{\mathrm{Re}}) \tag{11}$$

The Froude number, $N_{\mathrm{Fr}} = v/\sqrt{Lg}$, is similar to N_{Re}; it is a measure of the inertial stress to the gravitational force per unit area acting on a fluid. Its inclusion in Eq. (11) is justified when density differences are encountered; in the absence of substantive differences in density, e.g., for emulsions more so than for suspensions, the Froude term can be neglected. Dimensionless mixing time is independent of the Reynolds number for both laminar and turbulent flow regimes, as in-

[10] The interrelationships are embodied in variations of the Navier–Stokes equations, which describe mass and momentum balances in fluid systems [22].

dicated by the plateaus in Figure 1. Nonetheless, because there are conflicting data in the literature regarding the sensitivity of θ_m to the rheological properties of the formulation and to equipment geometry, Eq. (11) must be regarded as an oversimplification of the mixing operation. Considerable care must be exercised in applying the general relationship to specific situations.

Empirical correlations for *turbulent* mechanical mixing have been reported in terms of the following dimensionless mixing time relationship [23]:

$$\theta_m = t_m N = K\left(\frac{T}{D}\right)^a \tag{12}$$

where K and a are constants, T is tank diameter, N is impeller rotational speed, and D is impeller diameter. Under *laminar* flow conditions, Eq. (12) reduces to

$$\theta_m = H_0 \tag{13}$$

where H_0 is referred to as the *mixing number* or *homogenization number.* In the *transitional* flow regime,

$$H_0 = C(N_{\mathrm{Re}})^a \tag{14}$$

where C and a are constants, with a varying between 0 and -1.

Flow patterns in agitated vessels may be characterized as radial, axial, or tangential relative to the impeller but are more correctly defined by the direction and magnitude of the velocity vectors throughout the system, particularly in a transitional flow regime: While the dimensionless velocity, v^*, or v/ND, is essentially constant in the laminar and turbulent flow zones, it is highly dependent on N_{Re} in the transitional flow zone (Fig. 1). Initiation of tangential or circular flow patterns, with minimal radial or axial movement, is associated with vortex formation, minimal mixing, and, in some multiphase systems, particulate separation and classification. Vortices can be minimized or eliminated altogether by redirecting flow in the system through the use of baffles[11] or by positioning the impeller so that its entry into the mixing tank is off-center. For a given formulation, large tanks are more apt to exhibit vortex formation than small tanks. Thus, full-scale production tanks are more likely to require baffles, even when smaller (laboratory- or pilot-plant scale) tanks are unbaffled.

Mixing processes involved in the manufacture of disperse systems, whether suspensions or emulsions, are far more problematic than those employed in the blending of low-viscosity miscible liquids, due to the multiphasic character of the

[11] The usefulness of baffles in mixing operations is offset by increased cleanup problems (due to particulate entrapment by the baffles or congealing of product adjacent to the baffles). Furthermore, "overbaffling"—excessive use of baffles—reduces mass flow and localizes mixing, which may be counterproductive.

systems and deviations from Newtonian flow behavior. It is not uncommon for both laminar and turbulent flow to occur simultaneously in different regions of the system. In some regions, the flow regime may be in transition, i.e., neither laminar nor turbulent but somewhere in between. The implications of these flow regime variations for scale-up are considerable. Nonetheless, it should be noted that the mixing process is only completed when Brownian motion occurs to a sufficient extent that uniformity is achieved on a molecular scale.

B. Viscous and Non-Newtonian Materials

Mixing in high-viscosity materials ($\eta > \sim 10^4$ cPs) is relatively slow and inefficient. Conventional mixing tanks and conventional impellers (e.g., turbine or propellor impellers) are generally inadequate. In general, due to the high viscosity, N_{Re} may well be below 100. Thus, laminar flow is apt to occur rather than turbulent flow. As a result, the inertial forces imparted to a system during the mixing process tend to dissipate quickly. Eddy formation and diffusion are virtually absent. Thus, efficient mixing necessitates substantial convective flow, which is usually achieved by high velocity gradients in the mixing zone. Fluid elements in the mixing zone, subjected to both shear and elongation, undergo deformation and stretching, ultimately resulting in the size reduction of the fluid elements and an increase in their overall interfacial area. The repetitive cutting and folding of fluid elements also result in decreasing inhomogeneity and increased mixing. The role of molecular diffusion in reducing inhomogeneities in high-viscosity systems is relatively unimportant until these fluid elements have become small and their interfacial areas have become relatively large [24]. In highly viscous systems, rotary motion is more than compensated for by viscous shear, so baffles are generally less necessary [25].

Mixing equipment for highly viscous materials often involves specialized impellers and configurations that minimize high shear zones and heat dissipation. Accordingly, propeller-type impellers are not generally effective in viscous systems. Instead, turbines, paddles, anchors, helical ribbons, screws, and kneading mixers are resorted to, successively, as system viscosity increases. Multiple impellers or specialized impellers (e.g., sigma-blades, Z-blades) are often necessary, along with the maintenance of narrow clearances, or gaps, between impeller blades and between impeller blades and tank (mixing chamber) walls in order to attain optimal mixing efficiency [24,25]. However, narrow clearances pose their own problems. Studies of the power input to anchor impellers used to agitate Newtonian and shear-thinning fluids showed that the clearance between the impeller blades and the vessel wall was the most important geometrical factor: N_P at constant N_{Re} was proportional to the fourth power of the clearance divided by tank diameter [26]. Furthermore, although mixing is promoted by these specialized impellers in the vicinity of the walls of the mixing vessel, stagnation is often encountered in regions adjacent to the impeller shaft. Finally, complications (wall effects) may arise from the formation of a thin, particulate-free, fluid layer adja-

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cent to the wall of the tank or vessel that has a lower viscosity than the bulk material and allows slippage (i.e., nonzero velocity) to occur, unless the mixing tank is further modified to provide for wall-scraping.

Rheologically, the flow of many non-Newtonian materials can be characterized by a time-independent power law function (sometimes referred to as the Ostwald–deWaele equation):

$$\tau = \mathrm{K}\dot{\gamma}^{a} \qquad \text{or} \qquad \log \tau = \mathrm{K}' + \mathrm{a}(\log \gamma\acute{\mathrm{Y}}) \tag{15}$$

where τ is the shear stress, $\log \tau = \mathrm{K}' + \mathrm{a}(\log \dot{\gamma})$ is the rate of shear, K' is the logarithmically transformed proportionality constant K with dimensions dependent upon a, the so-called flow behavior index. For pseudoplastic or shear-thinning materials, $a < 1$; for dilatant or shear-thickening materials, $a > 1$; for Newtonian fluids, $a = 1$. For a power law fluid, the average apparent viscosity, η_{avg}, can be related to the average shear rate by the following equation:

$$\eta_{\mathrm{avg}} = K' \left(\frac{d\nu}{dy}\right)_{\mathrm{avg}}^{n'-1} \tag{16}$$

Based on this relationship, a Reynolds number can be derived and estimated for non-Newtonian fluids from

$$\left[N_{\mathrm{Re}} = \frac{L\nu\rho}{\eta}\right] \Rightarrow \left[N_{\mathrm{Re,nonN}} = \frac{ND_i^2\rho}{K'(d\nu/dy)_{\mathrm{avg}}^{n'-1}}\right] \tag{17}$$

Dispersions that behave, rheologically, as Bingham plastics require a minimum shear stress (the yield value) in order for flow to occur. Shear stress variations in a system can result in local differences wherein the yield stress point is not exceeded. As a result, flow may be impeded or absent in some regions compared to others, resulting in channeling or cavity formation and a loss of mixing efficiency. Only if the yield value is exceeded *throughout* the system will flow and mixing be relatively unimpeded. Helical ribbon and screw impellers would be preferable for the mixing of Bingham fluids, in contrast to conventional propeller or turbine impellers, given their more even distribution of power input [27]. From a practical vantage point, monitoring power input to mixing units could facilitate process control and help to identify problematic behavior. Etchells et al. [28] analyzed the performance of industrial mixer configurations for Bingham plastics. Their studies indicate that the logical scale-up path from laboratory to pilot plant to production, for geometrically similar equipment, involves the maintenance of constant impeller tip speed, which is proportional to $N \cdot D$, the product of rotational speed of the impeller (N) and the diameter of the impeller (D).

Oldshue [25] provides a detailed procedure for selecting mixing times and optimizing mixer and impeller configurations for viscous and shear-thinning materials that can be adapted for other rheologically challenging systems.

Gate and anchor impellers, long used advantageously for the mixing of viscous and non-Newtonian fluids, induce complex flow patterns in mixing tanks: both

primary and secondary flows may be evident. *Primary* flow or circulation results from the direct rotational movement of the impeller blade in the fluid; *secondary* flow is normal to the horizontal planes about the impeller axis (i.e., parallel to the impeller axis) and is responsible for the interchange of material between different levels of the tank [29]. In this context, rotating viscoelastic systems, with their normal forces, establish stable secondary flow patterns more readily than Newtonian systems. In fact, the presence of normal stresses in viscoelastic fluids subjected to high rates of shear ($\sim 10^4$ sec^{-1}) may be substantially greater than shearing stresses, as demonstrated by Metzner et al. [30]. These observations, among others, moved Fredrickson [31] to note that "neglect of normal stress effects is likely to lead to large errors in theoretical calculations for flow in complex geometries." However, the effect of these secondary flows on the efficiency of mixing, particularly in viscoelastic systems, is equivocal. On the one hand, vertical velocity near the impeller blade in a Newtonian system might be 2–5% of the horizontal velocity, whereas in a non-Newtonian system, vertical velocity can be 20–40% of the horizontal. Thus, the overall circulation can improve considerably. On the other hand, the relatively small, stable toroidal vortices that tend to form in viscoelastic systems may result in substantially incomplete mixing. Smith [29] advocates the asymmetric placement of small deflector blades on a standard anchor arm as a means of achieving a dramatic improvement in mixing efficiency of viscoelastic fluids without resorting to expensive alternatives, such as pitched blade anchors or helical ribbons.

Side-wall clearance, i.e., the gap between the vessel wall and the rotating impeller, was shown by Cheng et al. [32] to be a significant factor in the mixing performance of helical ribbon mixers not only for viscous and viscoelastic fluids but also for Newtonian systems. Bottom clearance, i.e., the space between the base of the impeller and the bottom of the tank, however, had a negligible, relatively insignificant effect on power consumption and on the effective shear rate in inelastic fluids. Thus, mixing efficiency in nonviscoelastic fluids would not be affected by variations in bottom clearance. For viscoelastic fluids, on the other hand, bottom clearance effects were negligible only at lower rotational speeds ($\leq$60 rpm); substantial power consumption increases were evident at higher rotational speeds.

The scale-up implications of *mixing*-related issues, such as impeller design and placement, mixing tank characteristics, new equipment design, and the mixing of particulate solids, are beyond the scope of this chapter. However, extensive monographs are available in the chemical engineering literature (many of which have been cited herein[12]) and will prove to be invaluable to the formulator and technologist.

[12] The reader is directed to previously referenced monographs by Oldshue and by Tatterson as well as to standard textbooks in chemical engineering, including the multivolume series authored by McCabe et al., and the encyclopedic *Perry's Chemical Engineers' Handbook.*

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C. Particle Size Reduction

Disperse systems often necessitate particle size reduction, whether it is an integral part of product processing, as in the process of liquid–liquid emulsification, or an additional requirement insofar as solid particle suspensions are concerned. (It should be noted that solid particles suspended in liquids often tend to agglomerate. Although milling of such suspensions tends to disrupt such agglomerates and produce a more homogeneous suspension, it generally does not affect the size of the unit particles comprising the agglomerates.) For emulsions, the dispersion of one liquid as droplets in another can be expressed in terms of the dimensionless Weber number, N_{We}:

$$N_{We} = \frac{\rho \nu^2 d_0}{\sigma} \tag{18}$$

where ρ is the density of a droplet, ν is the relative velocity of the moving droplet, d_0 is the diameter of the droplet, and σ is the interfacial tension. The Weber number represents the ratio of the driving force causing partial disruption to the resistance due to interfacial tension [33]. Increased Weber numbers are associated with a greater tendency for droplet deformation (and consequent splitting into still smaller droplets) to occur at higher shear, i.e., with more intense mixing. This can be represented by

$$N_{We} = \frac{D_i^3 N^2 \rho_{cont.}}{\sigma} \tag{19}$$

where D_i is the diameter of the impeller, N is the rotational speed of the impeller, and $\rho_{cont.}$ is the density of the continuous phase. For a given system, droplet size reduction begins above a specific critical Weber number [34]; above the critical N_{We}, average droplet size varies with $N^{-1.2} D_i^{-0.8}$, or, as an approximation, with the reciprocal of the impeller tip speed. In addition, a better dispersion is achieved, for the same power input, with a smaller impeller rotating at high speed [35].

As the particle size of the disperse phase decreases, there is a corresponding increase in the number of particles and a concomitant increase in interparticulate and interfacial interactions. Thus, in general, the viscosity of a dispersion is greater than that of the dispersion medium. This is often characterized in accordance with the classical Einstein equation for the viscosity of a dispersion,

$$\eta = \eta_o(1 + 2.5\phi) \tag{20}$$

where η is the viscosity of the dispersion, η_o is the viscosity of the continuous phase, and ϕ is the volume fraction of the particulate phase. The rheological behavior of concentrated dispersions may be demonstrably non-Newtonian (pseudoplastic, plastic, or viscoelastic) and its dependence on ϕ more marked due to disperse phase deformation and/or interparticulate interaction.

Maa and Hsu [36] investigated the influence of operation parameters for rotor/stator homogenization on emulsion droplet size and temporal stability in order to optimize operating conditions for small- and large-scale rotor/stator homogenization. Rotor/stator homogenization effects emulsion formation under much more intense turbulence and shear than that encountered in an agitated vessel or a static mixer. Rapid circulation, high shear forces, and a narrow rotor/stator gap ($<$0.5 mm) contribute to the intensity of dispersal and commingling of the immiscible phases, since turbulent eddies are essential for the breakup of the dispersed phase into droplets. Maa and Hsu's estimates of the circulation rates in small- and large-scale rotor/stator systems—based on the total area of the rotor/stator openings, the radial velocity at the openings (resulting from the pressure difference within the vortex that forms in the rotor/stator unit), and the centrifugal force caused by the radial deflection of fluid by the rotor—appear to be predictive for the scale-up of rotor/stator homogenization [36].

Dobetti and Pantaleo [37] investigated the influence of hydrodynamic parameters per se on the efficiency of a coacervation process for microcapsule formation. They based their work on that of Armenante and Kirwan [38], who described the size of the smallest eddies or vortices generated in a turbulent regime on a microscopic scale in the vicinity of the agitation source, i.e., microeddies,[13] as

$$d_e = \left(\frac{\nu^3}{P_s}\right)^{\frac{1}{4}} \tag{21}$$

where d_e is the diameter of the smallest microeddy, ν is the kinematic viscosity of the fluid (i.e., η/ρ, or viscosity/density), and P_s is the specific power, i.e., power input per unit mass. Hypothetically, if mass transfer of the coacervate and particle encapsulation occurred only within the microeddies, then the diameter of the hardened microcapsules would depend on the size of the microeddies produced by the agitation in the system. They dispersed a water-insoluble drug in a cellulose acetate phthalate (CAP) solution to which a coacervation-inducing agent was gradually added to facilitate microencapsulation by the CAP coacervate phase. The stirring rate and the tank and impeller configuration were varied to produce an array of microeddy sizes. However, the actual size of the hardened microcapsules was less than that calculated for the corresponding microeddies (Fig. 2). The authors attributed the inequality in sizes, in part, to relatively low agitation energies. Their conclusion is supported by their calculated N_{Re} values, ranging from 1184 to 2883, which are indicative of a flow regime ranging from laminar to transitional, rather than turbulent.

[13] Deduced in 1941 by A. N. Kolmogorov, it is generally referred to as the Kolmogorov length or dissipation scale [9].

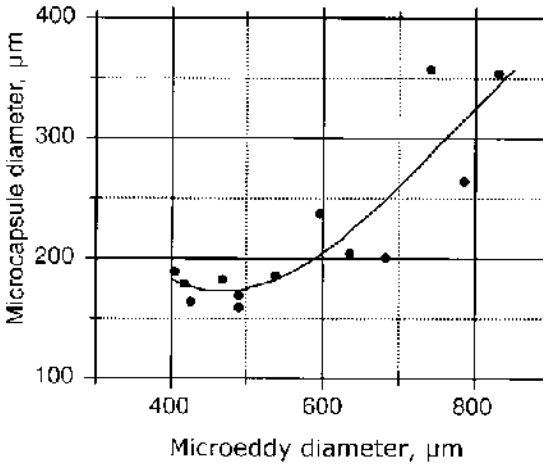

Figure 2 Microcapsule size as a function of calculated microeddy size. (Adapted from Ref. 37.)

Comminution, or particle size reduction of solids, is considerably different from that of the breakup of one liquid by dispersal as small droplets in another. Particle size reduction is generally achieved by one of four mechanisms: (1) compression, (2) impact, (3) attrition, or (4) cutting or shear. Equipment for particle size reduction or milling includes *crushers* (which operate by compression, e.g., crushing rolls), *grinders* (which operate principally by impact and attrition, although some compression may be involved, e.g., hammer mills, ball mills), *ultrafine grinders* (which operate principally by attrition, e.g., fluid-energy mills), and *knife cutters.* Accordingly, a thorough understanding of milling operations requires an understanding of fracture mechanics, agglomerative forces (dry and wet) involved in the adhesion and cohesion of particulates, and flow of particles and bulk powders. These topics are dealt with at length in the monographs by Fayed and Otten [39] and Carstensen [40,41].

As Austin [42] notes, the formulation of a general theory of the unit operation of size reduction is virtually impossible given the multiplicity of mill types and mechanisms for particulate reduction. The predictability of any comminution process is further impaired given the variations among solids in surface characteristics and reactivity, molecular interactions, crystallinity, etc. Nonetheless, some commonalities can be discerned. First, the particle size reduction rate is dependent upon particle strength and particle size. Second, the residence time of particles in the mill is a critical determinant of mill efficiency. Thus, whether a given mill operates in a single-pass or a multiple-pass (retention) mode can be a limiting factor insofar as characterization of the efficacy of comminution is concerned. Third, the energy required to achieve a given degree of comminution is an inverse

function of initial particle size. This is due to (1) the increasing inefficiency of stress or shear application to each particle of an array of particles as particle size decreases, and (2) the decreasing incidence of particle flaws that permit fracture at low stress [42].

If monosized particles are subjected to one pass through a milling device, the particle size distribution of the resultant fragments can be represented in a cumulative form. Subsequent passes of the comminuted material through the milling device often result in a superimposable frequency distribution when the particle sizes are normalized, e.g., in terms of the weight fraction less than size y resulting from the milling of particles of larger size x. The mean residence time, τ, of material processed by a mill is given by

$$\tau = \frac{M}{F} \tag{22}$$

where M is the mass of powder in the mill and F is the mass flow rate through the mill. Process outcomes for retention mills can be described in terms of residence time distributions, defined by the weight fraction of the initial charge at time $t = 0$ that leaves between $(t + dt)$. If the milling operation is scalable, the particle size distributions produced by a large and a small mill of the same type would be comparable and would differ only in the time scale of operation, i.e., the operation can be characterized as a $f(t/\tau)$. The prospect for scalability may be further enhanced when the weight fraction remaining in an upper range is a log-linear (first order) function of total elapsed milling time[14] [42]. Corroboration of the likelihood of scalability of milling operations is Mori's finding that most residence time distributions for milling conform to a log-normal model [43].

One estimate of the efficacy of a crushing or grinding operation is the crushing efficiency, E_c, described as the ratio of the surface energy created by crushing or grinding to the energy absorbed by the solid [44]:

$$E_c = \frac{\sigma_s(A_{wp} - A_{wf})}{W_n} \tag{23}$$

where σ_s is the specific surface or surface per unit area, A_{wp} and A_{wf} are the areas per unit mass of product particulates and feed particulates, i.e., after and before milling, respectively, and W_n is the energy absorbed by the solid per unit mass. The energy absorbed by the solid per unit mass is less than the energy W supplied to the mill per unit mass i.e., $W_n < W$. While a substantial part of the total energy input W is needed to overcome friction in the machine, the rest is available for crushing or grinding. However, of the total energy stored within a solid, only a small fraction is converted into surface energy at the time of fracture. Because

[14] Total elapsed milling time encompasses the time during which solids are subjected to a milling operation, whether the particulates undergo single or multiple passes through the mill.

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most of the energy is converted into heat, crushing efficiency values tend to be low, i.e., $0.0006 < E_c < 0.01$, principally due to the inexactness of estimates of σ_s [44].

A number of quasi-theoretical relationships have been proposed to characterize the grinding process: Rittinger's "law" (1867),

$$\frac{P}{\dot{m}} = K_R\left(\frac{1}{\bar{D}_p} - \frac{1}{\bar{D}_f}\right) \tag{24}$$

which states that the work required in crushing a solid is proportional to the new surface created, and Kick's "law" (1885),

$$\frac{P}{\dot{m}} = K_k \ln \frac{\bar{D}_f}{\bar{D}_p} \tag{25}$$

which states that the work required to crush or grind a given mass of material is constant for the same particle size reduction ratio. In Eqs. (24) and (25), $\bar{D}_p$ and $\bar{D}_f$ represent the final and initial average particle sizes,[15] P is the power (in kilowatts), and $\dot{m}$ is the rate at which solids are fed to the mill (in tons/hr). K_R and K_K are constants for the Rittinger equation and the Kick equation, respectively.

Bond's "law" of particle size reduction provides an ostensibly more reasonable estimate of the power required for crushing or grinding of a solid [45]:

$$\frac{P}{\dot{m}} = \frac{K_B}{\sqrt{D_p}} \tag{26}$$

where K_B is a constant that is *mill* dependent and *solids* dependent and D_p is the particle size (in mm) produced by the mill. This empirical equation is based on Bond's hypothesis that the work required to reduce very large particulate solids to a smaller size is proportional to the square root of the surface-to-volume ratio of the resultant particulate product. Bond's work index, W_i, is an estimate of the gross energy required, in kilowatt hours per ton of feed, to reduce very large particles (80% of which pass a mesh size of D_f mm) to such a size that 80% pass through a mesh of size D_p mm:

$$W_i = \frac{K_B}{\sqrt{D_p}} \tag{27}$$

Combining Bond's work index [Eq. (27)] with Bond's law [Eq. (26)] yields

$$\frac{P}{\dot{m}} = W_i\sqrt{D_p}\left(\frac{1}{\sqrt{D_p}} - \frac{1}{\sqrt{D_f}}\right) \tag{28}$$

[15] In this section, particle size refers to the nominal particle size, i.e., the particle size based on sieving studies or on the diameter of a sphere of equivalent volume.

which allows one to estimate energy requirements for a milling operation in which solids are reduced from size D_f to D_p (W_i for wet grinding is generally smaller than that for dry grinding: $W_{i,\text{wet}}$ is equivalent to $(W_{i,\text{dry}})^{3/4}$ [44].)

These relationships are embodied in the general differential equation

$$dE = -CdX/X^n \tag{29}$$

where E is the work done and C and n are constants. When $n = 1$, the solution of the equation is Kick's law; when $n = 2$, the solution is Rittinger's law; and when $n = 1.5$, the solution is Bond's law [46].

Although these relationships [Eqs. (24)–(29)] are of some limited use in scaling up milling operations, their predictiveness is limited by the inherent complexity of particle size reduction operations. Virtually all retentive or multiple-pass milling operations become increasing less efficient as milling proceeds, since the specific comminution rate is smaller for small particles than for large particles. Computer simulations of milling for batch, multiple-pass, and continuous modes have been outlined by Snow et al. [47]. They describe a differential equation for batch grinding for which analytical and matrix solutions have been available for some time:

$$\frac{dw_k}{dt} = \sum_{u=1}^{k} [w_u S_u(t)\ \Delta B_{k,u}] - S_k(t) w_k \tag{30}$$

Equation (30) includes a term S_u, a grinding-rate function that corresponds to

$$S_u = -\frac{dw_u/dt}{w_u} \tag{31}$$

i.e., the rate at which particles of upper size u are selected for breakage per unit time relative to the amount, w_u, of size u present, and a term $\Delta B_{k,u}$, a breakage function that characterizes the size distribution of particle breakdown from size u into all smaller sizes k. Equation (30) thus defines the rate of accumulation of particles of size k as the difference between the rate of production of particles of size k from all larger particles and the rate of breakage of particles of size k into smaller particles. Adaptation of Eq. (30) to continuous milling operations necessitates the inclusion of the distribution of residence time, $\tau = M/F$, as discussed earlier.

Additional complications in milling arise as fines build up in the powder bed [42]: (a) the fracture rate of *all* particle sizes decreases, the result, apparently, of a cushioning effect by the fines that minimizes stress and fracture; (b) fracture kinetics become nonlinear. Other factors, such as coating of equipment surfaces by fines, also affect the efficiency of the milling operation.

Nonetheless, mathematical analyses of milling operations, particularly for ball mills, roller mills, and fluid energy mills, have been moderately successful. There continues to be a pronounced need for a more complete understanding of

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micromeritic characteristics, the intrinsic nature of the milling operation itself, the influence of fines on the milling operation, and phenomena such as flaw structure of solids, particle fracture, particulate flow, and interactions at both macroscopic and microscopic scales.

D. Material Transfer

Movement of liquids and semisolids through conduits or pipes from one location to another is accomplished by inducing flow with the aid of pumps. The induction of flow usually occurs as a result of one or more of the following energy transfer mechanisms: gravity, centrifugal force, displacement, electromagnetic force, mechanical impulse, or momentum transfer. The work expended in pumping is the product of pump capacity, *Q,* i.e., the rate of fluid flow through the pump (in m^3/hr), and the dynamic head, *H:*

$$P = \frac{HQ\rho}{3.670 \times 10^5} \tag{32}$$

where P is the pump's power output, expressed in kW, H is the total dynamic head, in $N \cdot m \cdot kg^{-1}$, and ρ is the fluid density, in $kg \cdot m^{-3}$. Due to frictional heating losses, power input for a pump is greater than its power output. As pump efficiency is characterized by the ratio of power output to power input, the pumping of viscous fluids would tend to result in decreased pump efficiency due to the increase in power required to achieve a specific output. Another variable, ε, the surface roughness of the pipe, has an effect on pump efficiency as well and must also be considered. The Fanning friction factor f is a dimensionless factor that is used in conjunction with the Reynolds number to estimate the pressure drop in a fluid flowing in a pipe or conduit. The relative roughness, ε/D, of a pipe—where D is the pipe diameter—has an effect on the friction factor f. When *laminar* flow conditions prevail, f may be estimated by

$$f = \frac{16}{N_{\mathrm{Re}}} \tag{33}$$

When *turbulent* flow in smooth pipes is involved,

$$f = \frac{0.079}{N_{\mathrm{Re}}^{0.25}} \tag{34}$$

A useful discussion of incompressible fluid flow in pipes and the influence of surface roughness and friction factors on pumping is found in *Perry's Chemical Engineer's Handbook* [48].

The transfer of material from mixing tanks or holding tanks to processing equipment or to a filling line, whether by pumping or by gravity feed, is potentially problematic. Instability (chemical or physical) or further processing, (e.g.,

mixing, changes in the particle size distribution) may occur during the transfer of material (by pouring or pumping) from one container or vessel to another due to changes in the rate of transfer or in shear rate or shear stress. While scale-up-related changes in the velocity profiles of time-*independent* Newtonian and non-Newtonian fluids due to changes in flow rate or in equipment dimensions or geometry can be accounted for, time dependence must first be recognized in order to be accommodated.

Changes in mass transfer *time* as a consequence of scale-up are often overlooked. As Carstensen and Mehta [49] note, mixing of formulation components in the laboratory may be achieved almost instantaneously with rapid pouring and stirring. They cite the example of pouring 20 mL of liquid A, while stirring, into 80 mL of liquid B. On a production scale, however, mixing is unlikely to be as rapid. A scaled-up batch of 2000 L would require the admixture of 400 L of A and 1600 L of B. If A were pumped into B at the rate of 40 L min^{-1}, then the transfer process would take at least 10 min while additional time would also be required for the blending of the two liquids. If, for example, liquids A and B were of different pH (or ionic strength or polarity etc.), the time required to transfer all of A into B and to mix A and B intimately would allow some intermediate pH (or ionic strength or polarity etc.) to develop and to persist long enough for some adverse effect to occur, such as precipitation, adsorption, or change in viscosity. Thus, transfer times on a production scale need to be determined so that the temporal impact of scale-up can be accounted for in laboratory or pilot-plant studies.

E. Heat Transfer

On a laboratory scale, heat transfer occurs relatively rapidly, for the volume-to-surface-area ratio is relatively small; cooling or heating may or may not involve jacketed vessels. However, on a pilot-plant or production scale, the volume-to-surface-area ratio is relatively large. Consequently, heating or cooling of formulation components or product takes a finite time, during which system temperature, T°C, may vary considerably. Temperature-induced instability may be a substantial problem if a formulation is maintained at suboptimal temperatures for a prolonged period of time. Thus, jacketed vessels or immersion heaters or cooling units with rapid circulation times are an absolute necessity. Carstensen and Mehta [49] give an example of a jacketed kettle with a heated surface of A cm^2, with inlet steam or hot water in the jacket maintained at a temperature T_0°C. The heat transfer rate (dQ/dt) in this system is proportional to the heated surface area of the kettle and the temperature gradient, $T_0 - T$ (i.e., the difference between the temperature of the kettle contents, T, and the temperature of the jacket, T_0) at time t:

$$\frac{dQ}{dt} = C_p\left(\frac{dT}{dt}\right) = kA(T_0 - T) \tag{35}$$

where C_p is the heat capacity of the jacketed vessel and its contents and k is the heat transfer coefficient. If the initial temperature of the vessel is T_1°C, Eq. (35) becomes

$$T_0 - T = (T_0 - T_1)e^{-at} \tag{36}$$

where $a = kA/C_p$. The time t required to reach a specific temperature T_2 can be calculated from Eq. (36), if a is known, or estimated from time–temperature curves for similar products processed under the same conditions. Scale-up studies should consider the effect of longer processing times at suboptimal temperatures on the physicochemical or chemical stability of the formulation components and the product. A further concern for disperse system scale-up is the increased opportunity in a multiphase system for nonuniformity in material transport (e.g., flow rates and velocity profiles) stemming from nonuniform temperatures within processing equipment.

III. HOW TO ACHIEVE SCALE-UP[16]

Full-scale tests using production equipment and involving no scale-up studies whatsoever are sometimes resorted to when single-phase low-viscosity systems are involved and processing is considered to be predictable and directly scalable. By and large, these are unrealistic assumptions when viscous liquids, dispersions, or semisolids are involved. Furthermore, the expense associated with full-scale testing is substantial: Commercial-scale equipment is relatively inflexible and costly to operate. Errors in full-scale processing involve large amounts of material. Insofar as most liquids or semisolids are concerned then, full-scale tests are *not* an option.

On the other hand, scale-up studies involving relatively low scale-up ratios and few changes in process variables are not necessarily a reasonable alternative to full-scale testing. For that matter, experimental designs employing minor, incremental, changes in processing equipment and conditions are unacceptable as well. These alternative test modes are inherently unacceptable because they consume time, an irreplaceable resource [50] that must be utilized to its maximum advantage. Appropriate process development, by reducing costs and accelerating lead times, plays an important role in product development performance. In *The Development Factory: Unlocking the Potential of Process Innovation,* author Gary Pisano [51] argues that while pharmaceuticals compete largely on the basis of product innovation, there is a hidden leverage in process development and man-

[16] Reprinted in part, with revisions and updates, by courtesy of Marcel Dekker, Inc., from L. H. Block, "Scale-up of disperse systems: theoretical and practical aspects," in *Pharmaceutical Dosage Forms: Disperse Systems* (H. A. Lieberman, M. M. Rieger, and G. S. Banker, eds.), 2nd ed., Vol. 3, Marcel Dekker, New York, 1998, pp. 378–388.

ufacturing competence that provides more degrees of freedom, in developing products, to more adroit organizations than to their less adept competitors. Although Pisano focuses on drug synthesis and biotechnology process scale-up, his conclusions translate effectively to the manufacturing processes for drug dosage forms and delivery systems. In effect, scale-up issues need to be addressed jointly by pharmaceutical engineers and formulators as soon as a dosage form or delivery system appears to be commercially viable. Scale-up studies should not be relegated to the final stages of product development, whether initiated at the behest of the FDA (to meet regulatory requirements) or marketing and sales divisions (to meet marketing directives or sales quotas). The worst scenario would entail the delay of scale-up studies until after commercial distribution (to accommodate unexpected market demands).

Modular scale-up involves the scale-up of individual components or unit operations of a manufacturing process. The interactions among these individual operations comprise the potential scale-up problem, i.e., the inability to achieve sameness when the process is conducted on a different scale. When the physical or physicochemical properties of system components are known, the scalability of some unit operations may be predictable.

Known scale-up correlations thus may allow scale-up when laboratory or pilot plant experience is minimal. The fundamental approach to process scaling involves mathematical modeling of the manufacturing process and experimental validation of the model at different scale-up ratios. In a paper on fluid dynamics in bubble column reactors, Lübbert and coworkers [52] noted: "Until very recently fluid dynamical models of multiphase reactors were considered intractable. This situation is rapidly changing with the development of high-performance computers. Today's workstations allow new approaches to . . . modeling."

Insofar as the scale-up of pharmaceutical liquids (especially disperse systems) and semisolids is concerned, virtually no guidelines or models for scale-up have generally been available that have stood the test of time. Uhl and Von Essen [54], referring to the variety of rules of thumb, calculation methods, and extrapolation procedures in the literature, state, "Unfortunately, the prodigious literature and attributions to the subject [of scale-up] seemed to have served more to confound. Some allusions are specious, most rules are extremely limited in application, examples give too little data and limited analysis." Not surprisingly, then, the trial-and-error method is the one most often employed by formulators. As a result, serendipity and practical experience continue to play large roles in the successful pursuit of the scalable process.

A. Principles of Similarity

Irrespective of the approach taken to scale-up, the scaling of unit operations and manufacturing processes requires a thorough appreciation of the principles of sim-

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ilarity. "Process similarity is achieved between two processes when they accomplish the same process objectives by the same mechanisms and produce the same product to the required specifications." Johnstone and Thring [53] stress the importance of four types of similarity in effective process translation: (a) geometric similarity, (b) mechanical (static, kinematic, and dynamic) similarity, (c) thermal similarity, and (d) chemical similarity. Each of these similarities presupposes the attainment of the other similarities. In actuality, approximations of similarity are often necessary due to departures from ideality (e.g., differences in surface roughness, variations in temperature gradients, changes in mechanism). When such departures from ideality are not negligible, a correction of some kind has to be applied when scaling up or down: These scale effects must be determined before scaling of a unit operation or a manufacturing process can be pursued. It should be recognized that scale-up of multiphase systems, based on similarity, is often unsuccessful, since only one variable can be controlled at a time, i.e., at each scale-up level. Nonetheless, valuable mechanistic insights into unit operations can be achieved through similarity analyses.

1. Geometric Similarity

Point-to-point geometric similarity of two bodies (e.g., two mixing tanks) requires three-dimensional correspondence. Every point in the first body is defined by specific x-, y-, and z-coordinate values. The corresponding point in the second body is defined by specific x'-, y'-, and z'-coordinate values. The correspondence is defined by the following equation

$$\frac{x'}{x} = \frac{y'}{y} = \frac{z'}{z} = L \tag{37}$$

where the linear scale ratio L is constant. In contrasting the volume of a laboratory-scale mixing tank (V_1) with that of a geometrically similar production scale unit (V_2), the ratio of volumes (V_1/V_2) is dimensionless. However, the contrast between the two mixing tanks needs to be considered on a linear scale; e.g., a 1000-fold difference in volume corresponds to a 10-fold difference, on a linear scale, in mixing tank diameter, impeller diameter, etc.

If the scale ratio is not the same along each axis, the relationship between the two bodies is of a distorted geometric similarity, and the axial relationships are given by

$$\frac{x'}{x} = X, \qquad \frac{y'}{y} = Y, \qquad \frac{z'}{z} = Z \tag{38}$$

Thus, equipment specifications can be described in terms of the scale ratio L or, in the case of a distorted body, two or more scale ratios (X, Y, Z). Scale ratios facilitate the comparison and evaluation of different sizes of functionally comparable equipment in process scale-up.

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2. Mechanical Similarity

The application of force to a stationary or moving system can be described in static, kinematic, or dynamic terms that define the mechanical similarity of processing equipment and the solids or liquids within their confines. *Static* similarity relates the deformation under constant stress of one body or structure to that of another; it exists when geometric similarity is maintained even as elastic or plastic deformation of stressed structural components occurs [53]. In contrast, *kinematic* similarity encompasses the additional dimension of time, while *dynamic* similarity involves the forces (e.g., pressure, gravitational, centrifugal) that accelerate or retard moving masses in dynamic systems. The inclusion of time as another dimension necessitates the consideration of *corresponding times,* t' and *t,* for which the time scale ratio **t,** defined as $\mathbf{t} = t'/t$, is a constant.

Corresponding particles in disperse systems are geometrically similar particles that are centered on corresponding points at corresponding times. If two geometrically similar fluid systems are kinematically similar, their corresponding particles will trace out geometrically similar paths in corresponding intervals of time. Thus, their flow patterns will be geometrically similar and heat- or mass-transfer rates in the two systems will be related to one another [53]. Pharmaceutical engineers may prefer to characterize disperse systems' *corresponding velocities,* which are the velocities of corresponding particles at corresponding times:

$$\frac{v'}{v} = \mathbf{v} = \frac{L}{\mathbf{t}} \tag{39}$$

Kinematic and geometric similarity in fluids ensures geometrically similar streamline boundary films and eddy systems. If forces of the same kind act upon corresponding particles at corresponding times, they are termed *corresponding forces,* and conditions for dynamic similarity are met. While the scale-up of power consumption by a unit operation or manufacturing process is a direct consequence of dynamic similarity, mass and heat transfer—direct functions of kinematic similarity—are only indirect functions of dynamic similarity.

3. Thermal Similarity

Heat flow, whether by radiation, conduction, convection, or the bulk transfer of matter, introduces temperature as another variable. Thus, for systems in motion, thermal similarity requires kinematic similarity. Thermal similarity is described by

$$\frac{H'_r}{H_r} = \frac{H'_c}{H_c} = \frac{H'_v}{H_v} = \frac{H'_f}{H_f} = \mathbf{H} \tag{40}$$

where H_r, H_c, H_v, and H_f, are the heat fluxes or quantities of heat transferred per second by radiation, convection, conduction, and bulk transport, respectively, and **H,** the thermal ratio, is a constant.

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4. Chemical Similarity

This similarity state is concerned with the variation in chemical composition from point to point as a function of time. Chemical similarity, i.e., the existence of comparable concentration gradients, is dependent upon both thermal and kinematic similarity.

5. Interrelationships Among Surface Area and Volume Upon Scale-Up

Similarity states aside, the dispersion technologist must be aware of whether a given process is volume dependent or area dependent. As the scale of processing increases, volume effects become increasingly more important while area effects become increasingly less important. This is exemplified by the dependence of mixing tank volumes and surface areas on scale-up ratios (based on mixing tank diameters) in Table 1. The surface-area-to-volume ratio is much greater on the small scale than on the large scale; surface area effects are thus much more important on a small scale than on a large one. Conversely, the volume-to-surface-area ratio is much greater on the large scale than on the small scale; volumetric effects are thus much more important on a large scale than on a small scale. Thus, volume-dependent processes are more difficult to scale-up than surface-area-dependent processes. For example, exothermic processes may generate more heat than can be tolerated by a formulation, leading to undesirable phase changes or product degradation unless cooling coils, or other means of intensifying heat transfer, are added. A further example is provided by a scale-up problem involving a tenfold increase in tank volume, from 400 L to 4000 L, and an increase in surface area from 2 m^2 to 10 m^2. The surface-area-to-volume ratio is 1/200 and 1/400, respectively. In spite of the tenfold increase in tank volume, the increase in surface area is only fivefold, necessitating the provision of additional heating or cooling capacity to allow for an additional 10 m^2 of surface for heat exchange.

Table 1 Dependence of Area and Volume on Scale-Up Ratios

Scale	Tank diameter, m	Area, m^2	Volume, m^3	Area/volume	Volume/area
1	0.1	0.0393	0.000785	50	0.02
10	1	3.93	0.785	5	0.2
20	2	15.7	6.28	2.5	0.4
50	5	98.2	98.2	1	1

Assumptions: Tank is a right circular cylinder; batch height = tank diameter; area calculations are the sum of the area of the convex surface and the area of the bottom of the cylinder.
Source: Ref. 55.

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As Tatterson [55] notes, "There is much more volume on scale-up than is typically recognized. This is one feature of scale-up that causes more difficulty than anything else." For disperse systems, a further mechanistic implication of the changing volume and surface-area ratios is that particle size reduction (or droplet breakup) is more likely to be the dominant process on a small scale while aggregation (or coalescence) is more likely to be the dominant process on a large scale [55].

6. Interrelationships Among System Properties Upon Scale-Up

When a process is dominated by a mixing operation, another gambit for the effective scale-up of geometrically similar systems involves the interrelationships that have been established for impeller-based systems. Tatterson [56] describes a number of elementary scale-up procedures for agitated tank systems that depend upon operational similarity. Thus, when scaling up from level 1 to level 2,

$$\frac{(P/V)_1}{(P/V)_2} = \begin{cases} \left(\frac{N_1}{N_2}\right)^3 \left(\frac{D_1}{D_2}\right)^2 & \text{for turbulent flow} \\ \left(\frac{N_1}{N_2}\right)^2 & \text{for laminar flow} \end{cases} \tag{41}$$

power per unit volume is dependent principally on the ratio N_1/N_2 since impeller diameters are constrained by geometric similarity.

A change in size on scale-up is not the sole determinant of the scalability of a unit operation or process. Scalability depends on the unit operation mechanism(s) or system properties involved. Some mechanisms or system properties relevant to dispersions are listed in Table 2 [57]. In a number of instances, size has

Table 2 Influence of Size on System Behavior or Important Unit Operation Mechanisms

System behavior or unit operation mechanisms	Important variables[a]	Influence of size
Chemical kinetics	*C, P, T*	None
Thermodynamic properties	*C, P, T*	None
Heat transfer	Local velocities, *C, P, T*	Important
Mass transfer within a phase	N_{Re}, *C, T*	Important
Mass transfer between phases	Relative phase velocities, *C, P, T*	Important
Forced convection	Flow rates, geometry	Important
Free convection	Geometry, *C, P, T*	Crucial

[a] *C, P,* and *T* are concentration, pressure, and temperature, respectively.
Source: Adapted from Ref. 57.

little or no influence on processing or on system behavior. Thus, scale-up will not affect chemical kinetics or thermodynamics, although the thermal effects of a reaction could perturb a system, e.g., by affecting convection [57]. Heat or mass transfer within or between phases is indirectly affected by changes in size, while convection is directly affected. Thus, since transport of energy, mass, and momentum are often crucial to the manufacture of disperse systems, scale-up can have a substantial effect on the resultant product.

B. Dimensions, Dimensional Analysis, and the Principles of Similarity

Just as process translation or scaling up is facilitated by defining similarity in terms of dimensionless ratios of measurements, forces, or velocities, the technique of dimensional analysis per se permits the definition of appropriate composite dimensionless numbers whose numeric values are process specific. Dimensionless quantities can be pure numbers, ratios, or multiplicative combinations of variables with no net units.

Dimensional analysis is concerned with the nature of the relationship among the various quantities involved in a physical problem. An approach intermediate between formal mathematics and empiricism, it offers the pharmaceutical engineer an opportunity to generalize from experience and apply knowledge to a new situation [58,59]. This is a particularly important avenue, for many engineering problems—scale-up among them—cannot be solved completely by theoretical or mathematical means. Dimensional analysis is based on the fact that if a theoretical equation exists among the variables affecting a physical process, that equation must be dimensionally homogeneous. Thus, many factors can be grouped, in an equation, into a smaller number of dimensionless groups of variables [59].

Dimensional analysis is an algebraic treatment of the variables affecting a process; it does not result in a numerical equation. Rather, it allows experimental data to be fitted to an empirical process equation that results in scale-up being achieved more readily. The experimental data determine the exponents and coefficients of the empirical equation. The requirements of dimensional analysis are that (1) only one relationship exists among a certain number of physical quantities, and (2) no pertinent quantities have been excluded or extraneous quantities included.

Fundamental (primary) quantities, which cannot be expressed in simpler terms, include mass (M), length (L), and time (T). Physical quantities may be expressed in terms of the fundamental quantities: e.g., density is ML^{-3}, velocity is LT^{-1}. In some instances, mass units are covertly expressed in terms of force (F) in order to simplify dimensional expressions or render them more identifiable.

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The MLT and FLT systems of dimensions are related by the equations

$$\left.\begin{aligned} F = Ma = \frac{ML}{T^2} \\ M = \frac{FT^2}{L} \end{aligned}\right\}$$

According to Bisio [60], scale-up can be achieved by maintaining the dimensionless groups characterizing the phenomena of interest constant from small scale to large scale. However, for complex phenomena this may not be possible. Alternatively, dimensionless numbers can be weighted so that the untoward influence of unwieldy variables can be minimized. On the other hand, this camouflaging of variables could lead to an inadequate characterization of a process and a false interpretation of laboratory or pilot plant data.

Pertinent examples of the value of dimensional analysis have been reported recently in a series of papers by Maa and Hsu [19,36,61]. In their first report, they successfully established the scale-up requirements for microspheres produced by an emulsification process in continuously stirred tank reactors (CSTRs) [61]. Their initial assumption was that the diameter of the microspheres, d_{ms}, is a function of phase *quantities, physical properties* of the dispersion and dispersed phases, and *processing equipment parameters:*

$$d_{ms} = f(D\omega, D/T, H, B, n_{\text{imp}}, g_c, g, c, \eta_o, \eta_a, \rho_o, \rho_a, \nu_o, \nu_a, \sigma) \tag{42}$$

Gravitational acceleration, g, is included to relate mass to inertial force. The conversion factor, g_c, was included to convert one unit system to another. The subscripts o and a refer to the organic and aqueous phases, respectively. The remaining notation is as follows:

D	impeller diameter (cm)
ω	rotational speed (angular velocity) of the impeller(s) (sec^{-1})
T	tank diameter (cm)
H	height of filled volume in the tank (cm)
B	total baffle area (cm^2)
n	number of baffles
n_{imp}	number of impellers
ν_o, ν_a	phase volumes (mL)
c	polymer concentration (g/mL)
η_o, η_a	phase viscosities ($\text{g-cm}^{-1}\text{-sec}^{-1}$)
ρ_o, ρ_a	phase densities (g-mL^{-1})
σ	interfacial tension between organic and aqueous phases (dyne-cm^{-1})

The initial emulsification studies employed a 1-L "reactor" vessel with baffles originally designed for fermentation processes. Subsequent studies were suc-

cessively scaled-up from 1 L to 3, 10, and 100 L. Variations due to differences in reactor configuration were minimized by utilizing geometrically similar reactors with approximately the same D/T ratio (i.e., 0.36–0.40). Maa and Hsu contended that separate experiments on the effect of the baffle area (B) on the resultant microsphere diameter did not significantly affect d_{ms}. However, the number and location of the impellers had a significant impact on d_{ms}. As a result, to simplify the system, Maa and Hsu always used double impellers ($n_{imp} = 2$), with the lower one placed close to the bottom of the tank and the other located in the center of the total emulsion volume. Finally, Maa and Hsu determined that the volumes of the organic and aqueous phases, in the range they were concerned with, played only a minor role in affecting d_{ms}. Thus, by the omission of D/T, B, and ν_o, and ν_a, Eq. 42 was simplified considerably to yield

$$d_{ms} = f(D\omega, g_c, g, c, \eta_o, \eta_a, \rho_o, \rho_a, \sigma) \tag{43}$$

Equation (43) contains ten variables and four fundamental dimensions (L, M, T, and F). Maa and Hsu were able subsequently to define microsphere size, d_{ms}, in terms of the processing parameters and physical properties of the phases:

$$\frac{g(\rho_o - \rho_a)d_{ms}^2}{\sigma} = \Pi_2^{-0.280}\,\Pi_3^{-0.108}\,\Pi_4^{-0.056}\left(0.255\Pi_5^{e} + 0.0071\right) \tag{44}$$

where Π are dimensionless multiplicative groups of variables. [The transformation of Eq. (43) into Eq. (44) is described by Maa and Hsu [61] in an appendix to their paper.] Subsequently, linear regression analysis of the microsphere size parameter, $g(\rho_o - \rho_a)d_{ms}^2/\sigma$, as a function of the right-hand side of Eq. (43); i.e., $(\Pi_2^{-0.280}\,\Pi_3^{-0.108}\,\Pi_4^{-0.056}\,(0.255\Pi_5^{e} + 0.0071))$, resulted in $r \approx 0.973$ for 1-L, 3-L, 10-L, and 100-L reactors, at two different polymer concentrations. These composite data are depicted graphically in Figure 3.

Subsequently, Maa and Hsu [19] applied dimensional analysis to the scale-up of a liquid–liquid emulsification process for microsphere production utilizing one or another of three different static mixers, which varied in diameter, number of mixing elements, and mixing element length. Mixing element design differences among the static mixers were accomodated by the following equation:

$$d_{ms} = 0.483 d^{1.202} V^{-0.556} \sigma^{0.556} \eta_a^{-0.560} \eta_o^{0.004} n^h c^{0.663} \tag{45}$$

where d_{ms} is the diameter of the microspheres (μm) produced by the emulsification process, d is the diameter of the static mixer (cm), V is the flow rate of the continuous phase (mL-sec^{-1}), σ is the interfacial tension between the organic and aqueous phases (dyne/cm), η_a and η_o are the viscosities (g-cm^{-1}-sec^{-1}) of the aqueous and organic phases, respectively, n is the number of mixing elements, h is an exponent the magnitude of which is a function of static mixer design, and c

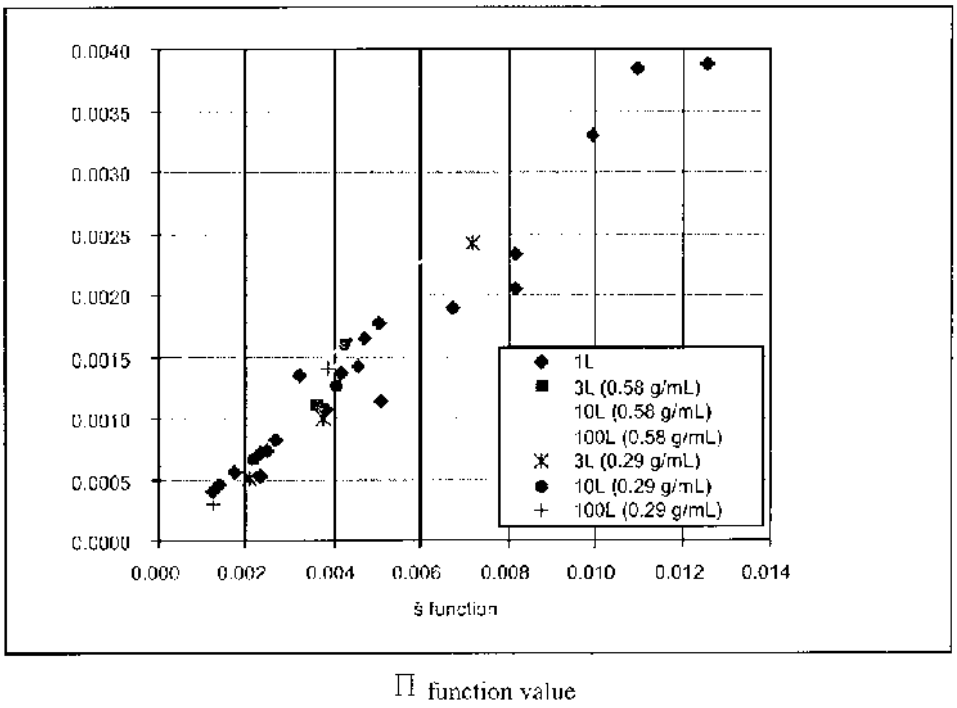

Figure 3 Microsphere diameter parameter, d_{ms}, as a function of processing parameters and physical properties of the phases (Π functions of the right-hand side of Eq. 31). (From Ref. 61.)

is the polymer concentration (g-mL^{-1}) in the organic phase. The relative efficiency of the three static mixers was readily determined in terms of emulsification efficiency, ε, defined as equivalent to $1/d_{ms}$: better mixing results in smaller microspheres. In this way, Maa and Hsu were able to compare and contrast continuously stirred tank reactors (CSTRs) with static mixers.

Houcine et al. [62] used a nonintrusive laser-induced fluorescence method to study the mechanisms of mixing in a 20 dm^3 CSTR with removable baffles, a conical bottom, a mechanical stirrer, and two incoming liquid jet streams. Under certain conditions, they observed an interaction between the flow induced by the stirrer and the incoming jets that led to oscillations of the jet stream with a period of several seconds and corresponding switching of the recirculation flow between several metastable macroscopic patterns. These jet feedstream oscillations or intermittencies could strongly influence the kinetics of fast reactions such as precipitation. The authors used dimensional analysis to demonstrate that the intermittence phenomenon would be less problematic in larger CSTRs.

Additional insights into the application of dimensional analysis to scale-up can be found in Chapter 1 of this volume, by Zlokarnik [63], and in his earlier monograph on scale-up in chemical engineering [64].

C. Mathematical Modeling and Computer Simulation

Basic and applied research methodologies in science and engineering are undergoing major transformations. Mathematical models of "real-world" phenomena are more elaborate than in the past, with forms governed by sets of partial differential equations that represent continuum approximations to microscopic models [65]. Appropriate mathematical relationships would reflect the fundamental laws of physics regarding the conservation of mass, momentum, and energy. Euzen et al. [66] list such balance equations for mass, momentum, and energy (e.g., heat), for a single-phase Newtonian system (with constant density, ρ, viscosity, η, and molar heat capacity at constant pressure, C_p) in which a process takes place in an element of volume, ΔV (defined as the product of *dx, dy,* and *dz*):

$$\left.\begin{aligned}
&\frac{\partial C_i}{\partial t} = -\left\{\nu_x\frac{\partial C_i}{\partial x} + \nu_y\frac{\partial C_i}{\partial y} + \nu_z\frac{\partial C_i}{\partial z}\right\} \\
&\qquad + \left\{D_{ix}\frac{\partial^2 C_i}{\partial x^2} + D_{iy}\frac{\partial^2 C_i}{\partial y^2} + D_{iz}\frac{\partial^2 C_i}{\partial z^2}\right\} + R_i \\
&\qquad\qquad \text{Mass balance} \\
&\rho\left\{\frac{\partial \nu_x}{\partial t} + \nu_x\frac{\partial \nu_x}{\partial x} + \nu_y\frac{\partial \nu_x}{\partial y} + \nu_z\frac{\partial \nu_x}{\partial z}\right\} \\
&\qquad = -\frac{\partial P}{\partial x} + \eta\left\{\frac{\partial^2 \nu_x}{\partial x^2} + \frac{\partial^2 \nu_x}{\partial y^2} + \frac{\partial^2 \nu_x}{\partial z^2}\right\} + \rho g_x \\
&\qquad\qquad \text{Momentum balance (e.g., in } x\text{-direction)}\} \\
&\rho C_p\left\{\frac{\partial T}{\partial t} + \nu_x\frac{\partial T}{\partial x} + \nu_y\frac{\partial T}{\partial y} + \nu_z\frac{\partial T}{\partial z}\right\} \\
&\qquad = \left\{k_x\frac{\partial^2 T}{\partial x^2} + k_y\frac{\partial^2 T}{\partial y^2} + k_z\frac{\partial^2 T}{\partial z^2}\right\} + S_R \\
&\qquad\qquad \text{Energy balance}
\end{aligned}\right\} \quad (46)$$

where P is pressure, T is temperature, t is time, ν is fluid flow velocity, k is thermal conductivity, and R_i, g_x, and S_R are kinetic, gravitational, and energetic parameters, respectively. Equation (46) is presented as an example of the complex

relationships that are becoming increasingly more amenable to resolution by computers, rather than for its express utilization in a scale-up problem.

However, most computational fluid dynamics (CFD) software programs available to date for simulation of transport phenomena require the user to define the model equations and parameters and specify the initial and boundary conditions in accordance with the program's language and code, often highly specialized. A practical interim solution to the computational problem presented by Eq. (46) and its non-Newtonian counterparts is at hand now in the form of software developed by Visimix Ltd. [67]—VisiMix 2000 Laminar and VisiMix 2000 Turbulent—for personal computers! These interactive programs utilize a combination of classical transport equations in conjunction with algorithms for computation of mixing processes and actual laboratory, pilot plant, and production data to simulate macro- and microscale transport phenomena. VisiMix's user friendly, menu-driven software uses physical and mathematical models of mixing phenomena based on fundamental transport equations and on extensive theoretical and experimental research [68–70]. Graphical menus allow the user to select and define process equipment from a wide range of options, including vessel shape, agitator type, jacketing, and baffle type. VisiMix not only addresses most unit operations with a mixing component (e.g., blending, suspension of solids, emulsification, dissolution, gas dispersion) but also evaluates heat transfer/exchange (e.g., for jacketed tanks). Tangential velocity distributions, axial circulation, macro- and microscale turbulence, mixing time, equilibrium droplet size distribution, and droplet breakup and coalescence are just some of the calculations or simulations that VisiMix can provide.

Liu and Neeld [71] used VisiMix software to calculate shear rates in laboratory-, pilot-plant-, and production-scale vessels. Their results (Table 3) showed marked differences, by as much as two orders of magnitude, in the shear rates calculated in the conventional manner (from tip speed and the distance from impeller tip to baffle, i.e., $\dot{\gamma} = ND/(T - D)$, and the shear rates computed by VisiMix. The latter's markedly higher shear rates resulted from VisiMix's definition of the shear rate in terms of Kolmogorov's model of turbulence and the distribution of flow velocities. Note that VisiMix's estimates of the respective shear rates in the vicinity of the impeller blade are comparable at all scales, while the shear rates in the bulk volume or near the baffle are not, except on the laboratory scale. If the efficacy of the mixing process were dependent upon the shear achieved adjacent to the impeller, the VisiMix scaling simulations would predict comparable outcomes for the equipment parameters employed. However, if the shear rate in the vicinity of the impeller were not the controlling factor in achieving similitude, then scale-up relying on adjustments in agitator speed or tip velocity would be unsuccessful.

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Table 3 Shear Rates at Different Processing Scales

Scale	Agitator speed, rpm	Tip velocity, m/s	Average shear rate = (tip speed/ distance from tip to baffle), 1/sec	VisiMix simulation: shear rate in bulk volume, 1/sec	VisiMix simulation: shear rate near the impeller blade, 1/sec	VisiMix simulation: shear rate near baffle, 1/sec
Laboratory reactor	700	3.11	37	902	12,941	902
Pilot plant reactor	250	5.98	118	2,470	12,883	4,146
Production plant reactor	77	8.60	15	1,517	11,116	1,678

Source: Adapted from Ref. 71.

IV. SCALE-UP PROBLEMS

As Baekland [72] said, "Commit your blunders on a small scale and make your profits on a large scale." Effective scale-up mandates an awareness of the relative importance of various process parameters at different scales of scrutiny. Heat transfer, molecular diffusion, and microscopic viscosity operate on a so-called microscopic or molecular scale. On a macroscopic scale, these parameters may not appear to have a noticeable effect, yet they cannot be ignored: Were there no energy, mass, or momentum transport at the microscopic scale, larger-scale processes would not function properly [55]. On the other hand, a system's flow regimes operate at both the microscopic and macroscopic levels. Turbulent flow, characterized by random swirling motions superimposed on simpler flow patterns, involves the rapid tumbling and retumbling of relatively large portions of fluid, or eddies. While turbulence, encountered to some degree in virtually all fluid systems, tends to be isotropic on a small scale, it is anisotropic on a large scale.

Among some of the more common scale-up errors are:

- Scaling based on wrong unit operation mechanism(s)
- Incompletely characterized equipment, e.g., multishaft mixers/homogenizers
- Insufficient knowledge of process; lack of important process information
- Utilization of different types of equipment at different levels of scale-up

- Unrealistic expectations (e.g., heat dissipation)
- Changes in product or process (e.g., altered formulation, phase changes, changes in order of addition) during scale-up

These last issues, in particular, are exemplified by the recent report of Williams et al. [73] on problems associated with the scale-up of an o/w cream containing 40% diethylene glycol monoethyl ether and various solid, waxy excipients (e.g., cetyl alcohol; polyoxyethylene-2-stearyl ether). Preparation of 300-g batches in the laboratory in small stainless steel beakers proceeded without incident while 7-kg batches made with a Brogli-10 homogenizer were subject to precipitation in or congealing of the external phase in the region between the sweep agitation blade and the discharge port. Low levels of congealed or precipitated excipient that went undetected on the laboratory scale, marked differences in the rate and extent of heat exchange at the two levels of manufacturing, and the presence of cold spots or nonjacketed areas in the Brogli-10 homogenizer contributed to the problem.

Unfortunately, the publication by Williams and coworkers is one of the only reports of a scale-up problem involving liquids or semisolids in the pharmaceutical literature. A number of papers that purport to deal with scale-up issues and even go so far as to compare the properties of small versus large batches fail to apply techniques such as dimensional analysis that could have provided the basis for a far more substantial assessment or analysis of the scale-up problem for their system. Worse yet, there is no indication of how scale-up was achieved or what scale-up algorithm(s), if any, were used. Consequently, their usefulness, from a pedagogical point of view, is minimal.

V. CONCLUSIONS

Process scale-up of liquids and semisolids not only is an absolutely essential part of pharmaceutical manufacturing but also is a crucial part of the regulatory process. The dearth of research publications to date must reflect either the avoidance of scale-up issues by pharmaceutical formulators and technologists due to their inherent complexity or a concern that scale-up experimentation and data constitute trade secrets that must not be disclosed lest competitive advantages be lost. The emergence of pharmaceutical engineering as an area of specialization and the advent of specialized software capable of facilitating scale-up warrant a change in these attitudes.

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4

Scale-Up Considerations for Biotechnology-Derived Products

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I. INTRODUCTION

This chapter covers the general principles involved in the scale-up of biotechnology-derived products. Sections I and II focus on technologies currently used in the manufacture of commercial products. Sections III and IV include a practical approach to process design and scale-up strategies used to translate process development to large-scale production.

In addition to basic engineering design principles, the scale-up of biotechnology products requires an understanding of the cellular and regulatory mechanisms that govern cell physiology and the biophysical and biochemical characteristics of products. A thorough understanding of process operations and process limitations is essential for successful technology transfer from development to manufacturing. The design and operation of the facility, including appropriate segregation of products, personnel and equipment at each stage of manufacturing, must comply with current regulatory guidelines. The true measure of successful scale-up is validation of the process at manufacturing scale and ultimate approval of the biopharmaceutical product.

Due to the complexity of biological systems and the physical and biochemical characteristics of the protein products, the design and scale-up of biological processes can be challenging. Batch sizes for the production of biotechnology-derived products can reach 10,000 L [1] to 12,500 L [2,3] and above. Although these

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scales of operation are often smaller than conventional fermentation, the high value of individual production lots requires careful planning and process control. For this reason, laboratory- and pilot-scale data together with actual experience are essential for the effective selection of scale-up strategies, equipment, and process parameters [4].

The efficient and timely completion of scale-up to commercial manufacture is critical to biotechnology companies. In some cases, novel unit operations or techniques are required to achieve adequate expression, recovery, quality, or integrity of the product, which may not be feasible with more conventional techniques. However, this may cause costly delays in product approval because the use of new technologies may be associated with a greater uncertainty as the scale of the operation increases. In addition, the ease of process validation may be an important factor influencing the selection of novel versus conventional process techniques [2,5]. For example, cell culture processes can be conducted either as a batch process or as a continuous process. However, the time required to validate a continuous process may be longer than that for a batch process. As a consequence, this may impact the time required for preparation and submission of documents to regulatory agencies as well as the time needed for review and approval. For many companies, the duration of clinical development and the strategy for efficacy studies may determine the difference between success in the marketplace and total failure.

The time lines needed to complete technology transfer may vary with the complexity of the process. A team composed of manufacturing and development personnel is responsible for facility design or integration of a process into an existing facility. The team is also responsible for equipment specifications and defining the physical relationship of process operations in order to comply with regulatory standards. The team must be aware of the relevant scale-up criteria to be used because their misapplication can lead to significant performance differences between benchtop and manufacturing-plant scales [6]. For this reason, stepwise scale-up is recommended. In addition, successful scale-up requires that manufacturing personnel be properly trained on process requirements and Good Manufacturing Practices to provide an efficient and seamless transition into commercial production within the shortest time possible.

Recent advances in safety, selectivity, quality, and integrity of molecules obtained from recombinant microorganisms and immortalized cell lines have provided a wide range of products used as therapeutic agents. Marketed biotechnology products can be classified into five categories [1]: coagulation factors, enzymes, hormones and growth factors, molecular inhibitors/antagonists, and vaccines. Examples of marketed biotechnology products are presented in Table 1. This table illustrates the diversity of cell lines (bacteria, yeast, and mammalian cells) used to produce licensed products. In addition to the expression systems listed later, other expression systems, such as insect cells, plant cells, and transgenic animals and plants, are currently being evaluated at preclinical and clinical stages.

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Table 1 Examples of Biotechnology-Derived Products

Protein	Clinical application	Production process
Coagulation factors		
Recombinate (F VIII)[a]	Hemophilia	rCHO, bleed-feed
Kogenate (F VIII)[a]	Hemophilia	rBHK-21, bleed-feed
Novo Seven (F VIIa)[a]	Hemophilia A	rBHK
Bene Fix (FIX)[a]	Hemophilia B	rCHO
Enzymes		
Pulmozyme (Dnase1)[a]	Cystic fibrosis	rCHO, suspension
Cerezyme[a]	Gaucher's disease	rCHO, microcarriers
Activase (tPA)[a]	Thrombolytic agent	rCHO, suspension
Abbokinase (Urokinase)	Pulmonary embolism	Human kidney cells
Growth factors and hormones		
Welferon (IFN alfa)[a]	Hep C treatment	Namalva
Roferon (IFN alfa-b)	Hep C treatment	r*E. coli*
Infergen (IFN alfa)	Hep C treatment	r*E. coli*
Intron A (IFN alfa)	Hairy cell lymphoma	r*E. coli*
Epogen (Epo)[a]	Stimulation of erithropoiesis	rCHO, Roller bottles
Avonex (IFN beta)[a]	Multiple sclerosis	rCHO
Betaseron (IFN beta)	Multiple sclerosis	r*E. coli*
Proleukin (IL)	Metastatic renal carcinoma	r*E. coli*
Gonal F (FSH)[a]	Induction of ovulation	rCHO
Saizen (hGH)[a]	Growth hormone deficiency	rC127, Roller bottles
Molecular inhibitors/antagonists		
Rituxan (Mab)	B-cell non-Hodgkin's lymphoma	rCHO
Synagis (Mab)	Prevention of RSV disease	rNS/0, suspension
Herceptin (Mab)	Breast cancer	rCHO, supension
OKT3 (Mab)[a]	Rescue of acute renal rejection/GVHD	Mouse ascites
Zenapax (Mab)	Prevention of acute renal rejection	rNS/0, suspension
Reopro (Mab)	Prevention of cardiac ischemic complications	rSP2/0
Leukine (GMCSF)	Induction chemotherapy for acute leukemia	rYeast
Neupogen (GCSF)	Treatment of neutropenia	r*E. coli*
Remicade (Mab)	Reumathoid arthritis	rSP2/0
Embrel	Rheumatoid arthritis	rCHO
Simulect (Mab)	Acute rejection kidney transplants	Recombinant myeloma
Mylotarg (Mab)	Relapsed acute myeloid leukemia	rNS/0, suspension
Campath (Mab)	B cell chronic lymphocytic leukemia	rCHO, suspension

continues

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Table 1 Continued

Protein	Clinical application	Production process
Vaccines		
Vaqta	Hep A Vaccine	MRC5 cells
Recombivax (HbsAg)	Hep B Vaccine	rYeast
Engerix-B (HbsAg)	Hep B vaccine	rYeast
GenHevac B (HbsAg)[a]	Hep B vaccine	rCHO, microcarriers
HB Gamma (HbsAg)[a]	Hep B vaccine	rCHO
Comvax (HbsAg)	Combination of PedvaxHIB and recombivax HB	Microbial fermentation
Infanrix	Tetanus toxoids, diphtheria, acellular pertussis vaccine	Bacterial fermentation
Certiva	Tetanus toxoids, diphtheria, acellular pertusis vaccine	Bacterial fermentation
LYMErix (OspA)	Lyme disease vaccine	r*E. coli*
RotaShield	Rotavirus vaccine	FRhk2
Varivax	Varicella vaccine	MRC5 cells

[a] Ref. 7.

II. FUNDAMENTALS: TYPICAL UNIT OPERATIONS

Comprehensive descriptions of the basic unit operations commonly used in the production of biotechnology products are available in the literature [8]. This section focuses on the typical unit operations currently used for production of biological molecules in cell culture and the technologies used for the purification of pharmaceutical proteins. For each of these operations, laboratory- and pilot-scale experiments provide the basis for scale-up, especially to define the expected range of process operating parameters.

A. Bioreactor Operation

Commercial manufacturing operations in biotechnology usually employ mechanical bioreactors or fermentors for product expression. In this discussion the term *fermentor* will refer to bacterial or fungal processes and the term *bioreactor* to animal cell cultures. While extensive description of the operation of fermentors is available elsewhere [6,8], this chapter will focus on bioreactors used in the manufacture of complex proteins.

There are a variety of types of bioreactors described in the literature. Among them, the stirred tank bioreactor is the most commonly employed due to its record of performance and ease of operation. Cells growing in bioreactors take up nutrients from the culture medium and release products, byproducts, and waste

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metabolites. Mass transport phenomena required for adequate supply of nutrients and removal of waste metabolites are greatly influenced by mixing and aeration rates. Agitation is used to maintain cells in suspension, to provide a homogeneous mix of nutrients, and to prevent the accumulation of toxic gases [9].

Aeration is also an essential requirement for aerobic cell lines. The design of aeration devices includes single-orifice tubes, sparger rings, and diffuser membranes. Bubble sizes may vary with each device, and optimization is required to achieve the maximum ratio of surface area to gas volume transfer rate that generates a minimal of foaming to prevent damaging effects on cell viability [10,11]. The effect of aeration on cell productivity is complex and depends on cell line, medium components (including cell proteins), and characteristics of foam formation and collapse. The optimal aeration rate then is determined empirically at each scale.

B. Filtration Operations

Filtration technologies are used extensively throughout the biotechnology industry [12,13]. Membranes and filters can be used for medium exchange during cell growth, cell harvest, product concentration, diafiltration, and formulation or for removal of viruses and control of bioburden. For example, microfiltration is used to replace spent medium with fresh medium [14] or to recover secreted proteins [3,14]. Ultrafiltration membranes with submicron pore sizes are used for product concentration and buffer exchange by diafiltration. Nanometer ultrafiltration using filters with tightly controlled pore sizes can be used for virus removal [15]. Filtration with 0.2-micron dead-end filters is used for removal of microorganisms [16]. Sterilizing filters are validated for product-specific bubble point, product compatibility, and microbial retention. The key process parameters for filtration scale-up are pressure, volume, operating time, temperature, flux rate, protein concentration, and solution viscosity.

C. Centrifugation

Centrifugation is used in fermentation processes as well as in blood serum fractionation. Scale-up of operations for separation of product-containing cells from supernatant fluid or secreted products from host cells is well established [17]. Although, batch centrifugation is often used at the laboratory scale, continuous centrifugation is preferred at production scale. When centrifugation is used for biotechnology applications, it is preferable to use high-throughput low-shear centrifuges to minimize the shear sensitivity of animal cells. For this reason, filtration may be the preferable unit operation for separating excreted products from host cells because of the relatively mild operating conditions. A second advantage of filtration is that the cleaning validation is relatively simple compared to the elaborated cleaning validation required for continuous centrifuges.

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D. Chromatography

Chromatography is a commonly used unit operation for the purification of proteins in biotechnology applications. It is capable of combining relatively high throughputs with high selectivity. A major advantage of this technique is that it can be optimized to achieve high resolution of the desired product from its contaminants. The selection of the appropriate gel is very much dependent on an understanding of the physical and chemical characteristics of the target protein product. Chromatography steps can be designated selectively to either capture the product or remove contaminants. For ion exchange gels, contaminant removal is achieved by optimizing the pH and conductivity of the equilibration, wash, and elution buffers. Affinity chromatography is often used as an initial capture step to provide high specificity, high selectivity, and volume reduction. However, affinity chromatography gels such as Protein A and Protein G are costly, especially in early process steps with crude product streams. The use of crude material on affinity matrices may require extensive cleaning, which contributes to the cost and can reduce the effective lifetime of the gel. Hydrophobic interaction chromatography (HIC), which takes advantage of the different hydrophobicity of proteins and contaminants, also exhibits selectivity and specificity. Because proteins bind effectively to HIC gels at high conductivity, HIC can be integrated effectively with both ion exchange and affinity chromatography. Key parameters for chromatography scale-up are gel capacity, linear velocity, buffer volume, bed height, temperature, cleanability, and gel lifetime.

E. Dimensional Analysis

Dimensional analysis is a useful tool for examining complex engineering problems by grouping process variables into sets that can be analyzed separately. If appropriate parameters are identified, the number of experiments needed for process design can be reduced, and the results can be described in simple mathematical expressions. In addition, the application of dimensional analysis may facilitate the scale-up for selected biotechnology unit operations. A detailed description of dimensional analysis is reviewed by Zlokarnik [18].

These analysis techniques provide a macroscopic description of the process and offer the possibility of qualitative assessment, although detailed mechanistic information is not captured. Due to the complexity of living systems, it may be impractical to provide a detailed description of the reaction parameters or to determine the specific dimensionless parameters for modeling cell growth and product production. However, models for mixing and aeration are well described in the literature. Similarly, for chromatography steps, it is often difficult to describe the purification of a single protein from a complex mixture of contaminants that range in concentration. However, parameters such as column volumes of solution (liters solution per liter of gel volume) may be used to maintain similarity between scales.

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The scale-up of fermenters and bioreactors has been based on chemical industry methods for design and operation of chemical reactors. Most of the correlations used in the scale-up of fermentors and bioreactors pertain to mixing and aeration. Because agitation rates have a strong effect on cell culture performance, these rates must be optimized at each production scale. Although the effect of mechanical agitation on cell culture has been examined extensively [19,20], it should be noted that models describing mass transfer in agitated vessels are of limited value when scaling up biological processes [6]. While the experience available from fermentation technology has been adapted for scale-up of suspension cultures of animal cells, the scale-up of anchorage-dependent cell lines is more complicated [21] and will not be addressed here.

In a 1991 study by Van Reis et al. [3], a filtration operation as applied to harvest of animal cells was optimized by the use of dimensional analysis. The fluid dynamic variables used in the scale-up work were the length of the fibers (*L,* per stage), the fiber diameter (*D*), the number of fibers per cartridge (*n*), the density of the culture (ρ), and the viscosity of the culture (μ). From these variables, scale-up parameters such as wall shear rate (γ_w) and its effect on flux (L-m^{-2}-hr^{-1}) were derived. Based on these calculations, an optimum wall shear rate for membrane utilization, operating time, and flux was found. However, because there is no single mathematical expression relating all of these parameters simultaneously, the optimal solution required additional experimental research.

III. SCALE-UP OF UPSTREAM OPERATIONS

Unit operations for biological products obtained from fermentation or cell culture can largely be subdivided into four parts: medium preparation, inoculum expansion, bioreactor, and harvest operations.

A. Medium Preparation

In development or small clinical production runs, complete liquid medium may be most convenient. Economic issues may dictate that at large scale, powdered or liquid concentrate medium be used. Shipment and storage of large volumes of complete liquid medium is less practical at scales greater than 1,000 L.

Culture medium is typically prepared by addition of the base powder or liquid concentrate mixtures to appropriate grade water. These base media mixtures usually contain aminoacids, vitamins, cell membrane precursors, antioxidants, and growth factors to mention some major categories of nutrients. Additional components such as proteins or lipids may need to be added separately, since they are usually not compatible in powder blends.

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At present, powdered medium is the formulation of choice for large-scale operations. Powdered medium is easy to ship and store and has a longer shelf life compared to liquid formulations. Medium components are reduced in particle size by ball milling or micronization, mixed, and charged into appropriate-sized containers. Regardless of which process is used to prepare the powder, homogeneity of the powder blend has always been a concern. Because each component will have a different particle size distribution, it may be difficult to be certain that each container of powder will have the exact same composition. Ray [22] reported on a study examining blend uniformity in powder-medium production. A model powder was used to demonstrate homogeneity of medium components that are present at high (glucose) and low (phenol red) concentrations. Large drums of powdered medium were sampled from several locations within the drum to demonstrate homogeneity of amino acids. One issue that has not been adequately addressed yet is whether powder-medium components settle and segregate during the course of shipping and storage.

Liquid-concentrate medium has emerged recently as an alternative to powdered medium [23,24]. For liquid-concentrate preparation, medium components are grouped according to solubility criteria. Liquid-medium concentrates allow for the preparation of medium in-line, by automated dilution of the concentrates with water of the appropriate quality [25]. This would be particularly useful in continuous or perfused processes that require constant preparation of medium. Medium cost and component stability make it a secondary option for batch or fed-batch processes.

B. Cell Culture Inoculum Expansion

The objective of inoculum expansion is to increase the number of cells to an appropriate amount for inoculation of the production bioreactor. Cells are cultured in successively larger flasks by adding fresh medium during exponential growth phase. Cells should be maintained in a rapidly growing state to ensure a vigorous culture for the production stage. If cells are allowed to reach the plateau phase, growth of the culture may lag or cease, depending on the cell line and growth medium used. Each step of expansion is determined in laboratory experiments where culture growth curves are measured. There is a minimum seed cell density necessary to minimize the lag phase, as well a maximum cell density to avoid losing the culture due to starvation or accumulation of toxic metabolites. In the case of fermentation, the usual culture expansion ratio is 1 volume of inoculum to 10 volumes of fresh medium. In the case of animal cells, this ratio may be as high as 1 volume of inoculum to 1 volume of fresh medium.

For the cultivation of animal cells, inoculum expansions have traditionally been conducted in T-flasks, shake flasks, spinner flasks, or roller bottles. Typi-

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cally, T-flasks and shake flasks are used for smaller volumes at the beginning of inoculum expansion, roller bottles or spinner flasks for the larger volumes. However, one drawback of roller bottle inoculum expansion is that an increase in process scale requires an increase in the number of bottles, rather than an increase in the volume of the roller bottles, in order to keep the optimum surface-to-volume ratio. This approach, however, can quickly become cumbersome and labor intensive. Unlike roller bottles, spinner flasks offer the convenience of using-larger sizes of flasks as the amount of inoculum increases. Thus, the number of inoculum vessels can be kept to a minimum, reducing the number of manipulations conducted under sterile conditions. However, it should be noted that in many cases the expansion of inoculum in these types of vessels may have significant oxygen transfer limitations. If larger flasks are to be used in the preparation of an inoculum train, an aeration strategy should be considered. Spinner flasks can be aerated either through the headspace or by sparging through a diptube. The inoculum can be expanded to 10–20 L using these types of flask systems. Beyond that volume, bioreactors of successively larger volume will be used for expansion of the cells until the working volume of the production bioreactor is reached. An alternative method for inoculum expansion is to grow cells in a disposable plastic bag on a rocking platform [26]. The bag can be configured with sterile hydrophobic filters to allow for aeration of the culture. Systems are currently available for culture volumes up to 100 L. Ultimately, the decision about choosing among the alternative methods will depend on cost, reliability, and confidence in the technique used to expand the inoculum.

One consideration to bear in mind during the design of inoculum expansion is to demonstrate the genetic stability of the cell line beyond the expected number of generations required to operate at large scale. This is usually accomplished by conducting measurements of product expression and genetic markers in cells from an extended cell bank (ECB).

C. Bioreactor Operation

Several different bioreactor configurations have been described for use in cell culture and fermentation applications. These include stirred tanks, airlift, and hollow-fiber systems. The majority of bioreactor systems in use for cell culture applications are still of the stirred-tank type. These systems have been used for batch, fed-batch, and perfusion operations. It would not be possible to adequately cover the field of stirred-tank scale-up in the space available here. Instead, this section will touch briefly on the important issues in bioreactor scale-up. For detailed methodologies on stirred-tank bioreactor scale-up, the reader is referred to several review papers on the topic [20,27,28].

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1. Stirred-Tank Bioreactor

As a stirred-tank bioreactor is scaled up, the majority of operating parameters would stay the same as found at bench scale. The optimal range for parameters such as temperature, dissolved oxygen, and pH are scale independent. Among the scale-dependent parameters are the mixing efficiency given by the impeller rate and aeration rate, and hydrostatic pressure. Agitation and aeration rates determine the quality of mixing, the gas–liquid mass transfer rates, and the hydrodynamic stress that the cells experience. Poor mixing can result in inhomogeneities in pH, nutrient concentration, and metabolic byproduct concentrations. In addition to the oxygen gas–liquid transfer rate, the carbon dioxide gas–liquid transfer rate should be taken into account. In the case of animal cells, carbon dioxide is a metabolic byproduct that can accumulate to inhibitory levels unless adequate ventilation is provided [9,29]. Strategies to minimize gas sparging (to reduce sparging-induced cell damage) can inadvertently result in accumulation of carbon dioxide [30,31].

The basic problem in scaling up a stirred tank bioreactor used in animal cell cultivation is that at larger scales, quality of mixing, gas–liquid mass transfer rates, and hydrodynamic stress to the cells cannot all be kept identical to conditions at bench scale. An impeller rate and sparge rate must be chosen that provide adequate mixing and gas–liquid mass transfer rates but minimize cell damage due to shear stress. Animal cells are especially sensitive to mechanical stress, because they lack the protective cell wall of bacteria and fungi. Although many correlations have been described for quality of mixing, gas–liquid mass transfer rates, and hydrodynamic stress, they should be used as guidelines rather than as a predictor of bioreactor performance at large scale. They will rarely predict accurately the properties of a bioreactor system under real operating conditions. For example, measurements of glucose and lactate in a murine hybridoma culture showed a shift toward anabolic metabolism at the 200-L scale that was not observed at the 3-L scale. This observation indicated that oxygen limitation was present at the larger scale, even by using constant impeller tip speed as a scale-up criterion. This problem could be obviated by, for instance, increasing the agitation rate at production scale or the set point for dissolved oxygen tension [14].

Quality of mixing is usually described in terms of a mixing (or circulation) time. Mixing times are generally determined by injecting a tracer into a bioreactor and monitoring the signal until it decays to a predetermined level (for example, 99% of the final value). The simplest tracer is either acid or base, with pH probes to monitor pH fluctuations. As bioreactor volumes increase, mixing times for equivalent impeller tip speeds inevitably increase. For instance, calculations of the theoretical mixing time in a 10-L bioreactor and a 10,000-L bioreactor, under

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typical operating conditions, show that this parameter can increase by an order of magnitude [32].

Aeration of stirred-tank bioreactors can be accomplished by several methods, including direct sparging of gas through the culture, surface aeration, and silicon-tubing aeration. Of these possibilities, direct sparging is the simplest method for supplying a production bioreactor with oxygen. The most commonly used parameter to quantify the gas transfer efficiency is the mass transfer coefficient expressed in terms of the total transfer area, or k_La. Correlations for oxygen mass transfer rates based upon tank and impeller geometry can be found in many sources [6,29]. However, it may not always be possible to find a correlation for a specific reactor configuration, i.e., geometry, impeller types, number of impellers, etc. Therefore, these correlations should be used as a rough estimation of the power input required to reach a certain gas transfer efficiency. Gas sparging has also been implicated in damaging animal cells [11]. The high velocity gradients that develop around bursting bubbles can generate enough mechanical stress to damage animal cells. Addition of surfactants to the culture medium, such as Pluronic F68™, may prevent the attachment of cell to rising bubbles, reducing their exposure to shear stress [10].

The impact of hydrodynamic stress on animals cells has been reviewed extensively [19,33]. Most of the work reported in the literature on cell damage in agitated bioreactors has been done at bench scale. Kunas and Papoutsakis [34] reported that in 1- to 2-L bioreactors equipped with a 7-cm-diameter pitched-blade impeller, cell damage was not observed until the impeller rate was raised to above 700 rpm (tip speed: 513 cm/sec) as long as air entrapment did not occur. However, it is not clear how these bench-scale observations translate into damaging impeller rates at manufacturing scale.

2. Mode of Operation of Bioreactors

The mode of operation of bioreactors can largely be classified as batch or continuous. The advantages or disadvantages of using either method are still the subject of controversy, for proponents and detractors for each method are always well prepared to defend their positions.

Batch cultivation is perhaps the simplest way to operate a fermentor or bioreactor. It is easy to scale up, easy to operate, quick to turn around, and reliable for scale-up. Batch sizes of 15,000 L have been reported for animal cell cultivation [2], and vessels of over 100,000 L for fermentation are also available. Continuous processes can be classified into cell retention and non-cell retention. The devices typically used for cell retention are spin filters, hollow fibers, and decanters. Large-scale operation of continuous processes can reach up to 2,000 L of bioreactor volume. Typically, the process is operated at 1–2 bioreactor volumes

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per day. Perfusion is one variation of a continuous process, in which cells are retained to achieve the highest level of product expression possible [35]. Usually, high productivity in cell culture is achieved by a high specific productivity and/or high cell density. The major limitation of a batch is the accumulation of toxic metabolites and the depletion of nutrients. This is resolved in continuous systems, such as perfusion, where spent medium is continuously removed from the culture vessel and replaced by fresh medium. It is claimed to sustain high productivity for months of continuous operation [35].

The main disadvantage of a continuous system is the long time required for validation and timely submission of product application to the appropriate regulatory agency. This time line is drastically reduced with the use of a batch system of equivalent volumetric productivity.

D. Harvest Operation

Biotechnology products synthesized by living cells either are contained within the cells (intracellular) or are secreted by the cells into the liquid broth (extracellular). A clarification step is employed to remove the cells and debris before the purification process is initiated. Typical unit operations available for performing the clarification step include tangential-flow filtration [3,14,36], dead-end filtration [37], and centrifugation [38]. *Tangential-flow filtration* is the most extensively used method because it minimizes cell damage and maximizes effective membrane surface use, flux, and membrane lifetime. It is readily scalable and can provide high processing rates with good efficiency without adversely affecting the cell viability. Critical operating parameters for optimizing the filtration condition are transmembrane pressure, retentate flow rate, and permeate flux. High-shear conditions should be avoided to minimize cell rupture that leads to increased levels of contaminating cellular proteins and nucleic acids. The resulting increase in cell debris under such conditions also reduces the capacity of downstream sterile filters. Conventional *dead-end filters* are designed for sterile filtration of relatively clean fluids. The high amount of cells and debris in a typical cell culture broth makes the dead-end filtration approach impractical in terms of equipment size and filtration cost. A viable alternative is the use of depth filters that typically have graded porosity, allowing substantially higher processing capacities. An in-line sterile filtration step is then used to eliminate the debris. Continuous *centrifugation* offers scalable high processing rates. Its disadvantages include higher equipment and maintenance costs. Typically, the clarification efficiency of centrifugation is lower than that of the filtration operations because of the lower resolution of particle densities compared to size differences. This leads to an increased burden for downstream sterile filtration and additional efforts to remove process contaminants such as DNA.

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IV. DOWNSTREAM OPERATIONS

A. Design of Purification Processes

From the many options available for purification, process design should be based on selecting among the multiple unit operations that maximize ease of purification, product purity, and overall yield. In general, a simple stepwise purification design utilizing orthogonal methods of purification with maximum compatibility between steps is preferred. The use of orthogonal purification techniques is important for the removal of process contaminants to trace levels and for robust viral clearance. The number of product manipulations as well as the quantities and number of buffers can be minimized by maximizing the compatibility of process steps. This consideration should be exercised early in the development of the process, for it may have a huge impact later on buffer-handling operations at large scale. Initial steps using highly selective capture chromatography facilitate volume reduction and effective removal of the most problematic process contaminants. Effective intermediate and final polishing steps are necessary for the removal of process contaminants to trace levels and virus inactivation and/or removal. The formulation step is designed to produce the final bulk dosage form of the product with appropriate concentration and long-term product stability. Careful and effective optimization for all process steps is essential for successful scale-up to manufacturing.

For purification, scale-up considerations are important even in the earliest phases of development. It is important to avoid the use of purification techniques of limited scale-up potential even for early clinical production, because thorough justification of process changes and demonstration of biochemical comparability are necessary prior to product licensure. For successful scale-up, it is important to understand the critical parameters affecting the performance of each purification step at each scale. Conversely, it is important to verify that the scaled-down process is an accurate representation of the scaled-up process so that process validation studies such as viral clearance and column lifetime studies can be performed at the laboratory scale.

B. Chromatography

The majority of the processes currently used to manufacture biotechnology products employ chromatography columns as the main tool for effective product recovery and purification. The scale-up [39] and validation [40] of this vastly popular unit operation is key for successful implementation of the overall production strategy at large scale and eventual product approval for commercialization.

If an ion exchange step will be used as an initial capture chromatography step, pH or conductivity adjustment of the conditioned medium might be necesary. At large scale, conductivity adjustment can be accomplished by in-line dilu-

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tion without increasing the number or volume of the vessels required. Some manufacturers carry out a concentration and/or diafiltration for buffer exchange and volume reduction prior to the capture chromatography step. In this case, whatever time and effort saved in loading the initial capture chromatography must be weighed against the time for the concentration/diafiltration, the time for cleaning and preparation of ultrafiltration cartridges, as well as additional buffer preparation time.

Many manufacturers prefer to use an initial capture affinity chromatography step. The affinity gels are highly selective and generally require little or no manipulation of a feedstream. Some possible disadvantages of using an initial affinity column step are the expense of the affinity matrix and the fact that repetitive exposure of the matrix to conditioned medium may require stringent cleaning procedures, which may reduce the effective lifetime of the gel. The cost issue can be obviated somewhat by using smaller columns and multiple cycles. However, this will extend processing time and increase labor costs. For subsequent chromatography steps, ion exchange frequently may follow or precede hydrophobic interaction chromatography (HIC). The HIC product is often eluted at low salt concentrations, which is compatible with the low conductivity necessary for binding to ion exchange gels. Conversely, an ion exchange product is often eluted at high salt conditions, which may provide conditions compatible with HIC chromatography.

C. Viral Clearance

Viral inactivation and/or removal steps are a critical part of the process design for biotechnology products derived from mammalian cell culture systems. Regulatory agencies are concerned with the presence of endogenous and/or adventitious agents in the cell lines an/or raw materials employed to manufacture pharmaceutical proteins from cell culture [41]. The best approach to ensure adequate viral clearance is to have multiple orthogonal virus-removal steps and at least one virus-inactivation step. Virus removal, demonstrated with spiking studies using model viruses, should be carried out with a scaled-down version of the purification process that accurately represents the process used at manufacturing scale. In addition, it is recommended that studies include the use of typical critical operating parameters for each step as well as conditions that represent a worst case for virus removal. For instance, for process validation of chromatography steps extremes of linear velocity, protein concentration, reduced bed height or contact time, and total protein capacity should be tested. Although it is often difficult to adequately quantitate viruses in various column fractions, it is important whenever possible to characterize viral removal in the product fraction as well as in the nonbound flowthrough, wash, and strip fractions. Viral-inactivation steps using chemical or physical conditions such as low pH, heat, irradiation, and chemical agents should be characterized by performing kinetic inactivation studies. For

these studies, typical and worst-case conditions should be evaluated. For example, if a product is eluted with a low pH buffer, a manufacturer might consider holding the product at the same low pH as the viral-inactivation step. However, because the product has some inherent buffering capacity, the final pH value of the eluted product may change based on the protein concentration or, as the process is scaled up, the eluted product pH may shift slightly due to subtle modifications in the collected-product peak. The low pH tested in viral-inactivation studies must be based on the maximum-eluted-product pH, which may not be known prior to scale-up. For these reasons, it may be preferable to define a separate inactivation step in a single vessel with subsurface addition and mixing of the inactivating agent to provide precise control of the hold time, temperature, and pH.

V. FACILITY DESIGN

Facility design is also an important consideration in process design and scale-up. Although it is easy to design a process to fit into a new facility, retrofitting an existing facility for commercial manufacture can be costly. Sometimes the design of a process has to consider the constraints imposed by an existing plant. In this case, it is helpful to create a spreadsheet template for scale-up calculations to test and evaluate the operation of the process in an existing environment with minimal changes in existing equipment. Examples of such calculations are found for buffer preparation, bioreactor and harvest operations, filtration operations, product and buffer tanks, chromatography controllers, hard piping, and flow patterns. For example, if existing product tanks are too small, chromatography column sizes can be reduced and multiple cycles need to be performed. However, the long-term costs associated with smaller chromatography columns and extended processing times must be weighed against the initial costs of purchasing and installing larger vessels or columns. The operational segregation of pre- and postviral clearance steps may also require redesign of a facility and should be considered in the early stages of process development.

A. Examples of Process Scale-Up

Once process design is complete and each of the process steps characterized, the process is ready for scale-up to pilot or manufacturing scale. A spreadsheet template for scale-up calculations is important and provides a mass balance of buffer volumes, column volumes, priming volumes, product volumes, and waste volumes as well as the tank size and column size. Product volumes can be expressed relative to column volume or can be calculated from a constant concentration, depending on the process step. In addition, starting volumes and titers of conditioned medium as well as step yields and gel or membrane capacity are necessary to cal-

culate bed volumes and membrane surface area for the purification steps. A worst-case approach assuming maximum step yields, product volume, and starting titer is recommended, except for cases where underloading a column or a membrane step is problematic.

Some general observations were made during the scale-up of a process using microfiltration operations at the bioreactor stage [14]. One was that when using tangential flow filtration, the ratio between retentate flow and permeate flow has to be at least 5 to 1 in order to avoid the effect know as "dead-end filtration." This finding clearly indicated the need for an additional control on the permeate flow that was not necessary in the small-scale experiments. Another observation was that the ratio of filtration area (FA) to process volume (PV) usually employed as a rule for scale-up may actually decrease as the scale of operation increases. This is due to a more efficient utilization of the membrane surface, with the consequent savings in filtration equipment.

It is also important to recognize the interaction between the scaling parameters. Simply multiplying an existing process by the next scale-up factor may lead to errors. For example, if a single 10-inch filter is used at 66% capacity in the pilot scale, a fourfold increase in scale does not require four 10-inch filters. Rather, three 10-inch filters or a single 30-inch filter can be used at 88% capacity.

Another example demonstrating the interaction between scaling factors comes from chromatography operation. As the process scale increases, the available column volume must increase, either by packing larger columns or by running multiple cycles. Columns are generally available with 30-, 45-, 60-, and 100-cm diameters. It is necessary to select a column diameter when doing calculations and then determine the resulting bed height based on the required volume. Using a narrower-diameter column will result in increased processing time because generally the linear velocity is held constant during scale-up. The alternative is to use a shorter, wider column, but there is a minimum bed height that can be used at large scales, generally 10 cm or larger. The use of a larger-diameter column will increase flow rate and decrease operating time. However, the use of a wider column may necessitate packing a column of larger volume than necessary from the given gel capacity. The larger-volume column means that greater volumes of buffer are needed and that product volumes will likely increase. It is important to determine if tanks are available for the additional volumes of product and buffers. In this example (Table 2), as the effective gel capacity decreases, the processing time decreases and the buffer volumes increase.

For buffer exchange or formulation steps using ultrafiltration, membrane capacity and processing time are closely linked. In contrast with the previous example, focusing on chromatography capacity, as membrane capacity decreases there is no dramatic increase in buffer usage. In general, decreasing the mem-

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Table 2 Sample Scale-Up Calculation for a Chromatography Step

		Units
Assumptions:		
Titer	0.5	g/L
Harvest volume	2000	L
Total product	1000	g
Maximum gel capacity	20.0	g/L gel
Minimum gel volume	50	L
Minimum bed height	10.0	cm
Linear velocity	300	cm/hr

	Case 1	Case 2
Column diameter (cm)	60	100
Calculated bed height (cm)	17.7	6.4
Actual bed height (cm)	17.7	10.0
Actual column volume (L)	50	79
Actual capacity used (g/L gel)	20.0	12.7
Flow rate (L/min)	14.1	39.3

Operation	Solution usage (L/L)	Solution volume (L)	Duration (min)	Solution usage (L/L)	Solution volume (L)	Duration (min)
Equilibration	5	250	17.7	5	393	10.0
Load		2000	141.5		2000	50.9
Post-load equilibration	3	150	10.6	3	236	6.0
Wash	5	250	17.7	5	393	10.0
Elution	6	300	21.2	6	471	12.0
Sanitization	3	150	10.6	3	236	6.0
Storage	3	150	10.6	3	236	6.0
Grand totals		3250	229.9		3964	100.9

brane capacity reduces processing time, because the gel layer is thinner and has less impact on permeate flux. However, as the membrane surface area increases, a larger size ultrafiltration system is required and larger pumps are required to maintain the recirculation flux. For a highly concentrated product, a large system hold-up volume increases the potential for product loss. For concentration/diafiltration operations, scale-up may require reoptimization of process parameters, especially if membrane capacities are changed. However, every effort should be made to keep recirculation flux constant with similar inlet and outlet pressures.

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VI. SUMMARY

Once the scale-up factors have been established, the scale-up of the process from pilot to manufacturing scale should be relatively straightforward. There are, of course, important considerations for working in a commercial manufacturing environment that have not been addressed in this chapter. These include, but are not limited to, cGMP and regulatory issues, segregation of pre- and postviral clearance steps, flow of material and personnel, waste handling, and environmental monitoring [27,42]. In order to scale up and transfer a process successfully from laboratory scale to pilot scale and multiple commercial manufacturing scales, a thorough understanding of the integration of scale factors, facility design, equipment design, and process performance is necessary. A scale-up template spreadsheet can be a useful tool to provide the critical integration of multiple factors.

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5 (1)
Batch Size Increase in Dry Blending and Mixing

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I. BACKGROUND

In the manufacture of many pharmaceutical products (especially tablets and capsules), dry particle blending is often a critical step that has a direct impact on content uniformity. Tumbling blenders remain the most common means for mixing granular constituents in the pharmaceutical industry. Tumbling blenders are hollow containers attached to a rotating shaft; the vessel is partially loaded with the materials to be mixed and rotated for some number of revolutions. The major advantages of tumbling blenders are large capacities, low shear stresses, and ease of cleaning. These blenders come in a wide variety of geometries and sizes, from laboratory scale ($<$16 qt) to full-size production models ($>$500 ft^3). A sampling of common tumbling blender geometries include the V-blender (also called the twin-shell blender), the double cone, the in-bin blender, and the rotating cylinder.

There are currently no mathematical techniques to predict blending behavior of granular components without prior experimental work. Therefore, blending studies start with a small-scale, try-it-and-see approach. The first portion of this chapter is concerned with the following typical problem: a 5-ft^3-capacity tumble blender filled to 50% of capacity and run at 15 rpm for 15 minutes produces the desired mixture homogeneity. What conditions should be used to duplicate these results in a 25-ft^3 blender? The following questions might arise.

1. What rotation rate should be used?
2. Should filling level be the same?
3. How long should the blender be operated?
4. Are variations to the blender geometry between scales acceptable?

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Unfortunately, there is no generally accepted method for approaching this problem; therefore, ad hoc approaches tend to be the rule rather than the exception. Further complicating the issue is that rotation rates for typical commercially available equipment are often fixed, obviating question 1 and suggesting that, under such conditions, true dynamic or kinematic scale-up may not be possible.

II. GENERAL MIXING GUIDELINES

A. Defining Mixedness

Before specifically addressing scale-up of tumbling blenders, this section discusses some general guidelines that cover the current understanding of the important issues in granular blending. The final objective of any granular mixing process is to produce a homogeneous blend. But even determining mixture composition throughout the blend is a difficulty for granular systems. As yet, no reliable techniques for on-line measuring of composition have been developed; hence, granular mixtures are usually quantified by removing samples from the mixture. To determine blending behavior over time, the blender is stopped at fixed intervals for sampling; the process of interrupting the blend cycle and repeated sampling may change the state of the blend. Once samples have been collected, the mean value and sample variance are determined and then often used in a mixing index. Many mixing indices are available; however, there is no "general mixing index," so the choice of index is left to the individual investigator [1]. Once a measure of mixedness has been defined, it is then tracked over time until suitable homogeneity is achieved. Ideally, this minimum level of variance would stay relatively constant over a sufficiently long time. This procedure is simple in concept, but many problems have been associated with characterization of granular mixtures [2].

One dangerous assumption is that a small number of samples can sufficiently characterize variability throughout the blend. Furthermore, sample size can have a large impact on apparent variability. Samples that are too small can show exaggerated variation, while too large a sample can blur concentration gradients. Unlike miscible fluids, which, through the action of diffusion are continually mixing on a microscale, granular blends mix only when energy is input to the system. Hence, it is important that a sufficient number of samples be taken representing a large cross section of the blender volume.

Another concern is assuming that standard sampling techniques retrieve samples that are truly representative of local concentration at a given location. Thief probes remain the most commonly employed instrument for data gathering. These instruments have been demonstrated to sometimes induce large sampling errors coming from poor flow into the thief cavity or sample contamination (carryover from other zones of the blender) during thief insertion [2]. Care and skep-

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ticism have to be employed whenever relying on thief probe data. One method to assess blend uniformity and blend sampling error is given in PDA Technical Report No. 25 [3].

Finally, the degree of mixedness at the end of a blending step is not always a good indicator of the homogeneity to be expected in the final product. Many granular mixtures can spontaneously segregate into regions of unlike composition when perturbed by flow, vibration, shear, etc. Once a good blend is achieved, the mixture still must be handled carefully to avoid any "de-mixing" that might occur. Chapter 5(2) deals with the scaling of flow from blenders, bins, and hoppers and the effect of segregation during handling.

B. Mixing Issues in Tumbling Blenders

Mixing in tumbling blenders takes place as the result of particle motions in a thin, cascading layer at the surface of the material, while the remainder of the material below rotates with the vessel as a rigid body. Current thinking describes the blending process as taking place by three essentially independent mechanisms: convection, dispersion, and shear. *Convection* causes large groups of particles to move in the direction of flow (orthogonal to the axis of rotation), the result of vessel rotation. *Dispersion* is the random motion of particles as a result of collisions or interparticle motion, usually orthogonal to the direction of flow (parallel to the axis of rotation). *Shear* separates particles that have joined due to agglomeration or cohesion and requires high forces. While all mechanisms are active to some extent in any blender, tumbling blenders impart very little shear, unless an intensifier bar (I-bar) or chopper blade is used (in some cases, high shear is detrimental to the active ingredient and so is avoided). While these definitions are helpful from a conceptual standpoint, blending does not take place as merely three independent, scalable mechanisms. However, attentive planning of the blending operation can emphasize or de-emphasize specific mechanisms and have significant impact on mixing rate.

Most tumbling blenders are symmetrical in design; this symmetry can be the greatest impediment to achieving a homogeneous mixture. The mixing rate often becomes limited by the amount of material that can cross from one side of the symmetry plane to the other [4–8]. Some blender types have been built asymmetrically (e.g., the slant cone, the offset V-blender), and show greater mixing proficiency. Furthermore, by rocking the vessel as it rotates, mixing rate can also be dramatically increased [9]. Asymmetry can be "induced" through intelligent placement of baffles, and this approach has been successfully tested on small-scale equipment [7,10–12] and used in the design of some commercial equipment. But when equipment is symmetrical and baffles unavailable, careful attention should be paid to the loading procedure, for this can have an enormous impact on mixing rate.

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Nonsystematic loading of multiple ingredients will have a dramatic effect on mixing rate if dispersion is the critical blending mechanism. For instance, in a V-blender, it is preferable to load the vessel either through the exit valve or equally into each shell. This ensures that there are near-equal amounts of all constituents in each shell of the blender. Care must be taken when loading a minor (~1%) component into the blender—adding a small amount early in the loading process could accidentally send most of the material into one shell of the blender and substantially slow the mixing process. Smaller blenders entail shorter dispersal distances necessary for complete homogeneity and thus may not be as affected by highly asymmetrical loading. As a final caution, the order of constituent addition can also have significant effects on the degree of final homogeneity, especially if ordered mixing (bonding of one component to another) can occur within the blend [13].

Intershell flow is the slowest step in a V-blender, because it is dispersive in nature, while intrashell flow is convective. Both processes can be described by similar mathematics, typically using an equation such as

$$\sigma^2 = Ae^{-kN} \tag{1}$$

where σ^2 is mixture variance, N is the number of revolutions, A is an unspecified constant, and k is the rate constant [6,14]. The rate constants for convective mixing, however, are orders of magnitude greater than for dispersive mixing. Thus, unequal loading across the symmetry plane places emphasis on dispersive mixing and is comparatively slow compared to top-to-bottom loading, which favors convective mixing.

C. Process Parameters

When discussing tumbling blender scale-up, one parameter consideration that arises is whether rotation rate should change with variations in size. Previous studies on laboratory-scale V-blenders and double cones have shown that, when far from the critical speed of the blender, the rotation rate does not have strong effects on the mixing rate [6,7] (the critical speed is the speed at which tangential acceleration due to rotation matches the acceleration due to gravity). These same studies showed that the number of revolutions was the most important parameter governing the mixing rate. Equation (1) was derived by assuming that the mixture went through a specific incremental increase in mixedness with each revolution (either by dispersion or by convection). While this approach has been shown to be successful at modeling increases in mixture homogeneity, no scaling rules have been determined for the rate constants that govern this equation, and this remains an open question for further inquiry.

Given a geometrically similar blender and the same mixture composition, it would seem obvious that the fill level should also be kept constant with changes in scale. However, an increase in vessel size at the same fill level may correspond

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to a significant decrease in the relative volume of particles in the cascading layer compared to the bulk—this could accompany a large decrease in mixing rate. It has been shown in 1-pint V-blenders that running at 40% fill brings about a mixing rate that is nearly three times faster than at 60% fill [6]. Thus, although fill level should be kept constant for geometric similarity, it may be impossible to match mixing rate per revolution across changes in scale if the depth of the flowing layer is a critical parameter.

III. SCALE-UP APPROACHES

In the literature, the Froude number ($\mathrm{Fr} \equiv \Omega^2 R/g$, where Ω is the rotation rate, R is the vessel radius, and g is the acceleration from gravity) is often suggested for tumbling blender scale-up [15–18]. This relationship balances gravitational and inertial forces and can be derived from the general equations of motion for a general fluid. Unfortunately, no experimental data have been offered to support the validity of this approach. Continuum mechanics may offer other dimensionless groups, if a relationship between powder flow and powder stress can be determined. However, Fr is derived from equations based on continuum mechanics, whereas the scale of the physical system for blending of granular materials is on the order of the mean free path of individual particles, which may invalidate the continuum hypothesis. A less commonly recommended scaling strategy is to match the tangential speed (wall speed) of the blender; however, this hypothesis also remains untested (Patterson-Kelly, personal communication, 2000).

We now look at our general problem of scaling the 5-ft^3 blender using Fr as the scaling parameter: The requisites are to ensure geometric similarity (i.e., all angles and ratios of lengths are kept constant) and to keep the total number of revolutions constant. With geometric similarity, the 25-ft^3 blender must look like a photocopy enlargement of the 5-ft^3 blender. In this case, the linear increase is $5^{1/3}$, or 71%. Also for geometric similarity, the fill level must remain the same. To maintain the same Froude number, since R has increased by 71%, the rpm (Ω) must be reduced by a factor of $(1.71)^{-1/2} = 0.76$, corresponding to 11.5 rpm. In practice, since most blends are not particularly sensitive to blend speed and available blenders are often of fixed speed, the speed closest to 11.5 rpm would be selected. If the initial blend time were 15 minutes at 15 rpm, the total revolutions of 225 must be maintained with the 25-ft^3 scale. Assuming 11.5 rpm were selected, this would amount to a 19.5-minute blend time. Though this approach is convenient and used often, it remains empirical.

Common violations of this approach that can immediately cause problems include the attempt to scale from one geometry to another (e.g., V-blender to in-bin blender), changing fill level without concern to its effect, and keeping blending time constant while changing blender speed.

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The lack of first-principle, reliable scale-up criteria can have major impacts on development time and costs. Nonsystematic means of scale-up can often lead to excessively long processing times and inefficient use of existing capacity. Long processing times can lead to unwanted side effects, such as particle sintering, heat buildup, attrition, and excessive agglomeration. The advantages to rigorous scale-up include decreased process uncertainty, for we "know" what is going on. It also cuts down on development time and on experimental failures because experiments are done in a systemic manner based on science (not art).

IV. NEW APPROACH TO THE SCALE-UP PROBLEM IN TUMBLING BLENDERS

Herein, we offer a first step toward the definition of rigorous scale-up rules for tumbling blenders. We begin by proposing a set of variables that may control the process. The driving force for flow in tumbling blenders is the acceleration from gravity, which must be included in our analysis. Vessel size is obviously a critical parameter, as is the rotation rate, which defines the energy input to the system. These variables define the system parameters (i.e., the driving forces) but do not cover the mixture response. In the case of Newtonian fluids, fluid viscosity connects the driving force (pressure gradients, gravity, shear) to the fluid response (velocity gradients). For granular mixtures, no similar parameter has been derived; hence, we will define particle size and particle velocity as our "performance variables." Particle size plays a large role in determining mixing (or segregation) rates because dispersion distance is expected to vary inversely with particle size. For granular processes, individual particles drive bulk mixture behavior and we have assumed particle velocity to be an important variable. Because all transport and mixing phenomena are driven by the motions of individual particles, it is a priori impossible to scale transport phenomena without first scaling the velocities of individual particles. Although previous studies have indicated that rotation rate (and, hence, probably particle velocities) does not affect mixing rate, these experiments were done in very small blenders. It is conceivable that at larger scales, these variables could become important. Given these assumptions, we can now address the development of nondimensional scaling criteria.

A. Applying Rayleigh's Method

Our hypothesized set of variables that is believed to govern particle dynamics in tumbling blenders is shown in Table 1. Using these variables and the Rayleigh method, we derive the following equation:

$$V = k\Omega^a R^b d^c g^e \tag{2}$$

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Table 1 Variables Important to Scaling Particle Velocities in Cylinders

Variable	Symbol	Dimensions
Particle velocity	V	L/T
Vessel rotation rate	Ω	1/T
Vessel radius	R	L
Acceleration from gravity	g	L/T^2
Particle diameter	d	L

L = length; T = time.

Applying the rule of dimensional homogeneity and making c and e the unrestricted constants leads to

$$V = k\Omega^{1-2e}R^{1-c-e}d^c g^e \tag{3}$$

To solve Eq. (3), a correlation relating particle velocities to vessel radius and rotation rate is discussed in the forthcoming sections.

B. Correlating Particle Velocities to Vessel Rotation Rate and Radius

In order to determine particle velocities, an empirical approach is taken. A digital video camera was used to record the positions of individual particles on the flowing surface in clear acrylic, rotating cylinders of 6.3-, 9.5-, 14.5-, and 24.8-cm diameter filled to 50% of capacity. Experiments were performed using nearly monodisperse 1.6-mm glass beads (Jaygo, Inc.) dyed for visualization. The displacement of particles from one frame to the next was converted into velocities. To calculate velocity, only the motion down the flowing layer was used, and all cross-stream (i.e., dispersive) motion was ignored. Figure 1 shows an example of the data obtained from a typical experiment. Moving top to bottom in the rotating cylinder is equivalent to moving left to right on this graph (see Ref. 19 for details).

Figure 2 shows the mean cascading velocity versus distance down the granular cascade for experiments run at the same tangential velocity. Despite a nearly fourfold difference in diameter, the velocity data all fall on nearly the same curve over the first 3 cm down the flowing layer. This agreement indicates that initial particle accelerations may be nearly equivalent, regardless of vessel size. Scatter in the experimental data shown in Figure 2 precludes direct calculation of accelerations, so least-square polynomials were fit to the experimental data. By differentiating the polynomial fit, we obtain an estimate of the downstream acceleration, shown in Figure 3. Over the initial upper third [0 to $(\frac{1}{3})$L] of the flowing layer, the acceleration profiles for all cylinders are nearly identical, with only mi-

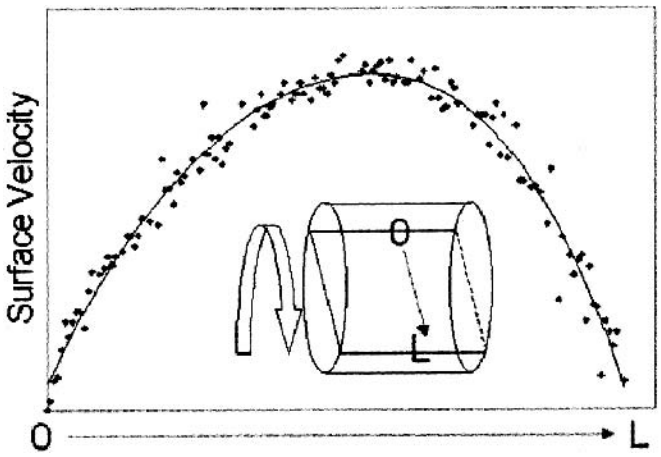


Figure 1 Typical velocity profile. Moving from top to bottom (O–L) in the rotating cylinder (inset) is equivalent to moving left to right in the graph.

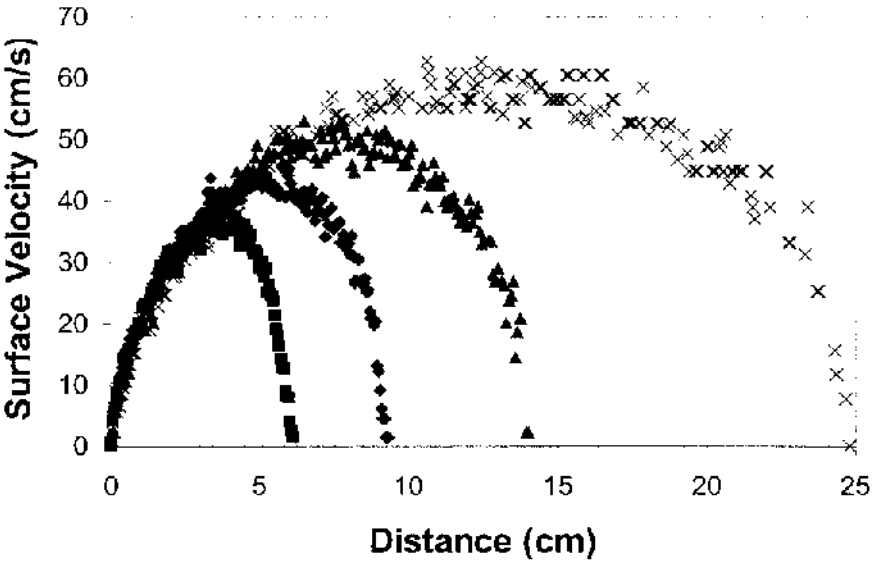


Figure 2 Velocity profiles for a series of experiments run at the same tangential velocity (26.4 cm/sec) in cylinders with inner diameters of 6.3 cm (■), 9.5 cm (◆), 14.4 cm (▲), and 24.8 cm (×), which correspond to rotation rates of 40 rpm, 26.5 rpm, 17.4 rpm, and 10.2 rpm, respectively.

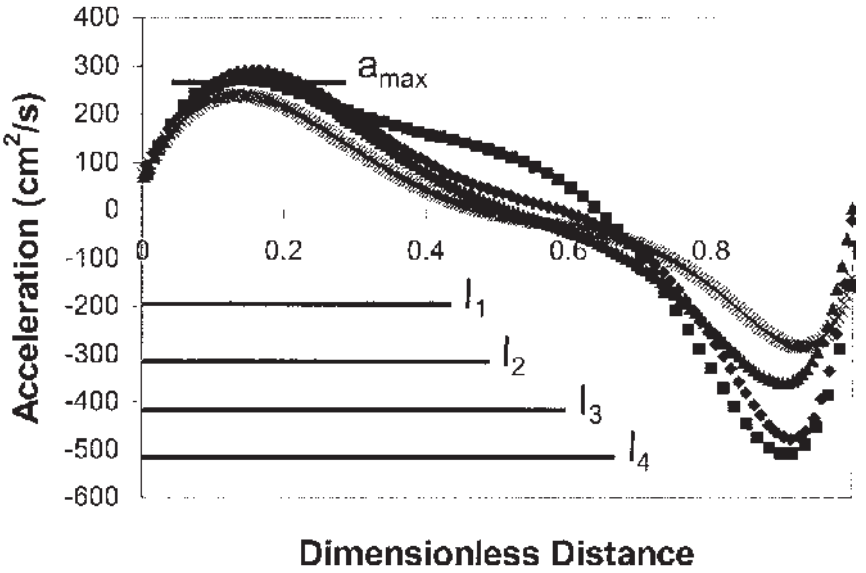


Figure 3 Acceleration profiles for experiments run at the same tangential velocity (13.2 cm/sec); ℓ marks the distance to reach 0 acceleration. The velocity profiles are shown in Figure 2.

nor variations in magnitude. Although the qualitative trend is the same for all curves, the distance taken to reach zero acceleration is very different, nearly two-thirds of the vessel diameter in the 6.3-cm cylinder as opposed to only half the diameter in the 24.8-cm cylinder.

In Figure 3, maximum accelerations are nearly equal, implying that tangential velocity may be proportional to maximum acceleration. Maximum accelerations were determined for all experiments; the results are plotted against the tangential velocity in Figure 4. An approximate linear fit

$$a_{\max} = \alpha \cdot \mathrm{TV} \tag{4}$$

where TV is the tangential velocity ($= 2\pi R\Omega$) and $\alpha = 17\ \mathrm{sec}^{-1}$, is seen relating acceleration and tangential velocity for all cylinders and rotation rates. While the data clearly display curvature, this linear fit is used as a first-order approximation for scaling purposes.

In Figure 3, the distance to reach zero acceleration varies greatly among the four different velocity profiles. This parameter, denoted ℓ, is quantitatively measured as the distance at which the relative change in velocity drops below a preset limit. However, by itself, the value of ℓ has little meaning; it is the parameter ℓ/r, where r is the cylinder radius, that has a quantitative effect on the velocity profile

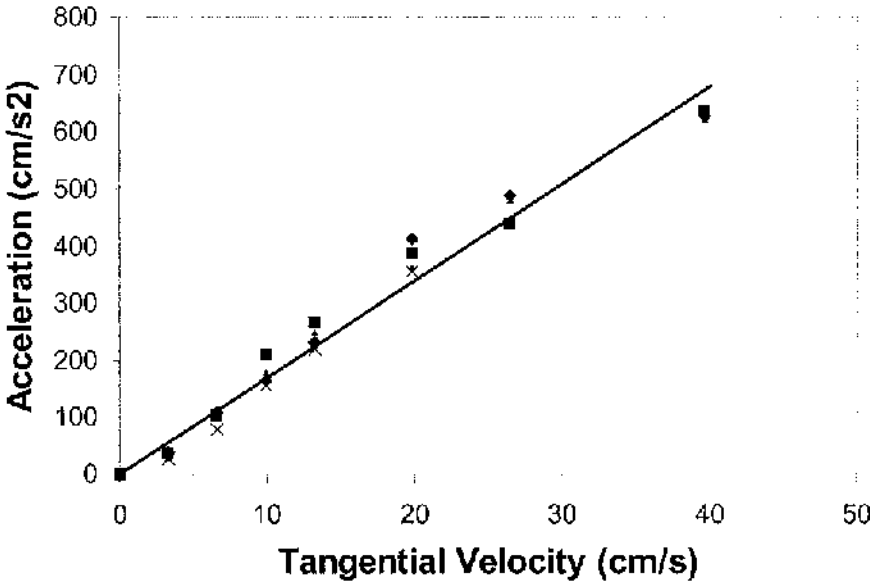


Figure 4 Plot of the maximum acceleration against the tangential velocity for all experiments; a near-linear relationship is noted. Data are calculated from experiments in 6.3-cm-(■), 9.5-cm-(◆), 14.5-cm-(▲), and 24.8-cm-(×) diameter cylinders.

and maximum velocities. When all values of ℓ/r were compiled, a strong correlation to rotation rate was noted. Because most pharmaceutical blenders are run at low rotation rates, we restrict the remaining discussion to vessel rotation rates below 30 rpm. Figure 5 plots ℓ/r against $\sqrt[3]{\Omega}$, showing a nearly linear relationship below ~30 rpm. An equation for ℓ/r becomes

$$\ell/r = \beta\sqrt[3]{\Omega}, \qquad \Omega \leq 30 \tag{5}$$

where $\beta = 0.37$ sec$^{1/3}$. Because ℓ/r determines the shape of the velocity profile, experiments run at the same rotation rate should show qualitatively similar velocity profiles, regardless of cylinder size.

C. Developing a Model

The simplest possible model for particle velocity relates velocity and distance when acceleration is constant,

$$V^2 = V_0^2 + 2ax \tag{6}$$

where V_0 is the initial downstream velocity and x is the downstream coordinate. Acceleration has been shown, though, to vary along the length of the flowing re-

gion. Also, the distance to reach zero acceleration depends on the rotation rate. It may be possible, however, to scale peak velocities using Eq. (6) subject to some simplifying assumptions:

1. Particles emerge into the flowing layer with zero initial downstream velocity ($V_0 = 0$).
2. Peak acceleration is proportional to the tangential velocity (TV), Eq. (4).
3. Particles accelerate over the distance ℓ.
4. Acceleration (a) is not constant over the distance ℓ, but the rate of change in acceleration scales appropriately with the value of ℓ (i.e., $a = a_{\max} f(\mathrm{x}/\ell)$, where x is the distance down the cascade).

Using these assumptions and Eqs. (4), (5), and (6), a new relation for particle velocity would be

$$\mathrm{V} \approx \mathrm{R}\Omega^{2/3}\sqrt{2\pi\alpha\beta} \tag{7}$$

Equation (7), which relates particle velocities to the rotation rate and the radius, can be used as the basis for scaling particle velocities with changes in cylinder diameter and rotation rate.

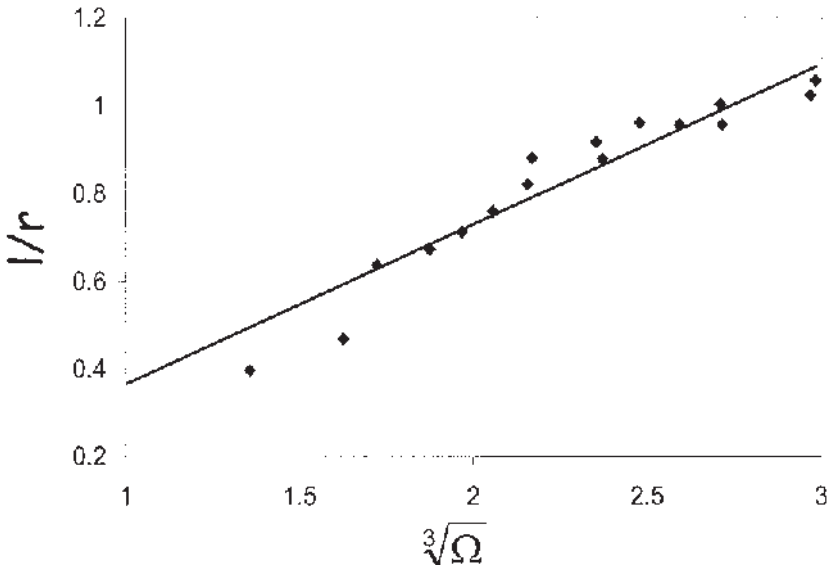
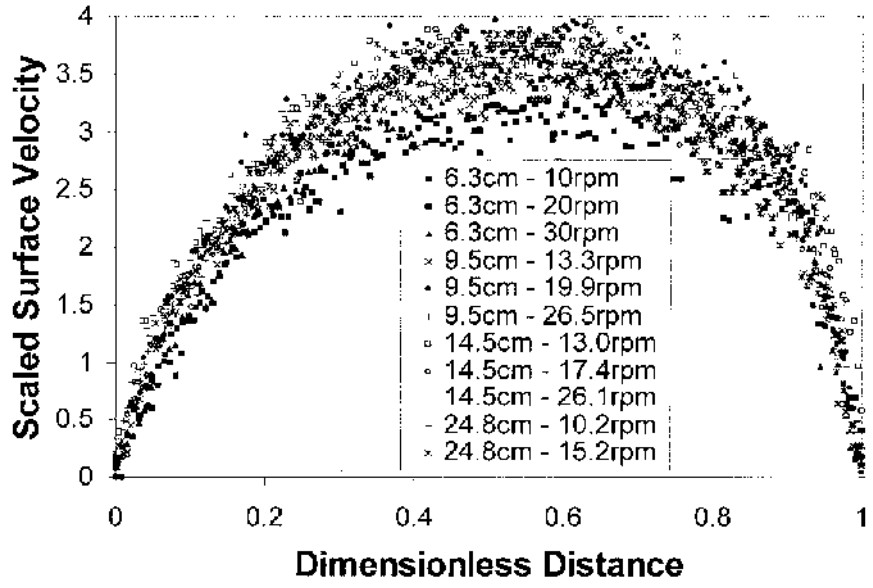
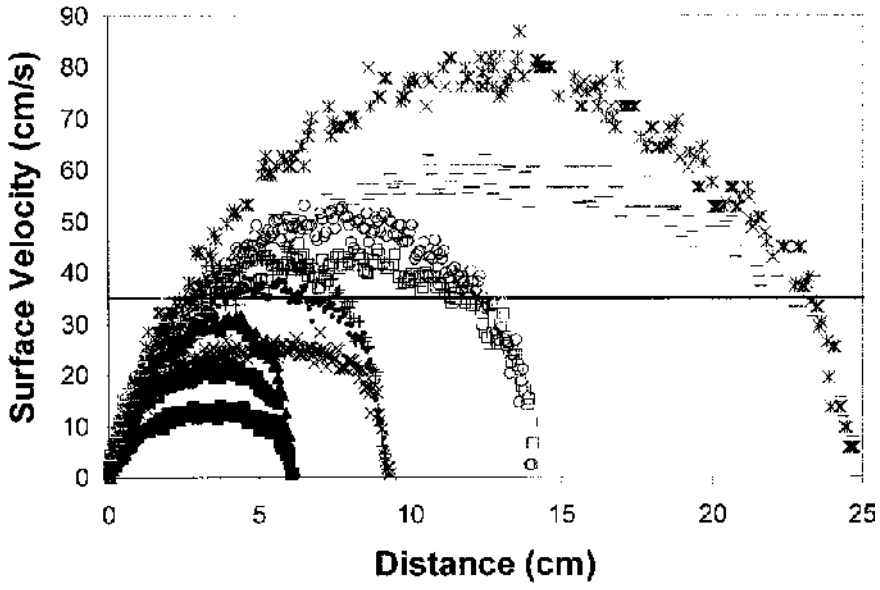


Figure 5 The value of ℓ/r is plotted against the cube root of rotation rate, showing a linear relationship.



(a)



(b)

Figure 6 (a) Scaled velocity profiles for all experiments run between 10 and 30 rpm; (b) unscaled profiles.

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D. Returning to Dimensional Analysis

Equation (7) gives a relationship between velocity, rotation rate, and cylinder radius that can be used to complete the dimensional analysis discussed earlier. Applying dimensional homogeneity and solving leads to

$$V = kR\Omega^{2/3}\left(\frac{g}{d}\right)^{1/6} \tag{8}$$

To test the scaling criteria suggested by Eq. (8), we will look at velocity profiles between 10 and 30 rpm. Figure 6(a) shows the scaled velocity profiles (i.e., all data are divided by using $R\Omega^{2/3}\,(g/d)^{1/6}$, and the distance down the cascade is divided by the cylinder diameter) for experiments run between 10 and 30 rpm [the unscaled data are shown in Figure 6(b)]. We see very good agreement in velocity magnitudes across all rotation rates and cylinder sizes (which incorporate a 4× range in vessel radii and a 3× range in rotation rates). Equation (8) indicates that particle size has an independent and measurable, though small, effect on particle velocities, which is further discussed elsewhere [19].

Returning to our example of scaling from a 5-ft^3 blender to a 25-ft^3 blender, again the relative change in length is 71%. This time, to scale surface velocities using this approach, the blending speed (Ω) must be reduced by a factor of $(1.71)^{-3/2} = 0.45$, corresponding to 6.7 rpm (assuming the particle diameter, *d,* remains constant). Again, the total number of revolutions would remain constant at 225, for a blend time of 33.6 min.

V. TESTING VELOCITY SCALING CRITERIA

Experimental work has not validated the preceding scaling procedure with respect to scale-up of blending processes. Since this approach also relies on empirical work, this model should not be favored over other approaches currently in use, though it may provide additional insight.

However, recent work has indicated that particle velocities may be critical for determining segregation dynamics in double-cone blenders and V-blenders [20,21]. Segregation occurs within the blender as particles begin to flow in regular, defined patterns that differ according to their particle size. Experimental work demonstrates how this occurs. In a 1.9-quart-capacity V-blender at fixed filling (50%), incrementally changing rotation rate induced a transition between two segregation patterns, as seen in Figure 7(a). At the lower rotation rate, the "small-out" pattern forms; the essential feature of the "small-out" pattern is that the smaller red particles dominate the outer regions of the blender while the larger yellow particles are concentrated near the center. At a slightly higher rotation rate, the "stripes" pattern forms; in this case, the small particles form a stripe near the mid-

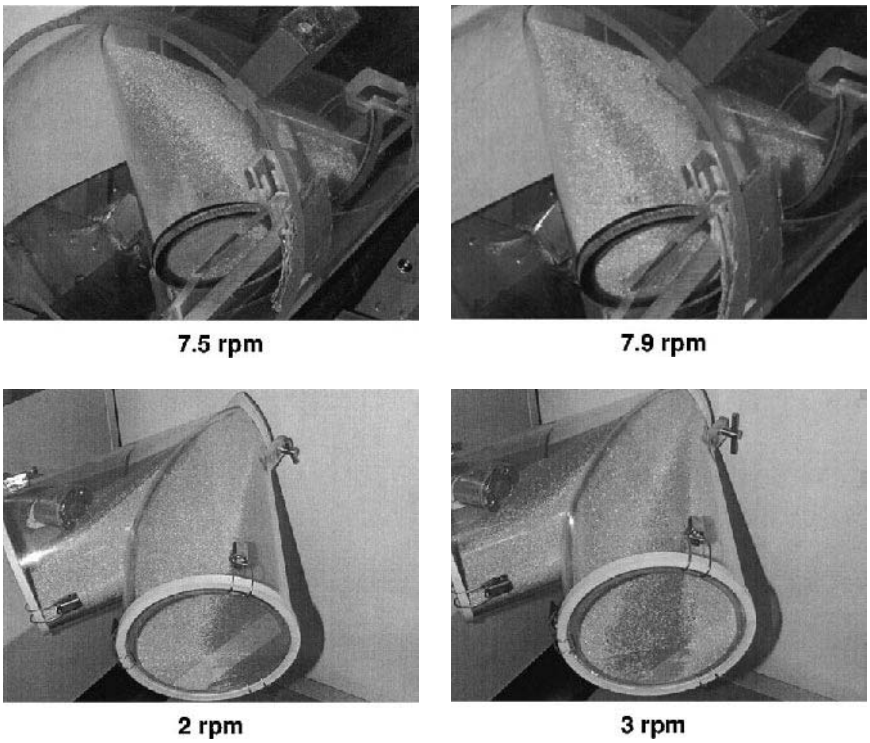

Figure 7 Changes in segregation pattern formation in the (a) 1.9-quart and (b) 12.9-quart V-blenders.

dle of each shell in the blender. Both patterns are symmetrical with respect to the central vertical symmetry plane orthogonal to the axis of rotation.

To validate both the particle velocity hypothesis and our scaling criteria, similar experiments were run in a number of different-capacity V-blenders. Vessel dimensions are shown in Table 2, along with a schematic, shown in Figure 8.

Table 2 Vessel Dimensions

Nominal capacity	Vessel volume (quarts)	L (cm)	R (cm)	D (cm)	θ
1 P	0.8	10.5	7.9	6.7	80°
1 Q	1.9	13.9	10.6	9.2	80°
4 Q	6.5	21.2	14.6	13.8	75°
8 Q	12.9	24.7	18.8	17.6	75°
16 Q	26.5	33	24.2	21.6	75°

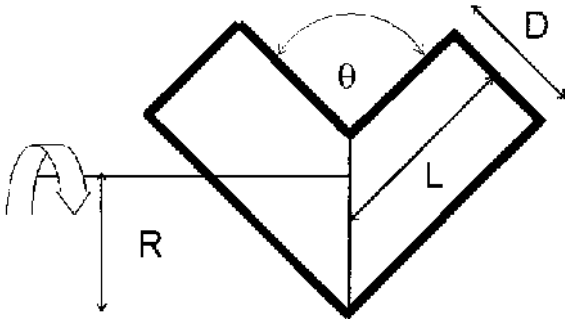

Figure 8 A sketch of the relevant dimensions for a V-blender; the actual values for the five blenders used are shown in Table 2.

All the vessels are constructed from clear plexiglass, enabling visual identification of segregation patterns.

For these experiments, a binary mixture of sieved fractions of 150-μ to 250-μ (nominally 200-μ) and 710-μ to 840-μ (nominally 775-μ) glass beads was used. A symmetrical initial condition (top-to-bottom loading) is implemented. The blender is run at constant rotation rate; a segregation pattern was assumed to be stable when it did not discernibly change for 100 revolutions. In many pharmaceutical operations, the mixing time is on the order of 100–500 revolutions, and experiments are run with regard to this timeframe.

The transition speeds (rotation rates) were determined for the change from the "small-out" pattern to "stripes" at 50% filling for all the blenders listed in Table 2 (Figure 7 shows results from the 1.9- and 12.9-quart blenders). As discussed earlier, the most commonly accepted methods for scaling tumbling blenders have used one of two parameters, either the Froude number (Fr) or the tangential speed of the blender. Earlier, we derived $R\Omega^{2/3}\,(g/d)^{1/6}$ and showed that it effectively scales particle velocities when the rotation rate is below 30 rpm. We note that all three of these criteria indicate an inverse relationship between rotation rate and blender size. Table 3 shows the parameter values at the transition ro-

Table 3 Parameter Values at Transition rpm

Blender size	Transition rotation rate	Fr, $\Omega^2 R/g$ ($\times 10^5$)	Tangential velocity ΩR (cm/sec)	$R\Omega^{2/3}\left(\frac{g}{d}\right)^{1/6}$ (cm/sec)
1 P	9.5	20	7.9	9.9
1 Q	7.7	18	8.5	11.5
4 Q	3.5	5	5.4	9.4
8 Q	2.5	3	4.9	9.6
16 Q	1.7	2	4.3	9.6

tation rate for $R\Omega^{2/3}\,(g/d)^{1/6}$, Fr, and the tangential velocity. The $R\Omega^{2/3}\,(g/d)^{1/6}$ parameter gives much better agreement than either Fr or tangential velocity; the relative standard deviation for $R\Omega^{2/3}\,(g/d)^{1/6}$ is 8.5%, compared to 89% for Fr and 30% for tangential velocity.

VI. RECOMMENDATIONS AND CONCLUSIONS

The analysis of particle velocities provides a good first step toward the rigorous development of scaling criteria for granular flow, but it is far from conclusive. While particle velocities may control the development of segregation patterns in small-capacity V-blenders, velocity may not be the most important dynamic variable affecting the mixing rate. If we regard mixing and segregation as competing processes, however, then knowing that one is velocity dependent and the other is not could be significant. Earlier, we discussed that mixing rate shows little change with rotation rate but large variation with changes in fill level. These results may indicate that a proportionality factor such as (mass of contents in motion)/(total mass) may be important for scaling the mixing process. It is important in granular systems to first determine the dynamic variable that governs the process at hand before determining scaling rules—the basic caveats that particle size, particle velocities, flowing layer depth, and the relative amount of particles in motion may all play a role in a given process, making it important to identify the crucial variables *before* attempting scale-up.

A systematic, generalized approach for the scale-up of granular mixing devices is still far from attainable. Clearly, more research is required both to test current hypotheses and to generate new approaches to the problem. Still, we can offer some simple guidelines that can help the practitioner wade through the scale-up process.

1. Make sure that changes in scale have not changed the dominant mixing mechanism in the blender (i.e., convective to dispersive). This can often happen by introducing asymmetry in the loading conditions.
2. Number of revolutions is a key parameter, but rotation rates are largely unimportant.
3. When performing scale-up tests, be sure to take enough samples to give an "accurate" description of the mixture state in the vessel. Furthermore, be wary of how you interpret your samples; know what the mixing index means and what your confidence levels are.
4. One simple way to increase mixing rate is to decrease the fill level—while this may be undesirable from a throughput point of view, decreased fill level also reduces that probability that dead zones will form.
5. Addition of asymmetry into the vessel, either by design or the addition of baffles, can have a tremendous impact on mixing rate.

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Until rigorous scale-up rules are determined, these cautionary rules are the state of the art for now. We offer a first step toward rigorous scaling rules by scaling particle surface velocities but caution that this work is only preliminary in nature. The best advice is to be cautious—understand the physics behind the problem and the statistics of the data collected. Remember that a fundamental understanding of the issues is still limited and luck is unlikely to be on your side; hence, frustrating trial and error is still likely (unfortunately) to be employed.

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5 (2)
Powder Handling

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I. INTRODUCTION

The goal in any blending operation is to have a properly blended powder mixture at the point in the process where it is needed, for example, during filling of the tablet die. This is not at all the same as requiring that all constituent powders in a blender be properly blended, since subsequent handling of a well-blended powder can result in significant deblending due to segregation. Segregation is as much a threat to product uniformity as poor or incomplete blending. An ability to control particle segregation during powder handling and transfer is critical to producing a uniform product. Understanding the flow behavior in bins and hoppers is a vital necessity for understanding segregation tendencies. Further consideration must be given to maintaining reliable flow of powder, since no flow or erratic flow can slow production or stop a process altogether.

The balance of this chapter will focus on achieving the uniformity requirements for the product, given a well-mixed blend has been achieved in the blender. Typical processing steps will be reviewed. The major concerns with powder flow through these steps will be illustrated, along with methods to determine the flow behavior in these processes. The mechanisms of segregation and methods to identify problems will be presented. Finally, with an understanding of these processes, scaling issues will be discussed.

Upon first reading the balance of this chapter, the reader will undoubtedly call into question why, for a chapter on blending, there is heavy emphasis on flow behavior in bins or a discussion of flow properties. The author's experience is that many pharmaceutical companies are equally likely to have problems with both producing a well-mixed blend and having an otherwise acceptable blend segregate upon further handling. Further, many firms have sufficient knowledge to diagnose

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and solve blending problems but lack understanding of powder flow behavior that results in the content uniformity problem that they may be facing. Lastly, these problems of no flow and segregation are less likely to occur at smaller scales and often appear for the first time at the full-scale batch, long after clinical trials are complete and the formulation and processing equipment are cast in stone.

II. REVIEW OF TYPICAL POWDER TRANSFER PROCESSES

Powder that has been blended in a blender must be discharged for further processing. Often, discharge is driven by gravity alone (such as out of a V-blender), though powder may also be forced out of the blender by way of mechanical agitation (e.g., a ribbon blender). The powder is often discharged into one or more portable containers, such as bins or drums, though some form of conveying system, such as vacuum transfer, may also be used. If drums are used, powder may be hand-scooped from the drums into downstream equipment, or a hopper may be placed on the drum, followed by inversion of the drum for gravity discharge. Powder in bins is usually discharged by gravity alone. Powder then feeds into one or more press hoppers, either directly or through a single or bifurcated chute, depending on the press configuration. With many modern presses, powder is fed by way of a feed frame or powder feeder from the press hopper into the die cavities.

Each of these transfer and handling steps is deceptively simple. Each of these steps can have a dramatic effect on the product quality, even if no effect is desired. Powder transfer should not be taken for granted and instead should be considered a critical unit operation for which bins, chutes, and press hoppers are major, design-critical pieces of equipment.

III. CONCERNS WITH POWDER-BLEND HANDLING PROCESSES

There are two primary concerns with powder handling that cannot be overlooked when scaling processes: achieving reliable flow and maintaining blend uniformity. To address these issues when scaling processes, knowledge of how powders flow and segregate is required.

A. How Powders Flow

A number of problems can develop as powder flows through equipment such as bins, chutes, and press hoppers. If the powder has cohesive strength, an arch or rathole may form. An *arch* is a stable obstruction that usually forms within the

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hopper section (i.e., converging portion of the bin) near the bin outlet. Such an arch supports the rest of the bin's contents, preventing discharge of the remaining powder. A *rathole* is a stable pipe or vertical cavity that empties out above the bin outlet. Powder remains in stagnant zones until an external force is applied to dislodge it. *Erratic flow* is the result of the blend's alternating between arching and ratholing, while *flooding* or *uncontrolled flow* may occur if a rathole spontaneously collapses. On the other hand, a deaerated bed of fine powder may experience flow rate limitations or no-flow conditions.

One of the most important factors in determining whether powder will discharge reliably from bins or hoppers is establishing the flow pattern that will develop as powder is discharged. The flow pattern is also critical in understanding segregation behavior.

1. Flow Patterns

Two flow patterns can develop in a bin or hopper: funnel flow and mass flow. In funnel flow (Fig. 1), an active flow channel forms above the outlet, which is surrounded by stagnant material. This is a first-in, last-out flow sequence. As the level of powder decreases, stagnant powder may slough into the flow channel if the material is sufficiently free flowing. If the powder is cohesive, a stable rathole may remain.

In mass flow (Fig. 2), all of the powder is in motion whenever any is withdrawn. Powder flow occurs throughout the bin, including at the walls. Mass flow provides a first-in, first-out flow sequence, eliminates stagnant powder, provides

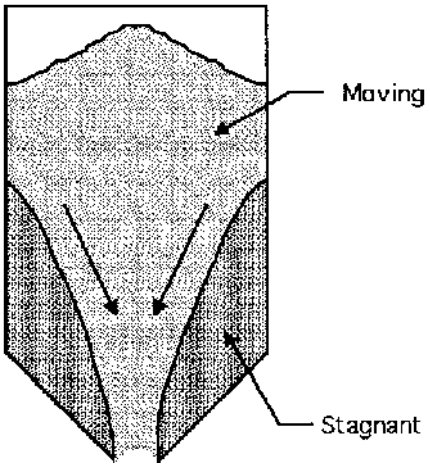

Figure 1 Funnel flow behavior in a bin.

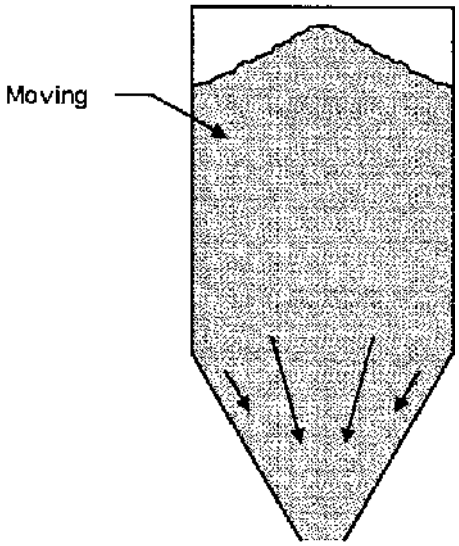

Figure 2 Mass flow behavior in a bin; all material is moving during discharge.

a steady discharge with a consistent bulk density, and provides a flow that is uniform and well controlled.

Requirements for achieving mass flow include sizing the outlet large enough to prevent arch formation and ensuring the hopper walls are steep and smooth enough to allow flow along them. Several flow properties are relevant to making such predictions. These properties are based on a continuum theory of powder behavior—namely, that powder behavior can be described as a gross phenomenon without describing the interaction of individual particles. The application of this theory using these properties has been proven over the last 40 years in thousands of installations handling the full spectrum of powders used in industry [1].

2. Flow Properties

In order to select, design, retrofit, or scale-up powder handling equipment, knowledge of the range of flow properties for all of the powders to be handled is critical. Formulators can also use these properties during product development to predict flow behavior in existing equipment. Though there are many tests that measure "flowability," it is important to measure flow properties relevant to the flow of equipment in the actual process [2]. The flow properties of interest to those involved with scale-up of processes include cohesive strength, wall friction, and compressibility.

a. Cohesive Strength. The consolidation of powder may result in arching and ratholing within transfer equipment. These behaviors are related to the cohesive strength of the powder, which is a function of the applied consolidation pressure. Cohesive strength of a powder can be measured accurately by a direct shear method. The most universally accepted method is described in ASTM standard D 6128-97 [3].

By measuring the force required to shear a bed of powder that is under various vertical loads, a relationship describing the cohesive strength of the powder as a function of the consolidating pressure can be developed [4]. This relationship, known as a *flow function,* FF, can be analyzed to determine the minimum outlet diameters for bins to prevent arching and ratholing.

b. Wall Friction. Used in a continuum model, wall friction (friction of powder sliding along a surface) is expressed as the wall friction angle ϕ', or coefficient of sliding friction μ [where μ = tangent (ϕ')]. This flow property is a function of the powder handled and the wall surface in contact with it. The wall friction angle can be measured by sliding a sample of powder in a test cell across a stationary wall surface using a shear tester (Fig. 3) [4]. Wall friction can be used to determine the hopper angles required to achieve mass flow. As the wall friction angle increases, steeper hopper walls are needed for powder to flow along them.

c. Bulk Density. The bulk density of a given powder is not a single or even a dual value, but varies as a function of the consolidating pressure applied to it. The degree to which a powder compacts can be measured as a function of the applied pressure [4]. For many materials, in a plot of the log of the bulk density, γ, vs. log of the consolidating pressure, σ, a straight-line curve fit is obtained. The resulting data can be used to accurately determine capacities for storage and transfer equipment of any scale, as well as to provide information to evaluate wall friction and feeder operation requirements.

If a flow problem is encountered in solids-handling equipment, at any scale, the most likely reason is that equipment was not based on the flow properties of the material handled. Often, when flow problems are encountered, the group re-

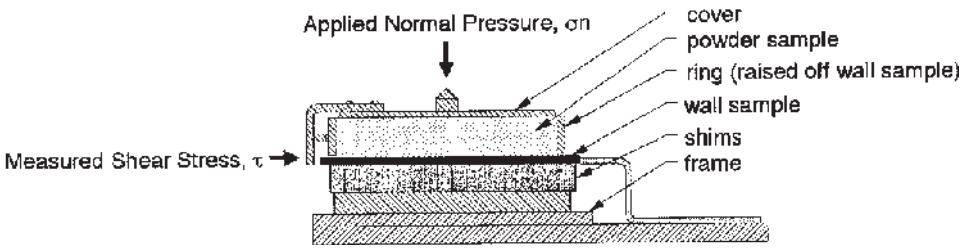

Figure 3 Setup of test apparatus for a wall friction test.

sponsible for selecting handling equipment had little or no knowledge of flow patterns or flow properties.

With an understanding of powder flow behavior and flow properties, segregation can be considered. Ultimately, as material is handled, stored, and transferred, the flow pattern that occurs will dictate how segregated the material will be when fed to downstream equipment.

B. How Powders Segregate

Segregation is the unwanted separation of differing components of the blend . This separation action is often referred to as a segregation mechanism. A second action is required for segregation to manifest itself, specifically, the flow from the blender to the creation of the dose. As material flows, the segregated zones may be reclaimed in such a way as to be effectively reblended; or these zones may be reclaimed one at a time, exacerbating segregation.

1. Segregation Mechanisms

Segregation can take place whenever forces are applied to the powder, for example, by way of gravity, vibration, or air flow. These forces act differently on particles with different physical characteristics, such as particle size, shape, and density. Most commonly, particles separate as a result of particle size differences. The result of segregation is that particles with different characteristics end up in different zones within the processing equipment (e.g., bin).

Typical pharmaceutical blends separate from each other by three common mechanisms: sifting/percolation, air entrapment (fluidization), and particle entrapment (dusting).

a. Sifting/Percolation. Under appropriate conditions, fine particles tend to sift or percolate through coarse particles. For segregation to occur by this mechanism there must be a range of particle sizes (a ratio of 2:1 is often more than sufficient). In addition, the mean particle size of the mixture must be sufficiently large (greater than about 100 microns), the mixture must be relatively free flowing, and there must be relative motion between particles. This last requirement is very important, since without it even blends of ingredients that meet the first three criteria will not segregate.

Relative motion can be induced, for example, as a pile is being formed, as particles tumble and slide down a chute. The result of sifting/percolation segregation is usually a side-to-side variation of particles. In the case of a bin, the smaller particles will generally be concentrated under the fill point, with the coarse particles concentrated at the outside of the pile (Fig. 4).

b. Air Entrainment (Fluidization). Handling of fine, aerated powders with variations in particle size or particle density often results in a vertical striation pattern, with the finer/lighter particles concentrated above larger/denser ones. This can

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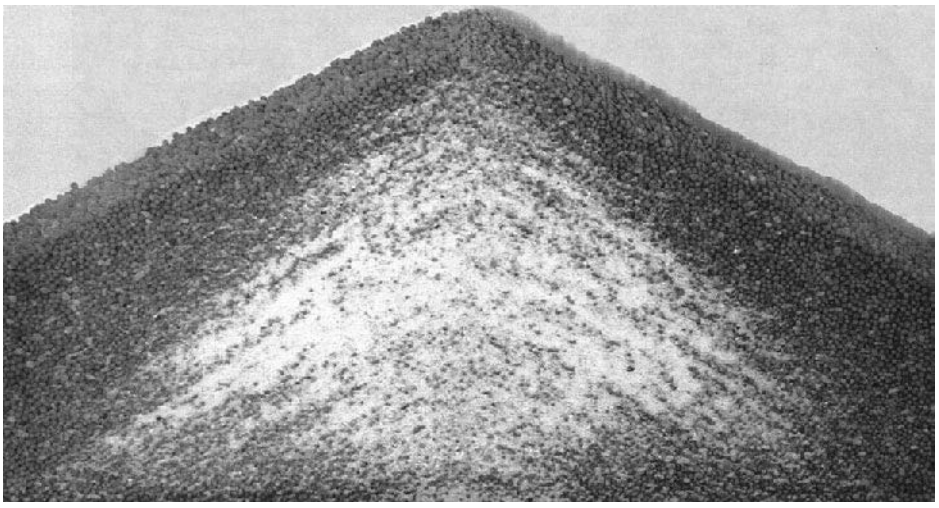

Figure 4 Photo of sifting segregation after pile formation; light-colored fines remain in the center, while darker, coarse particles concentrate at the perimeter.

occur, for example, during the filling of a bin. Whether or not the powder is pneumatically conveyed into the container or simply free-falls through an air stream, it may remain fluidized for an extended period after filling. In this fluidized state, larger and/or denser particles tend to settle to the bottom (Fig. 5). Air counterflow that occurs while filling an enclosed container can also cause these problems.

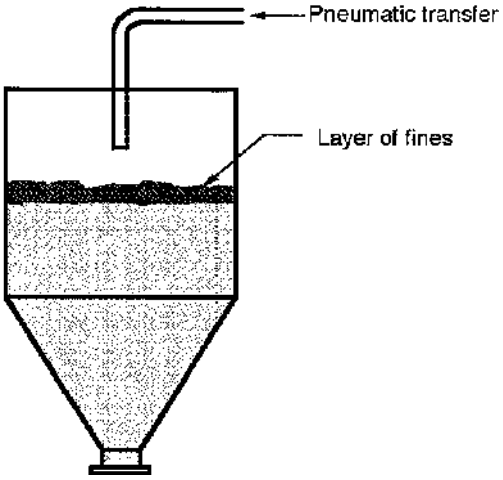

Figure 5 Fluidization segregation can take place when a bed of aerated material settles, driving fines to the top of the bin.

c. Particle Entrainment (Dusting). Similar to the air entrainment mechanism, particle entrainment, or dusting segregation, occurs primarily with fine powders that vary in particle size or density. Because of these variations, the finer/lighter particles remain suspended in air longer than larger/denser ones. For example, when powder drops into a container, the larger/denser particles will tend to remain concentrated in an area near the incoming stream, whereas smaller/lighter particles will be transported into slower-moving or even stagnant air (Fig. 6). This problem is particularly acute with pyramidal bins, as airborne fines that settle toward the walls eventually slide to the valleys (corners) of the bins. The powder in the corners of the bin discharges last, because of the funnel flow pattern that usually develops. The resulting trend across one bin usually involves a steady climb in the concentration of the finer components toward the end of the run.

2. Identifying Segregation Problems

a. At the Bench Scale. Two basic bench-scale evaluations serve as relative indicators of potential segregation problems. Neither approach provides a quantitative result that correlates to what could be expected at a pilot or production scale; however, they can be used as an indicator of the potential problems that may lie ahead. One approach is to sieve the blend and then assay individual screen cuts. If there is a wide variation of the assay across particle sizes, this serves as a warning that content uniformity problems may occur. The concern with this ap-

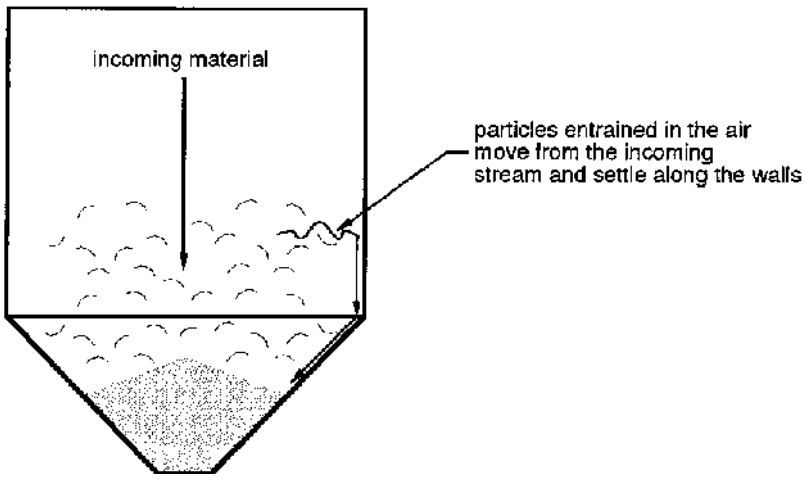

Figure 6 Dusting segregation can take place when airborne dust settles along the walls of a bin.

proach is that the sieving process may separate particles in a more vigorous manner than would be experienced in the actual process.

A second type of bench-scale evaluation is generically called a segregation test. In this type of test, the blend is subjected to forces expected to be induced in a "real" application. If the material is prone to segregation, these forces would segregate the material into different zones of the test apparatus. Samples are then collected and analyzed. Assay or particle size differences across different zones of the tester serve as a warning that segregation problems may occur. The quality of the information gleaned from these segregation tests is highly dependent upon the test method (how well the tester reproduces the forces induced in the process) as well as on avoiding sampling error (how samples from the segregation tester are collected, handled, and analyzed).

b. At a Pilot or Production Scale. The effects of segregation are usually recognized by comparing the standard deviation of samples of the final product (dosage form) to those collected either within a blender or upon blender discharge. The best way to diagnose problems is to take stratified, nested samples of powder from within the blender of dosage forms through the production run [5]. Segregation usually results in distinct trends across the run. To diagnose the problem, these trends must be correlated with the flow sequence (from the blender to the dosage formation) and the likely segregation mechanisms.

IV. SCALE EFFECTS

At the smaller scale, powder may be discharged from the blender into one or more containers and then hand-scooped from these containers into a small press hopper. Seldom is a batch left in storage for significant time after blending prior to compression. At this scale, the forces induced on the particles during bulk transport and handling are lower than full scale; further, distances across which the particles can separate are smaller, thereby reducing the tendency for segregation to occur. Hand-scooping obviates concerns about reliable discharge of powder from a bin. So if this process at the small scale works well, what must be considered when larger batch sizes are needed?

A. Analysis of Flow

In situations where a complete description of the physical behavior of a system is unknown, scale-up approaches often involve the use of dimensionless groups, as described in Chapter 1. Unlike flow behavior in a blender, the flow behavior of powder through bins and hoppers can be predicted by a complete mathematical relationship. In light of this, analysis of powder flow in a bin or hopper by dimen-

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sional relationships would be superfluous and, as will be illustrated, irrelevant, since nondimensional groups cannot be derived.

1. Bin or Hopper Outlet Size

If gravity discharge is used, the minimum outlet size required to prevent arching is dependent upon the flow pattern that occurs. Regardless of the flow pattern, though, the outlet size is determined with the powder's flow function, which is measured by way of cohesive strength tests described earlier.

The outlet size required to overcome no-flow conditions depends highly on the flow pattern that develops. If mass flow develops, the minimum outlet diameter, Bc to overcome arching is [4]:

$$Bc = H(\theta')f_{\text{crit}}/\gamma \tag{1}$$

$H(\theta')$ is a dimensionless function derived from first principles and is given by Figure 7 [for the complete derivation of $H(\theta')$, which is beyond the scope of this chapter, see Ref. 4]. f_{crit}, with units of force/area, is the unconfined yield strength at the intersection of the hopper flow factor (ff, a derived function based on powder flow properties and the hopper angle) and the powder flow function (FF) (see Fig. 8). Bulk density γ, with units of weight/volume, is the bulk density determined by compressibility tests described earlier. This calculation yields a dimensional value of Bc in units of length, which is scale independent. The opening size required is

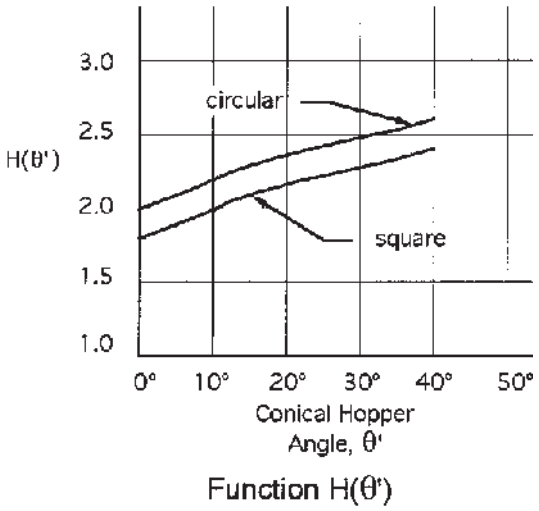

Figure 7 Plot showing derived function $H(\theta')$ used in calculating arching potential in mass flow bins.

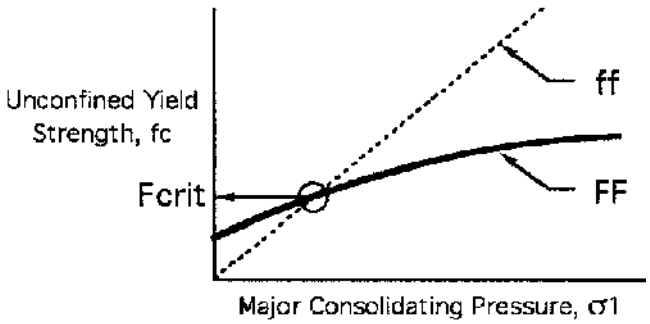

Figure 8 Sample flow function (FF) and flow factor (ff), showing Fcrit at their intersection.

not a function of the diameter or the height of the bin or the height-to-diameter ratio.

In other words, as a formulation is developed, one can run the shear tests described earlier to determine the cohesive strength (flow function). This material-dependent flow function, in conjunction with Eq. (1), will yield a minimum opening (outlet) size in order to avoid arching in a mass flow bin. For example, this opening size may be calculated to be 8 inches. This 8-inch diameter will be needed whether the bin holds 10 kilos or 1000 kilos, regardless of the hopper or cylinder height or diameter, and is scale independent. In this example, since an 8-inch-diameter opening is required, feeding this material through a press hopper or similarly small openings would pose real problems; it would be advisable to consider reformulating the product to improve flowability.

If funnel flow develops instead of mass flow, the minimum outlet diameter is given by the tendency for a stable rathole to occur, because this diameter is usually larger than that required to overcome arching. In this case, the minimum outlet diameter is:

$$\mathrm{Df} = G(\phi t) fc(\sigma 1)/\gamma \tag{2}$$

$G(\phi t)$ is also a derived function and is given by Figure 9. $fc(\sigma 1)$, the unconfined yield strength of the material, is determined by the flow function (FF) at the actual consolidating pressure $\sigma 1$. The consolidation pressure $\sigma 1$ is a function of the head or height of powder above the outlet of the bin, as given by Janssen's equation:

$$\sigma 1 = (\gamma R/\mu k)(1 - e^{-\mu kh/R}) \tag{3}$$

where R is the hydraulic radius (area/perimeter), μ is the coefficient of friction (tangent ϕ'), k is the ratio of horizontal to vertical pressures (often, 0.4 is used), and h is the depth of the bed of powder within the bin.

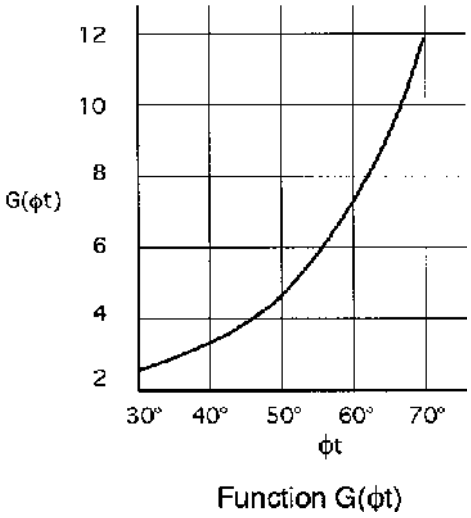

Figure 9 Plot showing derived function G(ϕt) used in calculating ratholing potential in funnel flow bins.

This relationship in Eq. (2) cannot be reduced further, for the function $fc(\sigma 1)$ is highly material dependent.

2. Hopper Angle

Design charts describe which flow pattern would be expected to occur, dependent on the hopper angle (θc, as measured from vertical), wall friction angle (ϕ'), and internal friction (δ) of the material being handled. An example of such a design chart for a conical hopper is shown in Figure 10. For any combination of ϕ' and θc that lies in the mass flow region, mass flow is expected to occur; if the combination lies in the funnel flow region, funnel flow is expected. The uncertain region is an area where mass flow is expected to occur but represents a 4° margin of safety on the design, to account for inevitable variations in test results and surface finish.

The wall friction angle ϕ' is determined by wall friction tests, as described earlier. The resulting wall yield locus (Fig. 11) is a function of the normal pressure against the surface. For many combinations of wall surfaces and powders, the wall friction angle changes depending on the normal pressure. When mass flow develops, the solids pressure normal to the wall surface is given by the following relationship:

$$\sigma n = (\sigma'/\gamma b) \times \gamma B. \tag{4}$$

Reference 4 provides charts giving $(\sigma'/\gamma b)$. Assuming $(\sigma'/\gamma b)$ and the bulk density γ are constant for a given powder and hopper (a reasonable assumption for a

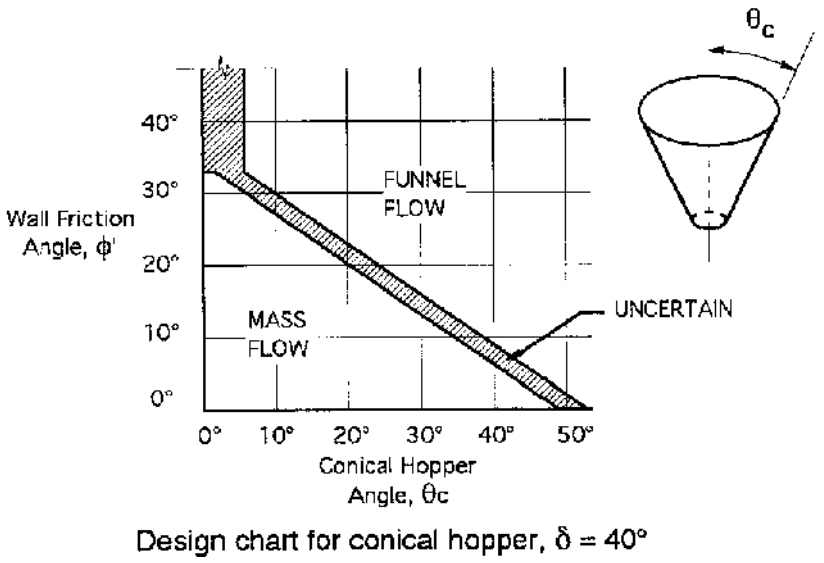

Figure 10 Mass flow/funnel flow design chart for a conical hopper handling a bulk material with a 40° effective angle of internal friction.

first approximation), the pressure normal to the wall is simply a linear function of the span of the hopper, *B,* at any given point. Generally, ϕ' increases with decreasing normal pressure, σn. Therefore, the critical point is at the outlet of the hopper; this is the smallest span *B,* with the correspondingly lowest normal pressure to the wall, σn. Hence, this point usually has the highest value of wall friction for a given design, so long as the hopper interior surface finish and angle remain constant above the outlet.

When considering scale effects, the implication of the foregoing analysis is that the hopper angle required for mass flow is principally dependent on the out-

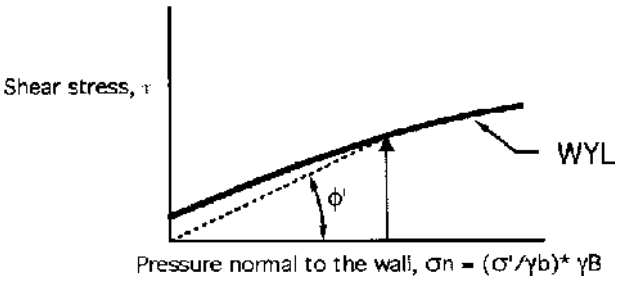

Figure 11 Sample wall yield locus generated from wall friction test data.

let size selected for the hopper under consideration. Note that the hopper angle required for mass flow is not a function of the flow rate, the level of powder within the hopper, or the diameter or height of the bin (as was also the case for minimum outlet size).

Since the wall friction angle generally increases with lower normal pressures, a steeper hopper is often required to achieve mass flow at smaller scales (smaller outlets). For example, assume that a specific powder discharges in mass flow from a bin with a certain outlet size. A second bin with an equal or larger outlet size will also discharge in a mass flow pattern for this powder, provided that the second bin has an identical hopper angle and surface finish. This is true regardless of the actual size of either bin; only the outlet size needs to be considered. The reverse, of using the same hopper angle with a bin with a smaller outlet, will not always provide mass flow.

Of course, mass flow is highly dependent upon conditions below the hopper; a throttled valve, a lip or other protrusion, or anything that can initiate a zone of stagnant powder can convert any hopper into funnel flow, regardless of the hopper angle or surface finish.

In scaling the flow behavior of powders, it is better to rely on first principles and material flow properties, as opposed to reliance on observations or data gleaned from the initial scale.

B. Scaling Segregation

Although basic concepts are understood, equations based on the physics of segregation within bins are not well described. At best, a list of relevant variables can be described, but such a list would likely be incomplete. Even the process of mathematically describing a segregated powder bed beyond a "mixing index" is not well defined. After all, in addition to quantifying the variability, the spatial arrangement of the different zones is also significant. These limitations make even simple dimensional analyses of segregation within bins impossible at this time. Instead, for the pharmaceutical scientist seeking guidance during scaling, there is heavy reliance on empirical considerations, experience, and judgment and on conservative design approaches. This may also put the scientist into a "hope-and-see" or reactionary position, an uncomfortable position given the repercussions of product uniformity failure.

C. Avoiding Segregation

There are three basic approaches to defeat segregation [6]:

1. Modify the powder in a way to reduce its inherent tendency to segregate.
2. Modify the equipment to reduce forces that act to segregate the powder.

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3. Remedy segregation that takes place by reblending the powder during subsequent transfer.

1. Modify the Powder to Reduce its Tendency to Segregate

There are several ways to change the powder to reduce its tendency to segregate. One way is to change the particle size distribution of one or more of the components. If the components have a similar particle size distribution, they will generally have a lesser tendency to segregate. Another option is to change the particle size such that the active segregation mechanism(s) become less dominant. For instance, one way to reduce fluidization segregation is to make the particles sufficiently large that the powder cannot fluidize. However, one must be careful in this approach not to activate a new segregation mechanism.

Another option is to change the cohesiveness of the powder, such that the particles in a bed of powder are less likely to move independent of each other. Increasing the tendency of one component to adhere to another will also reduce segregation. This is referred to as an ordered, adhesive, or structured blend. Granulation, whether wet or dry, is also implemented to, among other reasons, reduce segregation tendencies and improve powder flow. Bear in mind that, even if each particle is chemically homogeneous (which is never absolutely the case, even with granulations), segregation by particle size can result in variations that effect the end product, such as tablet weight or hardness.

2. Change the Equipment to Reduce the Chance of Segregation

Forces exerted on particles can induce segregation by many mechanisms. When handling a material where segregation is a concern, the designer must minimize these forces. Unfortunately, there are no scaling criteria available for guidance. Worse yet, when scaling up, forces acting on the particles increase significantly, as well as distances across which the particles can separate.

Here are some general guidelines:

Minimize transfer steps. With each transfer step and movement of the bin or drum, the tendency for segregation increases. Ideally, the material would discharge directly from the blender into the tablet press feed frame with no additional handling. In-bin blending is as close to this as most firms can practically obtain and is the best one can ask for—so long as a well-mixed blend can be obtained within the bin in the first place.

Minimize drop height. Drop height serves to aerate the material, induce dust, and increase momentum of the material as it hits the pile, increasing the tendency for each of the three segregation mechanisms described earlier.

Control dust generation. Dust can be controlled by way of socks or sleeves, to contain the material as it drops from the blender to the bin, for exam-

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ple. Some devices are commercially available specifically for this purpose.

Control fluidization of powder. Beware of processes, such as pneumatic conveying, that increase the potential for the material to become aerated.

Restriction. Slowing the fill rate can reduce fluidization and dusting segregation tendencies.

Venting. Air that is in an otherwise "empty" bin, for example, must be displaced from the bin as powder fills it. If this air is forced through material in the V-blender, perhaps sealed tight in the interest of containment, this can induce fluidization segregation within the blender. To avoid this, a separate pathway or vent line to allow the air to escape without moving through the bed of material can reduce segregation.

Distributor. A deflector or distributor can spread the material stream as it enters the bin. Instead of forming a single pile, the material is spread evenly across the bin. This reduces sifting segregation but may cause additional dust generation, making dusting segregation worse.

Proper hopper, Y-branch design. Press hoppers, transfer chutes, and Y-branches must be designed correctly, to avoid stagnant material and to minimize air counterflow.

Operate the valve correctly. Butterfly valves should be operated in full open position, not throttled to restrict flow. Restricting flow will virtually ensure a funnel flow pattern, which is usually detrimental to uniformity.

3. Change the Equipment to Provide Remixing

The concept of knowingly letting materials segregate and then counting on material transfer to provide reblending is frankly quite scary to both pharmaceutical scientists as well as regulatory personnel. Make no mistake, however, that this is a better approach than letting materials segregate and doing nothing about it. Ignorance is not bliss. The following concepts are not radical and, in fact, have been used for many decades in the pharmaceutical and other industries.

Use mass flow. In a mass flow pattern, material that has segregated in a side-to-side segregation pattern because of sifting or air entrainment will be reblended during discharge. In most applications, this reblending is sufficient to return the blend to its initial state of uniformity. However, a mass flow pattern will not remedy a top-to-bottom segregation pattern, such as caused by fluidization segregation; the top layer will discharge last. Note that if top-to-bottom segregation occurs, funnel flow will simply result in the top layer's discharging at some point in the middle of the run, also not providing any reblending.

Beware of velocity gradients. With mass flow, all the material is in motion during discharge, but the velocity will vary. The material will always be

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somewhat slower at the walls than at the center of the bin (assuming a symmetrical bin with a single outlet in the center). In critical applications, the velocity profile could effect uniformity, with the material at the walls discharging at a slightly slower rate than that from the center. While far superior to a funnel flow pattern, a mass flow pattern with high velocity gradients may not be desired. To remedy this, either a hopper that is designed well into the mass flow regime is needed, or a flow-controlling insert, such as a Binsert®, must be used. Velocity profiles, and their effect on blending material, can be calculated a priori given the geometry of the bin and measured flow properties. As a point of interest, velocity profiles can be carefully controlled to force a bin to behave as a static blender, used in other industrial applications.

The scientist seeking to scale blending processes must be well aware of the limitations of the state of science in this area. Equal consideration must be given to the state of the blend in the blender as well as the effects of subsequent handling.

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6
Scale-Up in the Field of Granulation and Drying

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I. INTRODUCTION

Today the production of pharmaceutical granules is still based on the batch concept. In the early stage of the development of a solid dosage form the batch size is small, e.g., for first clinical trials. In a later stage the size of the batch produced in the pharmaceutical production department may be up to a 100 times larger. Thus the scale-up process is an extremely important one. Unfortunately, in many cases the variety of the equipment involved does not facilitate the task of scale-up. During the scale-up process the quality of the granules may change. A change in granule size distribution, final moisture content, friability, compressibility, and compactibility of the granules may strongly influence the properties of the final tablet, such as tablet hardness, tablet friability, disintegration time, dissolution rate of the active substance, and aging of the tablet. In the following sections, the scale-up process is analyzed, taking into account mathematical considerations of scale-up theory [1], the search for scale-up invariants [2–5], the establishment of in-process control methods [6–9], as well as the design of a robust dosage form [10–13]. In this respect new concepts such as percolation theory [13] play an important role. Finally, a new concept concerning a quasi-continuous production line of granules is presented [14–20]. This concept permits the production of small-scale batches for clinical trials and of production batches using the same equipment. Thus scale-up problems can be avoided in an elegant and cost-efficient way.

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II. THEORETICAL CONSIDERATIONS

A. Principle of Similarity

1. Definition of Similarity and Dimensionless Groups

The important concept for scale-up is the principle of similarity [1–6]. When scaling up any mixer/granulator (e.g., planetary mixer, high-speed mixer, pelletizing dish) the following three types of similarity need to be considered: geometric, kinematic, and dynamic. Two systems are *geometrically* similar when the ratio of the linear dimensions of the small-scale and scaled-up system are constant. Two systems of different size are *kinematically* similar when, in addition to the systems' being geometrically similar, the ratio of velocities between corresponding points in the two systems are equal. Two systems of different size are *dynamically* similar when *in addition* to their being geometrically and kinematically similar, the ratio of forces between corresponding points in the two systems are equal.

a. Similarity Criteria. There are two general methods of arriving at similarity criteria:

1. When the differential equations, or in general the equations, that govern the behavior of the system are known, they can be transformed into dimensionless forms.
2. When the differential equations, or in general the equations, that govern the behavior of a system are not known, such similarity criteria can be derived by means of dimensional analysis.

Both methods yield dimensionless groups, which correspond to dimensionless numbers [1], e.g.:

Reynolds number Re
Froude number Fr
Nusselt number Nu
Sherwood number Sh
Schmidt number Sc etc. [2]

The classical principle of similarity can then be expressed by an equation of the form

$$\pi_1 = F(\pi_2, \pi_3, \ldots) \tag{1}$$

This equation may be a mechanistic one (case A) or an empirical one (case B).

Case A: $\pi_1 = e^{-\pi_2}$, with the dimensionless groups:

$$\pi_1 = \frac{P(x)}{P(0)}$$

where

$P(x)$ = pressure at level x

$P(0)$ = pressure above sea level ($x = 0$)

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$$\pi_2 = \frac{E(x)}{RT} \tag{2}$$

with

$$E(x) = Mgx$$

where

$E(x)$ = molar potential energy
M = molecular weight
g = gravitational accelaration
x = height above sea level
RT = molar kinetic energy

Case B:

$$\pi_1 = a(\pi_2)^b \cdot (\pi_3)^c \tag{3}$$

The unknown parameters *a, b, c* are usually determined by nonlinear regression calculus.

2. Buckingham's Theorem

For a correct dimensional analysis it is necessary to consider Buckingham's theorem, which may be stated as follows [3,4]:

1. The solution to every dimensionally homogeneous physical equation has the form

$$F(\pi_1, \pi_2, \pi_3 \ldots) = 0$$

in which $\pi_1, \pi_2, \pi_3 \ldots$ represent a complete set of dimensionless groups of the variables and the dimensional constants of the equation.

2. If an equation contains n separate variables and dimensional constants and these are given dimensional formulas in terms of m primary quantities (dimensions), the number of dimensionless groups in a complete set is $(n - m)$.

III. SCALE-UP AND MONITORING OF THE WET GRANULATION PROCESS

A. Dimensionless Groups

Because the behavior of the wet granulation process cannot yet be described adequately by mathematical equations, the dimensionless groups have to be deter-

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mined by a dimensional analysis. For this reason the following idealized behavior of the granulation process in the high-speed mixer is assumed:

The particles are fluidized.
The interacting particles have similar physical properties.
There is only a short-range particle–particle interaction.
There is no system property equivalent to viscosity, i.e., (1) there are no long-range particle–particle interactions and (2) the viscosity of the dispersion medium air is negligible.

According to Buckingham's theorem, the following dimensionless groups can be identified:

$\pi_1 = \dfrac{P}{r^5\omega^3\rho}$ Power number

$\pi_2 = \dfrac{qt}{V\rho}$ Specific amount of granulation liquid

$\pi_3 = \dfrac{V}{V^*}$ Fraction of volume loaded with particles

$\pi_4 = \dfrac{r\omega^2}{g}$ Froude number (centrifugal/gravitational energy)

$\pi_5 = \dfrac{r}{d}$ Geometric number (ratio of characteristic lengths)

where

P = Power consumption
r = Radius of the rotating blade (first characteristic length of the mixer)
ω = Angular velocity
ρ = Specific density of the particles
q = Mass (kg) of granulating liquid added per unit time
t = Process time
V = Volume loaded with particles
V^* = Total volume of the vessel (mixer unit)
g = Gravitational acceleration
d = Diameter of the vessel (second characteristic length of the mixer)

In principle the following scale-up equation can be established:

$$\pi_1 = a(\pi_2)^b \cdot (\pi_3)^c \cdot (\pi_4)^d \cdot (\pi_5)^e \quad (4)$$

In general, however, it may not be the primary goal to know exactly the empirical parameters *a, b, c, d, e* of the process under investigation, but to check or monitor pragmatically the behavior of the dimensionless groups (process variables, dimensionless constant) in the small- and large-scale equipment. The ultimate goal would be to identify scale-up invariants.

B. Experimental Evidence for Scale-Up Invariables

In the case of the wet granulation process in a mixer/kneader, the granulation process can easily be monitored by the determination of the power consumption [6–9] (Fig. 1).

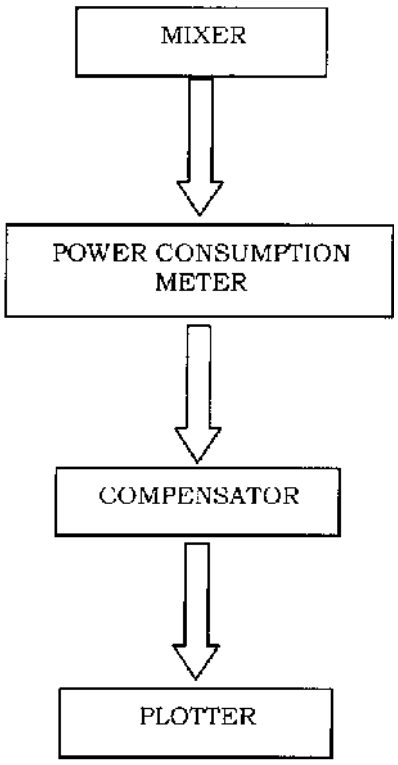

Figure 1 Block diagram of measuring equipment.

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The typical power profile consists of five different phases (Fig. 2). Usable granulates can be produced in a conventional way only within the plateau region S_3–S_4 according to the nomenclature in Figure 2. As Figure 3 indicates, changing the type of mixer has only a slight effect on the *phases* of the kneading process. However, the actual power consumption of mixers of different type differs greatly for a given granulate composition.

The important point now is that the power consumption profile as defined by the parameters S_3, S_4, S_5 is independent of the batch size. For this investigation, mixers of the planetary type (Dominici, Glen, Molteni) were used. The batch size ranged from 3.75 kg up to 60 kg. To obtain precise scale-up measurements, the excipients used belonged to identical lots of primary material (10% (W/W) corn starch, 4% (W/W) polyvinylpyrrolidone as binder, and 86% (W/W) lactose). As can be seen from Figure 4, the amount of granulating liquid is linearly dependent on the batch size. During the scale-up exercise the rate of addition of the granulation liquid was enhanced in proportion to the larger batch size. Thus the power profile, which was plotted on the chart recorder, showed the characteristic S_3, S_4, S_5—values independent of batch size within the same amount of time since the start of the addition of granulation liquid. This fact is not surprising because in terms of scale-up theory, the functional dependencies of the dimensionless group numbers π_1 and π_2— were measured:

$$\pi_1 = F(\pi_2) \tag{5}$$

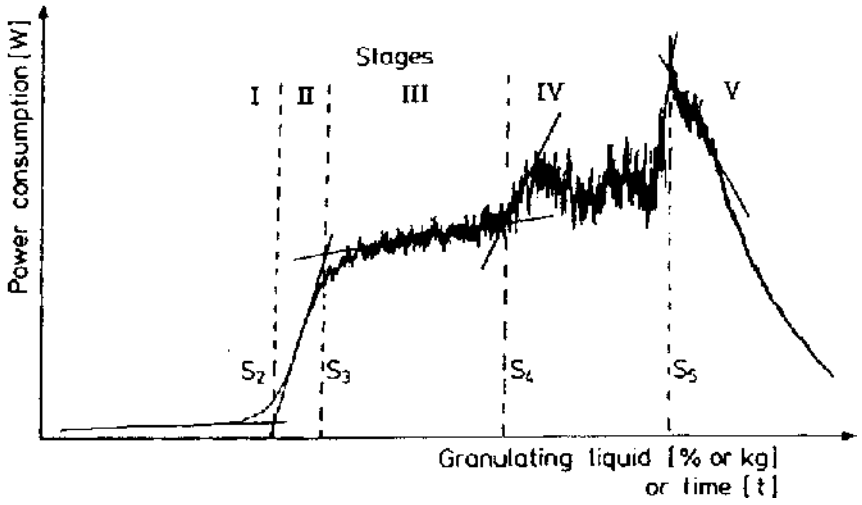

Figure 2 Division of a power consumption curve. (From Ref. 8.)

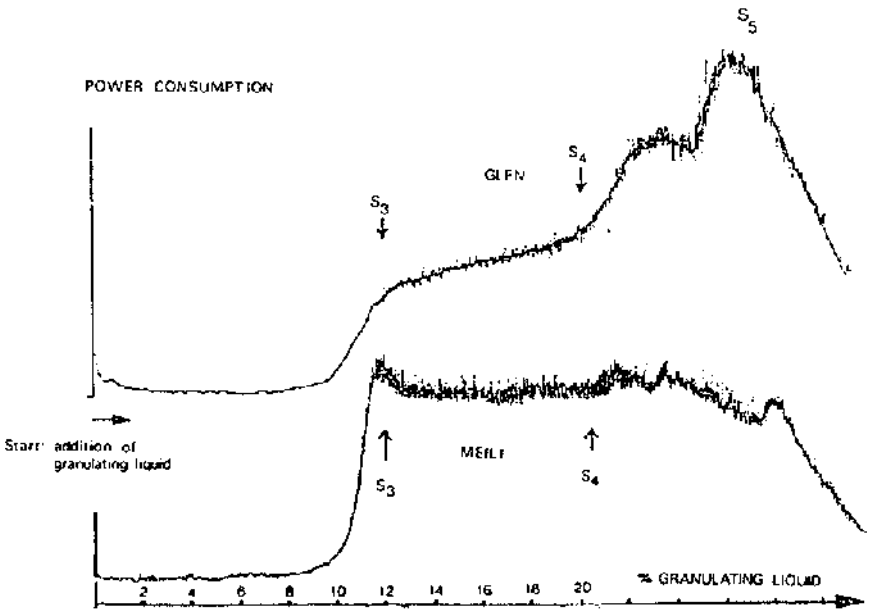

Figure 3 Power consumption profiles of two types of a mixer/kneader.

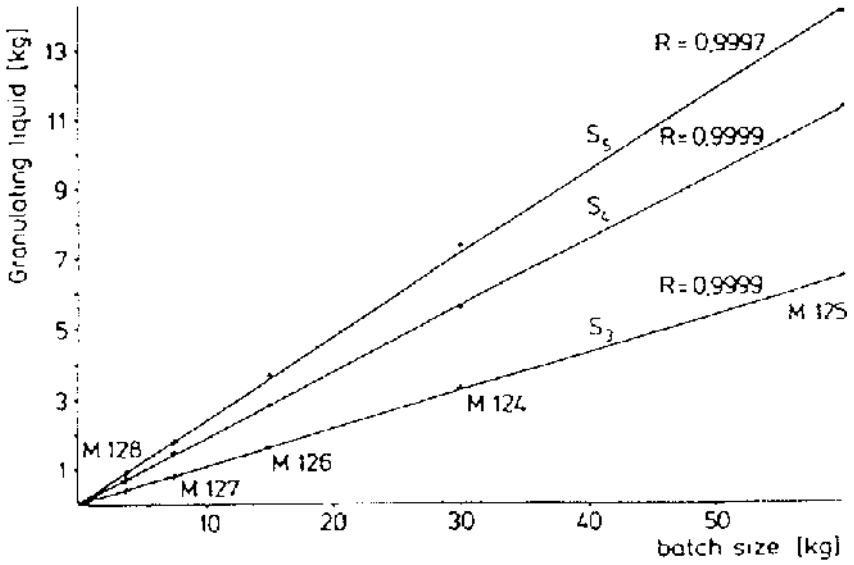

Figure 4 Scale-up precision measurements with identical charges. (From Ref. 6.)

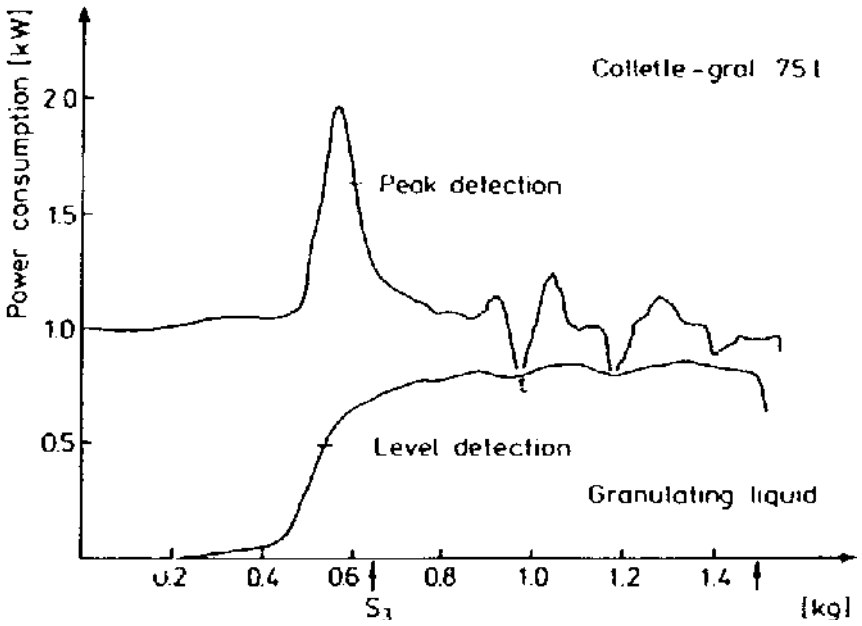

Figure 5 Power consumption profile of a high-speed-mixer (Collette–Gral 75 l) with peak and level detection. (From Ref. 8.)

The other numbers π_3, π_4, π_5, were kept essentially constant. From these findings one can conclude that the correct amount of granulating liquid per amount of particles to be granulated is a scale-up invariable [6–9]. It is necessary, however, to mention that during this scale-up exercise only a low-viscous granulating liquid was used. The exact behavior of a granulation process using high-viscous binders and different batch sizes is unknown. It is evident that the first derivative of the power consumption curve is a scale-up invariant and can be used as an in-process control and for a fine-tuning of the correct amount of granulating liquid (see Fig. 5).

C. Use of the Power Consumption Method in Dosage Form Design

Robust formulations are today an absolute prerequisite. Concerning the production of granules, the granule size distribution should not vary from batch to batch. The key factors are the correct amount and the type of granulating liquid. The interpretation of the power consumption method can be very important for an optimal selection of the type of granulating liquid. The possible variation of the initial particle size distribution of the active substance and/or excipients can be compen-

sated in case of an intelligent in-process control method, e.g., based on the power consumption profile (see Table 1). However, the formulation may not be very robust if the volume-to-volume ratio of certain excipients, such as maize starch and lactose, correspond to a critical ratio or percolation threshold.

With dosage form design it is often necessary to compare the performance of two different granule formulations. These two formulations differ in composition and as a consequence vary also in the amount of granulating liquid required. Thus the following question arises: How can the quantity of granulating liquid be adjusted to achieve a correct comparison? The answer is not too difficult, because it is based on identified physical principles. A correct comparison between two formulations is often a prerequisite because the dissolution process of the active substance in the final granulate or tablet can be affected by both the amount of granulating liquid and the qualitative change (excipients) in the formulation. In order to calculate corresponding, i.e., similar amounts of, granulating liquid in different compositions, it is necessary to introduce a dimensionless amount of granulating liquid π. This amount π can be defined as degree of saturation of the interparticulate void space between the solid material:

$$\pi = \frac{S - S_2}{S_5 - S_2}$$

where

S = Amount of granulating liquid (in liters)

S_2 = Amount of granulating liquid (in liters) necessary, which corresponds to a moisture equilibrium at approx. 100% relative humidity

S_5 = Complete saturation of interparticulate void space before a slurry is formed (amount in liters)

Power consumption is used as an analytical tool to define S values for different compositions. Thus the granule formation and granule size distribution of a

Table 1 Comparison Between the Manual and the Automatic Mode of Controlling the Moist Agglomeration Process

Type of mode	Yield (% w/w) 90–710 μm	% Undersize <710 μm	% Undersize <90 μm
Manual mode, $n = 20$ batches	82.03 ± 2.42	88.30 ± 2.05	6.80 ± 0.51
Automatic mode, $n = 18$ batches	91.45 ± 0.36	96.80 ± 0.31	5.40 ± 0.35

Source: Ref. 9.

Table 2 Physical Properties of Lactose and Corn Starch

Property	Lactose	Corn starch
Bulk density (g/cm^3)	0.58	0.49
Tapped density (g/cm^3)	0.84	0.65
True density (g/cm^3)	1.54	1.50
S_m (mass specific surface) (cm^2/g)	3055	
Mean diameter (μm)	40	25

binary mixture of excipients are analyzed as a function of the dimensionless amount of granulating liquid π. This strategy allows an unbiased study of the growth kinetics of granules consisting of a single substance or of a binary mixture of excipients. Thus it is important to realize that the properties of the granule batches are analyzed as a function of the dimensionless amount of granulating liquid [6–9].

1. Materials

The physical characteristics of the starting materials are compiled in Table 2. Polyvinylpyrrolidone was added in a dry state to the powder mix of lactose and corn starch at a level of 3% (w/w). As a granulating liquid, demineralized water was used and pumped to the powder mix at constant rate of 15 g min^{-1}kg^{-1}.

2. Methods

The principle of power consumption method was described in detail in Refs. 6–9 and 14. As a high-shear mixer, a Diosna V 10 was used, keeping constant impeller speed (270 rpm) and chopper speed (3000 rpm) during the experiments.

In order to reduce the possible effects of friability or second agglomeration during a drying process in dish dryers on the granule size distribution as a function of the amount π of granulating liquid added, the granules are dried for 3–5 min in a fluidized bed (Glatt Uniglatt) and subsequently for 15–25 min in a dish dryer to obtain moisture equilibrium corresponding to 50% relative humidity of the air at ambient temperature (20°C). The particle size distributions were determined according to DIN 4188 using ISO-norm sieve sizes [9].

IV. ROBUST FORMULATIONS AND DOSAGE FORM DESIGN

In the case of binary mixtures consisting of different substances, which, individually, may have a considerable effect on the physical properties (e.g., electrical con-

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ductivity) of the final product (granules, tablets, etc.), the ratio of components is essential. Thus with a mixture between Al_2O_3 (an electrically insulating material) and copper powder, electrical conductivity of the Al_2O_3/copper tablet is observed only if the copper powder forms an electrical pathway between the electrodes attached to the surface of the tablet produced. The critical ratio where conductivity is measured corresponds to the so-called percolation threshold p_c [10]. In the case of a fixed normalized amount π of granulating liquid, it is interesting to note that the granules obtained from a lactose/corn starch powder mixture lead to granule size distributions equivalent to the granule size distribution of either lactose or corn starch. This result can be interpreted on the basis of percolation theory (Fig. 6), i.e., that the properties differ for compositions below or above a critical ratio p_c of components between lactose and corn starch (Table 2).

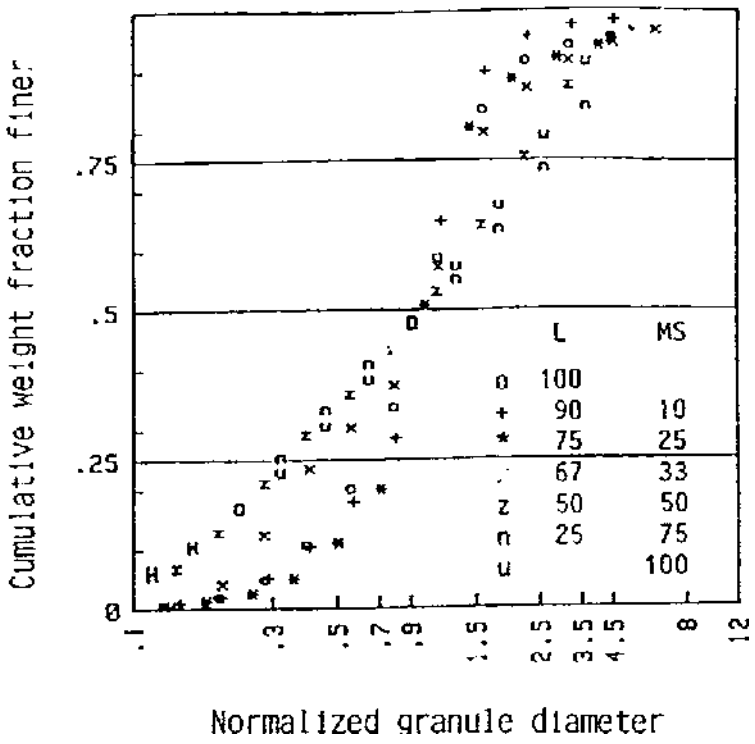

Figure 6 Cumulative particle size distribution of the agglomerates at a fixed normalized amount π (= 0.62) of granulating liquid for different ratios of the binary powder mixture lactose/corn starch.

V. A QUASI-CONTINUOUS GRANULATION AND DRYING PROCESS (QCGDP) TO AVOID SCALE-UP PROBLEMS

A. Continuous Processes and the Batch Concept

In the food and chemical industries, continuous production lines play an important role, whereas pharmaceutical industry production is based mainly on a batch-type procedure. Concerning the safety of a dosage form and quality assurance, the batch concept is very convenient. Thus a well-defined batch can be accepted or rejected.

In the case of a continuous process, a batch has to be defined somehow artificially, i.e., the amount of product, e.g., amount of granules produced within 6–8 hours. On the other hand, continuous processes offer two important advantages: (1) there is no difficult scale-up exercise necessary for larger "batches"; (2) a 24-hour automatic production line should be possible.

B. Development of the Quasi-Continuous Production Line for Granules

In order to combine the advantages of batch-type and continuous production, a prototype for a quasi-continuous production line was developed [15–18]. The principle of this quasi-continuous production line is based on a semicontinuous production of minibatches in a specially designed high-shear mixer/granulator connected to a continuous multicell-fluidized-(Glatt Multicell®) bed dryer (see Fig. 7).

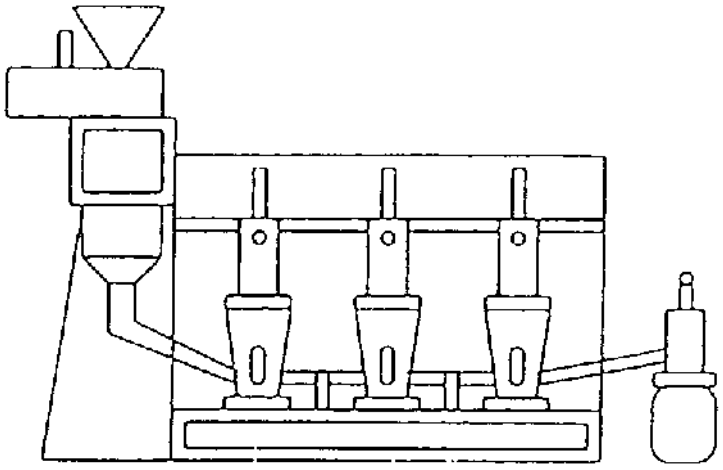

Figure 7 A quasi-continuous production line for granules with three drying cells (Glatt AG, CH-4133 Pratteln).

In order to study the feasibility of such a quasi-continuous production line, different formulations were tested and compared with a conventional batch process. The weighing system available on the market was not involved in the first experiments. Thus a prefixed amount of powder of the placebo formulation was added to the specially designed high-shear mixer and thoroughly mixed. Subsequently this amount of powder is granulated by continuously adding granulating liquid up to a fixed amount. The ideal amount of granulating can be defined according to the results of a power consumption measurement [6–9]. Afterwards the moist granules are discharged through a screen into the first cell of the multicell-fluidized-bed dryer unit to avoid any formation of lumps. Thus the quasi-continuous production of granules can be described as a train of minibatches passing like parcels through the compartments of dry mixing, granulation, and drying. The multicell dryer consists in general of three cells designed for different air temperatures; i.e., in the first cell the granules are dried at a high temperature, e.g., 60°C, and in the last cell ambient air temperature and humidity can be used to achieve equilibrium conditions. If appropriate, more cells can be added.

Due to this principle, a batch defined for quality control purposes consists of a fixed number of *n* minibatches. Thus a tight in-process control of the mixing/granulation [6–9] and drying step [14] provides an excellent "batch record" of the quasi-continuous production of granules and an excellent opportunity for a continuous validation of the process and the equipment [14–20].

Thus, based on the positive results obtained with the thesis work of Schade and Leuen berger [15] and B. Dörr [17] a new plant for quasi-continuous wet granulation and multiple-chambered fluid-bed drying was developed by Glatt AG CH-Pratteln in cooperation with F. Hoffmann-La Roche Ltd. Basel and the Institute of Pharmaceutical Technology of the University of Basel. For this achievement the Institute of Pharmaceutical Technology received the Innovation Award of the Cantons Basel–City and Basel–Country in 1994.

The system provides a new possibility for industrial manufacturing and galenical development of pharmaceutical solids specialties and has following purposes: to make possible automated, unattended production, withdrawing from scale-up experiments, and thus a shorter development time for new specialties, with the aim of a shorter time to market. Manufacturing procedures can be simplified and validated faster, and the quality of granules, tablets, and kernels compared to common production is equal or better. Different solids specialties have been tested and validated.

1. Goals of the Quasi-Continuous Granulation and Drying Line

a. Unattended Production. One of the general aims of quasi-continuous granulation and fluid-bed drying is unattended production. The production of

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small subunits of 7–9 kg instead of a whole batch allows an automated, iterative granulation and drying procedure. The division of the process into different compartments (mixing, sieving, and drying compartments) guarantees the reproducibility of the galenical properties of each subunit.

b. No Necessity for Scale-Up Experiments. The granulation and drying of subunits of 7–9 kg instead of a whole batch leads to the possibility of using the plant for laboratory and production scale, because the batch size is no longer characterized by machine size but by the number of produced subunits. Using the same plant in galenical research, development and production may shorten the time to market for new solids specialties.

c. Simplification of Manufacturing Procedures. Existing manufacturing procedures can be taken over from common equipment without changing components. In certain cases it's possible to simplify the procedures. The small mixer size and the geometry of the mixing elements allow the binders to be added to the premixture and granulation just with water.

d. Identical or Better Quality of Granules and Tablets. The quality of the produced granules and tablets has to be equal or better and fulfill product specifications.

2. Results

Constant values and the reproducibility of the process are important benefits of quasi-continuous granulation. The tests could also show equal or better quality of granules and tablets compared to common granulation equipment (Diosna P-600 high-speed granulator). Figures 8–13 show the results obtained during the devel-

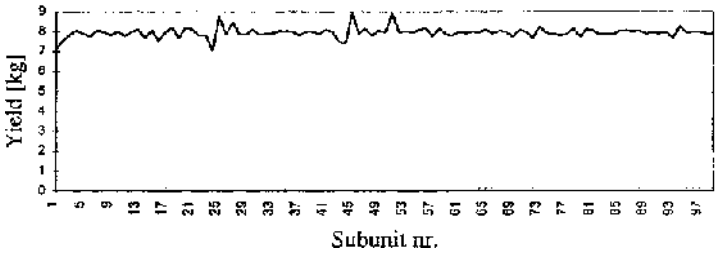

Figure 8 Yield (Formulation 1).

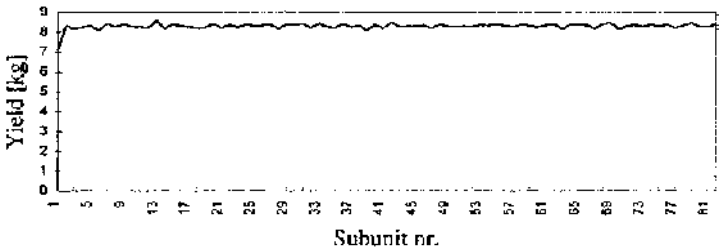

Figure 9 Yield (Formulation 2).

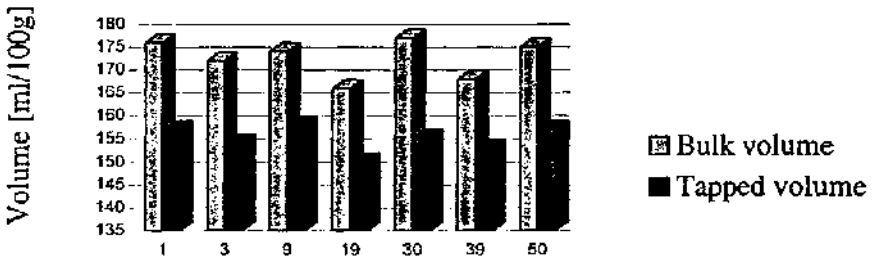

Figure 10 Bulk volume/tapped volume (Formulation 1).

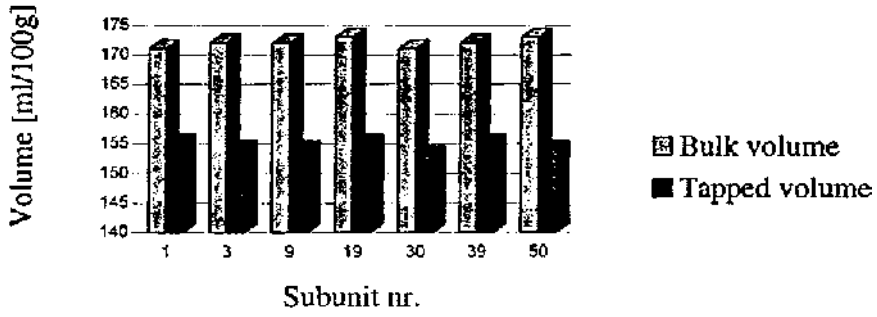

Figure 11 Bulk volume/tapped volume (Formulation 2).

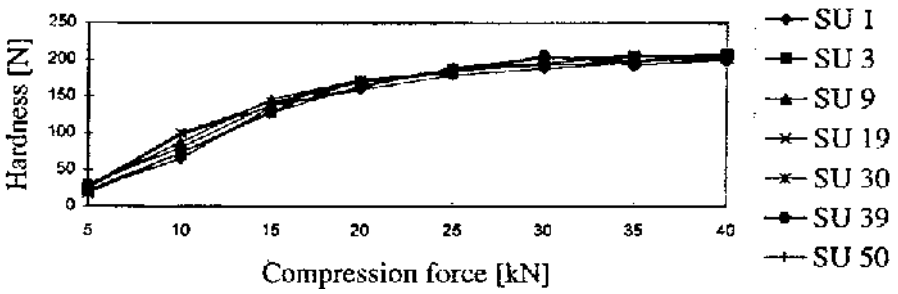

Figure 12 Compression force/hardness profile (Formulation 1).

opment of the equipment, where the high-shear mixer/granulator was operated separately from the subsequent drying system. The tests show the performance of the individual minibatches as a function of the subunit number. Because the subunits are collected in the container (see Layout 1) for the preparation of the final tablet blend, these tests are not necessary with the fully equipped quasi-continuous system.

In case of the yield (e.g., mass) per subunit, a negative deviation from the mean was followed by a positive deviation, showing the "self-cleaning" property of the mixer (Figs. 8–9). This test is not needed if the system is

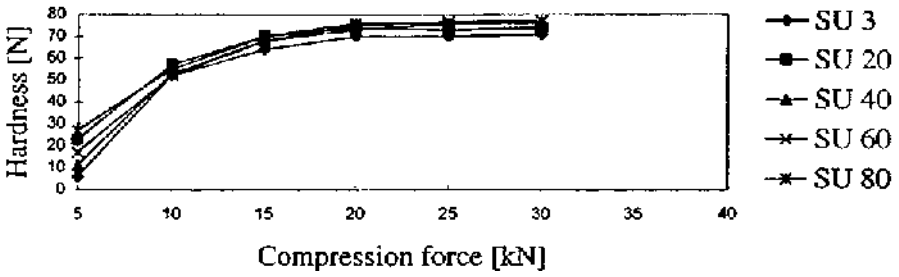

Figure 13 Compression force/hardness profile (Formulation 2).

equipped with an in-process control based on power consumption measurement [6–9].

3. Materials and Methods

a. Materials.

Formulation 1		Formulation 2	
Lactose 350 M	65.5%	Lactose 350 M	68.7% (W/W)
Maize starch	25.5%	Maize starch	27.0% (W/W)
Povidone K-30	6.5%	HPMC 2910/3 cP	4.3% (W/W)
Primojel	2.5%	Granulation liquid: Aqua purificata Ph. Eur. II	
Granulation liquid: Aqua purificata Ph. Eur. II			

b. Production Parameters.

Subunit size: 7.0 kg
Rotational speed of mixer: 206 rpm
Granulation liquid per subunit: 1.0 kg (Formulation 1); 1.3 kg (Formulation 2)
Spray rate: 800 g/min (Formulation 1); 900 g/min (Formulation 2)
Mixing time: 85 sec (Formulation 1); 90 sec (Formulation 2)
Sieve diameter: 5 mm wet sieving, 1.5/1.0 mm dry sieving
Drying temperature: 60°C
Inlet air quantity: 600 m^3/hr

c. Test Methods.

Relative humidity (Rotronic® hygroscope)
Loss on drying (Mettler® LP 16/PM 480 Deltarange infrared balance)
Sieve analysis (Fritsch® Analysette laboratory sieving machine)
Bulk volume/tapped volume (Jel STAV® 2003 volumeter)
Compression force/hardness profile (Manesty® Deltapress tableting machine with Tegimenta® Pharmatest PTB 301 hardness tester)
Hardness (Tegimenta® Pharmatest PTB 301 and Kramer® Computest hardness tester)
Disintegration time (Tegimenta® Pharmatest PT 21 and Kramer® DES-2A disintegration tester)
Friability/abrasion (Roche® friabilator)

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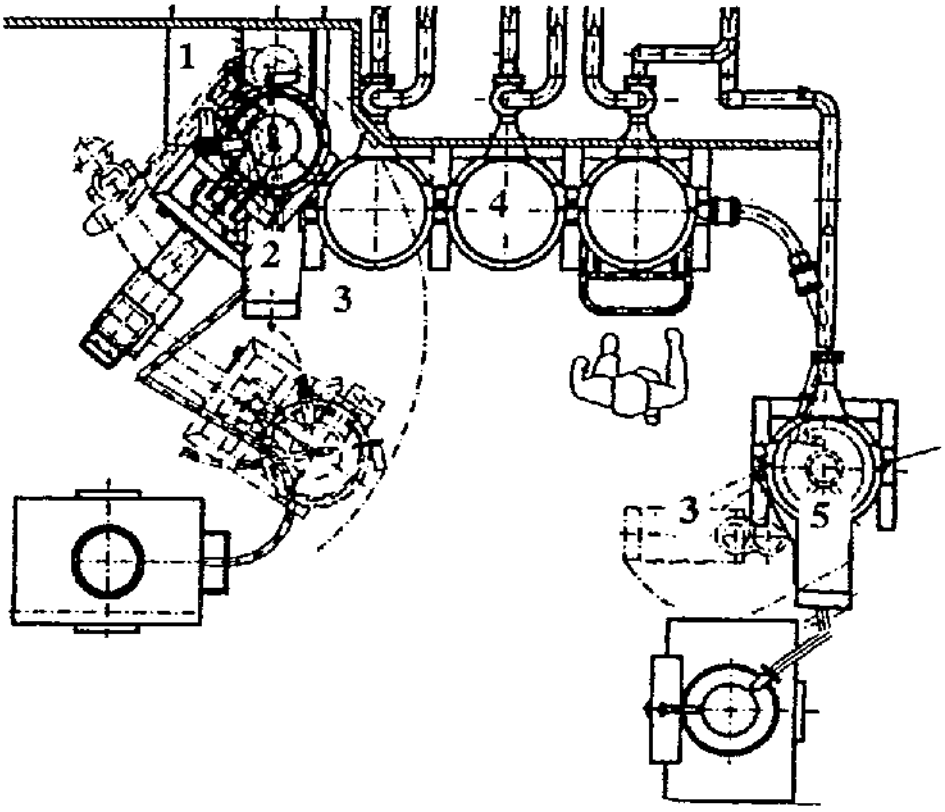
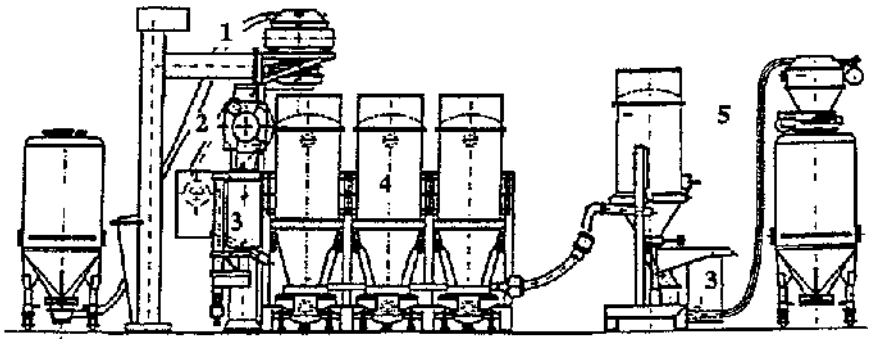
VI. DESCRIPTION OF THE PRODUCTION PLANT

The Glatt Multicell® unit for quasi-continuous granulation and fluid-bed drying (see Layouts 1 and 2) consists of the following elements: a transport and dosage system for mixer filling (1), a horizontal high-speed plough-share mixer (subunits of 4–9 kg of premixture can be granulated) with an airless spray pump for the granulation liquid (2), rotary sieving machines for wet and final sieving (3), a three-chambered fluid-bed dryer for predrying, final drying, and cooling down to room temperature (4), a transport system to collect the granulated subunits in a container (5), and an integrated washing-in-place or cleaning-in-place (CIP) system.

A. Layout



Layout 1 Top view of the Glatt Multicell®.



Layout 2 Front view of the Glatt Multicell®.

1. Transport and dosage system for mixer filling
2. Horizontal high-speed plough-share mixer
3. Rotary sieving machines for wet and final sieving
4. Three-chambered fluid-bed dryer
5. Transport system

B. Advantages of the Quasi-Continuous Granulation and Drying Line (Glatt Multicell®)

Such a production line is now successfully in operation at the Roche pharma production plant in Basel. A further-developed version has been installed at the technology center at Goedecke (Pfizer Group) in Freiburg, Germany. From the experience obtained so far the following conclusions can be drawn: The production line can be fully automated and equipped with a a CIP (cleaning-in-place) system. The moist agglomeration process can be monitored for each subunit by a power consumption in-process control device. Due to the three different cells of the Glatt Multicell® drying equipment, a gentle drying of temperature-sensitive drug substances is possible. According to need, a "just-in-time" production of the desired batch size B can be implemented. Early, small-sized batches can be already considered as production batches of identical quality. Thus these early batches can be put on a long-term stability test even at the beginning of the development of the dosage form. Because the early clinical batches are produced on exactly the same equipment as the large production batches, no bioequivalence test between early clinical batches and later production batches is needed. Due to these facts, no scale-up development is necessary. Thus the development time and the time needed to get to market can be reduced.

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7
Batch Size Increase in Fluid Bed Granulation

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I. INTRODUCTION

The size enlargement of primary particles has been carried out in the pharmaceutical industry in a variety of ways. One of the most common unit operations used in the pharmaceutical industry is fluid bed processing. Batch size increase using fluid bed granulation requires a good understanding of equipment functionality, the theoretical aspects of fluidization, excipient interactions, and, most of all, identifying the critical variables that affect the process of agglomeration.

This chapter* will provide an essential understanding of fluidization theory, describe the system that makes up the fluid bed processor, and discuss the critical variables associated with the equipment, the product, and the process. Upon gaining this basic understanding, one can design scale-up protocols. These protocols should be able to ensure successful transition from R&D batch sizes to pilot-size batches and ultimately to the commercial scale. As in any unit operation that requires batch size increase, the fluid bed process must undergo process qualification to establish its robustness. If these process variables are identified at an early stage of product development and then extrapolated, these variables, based on a knowledge of equipment variables and tolerances and material handling considerations, will provide a trouble-free batch size increase.

*Reprinted in part, with revisions and updates, from Ref. 98.

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A. Fluidization Theory

A fluidized bed is a bed of solid particles with a stream of air or gas passing upward through the particles at a rate great enough to set them in motion, this velocity, according to Kulling and Simon [1], is higher than the incipient fluidizing velocity but lower than the entrainment velocity. When the rate of flow of gas increases, the pressure drop across the bed also increases until, at a certain rate of flow, the frictional drag on the particles equals the effective weight of the bed. These conditions, and the velocity of gas corresponding to it, are termed *incipient fluidization* and *incipient velocity,* respectively. The relationship between air velocity and pressure drop is as shown in Figure 1 [2]. At low gas velocities, the bed of particles is practically a packed bed, and the pressure drop is proportional to the superficial velocity. As the gas velocity is increased, a point is reached at which the bed behavior changes from fixed particles to suspended particles. The superficial velocity required to first suspend the bed particles is known as *minimum fluidization velocity* (umf). The minimum fluidization velocity sets the lower limit of possible operating velocities, and the approximate pressure drop can be used to approximate the pumping energy requirements. Air velocity required for the agglomeration process in the fluid bed processor is normally five to six times the minimum fluidization velocity.

At the incipient point of fluidization, the pressure drop of the bed will be very close to the weight of the particles divided by the cross-sectional area of the bed (W/A). For the normal gas fluidized bed, the density of the gas is much less than the density of the solids and the balance of forces can be shown as

$$\Delta P\text{mf} = W/A$$

where

$W = (1 - \epsilon\text{mf})\rho p \cdot g/\text{gc}$

Δp = pressure drop

ϵmf = minimum fluidization void fraction

A = cross-sectional area,

W = weight of the particles

ρp = density of particles

g/gc = ratio of gravitational acceleration and gravitational conversion factor.

As the velocity of the gas is increased further, the bed continues to expand and its height increases with only slight increase in the pressure drop. As the velocity of the gas is further increased, the bed continues to expand and its height increases, whereas the concentration of particles per unit volume of the bed decreases. At a certain velocity of the fluidizing medium, known as the entrainment velocity, particles are carried over by the gas. This phenomenon is called *entrainment.* When the volumetric concentration of solid particles is uniform throughout the bed at all times, the fluidization is termed *particular.* When the concentration of solids is

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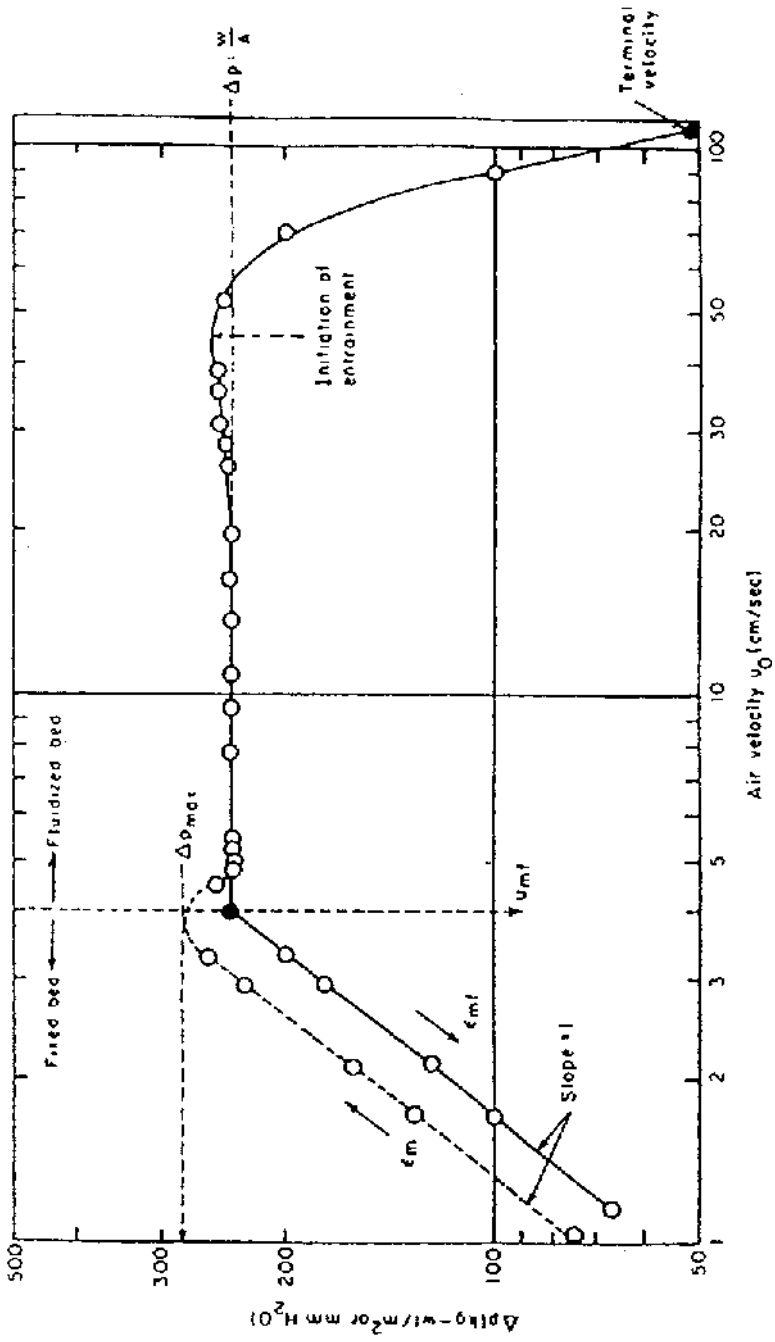

Figure 1 Typical pressure drop as a function of gas velocity. (From Ref. 2.)

not uniform throughout the bed, and if the concentration keeps fluctuating with time, the fluidization is called *aggregative fluidization.* A *slugging bed* is a fluid bed in which the gas bubbles occupy entire cross sections of the product container and divide the bed into layers. A *boiling bed* is a fluid bed in which the gas bubbles are approximately the same size as the solid particles. A *channeling bed* is a fluid bed in which the gas forms channels in the bed through which most of the air passes. A *spouting bed* is a fluid bed in which the gas forms a single opening through which some particles flow and fall on the outside. Figure 2 shows various types of fluid beds [3].

The mechanisms by which air affects fluidization have been discussed by various researchers [4–9]. When the fluidizing velocity is greater than the incipi-

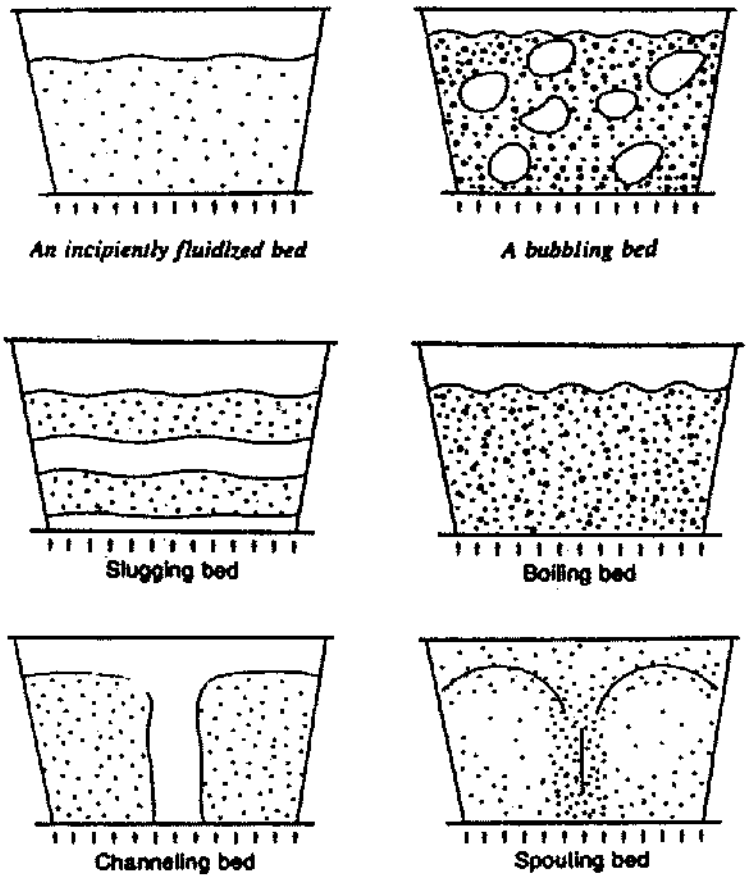

Figure 2 Various types of fluid beds. (From Ref. 3.)

ent velocity, bubbles of air rise through the bed, causing mixing of particles. Mixing does not generally occur when the bed is fluidized at very low or zero *excess* gas velocities, because insufficient bubbles are formed to cause bulk displacement of particles. It is the gas passing through the bed in the form of bubbles that determines the degree of mixing. The extent of mixing appears to vary with particle size. Mixing of particles having a mean particle size of less than approximately 150 μm decreases as the mean size approaches zero. Different types of beds, described earlier, are formed depending upon the movement of bubbles through the bed. The pattern of movement of the gas phase in and out of bubbles depends upon several factors, including minimum fluidization velocity and particle size. These movements affect heat transfer between air bubbles and particles. The air distributor at the bottom of the container has a controlling influence on the uniform distribution of gas, minimization of dead areas, and maximization of particle movement. The most common reason for mixing problems such as segregation in the fluid bed are the particle density differences. The extent of segregation can be controlled in part by maintaining high fluidizing velocities and a high bowl-height-to-bowl-diameter ratio. There are standard air velocities for various processes that can be used as guidelines.

The standard velocities are based upon the cross-sectional area at the bottom of the product container. This is calculated by using the following formula for calculating air velocity:

$$\text{velocity (m/sec)} = \text{air flow \{cubic meters per hour (CMH)\}} \div \text{area (square meters)} \times 3600$$

where

$$\text{air flow in cubic meters per hour (CMH)} = \text{air flow (CFM)} \times 1.696$$

Standard air velocities are based on the application. Low air velocities, such as 0.8–1.4 meters/second, are required for drying. The velocities are higher during the early stages of drying because of the wet mass present in the bowl, but will be reduced when the product loses its moisture. The objective is to have good particle movement but to keep the material out of filters. Particle movement and quick drying are important during the agglomeration process. Air flow velocities are normally 1.0–2.0 meters/second.

An indication of good fluidization is a free downward flow of the granulation at the sight glass of the drying container. However, improper fluidization can also be detected by monitoring the outlet air temperature. Every product has a unique constant rate of drying in which the bed temperature remains relatively constant for a significant length of time. Therefore, if the outlet temperature rises more rapidly than anticipated, it will indicate an improper fluidization and the process may have to be stopped and manual or mechanical intervention may be required to assist the fluidization.

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B. Fluidization and Fluid Bed Granulation

Fluidization is the operation by which fine solids are transformed into a fluidlike state through contact with a gas. At certain gas velocities, the fluid will support the particles, giving them freedom of mobility without entrainment. Such a fluidized bed resembles a vigorously boiling fluid with solid particles undergoing extremely turbulent motion, which increases with gas velocity.

Fluidized bed granulation is a process by which granules are produced in a single piece of equipment by spraying a binder solution onto a fluidized powder bed. This process is sometimes classified as the one-pot system. The fluid bed granulation process has received considerable attention within the pharmaceutical industry. However, other process industries, such as food, agrochemical, dyestuffs, and other chemical industries, have adopted the fluid bed granulation process to address particle agglomeration, dust containment, and material handling. The fluidization technique as it is known today began with the work of the Standard Oil Company (now known as Exxon in the United States) and M. W. Kellogg Company in an effort to produce the first catalytic cracking plant on a commercial scale in 1942 [10].

The fluid bed processing of pharmaceuticals was first reported by Dale Wurster, who used the air suspension technique to coat tablets [11,12]. In 1960, he reported on granulating and drying a pharmaceutical granulation, suitable for the preparation of compressed tablets, using the air suspension technique. In 1964 Scott et al. [13] and Rankell et al. [14] reported on the theory and design considerations of the process using a fundamental engineering approach and employing mass and thermal energy balances. They expanded this application to the 30-kg-capacity pilot model designed for both batch and continuous operations. Process variables such as air flow rate, process air temperature, and liquid flow rate were studied. Contini and Atasoy [15] later reported the processing details and advantages of the fluidized bed process in one continuous step. Wolf [16] discussed the essential construction features of the various fluid bed components, and Liske and Mobus [17] compared the fluidized bed and traditional granulation process. The overall results indicated that the material processed by fluid bed granulator was finer and more free flowing, and had homogeneous granules, which after compression produced stronger and faster disintegration of tablets than the materials processed by conventional wet granulation. Reviews by Sherrington and Oliver [18] and Pietch [19] and a series published on the topic of "Fluidization in the Pharmaceutical Industry" [20–25] provide an in-depth background on the fundamental aspects of the fluidized bed and other granulating technologies. The fluidized bed was used only for drying the pharmaceutical granulation efficiently in the early days, but now it is employed routinely for drying, agglomerating, pelletizing, and producing modified-release dosage forms using air suspension coating. Because of this, these units are normally called multiprocessor fluid bed units.

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II. SYSTEM DESCRIPTION

A *fluid bed processor* is a system of unit operations involving heating process air, directing it through the material to be processed, and having the same air (usually laden with moisture) exit the unit, void of the product. Figure 3 shows a typical fluid bed processor with all the components. These components and their utility for the granulation will be reviewed.

At the downstream end of the fluid bed processor, an exhaust blower or fan is situated to draw the air through the entire unit. This arrangement provides negative pressure in the fluid bed, which is necessary to facilitate material loading, maintain safe operation, prevent material escape, and carry out the process under good manufacturing practices guidelines, all of which will be discussed later in the chapter.

A. Air Handling Unit (AHU)

A typical air preparation system includes sections for air filtering, air heating, air cooling, and humidity removal. Generally, outside air is used as the fluidizing medium in a fluid bed processor. For the air to be used for pharmaceutical products, it must be free of dust and contaminants. This is achieved by placing coarse-dust filters (30–85%) in the AHU. Figure 4 shows the typical air handling unit.

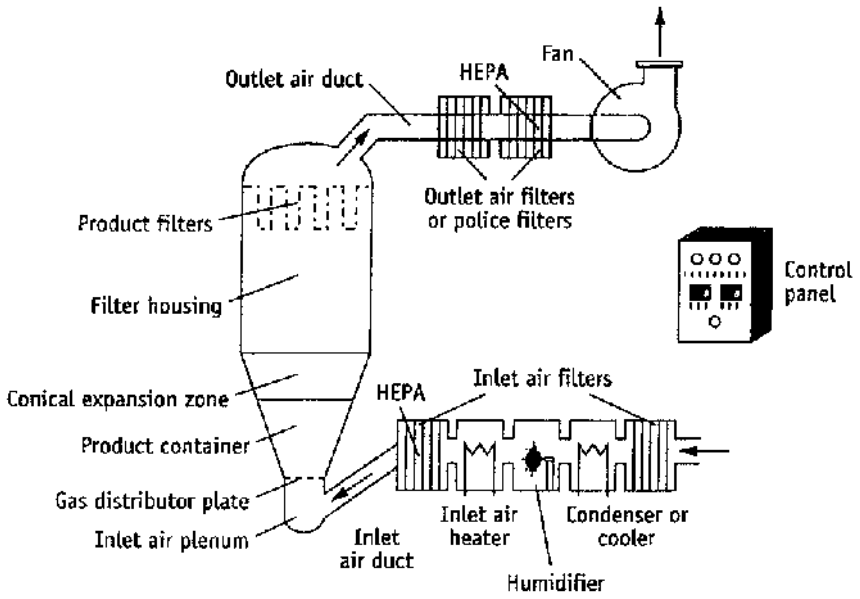

Figure 3 Typical components of a fluid bed processor.

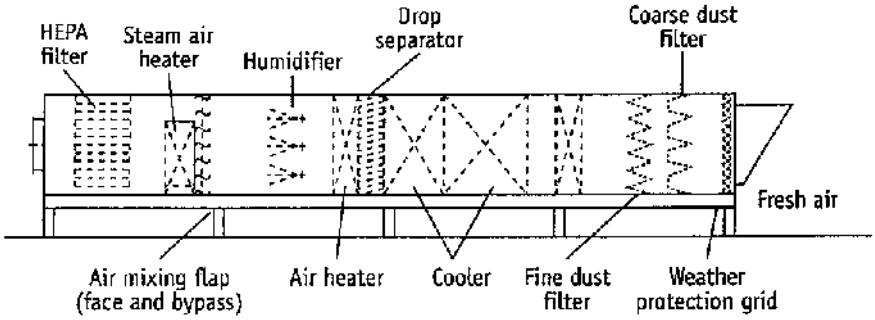

Figure 4 Typical Air Handling Unit for the fluid bed processor.

After installation of the filters, distinct heating or cooling sections are installed in the air handler, depending upon the geographical location of the plant. In a extremely cold climate, where cooling coils (needed in summer months for maintaining a uniform dew point) can freeze in winter, a preheating section is placed ahead of the cooling coils. A typical range for the air after pretreatment that one should aim at achieving is 15–30°C dry bulb and 3–5°C wet bulb. If the unit is located in a tropical or humid climate, the humidity removal section is employed first. The dehumidification of the air is extremely important where the outside air moisture varies over a wide range. In summer, when the outside humidity is high, dehumidification of the process air is required to maintain a specific dew point of the incoming process air. Rehumidification may be necessary during the winter months in some regions. A steam injector is used for rehumidifying the dry air. Generally, the lower the process-air dew point, the higher the affinity to entrain moisture and the shorter the process time. When granulating extremely fine powders, inlet-air dew point of 15°C is beneficial to reduce static charges and facilitate uniform fluidization. In many processes, when preheating is required, a bypass loop can be used for preconditioning the air. This loop allows the required process temperature and humidity to be attained within the system ducts before the product is subjected to fluidization. After the conditioned air leaves the humidification/dehumidification section of the AHU, it is finally heated to the desired process-air temperature and then passed through a high-efficiency particulate air (HEPA) filter of about 99.90–99.99% capacity. As the process air is treated and filtered, it is transported by the inlet duct. The air is thus brought into the process vessel in the lower plenum.

B. Product Container and Air Distributor

With the air at the desired humidity and temperature, it is ready to be passed through the bed of solids. Figure 5 shows a typical product container with the air

distributor. The air must be introduced evenly at the bottom of the product container through an inlet-air plenum. Proper air flow in the inlet-air plenum is critical to ensure that equal air flow velocities occur at every point on the air distributor plate. If the air is not properly distributed before it reaches the bottom of the container, uneven fluidization can occur.

To properly fluidize and mix the material in the container, the correct choice of container and air distributor must be made. The container volume should be chosen such that the bowl is filled to at least 35–40% of its total volume and no more than 90% of its total volume. The correct choice of air distributor is important. These distributors are made of stainless steel and are available with a 2–30% open area. Typically, the distributor should be chosen so that the pressure drop across the product bed and air distributor is 200–300 mm of water column. A fine screen of 60–325 mesh normally covers the air distributor and retains the product in the container. This type of sandwiched construction has been used for the last 30 years in the fluid bed processors. The classic air distributor with the fine-product-retaining screen is shown in Figure 5.

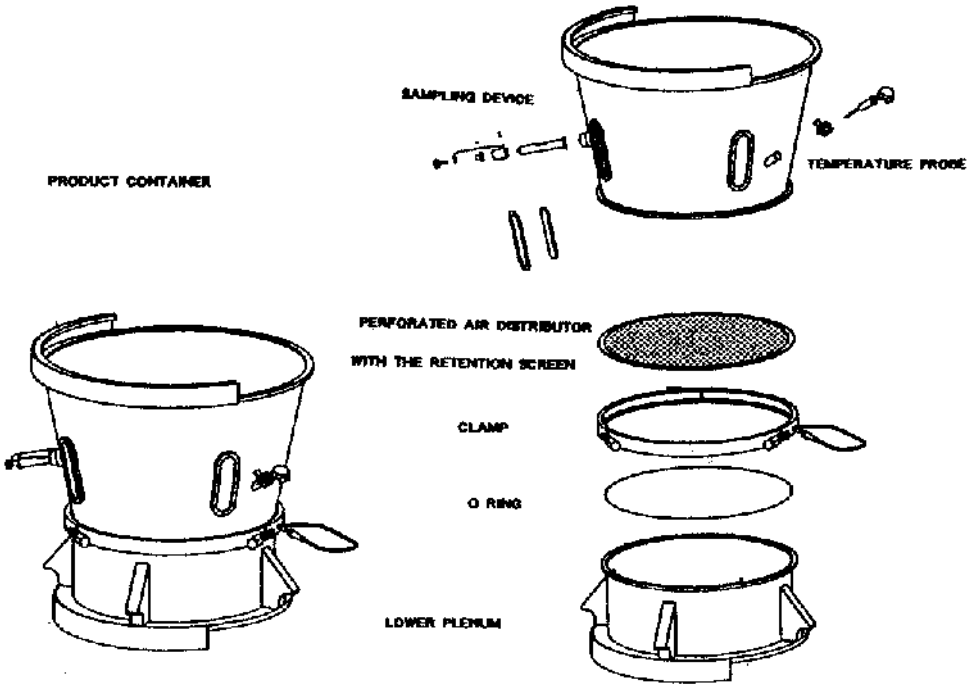

Figure 5 Typical product container with air distributor.

Keeping the screen and air distributors clean has been challenging. Partially to address the cleaning problems and partially to provide the efficient processing, a new overlap gill plate, shown in Figures 6a and b, was introduced in 1990 [26]. These new overlap gill air distributors eliminate the need for a fine screen and perform dual functions as the efficient air distributor and product retainer. Other advantages claimed by the manufacturer are validatable clean-in-place (CIP), controlled fluidization and directional flow of air to discharge the processed product from the container.

C. Spray Nozzle

A *spray* is a zone of liquid drops in a gas, and *spraying* is the act of breaking up a liquid into a multitude of these droplets. The general purpose of spraying is to increase the surface area of a given mass of liquid to disperse it over the product area. The two-fluid (binary) nozzle, in which the binder solution (one fluid) is atomized by compressed air or gas (second fluid), is the most commonly used nozzle for fluid bed granulation (Fig. 7a). These nozzles are available as a single-port or multiple-port design. Generally, the single-port nozzles are adequate for a batch of up to 100 kg, but for larger-sized batches a multiport (either three- or six-port) nozzle is required. When these nozzles are air-atomized, the spray undergoes three distinct phases. In the first, the compressed air (or gas) expands, essentially adiabatically, from the high pressure at the nozzle to that of the fluid bed chamber. The gas undergoes a Joule-Thomson effect, and its temperature falls. In the second, the liquid forms into discrete drops. During this atomization, the liquid's specific surface usually increases 1000 times. In the third, the drops travel, after being formed, until they become completely dry or impinge on the product particles.

During this phase, the solvent evaporates, and the diameter of the drop increases. The energy required to form a drop is the product of the surface tension and the new surface area. About 0.1 cal/g is needed to subdivide 1 g of water into 1-μm droplets. The air pressure required to atomize the binder liquid is set by means of a pressure regulator. The spray pattern and spray angle are adjusted by adjusting the air cap.

The binder solution is delivered to the nozzle port through a spray lance and tubing (Fig. 7b). The peristaltic, or positive displacement, pump is commonly used to pump the binder solution. The pneumatically controlled nozzle needle prevents the binder liquid from dripping when fluid flow is stopped. Nozzle port openings 0.8 and 2.8 mm in diameter are most common and are interchangeable.

D. Disengagement Area and Process Filters

Once the air leaves the product bed, fine particles need to be separated from the air stream; two zones are used in the fluid bed for this process: the disengagement area and the exhaust filters. In the disengagement area, larger particles lose mo-

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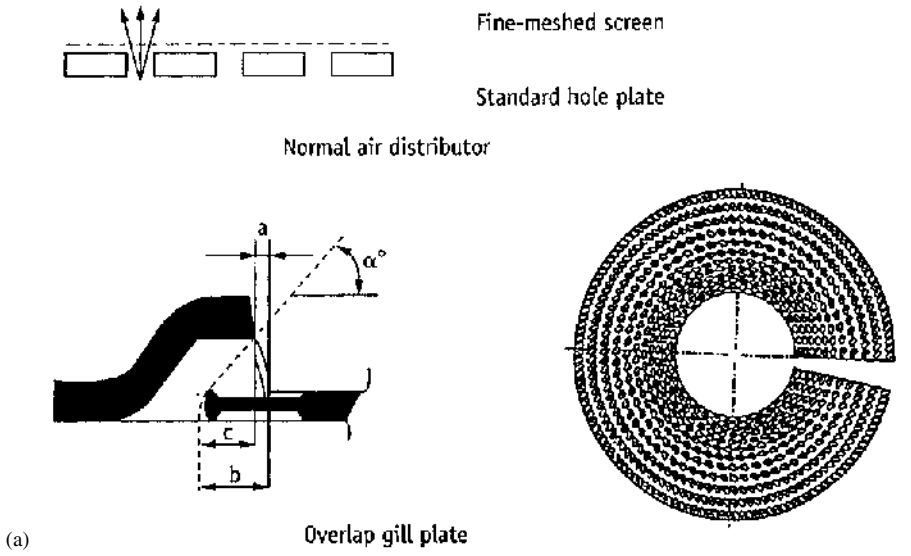
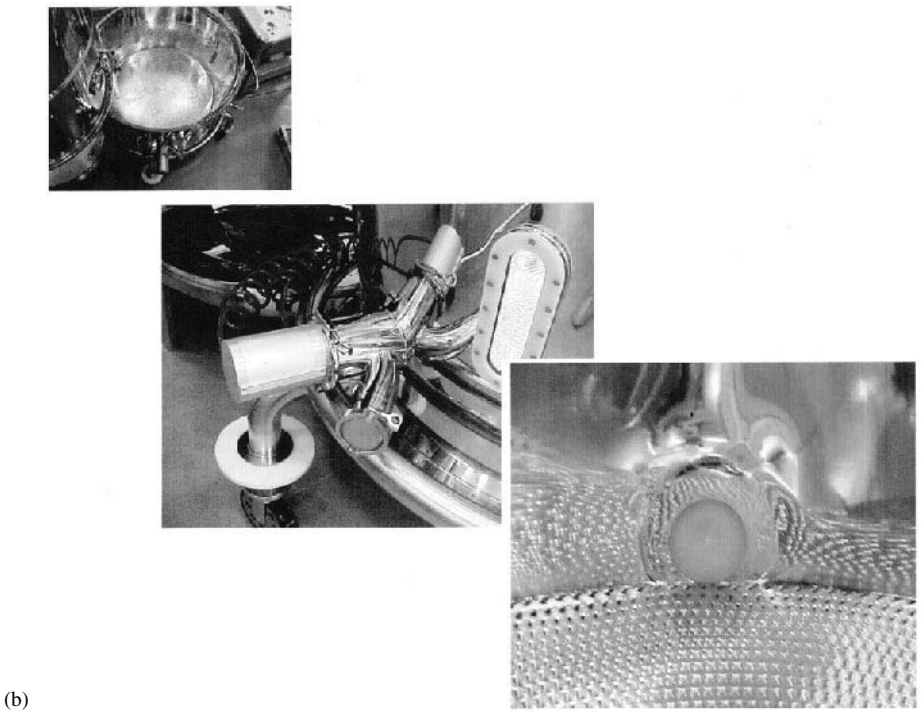


(a)



(b)

Figure 6 (a) Schematic of an overlap gill air distributor. (b) Container with the overlap air distributor and side discharge opening.

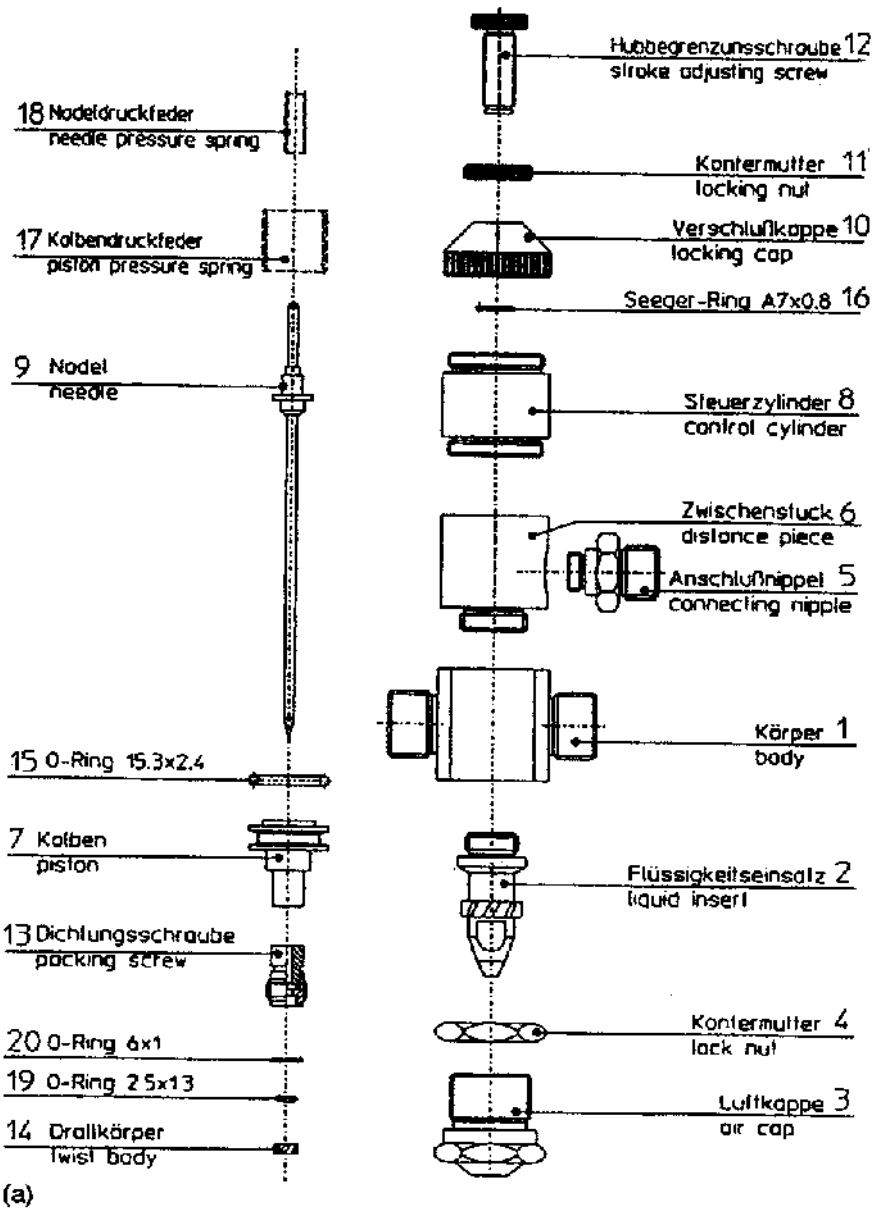


Figure 7 (a) Schematic of a nozzle showing different parts.

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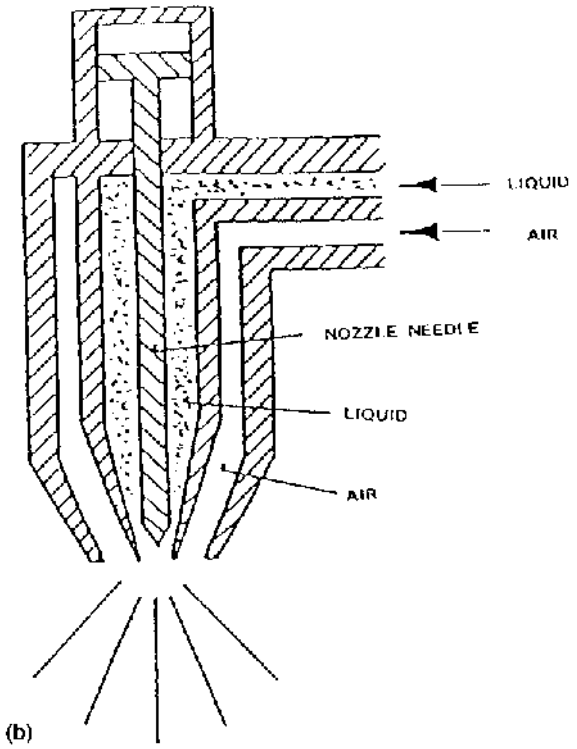

Figure 7 (b) Schematic of a two-fluid nozzle showing liquid and air pathways.

mentum and fall back into the bed. The velocity of the process air is highest at the center of the processor and approaches zero at the side walls. A process air filter system removes the particles from the exhaust air. The process air is filtered by using bags or cartridges. The bags can be constructed out of nylon, polyester, polypropylene, and/or polytetrafluroethylene- (PTFE) lined materials. To dissipate the potential static charges from the product particles, conductive fabrics are also available and are recommended. Cartridge filters lined with PTFE were introduced to the industry in 1980s [27]. Recently, cartridges made of stainless steel suitable for CIP have been introduced [28]. These process filters are cleaned during the granulation process by mechanical means or by using a low-pressure blowback system. Figure 8 shows various filters used in the fluid bed processors.

E. Exhaust Blower or Fan

Once the air leaves the exhaust filters, it travels to the fan. The fan is on the outlet side of the system, which keeps the system at a lower pressure than the surround-

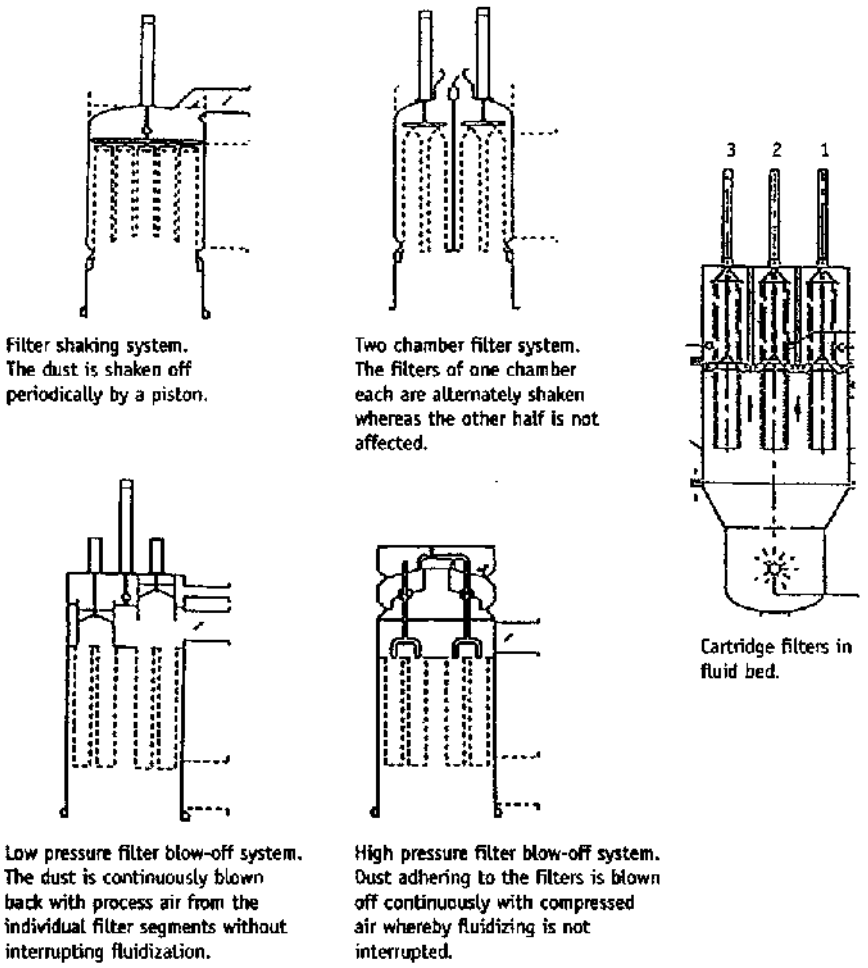

Figure 8 Various process filters and cleaning mechanisms.

ing atmosphere. The air flow is controlled by a valve or damper installed just ahead of or after the fan. The selection of the fan is normally done by the manufacturer based upon the layout and complexity of the system. Fan size is determined by calculating the pressure drop (ΔP) created by all the components that make up the fluid bed processor, including product at the highest design airflow volume.

F. Control System

A fluid bed granulation process can be controlled by pneumatic analog control devices or by using state-of-the-art programmable logic controllers (PLCs) or com-

puters. The electronic-based control system offers not only reproducible batches according to the recipe but a complete record and printout of all the process conditions. Process control technology has changed very rapidly, and it will continue to change as advances in computer technology take place and as the cost of control systems fall.

G. Solution Delivery System

A peristaltic pump capable of delivering binder solution at a controlled rate is desirable. The liquid is transported from the solution vessel through the tubing and then atomized, using a two-fluid (binary) nozzle, in the fluid bed processor.

III. PARTICLE AGGLOMERATION AND GRANULE GROWTH

Agglomeration can be defined as the size enlargement process, in which the starting material is fine particles and the final product is an aggregate in which primary particles can still be identified. The granules are held together with bonds formed by the binder used to agglomerate. Various mechanisms of granule formation have been described in the literature [29–31]. To summarize, three mechanisms for granule formation have been suggested by the researchers:

1. Bridges due to *immobile liquids* form adhesional and cohesional bridging bonds. Thin adsorption layers are immobile and can contribute to the bonding of fine particles under certain circumstances.
2. *Mobile liquids,* where interfacial and capillary forces are present.
3. *Solid bridges* formed due to crystallization of dissolved substances during drying.

The type of bonds formed approaches through four transition states, described by Newitt and Conway-Jones [29] as:

1. Pendular
2. Funicular
3. Capillary
4. Droplet, which normally happens during spray-drying

Most of the fluid bed granulated products require an amount of wetting much less than the high-shear granulation or spray-dryer-processed product. In the fluid bed granulation process, the particles are suspended in the hot air stream and the atomized liquid is sprayed on it. The degree of bonding between these primary particles to form an agglomerated granule depends on the binder used, physicochemical characteristics of the primary particles being agglomerated, and process parameters.

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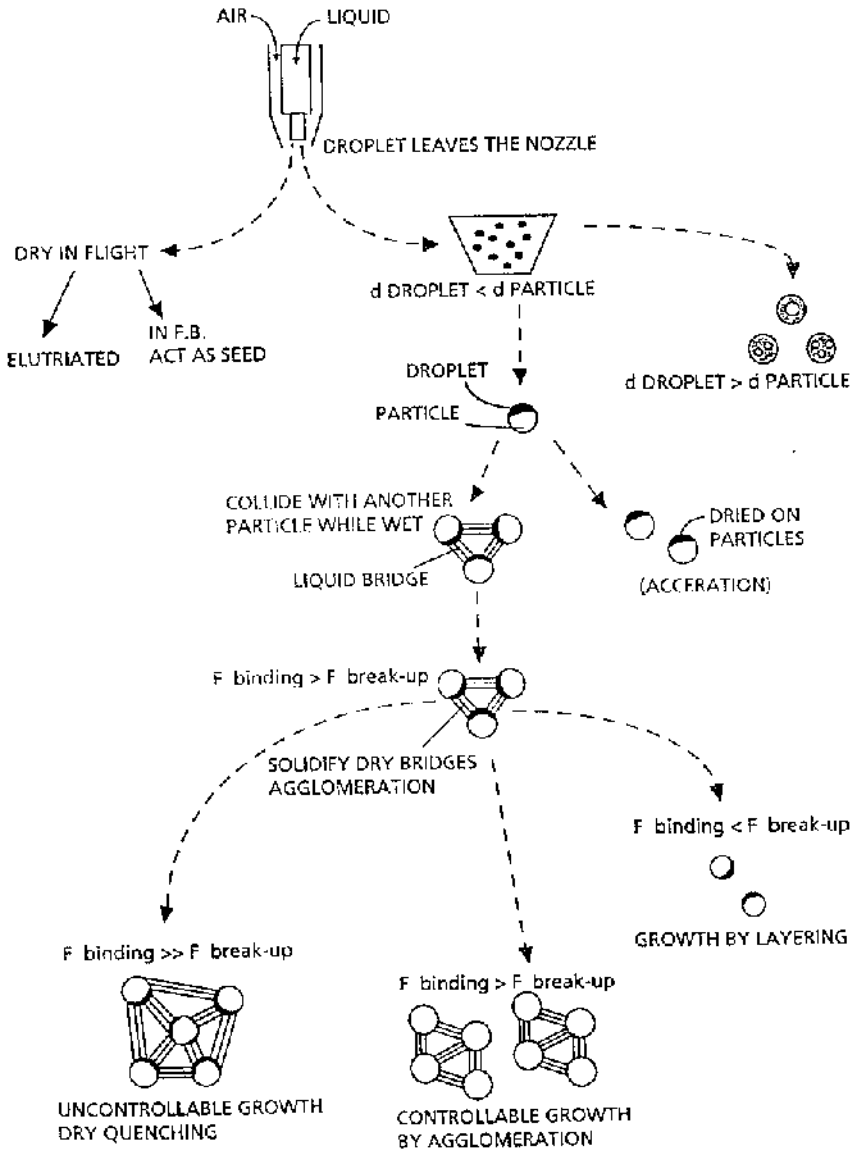

Figure 9 Mechanism of granulation in fluid bed. (Adapted from Ref. 36.)

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Schaefer and Worts [32] and Smith and Nienow [33] have reported a description of the growth mechanisms in the fluid bed, where the bed particles are wetted by liquid droplets in the spray zone. Atomized liquid from the nozzle tends to spread over the particle surface as long as there is a adequate wettability of the particle by the fluid [34]. Wet particles, on impact, form a liquid bridge and solidify as the agglomerate circulates throughout the remainder of the bed. Solid bridges then hold the particles together. The strength of the binder determines whether these particles stay as agglomerates. These binding forces should be larger than the breakup forces and this in turn depends on the size of the solid bridge. The breakup forces arise from movement of the randomized particles colliding with each other and are related to the excess gas velocity and particle size.

If the binding forces are in excess of the breakup forces, either in the wet state or in the dry state, uncontrolled growth will proceed to an overwetted bed or production of excessive fines, respectively. If a more reasonable balance of forces is present, controlled agglomeration will occur, growth of which can be controlled. Maroglou and Nienow presented a granule growth mechanism in the fluid bed by the use of model materials and scanning electron microscope [35]. Figure 9 shows the various paths a liquid droplet can take and the consequences on particle growth.

The mechanism of formation of a granule and subsequent growth progresses primarily through three stages:

1. Nucleation
2. Transition
3. Ball growth

Figure 10 shows the growth of the granule relative to the liquid added. In the beginning of the spraying stage, primary particles form nuclei and are held together by liquid bridges in a pendular state. The size of these nuclei depends upon the droplet size of the binder solution. As the liquid addition continues, more and more nuclei agglomerate and continue the transition from the pendular state to the capillary state.

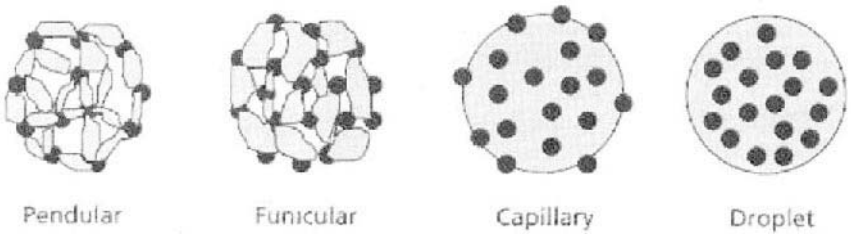

Figure 10 States of liquid saturation.

The uniqueness of the fluid bed agglomeration process is how the liquid addition and drying (evaporation) steps are concurrently carried out. When the granulation liquid is sprayed into a fluidized bed, the primary particles are wetted and form, together with the binder, relatively loose and very porous agglomerates. Densification of these agglomerates is brought about solely by the capillary forces present in the liquid bridges. It is therefore important that the quantity of liquid sprayed into the bed be relatively large compared with that used in high-shear granulation.

Drying a wet product in a fluid bed is a separate topic, but during the granulation process it becomes an integral part of the process, hence understanding fluid bed drying is important before we review the agglomeration process.

IV. FLUID-BED DRYING

Drying is usually understood to be removal of moisture or solvent. Drying involves heat transfer and mass transfer. Heat is transferred to the product to evaporate liquid, and mass is transferred as a vapor in the surrounding gas; hence these two phenomenon are interdependent. The drying rate is determined by the factors affecting the heat and mass transfer. The transfer of heat in the fluid bed takes place by convection. *Convection* is the transfer of heat from one point to another within a fluid (gas, solid, liquid) by the mixing of one portion of the fluid with another. The removal of moisture from a product granulated in the fluid bed granulator or in other equipment essentially removes the added water or solvent. This *free moisture content* is the amount of moisture that can be removed from the material by drying at a specified temperature and humidity. The amount of moisture that remains associated with the material under the drying conditions specified is called the *equilibrium moisture content,* or *EMC.* The rate of evaporation of liquid film surrounding the granule being dried is related to the rate of heat transfer by the following equation:

$$dw/dt = h \cdot A/H \cdot \partial T$$

where

dw/dt is the mass transfer rate (drying rate)

h is the heat transfer coefficient

A is the surface area

H is the latent heat of evaporation

∂T is the temperature difference between the air and the material surface

Because fluid bed processing involves drying of a product in suspended hot

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air, the heat transfer is extremely rapid. In a properly fluidized processor, product temperature and the exhaust air temperatures should reach equilibrium.

Improper air distribution, hence poor heat transfer in fluidized bed, causes numerous problems, such as caking, channeling, and sticking. The capacity of the air (gas) stream to absorb and carry away moisture determines the drying rate and establishes the duration of the drying cycle. Controlling this capacity is the key to controlling the drying process. The two elements essential to this control are inlet-air temperature and air flow. The higher the temperature of the drying air, the greater its vapor-holding capacity. Since the temperature of the wet granules in a hot gas depends on the rate of evaporation, the key to analyzing the drying process is psychometry [37–39].

Psychometry is defined as the study of the relationships between the material and energy balances of water vapor–air mixture. Psychometric charts (Fig. 11) simplify the crucial calculations of how much heat must be added and how much moisture can be added to the air. The process of drying involves both heat and mass transfer. For drying to occur, a concentration gradient must exist between the moist granule and the surrounding environment. As in heat transfer, the maximum rate of mass transfer that occurs during drying is proportional to the surface area, the turbulence of the drying air, the driving force between the solid and the air, and the drying rate. Because the heat of vaporization must be supplied to evaporate the moisture, the driving force for mass transfer is the same driving force required for heat transfer, which is the temperature difference between the air and the solid.

Schaefer and Worts [40] have shown that the higher the temperature difference between incoming air and the product, the faster the drying rate. Therefore, product temperature should be monitored closely to control the fluidized-bed drying process. During fluid bed drying, the product passes through three distinct temperature phases (Fig. 12). At the beginning of the drying process, the material heats up from the ambient temperature to approximately the wet bulb temperature of the air in the dryer. This temperature is maintained until the granule moisture content is reduced to the critical level. At this point, the material holds no free surface water, and the temperature starts to rise further.

The drying capacity of the air depends upon the relative humidity (RH) of the incoming air. At 100% RH, the air is holding the maximum amount of water possible at a given temperature. But if the temperature of the air is raised, the relative humidity drops and the air can hold more moisture. If air is saturated with water vapor at a given temperature, a drop in temperature will force the air mass to relinquish some of its moisture through condensation. The temperature at which moisture condenses is the dew point temperature. Thus, the drying capacity of the air varies significantly during processing. By dehumidifying the air to a preset dew point, incoming air can be maintained at a constant drying capacity (dew point) and hence provide reproducible process times.

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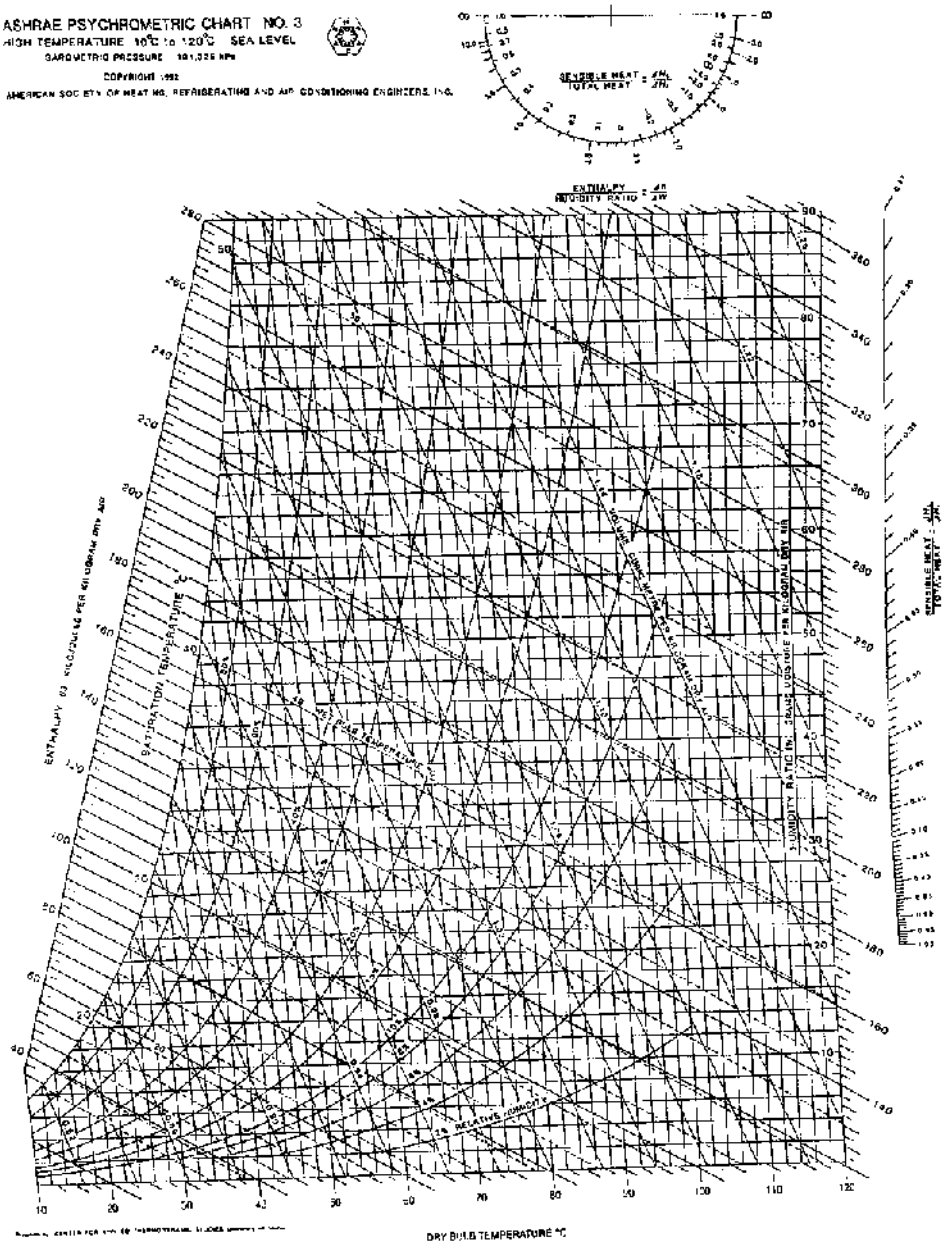

Figure 11 Psychrometric chart.

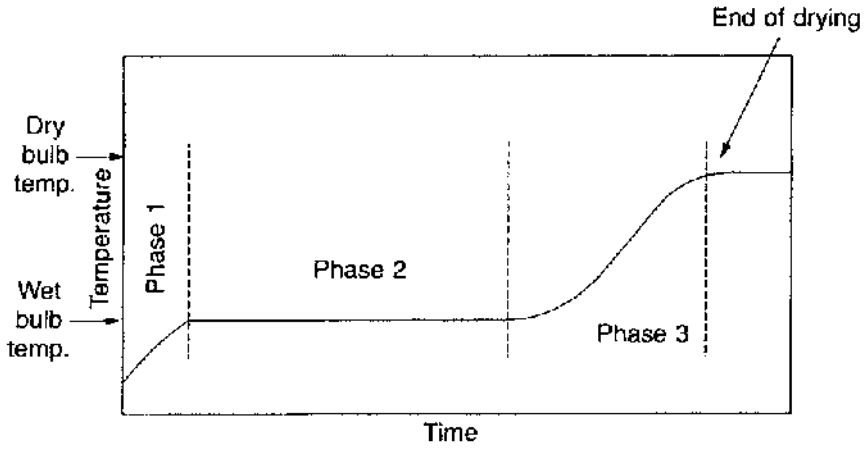

Figure 12 Product temperature changes during drying in a fluid bed processor. (From Ref. 20.)

V. PROCESS AND VARIABLES IN GRANULATION

A. Process

As with any granulating system, in fluid bed granulation processing the goal is to form agglomerated particles through the use of binder bridges between the particles. To achieve a good granulation, particles must be uniformly mixed, and liquid bridges between the particles must be strong and easy to dry. Therefore, this system is sensitive to the particle movement of the product in the unit, the addition of the liquid binder, and the drying capacity of the air. The granulation process in the fluid bed requires a binary nozzle, a solution delivery system, and compressed air to atomize the liquid binder. Figure 13 shows the equipment set up for granulation using the fluid bed processor.

Thurn [41], in a 1970 thesis, investigated details of the mixing, agglomerating, and drying operations that take place in the fluid bed process. Results indicated that the mixing stage was particularly influenced by air flow rate and air volume. It was suggested that the physical properties of the raw materials, such as hydrophobicity, may exert a strong influence upon the mixing stage. At the granulation stage, particular attention was paid to the nozzle and it was concluded that a binary-design (two-fluid) nozzle gave a wide droplet size distribution, yielding a homogeneous granule. The need for strong binders was recommended to aid granule formation and it was suggested that the wettability of the raw materials required particular attention. Several research papers have been published on the influence of raw material [40–57], binder type [14,17,40,41,51,53,58–68], binder concentration, and binder quantity [17,44,49,53,55,58,60–62,65–67,69–85].

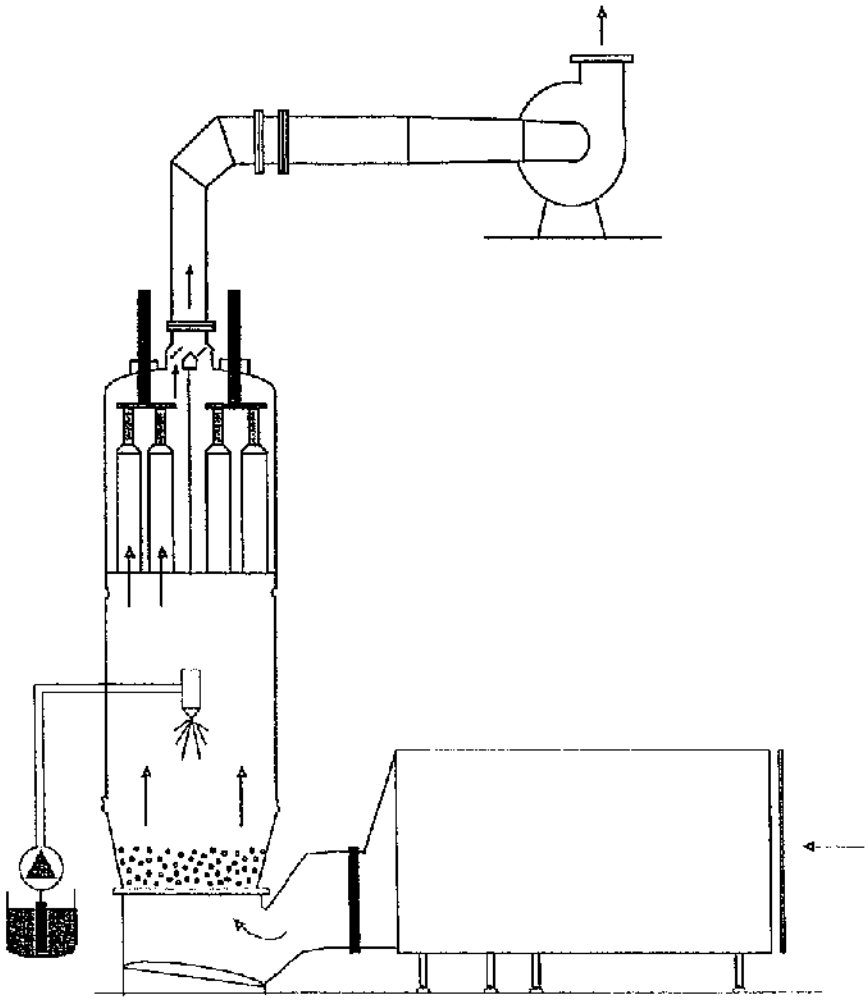

Figure 13 Typical fluid bed processor set up for the fluid bed granulation process.

Each phase of the granulation process must be controlled carefully to achieve process reproducibility. When binder liquid is sprayed into a fluidized bed, the primary particles are wetted and form, together with the binder, relatively loose and very porous agglomerates. Densification of these agglomerates is brought about almost solely by the capillary forces present in the liquid bridges. It is therefore important that the liquid binder sprayed into the bed be relatively large in quantity compared with that used in high- or low-shear granulation process. During spraying, a portion of the liquid is immediately lost by evaporation, so the

system has little tendency to pass beyond the liquid bridge phase. The particle size of the resulting granule can be controlled to some extent by adjusting the quantity of binder liquid and the rate at which it is fed, i.e., the droplet size. The mechanical strength of the particles depends principally on the composition of the primary product being granulated and the type of the binder used. Aulton et al. [75] found that lower fluidizing air temperature, a dilute solution of binder fluid, and a greater spray rate produced better granulation for tableting.

B. Variables

The factors affecting the fluid bed granulation process can be divided into three broad categories:

1. Formulation-related variables
2. Equipment-related variables
3. Process-related variables

1. Formulation-Related Variables

a. Properties of Primary Material. Ideally, the particle properties desired in the starting material include a low particle density, a small particle size, a narrow particle size range, the particle shape approaching spherical, a lack of particle cohesiveness, and a lack of stickiness during the processing. Properties such as cohesiveness, static charge, particle size distribution, crystalline vs. amorphous nature, and wettability are some of the properties that have an impact on the properties of granules formed. The cohesiveness and static charges on particles present fluidization difficulty. The same difficulties were observed when the formulation contained hydrophobic material or a mixture of hydrophilic and hydrophobic materials. The influence of hydrophobicity of primary particles has been shown by Aulton and Banks [25]. They demonstrated that the mean particle size of the product was directly related to the wettability of the primary particles, expressed as cos θ (where θ is the contact angle of the particles). It was also reported that as the hydrophobicity of the mix is increased, a decrease in granule growth is observed. Aulton et al., in a later publication, showed that addition of a surface-active agent such as sodium laurel sulfate improves the fluidized bed granulation [56]. In a mixture containing hydrophobic and hydrophilic primary particles, granule growth of hydrophilic materials takes place selectively, creating content uniformity problems. Formulating a controlled-release granulation can be accomplished by using fluid bed granulation. A controlled-release matrix formulation of naproxin was successfully developed using fluid bed granulation [86].

b. Low-Dose Drug Content. Wan et al. [87] studied various methods of incorporating a low-dose drug such as chlorphenarmine maleate in lactose formu-

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lation with PVP as the granulating solution. They concluded that the randomized movement of particles in the fluid bed may cause segregation of the drug and that uniform drug distribution was best achieved by dissolving the drug in granulating solution. The mixing efficiency of drug particles with the bulk material was found to increase in proportion with the granulating liquid used to dissolve the drug. The optimum nozzle atomizing pressure was deemed to be important to avoid spray-drying the drug particles or overwetting, which creates uneven drug distribution. Higashide et al. [88] studied the fluidized bed granulation using 5-fluorouracil in concentration of 0.3% in 1:1 mixture of starch and lactose. Hydroxy propyl cellulose (HPC) was used as the binder. The ratios of starch and lactose contained in the granules were measured gravimetrically. The researchers found that a bigger amount of the drug and starch was found in larger granules than in smaller granules. The results were attributed to the hydrophobicity of the 5-fluorouracil, starch, and the hydrophilicity of lactose.

c. Binder. A more general discussion on the types of binders used in the pharmaceutical granulations and their influence on the final granule properties was presented in Ref. 88a. Different binders have different binding properties, and the concentration of individual binder may have to be changed to obtain similar binding of primary particles. Thus the type of binder, the binder content in the formulation, and the concentration of the binder have a major influence on granule properties. These properties include friability, flow, bulk density, porosity, and size distribution.

Davies and Gloor [89,90] reported that the types of binder, such as povidone, acacia, gelatin, and hydroxypropyl cellulose (HPC), all have different binding properties that affect the final granule properties just mentioned. Hontz [83] investigated the effects of microcrystalline cellulose concentration, inlet-air temperature, binder (PVP) concentration, and binder solution concentration on tablet properties. Binder and microcrystalline cellulose concentration were found to have a significant effect on tablet properties. Alkan et al. [68] studied binder (PVP) addition in solution and as a dry powder in the powder mix. They found a larger mean granule size when the dry binder was granulated with ethanol. However, when the binder was in solution, the granules produced were less friable and more free-flowing. This same finding was confirmed by other researchers [84,85]. Binder temperature affects the viscosity of the solution, which in turn affects the droplet size. Increased temperature of the binder solution reduces the viscosity of the solution, reducing the droplet size and hence producing smaller mean granule size. Binder solution viscosity and concentration affect the droplet size of the binder. Polymers, starches, and high-molecular-weight PVP cause increased viscosity, which in turn creates larger droplet size and subsequently larger mean granule particle size [60].

Diluted binders are preferred because they facilitate finer atomization of the binder solution, provide the control of the particle size, reduce friability, and in-

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crease the bulk density even though the tackiness or binding strength may suffer [17,61,71,75,90].

d. Binder Solvent. In most instances water is used as a solvent. The selection of solvent, such as aqueous or organic, depends upon the solubility of the binder and the compatibility of product being granulated. Generally organic solvents, due to their rapid vaporization from the process, produce smaller granules than the aqueous solution. Different solvents have different heats of vaporization as shown in Table 1. Requirement of solvent for the binder can be eliminated by incorporating binder or a mixture of binders of low melting point and incorporating it with the drug substance in the dry form. The temperature of the incoming air is sufficient to melt the binder and form the granules.

2. Equipment-Related Variables

a. Design. The various fluid bed processors available from different equipment suppliers are essentially similar. The differences in design sometimes engender difficulty in scaling up from the laboratory units to production units in a linear scale.

To fluidize and thus granulate and dry the product, a certain quantity of process air is required. The volume of air required will vary based upon the amount of material that needs to be processed. The ratio of drying capacity of the process air to quantity of the product needs to be maintained constant throughout the scaling-up process. However, some equipment suppliers provide higher drying capacity for their laboratory unit but cannot maintain the same ratio for the production units. This lack of proportionality reduces the drying capacity per unit volume of process air, resulting in a longer process time in the production units. The current design of the fluid bed is a modular one, where multiple processes, such as drying, granulating, coating, and rotoprocessing, can be carried out by simply changing the container specially designed for the process.

b. Air Distributor Plate. The process of agglomeration and attrition due to random fluidization requires control of the particle during the granulation pro-

Table 1 Heat of Vaporization for Commonly Used Solvents

Solvent	Boiling point (°C)	Density (g/mL)	Heat of vaporization (kcal/g)
Methylene chloride	40.0	1.327	77.0
Acetone	56.2	0.790	123.5
Methanol	65.0	0.791	262.8
Ethanol	78.5	0.789	204.3
Isopropanol	82.4	0.786	175.0
Water	100.0	1.000	540.0

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cess. Optimization of the process requires control over fluidized particles. This is a complex phenomenon due to the prevailing fluidizing conditions and a particle size distribution that undergoes changes during the process. As the conditioned air is introduced through the lower plenum of the batch fluid bed, the fluidizing velocity of a given volume of air determines how fluidization will be achieved.

Perforated air distributor plates covered with the 60-325 mesh fine stainless steel screen, described previously, provide an appropriate means of supplying air to the product. These plates are identified by their percentage of open area. Air distributors plates that have 4–30% open area are normally available. These interchangeable plates provide a range of loading capacities so that batches of various sizes can be produced efficiently and with uniform quality. To prevent channeling, an operator can select a plate with optimum lift properties. For example, a product with low bulk density requires low fluidizing velocity. A distributor plate having a small open area to give a large enough pressure drop may provide uniform fluidization of such a product without reaching entraining velocity and impinging the process filters. Alternatively, a product with higher bulk density can be fluidized and processed using a plate with a larger open area. The air distributor plate consists of a perforated plate and a fine-mesh screen. This arrangement sometimes causes problems, like product leakage due to a torn screen, and difficulty in cleaning without separating the perforated plate and the fine-mesh screen. To overcome these deficiencies, an overlap gill plate has recently been introduced. These plate designs were discussed earlier in the chapter.

c. Pressure Drop. Flow of air through the fluid bed processor is created by the blower or a fan located downstream from the process chamber. This fan imparts motion and pressure to air using a paddle-wheel action. The moving air acquires a force or pressure component in its direction of motion because of its weight and inertia. This force, called *velocity pressure,* is measured in inches or millimeters of water column. In operating duct systems, a second pressure that is independent of air velocity or movement is always present. Known as *static pressure,* it acts equally in all directions. In exhaust systems such as fluid bed processors, a negative static pressure exists on the inlet side of the fan. Total pressure is thus a combination of static and velocity pressures. Blower size is determined by calculating the pressure drop (∂P) created by all the components of the fluid bed processing system. Proper selection of blower is essential in fluid bed design. A blower with appropriate ∂P will fluidize the process material adequately. However, a blower without enough ∂P will not allow proper fluidization of the product, resulting in longer process time and improper granulation. A similar effect can be seen when a product with unusually high bulk density is processed in place of normal pharmaceutical materials or when there is an air distributor plate offering high resistance due to its construction. This creates a pressure drop that the blower was not designed to handle. A proper-sized blower or fan should develop sufficient ∂P so that the exhaust damper can be used in the 30–60% open position.

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Any additional components, such as scrubbers, exhaust HEPA, police filters or other components in the air handling unit, would require a larger blower/static pressure, which can be recommended by the supplier of the fluid bed processor.

d. Shaker/Blow-Back Cycle Mechanism. To retain entrained particles of a process material, process filters are used. To maintain these filters from building up layers of fine process material and causing higher pressure drop and thus improper fluidization; these filters are cleaned during the granulation process. When bag filters are used, mechanical means are used to clean them. This mechanical cleaning of the bag filters requires a cessation of air flow, and thus of the fluidization, during the filter cleaning process. In units with a single bag house, this results in a momentary *dead bed,* where no fluidization takes place. This interruption in the process extends the process time. To avoid process interruptions, a multishaking filter bag arrangement is desired, where granulation process is continuous. The continuous process is also achieved by using bag filters with a blow-back or using stainless steel filter bags where air under pressure is pulsed through the filters. Generally, filters should be cleaned frequently during the granulation step so as to incorporate the fines in the granulation. This is possible if the cleaning frequency is high and the period between the filter cleaning short. Rawley [91] reported the effect of bag-shake/interval cycle. He discussed the possibility of improving particle size distribution by optimizing the shake time and the corresponding interval between bag shakes.

The following general guidelines for filter cleaning frequency and duration are recommended.

Single-shaker unit: Frequency of 2–10 minutes between filter cleaning, 5–10 seconds for shaking. This may vary because the fine powders form granules, and the frequency between the shakes or the duration of the shaking interval can be extended. In any case, the dead bed time should be kept at a minimum in a single-shaker unit.

Multiple-shaker unit: Since this is a continuous process, the frequency of shaking for each section is approximately 15–30 seconds between filter cleanings and about 5 seconds for shaking the filters. If a low-pressure blow-back system is used for the bags, the frequency of cleaning is about 10–30 seconds.

Cartridge filters: These offer continuous processing and require cleaning frequency of 10–30 seconds.

The cleaning frequency and cleaning duration is now offered as an automated system where instead of having base the cleaning frequency on time, the trigger point for filter cleaning is the buildup of a pressure drop across the filters. This automates the process and eliminates operator input.

e. Other Miscellaneous Equipment Factors. Granulator bowl geometry is considered to be a factor that may have an impact on the agglomeration process.

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The fluidization velocity must drop from the bottom to the top rim of the bowl by more than half to prevent smaller, lighter particles from being impinged into the filter, creating segregation from heavier product components in the bowl. Generally, a conical shape of the container and expansion chamber is preferred, where the ratio of the cross-sectional diameter of the distributor plate to the top of the vessel is 1:2. Most of the suppliers of this equipment offer units with a multiprocessor concept, where a single unit can be used for drying, agglomerating, air suspension coating, or rotoprocessing by changing the processing container while the rest of the unit is common. This approach does eliminate the concerns about the geometry of the processor because of the way these units are constructed.

3. Process-Related Variables

The agglomeration process is a dynamic process where a droplet is created by a two-fluid nozzle and deposited on the randomly fluidized particle. The binder solvent evaporates, leaving behind the binder. Before all of the solvent is evaporated, other randomized particles form bonds on the wet site. This process is repeated numerous times to produce the desired agglomerated product. There are a number of process variables that control the agglomeration. The process variables most important to consider are:

Process inlet-air temperature
Atomization-air pressure
Fluidization-air velocity and volume
Liquid spray rate
Nozzle position and number of spray heads
Product and exhaust-air temperature
Filter porosity and cleaning frequency
Bowl capacity

These process parameters are interdependent and can produce desirable product if this interdependency is understood. Inlet-process-air temperature is determined by the choice of binder vehicle, whether it is aqueous or organic, and the heat sensitivity of the product being agglomerated. Generally, aqueous vehicles will enable the use of temperatures between 60 and 100°C. On the other hand, organic vehicles will require the use of temperatures from 50°C to below room temperature. Higher temperatures will produce rapid evaporation of the binder solution and will produce smaller, friable granules. On the other hand, lower temperatures will produce larger and fluffier and denser granules. Figure 14 shows the relationship of inlet-air and product-air temperature and outlet air humidity during the granulation process.

The process of drying while applying spraying solution is a critical unit operation. This mass transfer step was previously discussed. The temperature, humidity, and volume of the process air determines the drying capacity. If the

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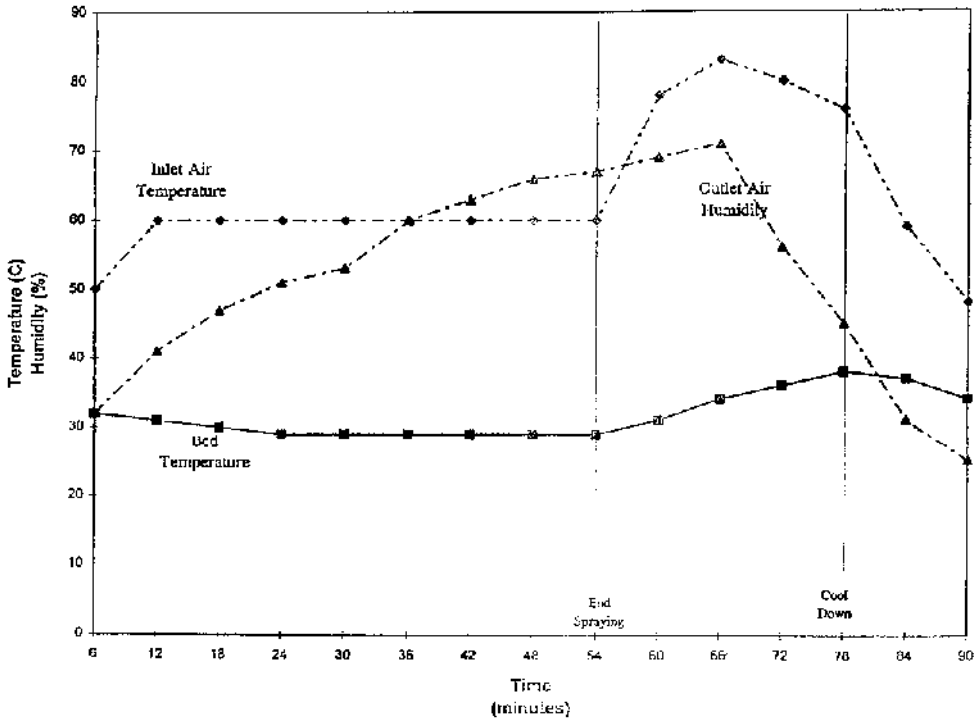

Figure 14 Temperature and humidity changes during the granulation process.

drying capacity of the air is fixed from one batch to the next, then the spray rate can also be fixed. If the drying capacity of the air is too high, the binder solution will have a tendency to spray-dry before it can effectively form bridges between the primary particles. If, on the other hand, the drying capacity of the air is too low, the bed moisture level will become too high and particle growth may become uncontrollable. This will result in unacceptable movement of the product bed.

As previously discussed, the appropriate process-air volume, inlet-air temperature, and binder spray rate are critical to achieving proper and consistent particle size distribution and granule characteristics. There are many ways to arrive at the proper operating parameters. The following procedure was found by the authors to be one of the ways one can set the operating parameters when granulating with fluid bed processors.

1. Determine the proper volume of air to achieve adequate mixing and particle movement in the bowl. Avoid excessive volumetric air flow so as to entrain the particles into the filters.

2. Choose an inlet-air temperature that is high enough to negate weather effects (outside-air humidity or inside-room conditions). The air temperature should not be detrimental to the product being granulated. (To achieve consistent process year round, a dehumidification/humidification system is necessary, which provides the process air with a constant dew point and hence a constant drying capacity).
3. Achieve a binder solution spray rate that will not dry while spraying (spray-drying) and will not overwet the bed. This rate should also allow the nozzle to atomize the binder solution to the required droplet size.
4. As stated earlier, a typical air velocity used for spray granulation is from 1.0 to 2.0 meters/second. Table 2, which is based upon the psychometric chart, gives a first guess at determining the proper spray rate for a spray granulation process in a fluid bed processor.

The variables in the fluid bed granulation process and its impact on the final granulation were summarized by Davies and Gloor Jr. [92]; they state that the

Table 2 Calculation of Fluid Bed Spray Rate

Given process data

Air volume range:
- Minimum (1.2 m/sec) _____ m^3/hr
- Maximum (1.8 m/sec) _____ m^3/hr

Inlet-air temperature and humidity to be used: _____ °C _____ % RH

% solids in sprayed solution _____ % solids

From psychrometric chart
- Air density at point where air volume is measured: _____ m^3/kg air
- Inlet air absolute humidity (H): _____ g H_2O/kg air
- Maximum outlet air absolute humidity (H): _____ g H_2O/kg air
  (follow line of constant adiabatic conditions)
- Use 100% outlet RH for spray granulator or 30–90% (as required) for column coating

Calculations for spray rate

Step 1. Convert air volumetric rate to air mass rate:

Minimum _____ m^3/hr ÷ (60 × _____ m^3/kg air) = _____ kg air/min

Maximum _____ m^3/hr ÷ (60 × _____ m^3/kg air) = _____ kg air/min

Step 2. Subract inlet-air humidity from outlet-air humidity:

_____ (g H_2O/kg air) H out − _____ (g H_2O/kg air) H in =
_____ g H_2O removed/kg air

Step 3. Calculate (minimum and maximum) spray rate of solution:

(This will provide a range of generally acceptable spray rates based on the airflow used in the unit.)

Step 1 (minimum) _____ × Step 2 _____ ÷ [1 − (_____ % solids ÷ 100)] = _____ spray rate (g/min) at minimum airflow

Step 1 (maximum) _____ × Step 2 _____ ÷ [1 − (_____ % solids ÷ 100)] = _____ spray rate (g/min) at minimum airflow

Table 3 Effect of Process Parameters on Granular Properties

Process parameter	Effect on process	Refs.
Inlet-air temperature	Higher inlet temperature produces finer granules, and lower temperature produces larger, stronger granules.	75, 94
Humidity	Increase in air humidity causes larger granule size, longer drying times.	40
Fluidizing air flow	Proper air flow should fluidize the bed without clogging the filters. Higher air flow will cause attrition and rapid evaporation, generating smaller granules and fines.	3, 75
Nozzle and nozzle height	A binary nozzle produces finest droplets and is preferred. The size of the orifice has an insignificant effect except when binder suspensions are to be sprayed. Optimum nozzle height should cover the bed surface. Too close to the bed will wet the bed faster, producing larger granules, whereas too high a position will spray-dry the binder, create finer granules, and increase granulation time.	60
Atomization air volume and pressure	Liquid is atomized by the compressed air. This mass/liquid ratio must be kept constant to control the droplet size and, hence, the granule size. Higher liquid flow rate will produce larger droplet and larger granules and the reverse will produce smaller granules. At a given pressure, an increase in orifice size will increase droplet size and liquid throughput.	40, 60, 92, 95
Binder spray rate	Droplet size is affected by liquid flow rate, binder viscosity, and atomizing air pressure and volume. The finer the droplet, the smaller the resulting average granules.	57, 74, 75, 95

physical properties of granulation are dependent upon both the individual formulations and the various operational variables associated with the process. The solution spray rate increase and subsequent increase in average granule size resulted in a less friable granulation, higher bulk density, and a better flow property for a lactose/corn starch granulation. Similar results were obtained by an enhancing the binder solution, decreasing the nozzle air pressure, or lowering the inlet-air temperature during the granulation cycle. The position of the binary nozzle with respect to the fluidized powders was also studied. It was concluded that by lowering the nozzle, binder efficiency is enhanced, resulting in average granule size and a corresponding decrease in granule friability. The significant process parameters and their effect on the granule properties are summarized in the Table 3.

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Table 4 Granulation Parameters Affecting the Type and Rate of Growth in Batch Fluidized Granulation

Operating parameters	
Droplet size	NAR[a]
	Atomization air velocity
	Rheology
	Surface tension
	Nozzle position
	Nozzle type
Bed moisture content	Solution type and feed rate
	Bed temperature
	Fluidization velocity
Attrition	Fluidization velocity
	Aspect ratio
	Nozzle position and atomization air velocity
	Distributor design
	Jet grinding
Solution (binder) concentration	Bridge strength and size
	Rheology
Material parameters	
Solution (binder) concentration	Bridge strength and size
	Rheology
Type of binder & wettability	Molecularlength and weight
	Particle–solvent interaction
	Surface tension
	Viscosity
Material to be granulated	Average size
	Size distribution[b]
	Shape
	Porosity
	Drying characteristics
	Density and density difference[b]

[a] NAR is the ratio of air to liquid flow rates through the nozzle of a twin-fluid atomizer, expressed either in mass units or in volume units (air at STP).
[b] Especially important relative to elutriation and segregation.

Maroglou and Nienow [36] listed various parameters affecting the type and rate of growth in batch fluidized granulation (Table 4) and showed the influence of the process parameters and the material parameters on the product.

VI. PROCESS CONTROLS AND AUTOMATION

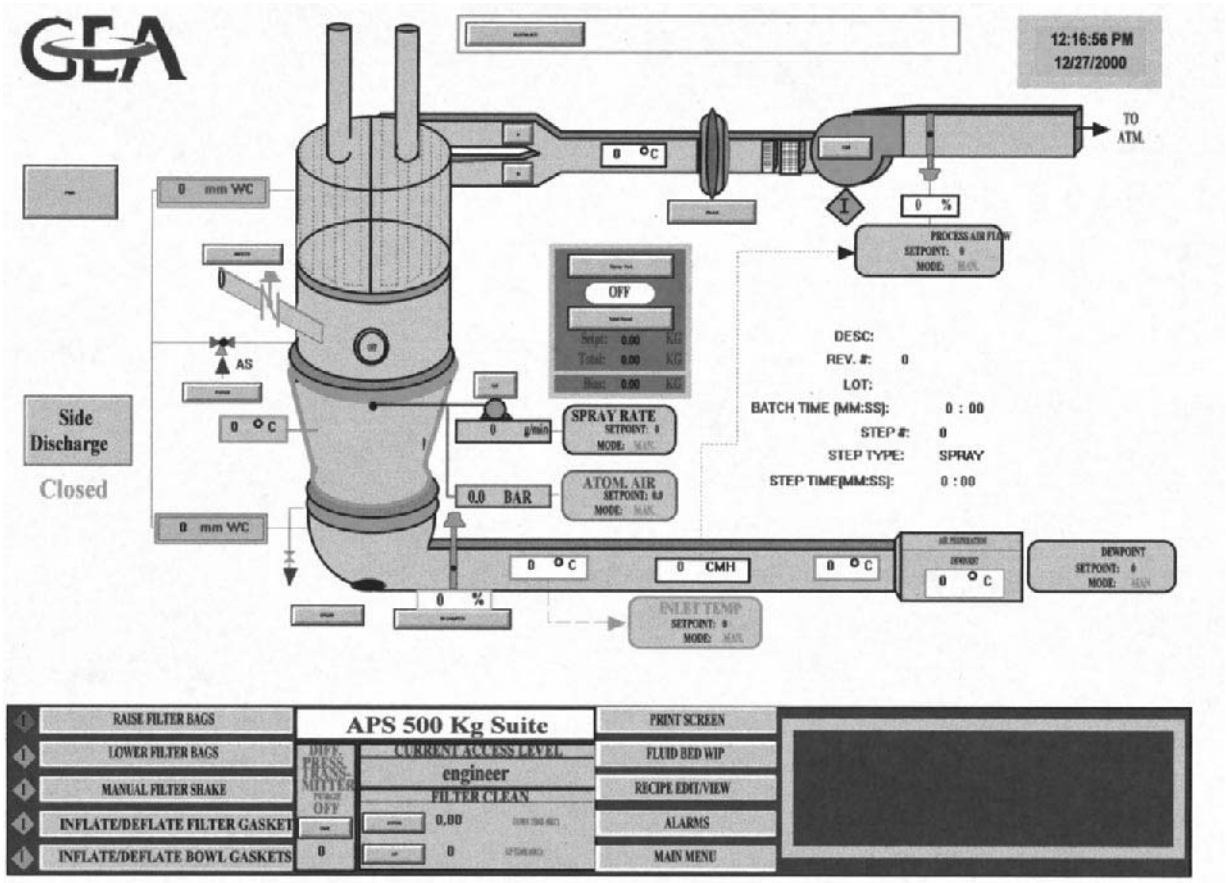
The agglomeration process is a batch process, and accurate repeatable control of all critical process parameters is necessary for a robust system. Earlier designs of

the fluid bed processor used pneumatic control, which provided safe operation in hazardous areas but relied heavily on human actions to achieve repeatable product quality and accurate data acquisition. Current designs use programmable logic controllers (PLCs) and personal computers (PCs) to achieve sophisticated control and data acquisition. The operating conditions are controlled to satisfy parameters of multiple user-configured recipes, and critical data is collected at selected time intervals for inclusion in an end-of-batch report. Access to all user-configured data is protected by security levels, with passwords permitting access only to selected functions. With the appropriate security level, not only are operating conditions configured, but also identification of each valid recipe and operator is entered. The identification is verified before any operator actions are permitted and is included with the end-of-run report. The use of computer-related hardware requires some additional validation; but with coordination between the control system provider and the end user, the validation of software can be managed. Figure 15a shows a PLC-based control panel; and Figure 15b shows a typical operation screen.

The most important sensors for control of the drying process are those for inlet-air and exhaust-air temperature and the sensor for air flow measurement, located in the air transport system. Other sensors for the spray agglomeration process include those for atomization air pressure and volume, pressure drops (across

(a)

Figure 15 (a) PLC-based control panel. *(continues)*



(b)

Figure 15 Continued. (b) PLC-based screen providing graphic representation of a process. (Courtesy of Atlantic Pharmaceutical Services Inc.)

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the inlet filter, the product container with the product being processed and outlet process air filter), inlet-air humidity or dew point, process filter cleaning frequency and duration, spray rate for the binder solution, and total process time. All of these sensors provide constant feedback information to the computer. These electronic signals may be stored in the computer's memory and then recalled as a batch report. With this ability to recall data analysis, a greater insight can be gained into the process.

VII. PROCESS SCALE-UP

A. Regulatory

Scale-up is normally identified with an incremental increase in batch size until a desired level of production is obtained. In 1991, the American Association of Pharmaceutical Scientists (AAPS), along with the U.S. FDA held, a workshop on scale-up [93]. Several speakers presented scale-up issues from the industrial and regulatory perspectives. For example, Shangraw divided scale-up problems in two general categories: those related to raw materials or formulation and those related to processing equipment. He also indicated that it is essential to ascertain whether or not changes in raw materials have occurred before one looks at processing/equipment changes as a source of any problem. The workshop report as it pertains to the process and equipment is reproduced here.

> It is generally recognized that many NDAs and ANDAs contain provision for multiple manufacturers of the drug substance(s), and that not all drug substance suppliers, a priori, produce equivalent material. There is then a need for material quality control to assure the performance and reproducibility of the finished product. Particle size and distribution, morphology, and intrinsic dissolution of the drug substance are important considerations. Polymorphism, hygroscopicity, surface area, wettability, density (bulk and tapped), compressibility (for dry blending), and powder flow effects should be controlled. Additionally, the process should be controlled by employment of a validation protocol, which defines the critical parameters and also establishes the acceptance criteria for the granulation or blend; which may include sieve analysis, flow, density, uniformity, and compressibility, moisture content, etc. In the milling, blending, *granulating, and/or drying processes,* the operating principles of the equipment employed should be defined and the variables determined. The impact and mechanism of measurement on in-process variables should be defined. Time, temperature, work input of equipment, blend/granulation volume, and granulating rate should be determined. . . . The parameters selected should be appropriate for the process. . . . In those cases where the manufacturing process has been controlled and validated as specified in the foregoing discussion; batch scale-up, changes in site of manufacture, allowance for equipment change (where the operating principle is the same),

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minor formulation changes, etc., should be determined on the basis of the comparability of both the blend/granulation and the final product, as assured by: (a) appropriate tests; (b) specifications; (c) process validation; and (d) comparative accelerated stability.

B. Scale-Up and Equipment Design

The scale-up from laboratory equipment to production-size units is dependent on equipment design, which may or may not have been scalable as far as its selected dimensional features or components is concerned. The importance of scalability is well understood and accepted by the manufacturers of fluid bed processors. Various sizes in their product line are logically designated and manufactured. Air flow in the fluid bed process is a critical parameter. The design and selection of the processor is very important for the laboratory and the production unit. Because air flow is one of the components of the drying capacity of a fluid bed system, the ratio of air volume per kg or liter of the product is very critical to achieve scale-up that is linear. The other critical design feature is the cross-sectional area of the product container and how it has been designed throughout the various sizes that a manufacturer supplies. The relationship between various sizes of the process containers can be utilized to calculate the scale-up of binder spray rate; if the cross-sectional area is designed linearly, then the spray rate scale-up can be linear.

C. Scale-Up and Process Factors

The fluid bed agglomeration process is a combination of three steps: dry mixing, spray agglomeration, and drying to a desired moisture level. These process steps are equally important. But the quality of the granules is really determined during the spraying stage, the process where constant building of granules and evaporation of binder solvent is taking place. Granule size is directly proportional to the bed humidity during granulation [40]; hence, control of this humidity during scale-up is essential.

Gore et al. [94] studied the factors affecting the fluid bed process during scale-up. The authors found that the processing factors that most affected granule characteristics were process-air temperature, height of the spray nozzle from the bed, rate of binder addition, and degree of atomization of the binder liquid.

The atomizing air pressure and the wetness of the bed are two of the most important elements of fluid bed granulation. A higher atomizing air pressure yields a finer droplet of binder solution. Therefore granule growth, as described earlier in this section, will be affected by the atomizing air pressure. A major factor that must be considered during the scale-up of a fluid bed granulation process is maintaining the same droplet size of the binder for ensuring successful scale-up. A more recent study [95] confirmed the influence of the spray nozzle setup parameters and the drying capacity of the air. The study concluded that more attention should be given

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to the easily overlooked nozzle atomizing air pressure and volume. When considering the atomizing air pressure, attention must be paid to ensure that enough air is delivered to the nozzle tip. This can be ensured by placing air pressure and volume measurement devices at the nozzle. The data also show that the drying capacity of the process air influences the final granulated particle size. Jones [96] has suggested the following process-related factors that should be considered during the scale-up of fluid bed processing: Due to the higher degree of attrition in the larger unit as compared to the smaller unit, the bulk density of the granulation from the larger fluid bed is approximately 20% higher than that of the smaller unit. He also reemphasized the importance of keeping the bed moisture level below a critical moisture level to prevent the formation of larger agglomerates. Since the higher air flow, along with the temperature (drying capacity) in a larger unit, provides a higher evaporation rate, one must maintain the drying capacity in the larger unit such that the bed temperature is similar to the smaller unit's bed temperature. This can be accomplished either by increased spray rate, increased air temperature, increased air flow, or a combination of these variables to obtain suitable results. Since the ratio of bed depth to the air distributor increases with the size of the equipment, the fluidization air velocity is kept constant by increasing the air volume.

In the past, scale-up was carried out by selecting best-guess process parameters. The recent trend is to employ the factorial and modified factorial designs and search methods. These statistically designed experimental plans can generate mathematical relationships between the independent variables, such as process factors, and the dependent variables, such as product properties. This approach still requires an effective laboratory/pilot-scale development program and an understanding of the variables that affect the product properties.

In summary, when scaling up, the following processing conditions should be similar to those in the pilot-scale studies.

Fluidization velocity of the process air through the system
Ratio of granulation spray rate to the drying capacity of the fluidization air volume
Droplet size of the binder spray liquid

Each of these values must be calculated based on the results of the operation of the pilot-size unit. Pilot-size equipment studies should also be conducted in a wide range to determine the allowable operating range for the process.

VIII. CASE STUDY

The following case study illustrates how a product is scaled up from 15 kg to 150 kg in equipment supplied by Aeromatic when one understands the critical process parameters used when scaling up.

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A spray granulation process was developed for a common pharmaceutical compound. The granulation process involved spraying a 5% w/w binder solution onto the fluidized powder. Table 5 shows the data from the 15-kg run and the resulting successful 150-kg run condition for a spray agglomeration process [97].

A. Air Flow Calculations

To maintain the same fluidization velocity, the air volume in a larger unit must be increased, based upon the cross-sectional area of the product bowl. In this case, the cross-sectional area of the base of the larger container was 0.77 m^2 and the smaller was 0.06 m^2. The correct air flow should be calculated as

$$300 \times (0.77/0.06) = 3850 \text{ CMH}$$

This number was further modified, after considering the increase in bed depth in a larger unit, to 4000 CMH.

B. Spray Rate Calculations

To maintain the same particle size, the triple-headed nozzle could spray three times the pilot-unit spray rate at a 2.5 atomization air pressure. However, this could result in a longer process time. Another approach to maintain a similar droplet size is to maintain the mass balance of spray rate and the atomization pressure. Thus by increasing the atomization pressure to 5 bar, the spray rate was increased to 800 grams per minute, keeping the same droplet size and hence obtaining granulation with desired characteristics.

C. Temperature Calculations

Finally, the required inlet temperature was recalculated based upon the change in the ratio of air volume to spray rate. Because the air volume was increased over 13 times but the spray rate was increased only 8 times, the inlet tempera-

Table 5 Scale-Up of Fluid Bed Granulation Process Parameters

Process parameter	15 kg	150 kg
Airflow (m^3h^{-1})	300	4000
Inlet-air temperature (°C)	55	50
Spray rate (g min^{-1})	100	800
Nozzle air pressure (bar)	2.5	5
Container cross-sectional area of the base (m^2)	0.06	0.77
Numbers of nozzles	1	3

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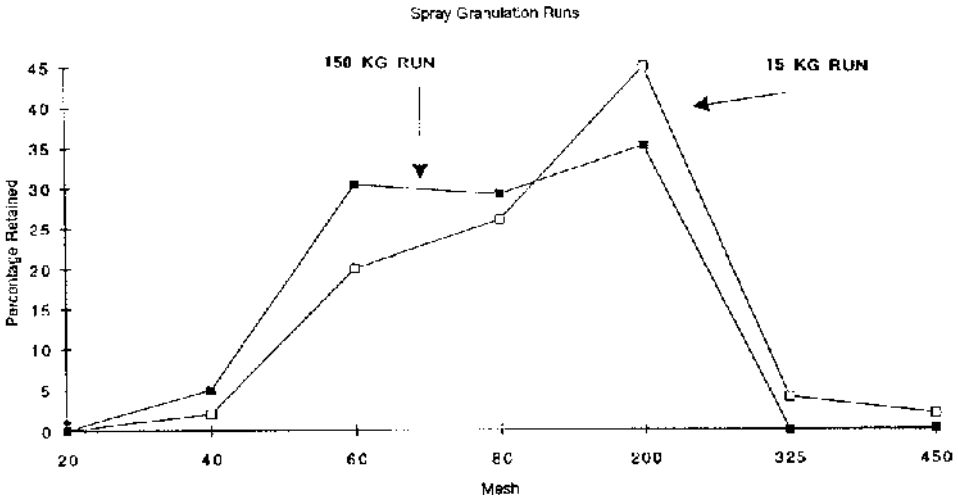

Figure 16 Scale-up case study and resultant particle size distribution.

ture was reduced to 50°C. This adjustment in drying capacity was necessary to avoid spray-drying the spray solution. (A three-headed nozzle used in this scale-up can be replaced by a six-headed nozzle. This would have resulted in the ability to increase the spraying rate 13 times above the pilot-size unit to match the air flow. The maintenance of droplet size and temperature could have been achieved with the six-headed nozzle. The end result would be reduced process time.) Figure 16 shows the particle size distribution produced using the 15-kg unit and the 150-kg unit.

IX. MATERIAL HANDLING

The transfer of materials to and from a fluid bed processor is an important consideration. The loading and unloading of the processing bowl can be accomplished by manual mode or by automated methods.

A. Loading

The contemporary method for loading the unit is to remove the product bowl from the unit, charge the material into the bowl, and then place the bowl back into the unit. This loading is simple and cost effective. Unfortunately, it has the potential of exposing the operators to the product and contaminating the working area. To avoid making the product a dust and cleaning hazard, a system should be installed

to collect the dust before it spreads. A manual process also depends on the batch size and on the operator's physical ability to handle the material and the containerful of product. Furthermore, this can be time consuming, since the material must be added to the product container one material at a time.

The loading process can be automated and isolated to avoid worker exposure, minimize dust generation, and reduce loading time. There are two main types of loading systems, which are similar because both use the fluid bed's capability to create a vacuum inside the unit. Here the product enters the fluid bed through a product in-feed port on the side of the unit. This is done by having the fan running and the inlet-air control flap set so that minimum air flow may pass through the product container and the outlet flap is almost fully open. Once the material has

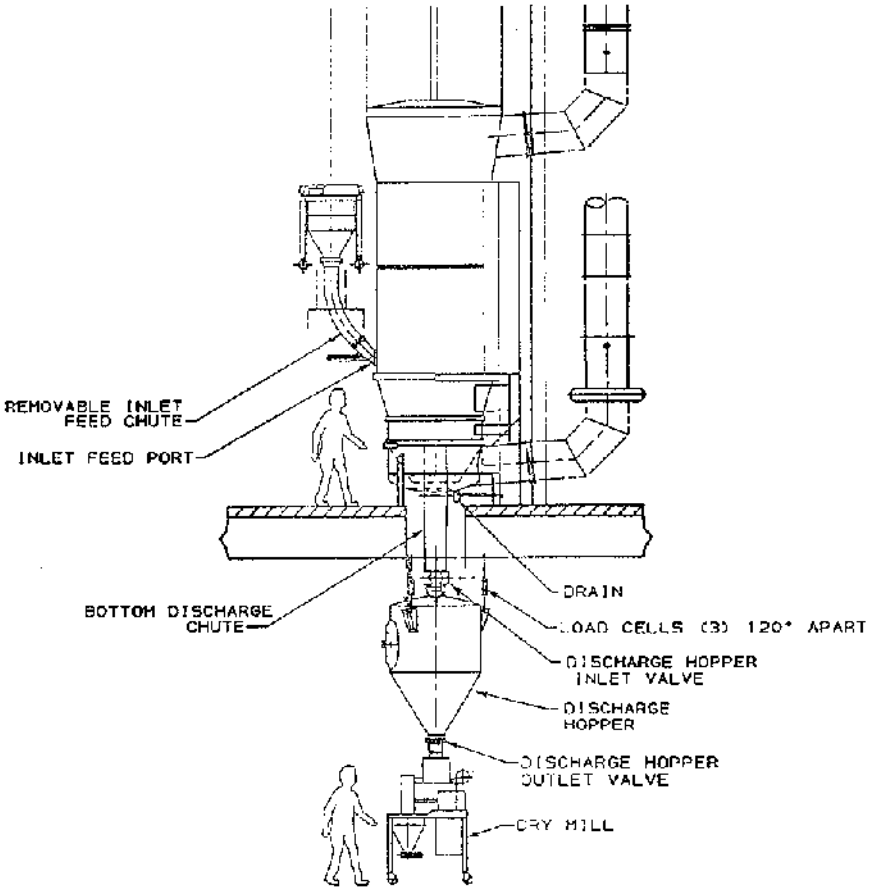

Figure 17 Loading the fluid bed through the product in-feed port and unloading through the bottom of the fluid bed processor. (Courtesy of Niro Pharma Systems.)

been charged to the fluid bed, the product in-feed valve is closed and the granulating process started. This transfer method uses some amount of air to help the material move through the tube. Figure 17 shows the setup for loading the fluid bed. Loading can be done either vertically, from an overhead bin, or from the ground. Less air is required through the transfer pipe when the material is transferred vertically, because gravity is working to help the process. Vertical transfer methods do require greater available height in the process area. Loading by this method has the advantages of limiting operator exposure to the product, allowing the product to be fluidized as it enters the processor, and reducing the loading time. The disadvantage of this type of system is that cleaning is required between different products.

B. Unloading

As with loading, the standard method for unloading is to remove the product bowl from the unit. Once the bowl is removed, the operator may scoop the material from the bowl, which is the most time-consuming and impractical method, because of the potential for exposure to the product. Alternatively, the product can be vacuum-transferred to a secondary container or unloaded by placing the product bowl into a bowl dumping device, as shown in Figure 18. This hydraulic device is installed in the pro-

(a)

Figure 18 (a) Product discharge with a bowl dumping device. *(continues)*

(b)

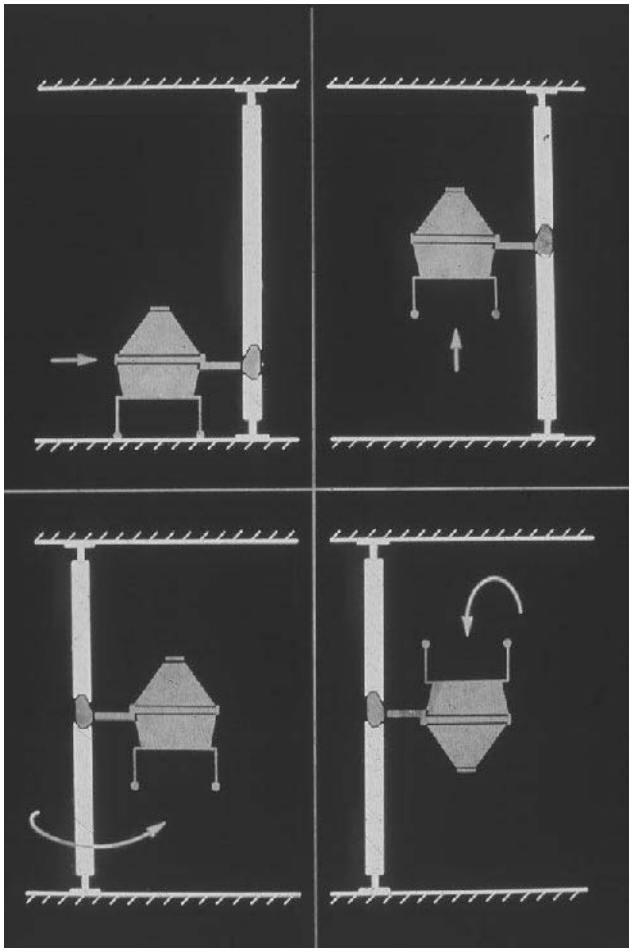

Figure 18 Continued. (b) Mechanism of bowl lifting, raising, inverting, and bringing it down for discharging. (Courtesy of Atlantic Pharmaceutical Services Inc.).

cessing area. The mobile product container of the fluid bed processor is pushed under the cone of the bowl dumper and coupled together by engaging the toggle locks. Subsequently, the container is lifted hydraulically, pivoted around the lifting column, and rotated 180° for discharging. Use of the bowl dumping device or vacuum unloading device still requires the product bowl to be removed from the unit.

There are contained and automated methods for unloading the product while the product bowl is still in the fluid bed processor. The product may be unloaded either out of the bottom of the product container or from the side. Until recently,

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the most common contained method was to unload the material from the bottom of the unit. This requires a ceiling high enough to accommodate the operation, or the installation becomes a multistoried installation. There are two types of bottom discharge options: gravity and pneumatic (Fig. 19). Gravity discharge allows for collection of the product into a container, which is located below the lower plenum. If the overall ceiling height limitation prevents discharge by gravity, a gravity/pneumatic transfer combination can be considered. Gravity discharge poses cleaning problems, since the process air and the product discharge follow the same path; assurance of cleanliness is always of prime concern.

The desire to limit the processing area, and the development of the overlap gill air distributor mentioned earlier in the chapter, has prompted the consideration of side discharge as an option. The product bowl is fitted with the discharge gate as shown in Figure 20. Most of the product, being free-flowing granules,

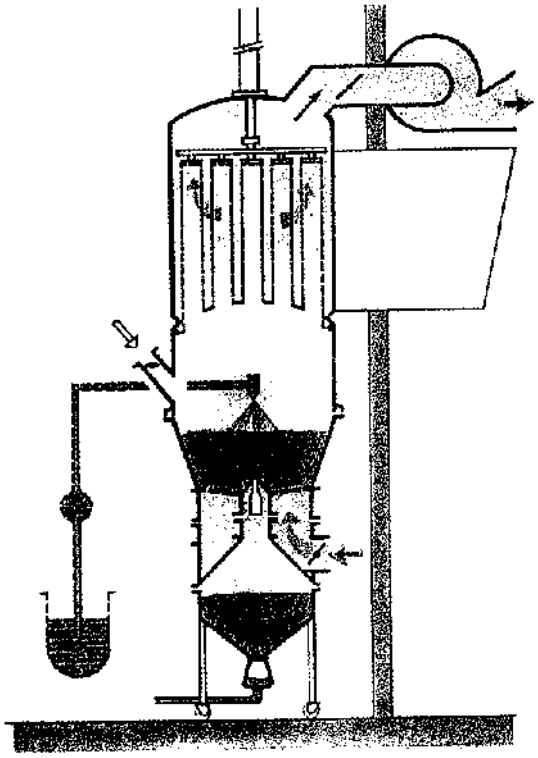

Figure 19 Product discharge through the bottom (pneumatic or gravity). (Courtesy of Niro Pharma Systems.)

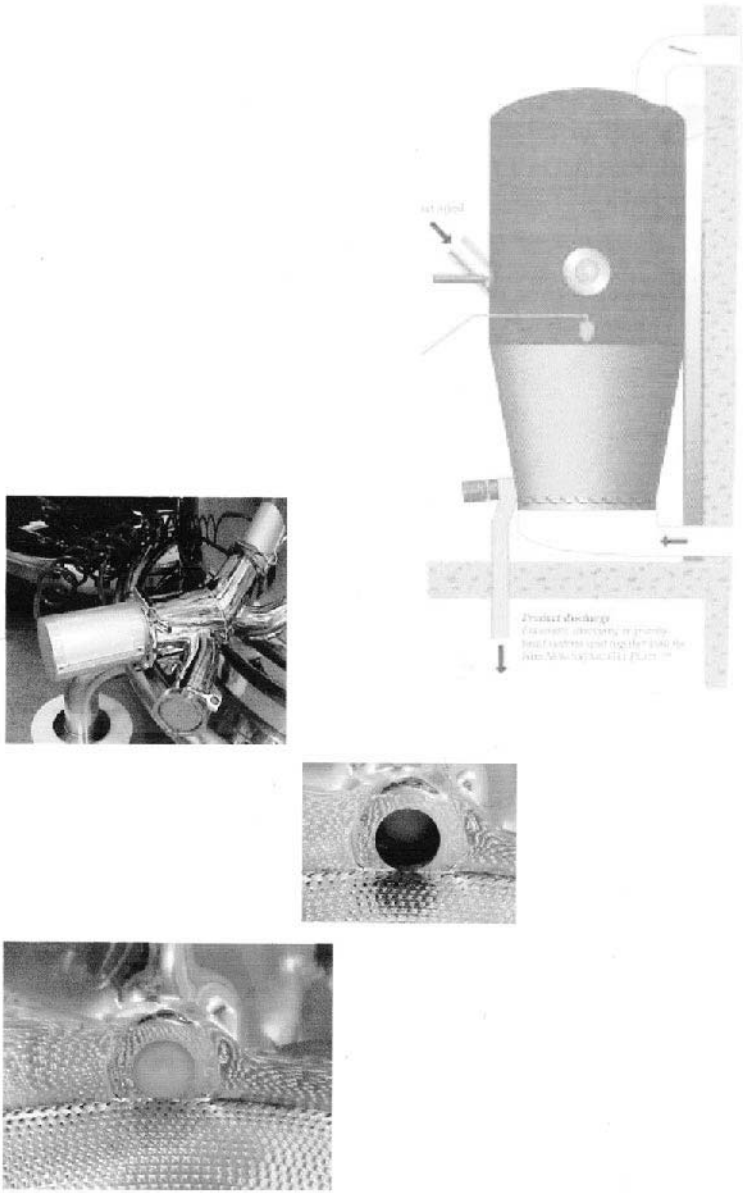

Figure 20 Product discharge through the side, showing closed and open discharge with overlap gill air distributor. (Courtesy of Atlantic Pharmaceutical Services Inc.)

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flows through the side discharge into a container. The remainder of the product is then discharged by manipulation of the air flow through the overlap gill air distributor. The discharged product can be pneumatically transported to an overhead bin if dry milling of the granulation is desired.

The contained system for unloading the product helps to isolate the operator from the product. The isolation feature also prevents the product from being contaminated via exposure to the work environment. Material handling must be thought of early in the equipment procurement process. With fluid bed processing, whether it's an integral part of a high-shear mixer/fluid bed dryer or a granulating equipment option, production efficiency and eventual automation can be enhanced by considering these loading and unloading options.

X. SUMMARY

The fluid bed process, similar to other granulation techniques, requires an understanding of the importance of characterizing the raw materials (especially for a active pharmaceutical ingredient), the process equipment, the limitations of the selected process, the establishment of an in-process control specifications, the characterization of the finished product, and cleaning and process validation. It is equally important that the formulation and development scientists not lose sight of the fact that the process being developed in the pilot plant must be transferred to the production floor. The scientists should spend enough time in the production department to understand the scale of operation that the desired process is being developed to.

Process scale-up can become very challenging if issues other than the fluid bed process are not addressed as one scales up. The selection of the solution delivery system could have significant impact on the process scale-up. For example, as you scale up the solution preparation step, the ingredient addition sequence and its impact, if any, need to be evaluated; the size and type of the impeller could determine if the homogenous binder solution is prepared to provide uniform binder concentration. Sometimes the length of the tubing from the solution tank to the processor creates problems, such as settlement of particles (where suspension is being sprayed as a binder) and possible breakage or back pressure developed from the clogged nozzle port. The control of spray rate to deliver the adequate quantity of solution can depend on the selection of the pump, the size of the liquid transfer lines, the size of the nozzle orifice, etc.

Similarly, scientists must think through how the material will be added and taken away from the processor. Without this forethought, processes that come to production can wind up very labor intensive. If the development scientists work with the production and engineering departments from early on, such difficulties can be avoided.

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Scale-Up of the Compaction and Tableting Process

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I. INTRODUCTION

A pharmaceutical *tablet* is a solid compact in any shape, containing drug and/or excipients, prepared from powder by the application of compressional force, and exhibiting some degree of strength. *Compaction* is the pharmaceutical unit operation of applying pressure or force to the powder to densify it and generate the physical bonds between the powder particles to create this strength.

To consider the subject of scale-up of the compaction and tableting process, one must consider the production of one tablet in 30 minutes, if one were a new graduate student using the Carver Hydraulic Laboratory Press for the first time, to a single-stroke Model E or Model F press at 60 tablets per minute, to a full-scale rotary tablet press at more than 2000 tablets per minute.

The principles of compaction/compression are the same. The critical parameters are (1) the material properties of the particles being compacted and (2) the equipment used for the compaction operation. Some general compaction concepts should be kept in mind.

1. Tablet presses fill by volume. This volume is controlled by the position of the lower punch in the die. This, in turn, controls tablet weight and, therefore, dose.
2. Tablet shape is fixed by the shape of the die cavity and the punch faces.
3. On all presses, the upper punch is set to come down to a specific point in the die cavity; this position, which is set by the operator, controls tablet thickness. More specifically, this setting controls the compaction force (pressure) and, in turn, tablet hardness.

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The only real test to determine that the scale-up batch will run well on the selected tablet press in production is a "use test"; i.e., the batch must be run. Although there is no completely accurate prediction of compaction behavior during scale-up, there are many excellent test methods that can provide an evaluation of specific material properties (flow, lubrication, etc.) and provide an understanding of the material properties of one's formulation. If proper science is applied, these measurements and approaches can provide assurance that scale-up can occur with a minimum of problems.

II. COMPACTION

The basic mechanical unit of compaction/compression consists of three parts: (1) an upper punch, (2) a lower punch, and (3) a die. Producing a finished tablet involves the compaction of a powdered solid between two punches and within the confines of a die, with the application of an external force [1].

There are three definitions needed to accurately describe this process. (1) *Compaction* is the compression and consolidation of a two-phase (particulate solid/gas) system by the application of an external force; (2) *compression* causes an increase in the apparent density (or a reduction in volume) by the displacement of air; and (3) *consolidation* is defined as an increase in mechanical strength due to particle–particle interaction [1,2].

When the external force is applied to the powder in the die cavity, the bulk volume will decrease through the following mechanism: (1) initially it occurs through repacking of the particles (this effect is limited because the mass will quickly become more like a single body); (2) with an additional load, densification occurs through elastic deformation (a reversible process); and (3) if the elastic limit of the material is exceeded, then "plastic deformation" and/or "brittle fracture" will occur. The exact type and mechanism of the material deformation will be dependent on its viscoelastic properties. It should be noted that when the upper punch moves away to release the applied load and allow ejection from the die, the viscoelastic behavior of the material, i.e., the relaxation of the compacted material combined with the forces necessary for ejection, can determine whether the tablet will survive intact or whether lamination or capping might occur. It is generally accepted that this decompression behavior is equally as important as the compression behavior. (Note that if ejection of the tablet represents a problem in production, the use of tapered dies sometimes alleviates the problem.)

As discussed later, compression and densification during compaction can be followed by monitoring and measuring density and porosity. The monitoring of the consolidation, i.e., the bonding process to create the tablet strength, is more difficult. It should be clear, and can be emphasized again, that the important parameters in this operation are the physicochemical properties of the powder and the equipment used to perform this operation.

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III. MATERIAL PREPARATION

The required material properties for compression/compaction are that the material be:

Free-flowing (so that the powder flows uniformly into the die cavity)
Cohesive, i.e., that it possess binding properties so the powder will hold together when it is compressed
Lubricated (to prevents the powder/granulation and the tablet from sticking to punches and die, and to enable the formed tablet to be ejected from the die wall and released cleanly from the punch faces)

There are other desirable properties for the powder, such as exhibiting a hydrophilic surface, but these are related to tablet performance, to product stability (antioxidant), or to esthetic characteristics (e.g., colors, flavors).

One should consider desirable tablet characteristics from the very first stages of formulation to the final stage of process scale-up. These might include:

Physical strength
Pharmaceutical elegance
Biologically available drug substance(s)
Stability (chemical and physical)
Reproducibility (uniformity)

It should be noted that a good formulator will also consider scale-up parameters from the first stages of a project. One must keep in mind the large-scale requirements for each operation required by the formula he or she is developing.

As for the three required properties for manufacture (i.e., flowability, cohesiveness, and lubrication), most of the drug substance in the pharmaceutical industry do not exhibit them. The two methods by which one may impart these characteristics to the final powder mixture are:

1. Formulation (selection of excipients)
2. Processing (selection of method of manufacture)

A discussion of *formulation* is beyond the scope and objectives of this chapter. A description of the three methods of manufacture is well summarized elsewhere [3–6]. As a summary, here are the methods of preparation/manufacture for tablets:

Wet granulation method
Dry granulation method
Direct compression (or simple blending)

Although there may be other reasons for selecting a method/process (such as economics), the manufacturing dictates can be summarized as follows:

1. If a material or mixture *flows* and is *compressible,* one can use *direct compression.*

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2. If a material or mixture is *compressible* (but exhibits poor flow), one can use *dry granulation.*
3. If a material or mixture neither flows nor is compressible, one must use *wet granulation.*

Remember that the first category can be accomplished by prudent selection of direct compression diluents and that wet granulation need not be aqueous (note for drugs that might be labile).

A final list should be kept in mind from the first formulation attempts through the production stage, i.e., the list of important tablet characteristics from a performance point of view. These, of course, are the specifications one sets on the final product, and they include:

Tablet weight
Tablet hardness (or tensile strength)
Tablet thickness
Disintegration time
Friability
Assay
Uniformity of dosage units
  Content uniformity
  Weight variation
Dissolution

IV. FORMULA PROPERTIES

The most important characteristics of the final formulation to be compacted are particle size and particle size distribution, density and/or porosity, powder flow, cohesiveness, and lubrication. Particle size, particle size distribution, and density and porosity of the formula will not be addressed here because they are the result of other operations in the scale-up sequence, such as granulation and milling. They should be evaluated as part of those specific operations. It should be noted, however, that the influence of particle size on powder flow and, therefore, on uniform die fill is very important to the compaction operation, but is not a result of it. The one consideration to keep in mind during scale-up is the speed of the press, which will directly affect the time available for the die filling to occur. This is an important parameter to observe carefully.

Although there are laboratory tests that one can perform to quantitate the flow of a final lubricated granulation, such as angle of repose and flow time through a funnel [7], they are best used as comparison techniques to choose between two or more formulations. If one considers the many different tablet presses available, the use of force feeders on most modern presses, and the fine-

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tuning an operator can perform with the press, these laboratory tests provide no predictive quantitation. Again the real test will be performed on the specific production press selected.

Cohesiveness, compactibility, and lubrication can be evaluated on research instrumented tablet presses, as discussed later. Such measurements should give a degree of assurance that the material will compress and eject properly. Only high-speed compaction simulators or other equipment that controls dwell time, however, will give any indication of potential problems with high-speed presses.

V. MATERIAL PROPERTIES

The specific material properties of most import to the compaction operation are elastic deformation behavior, plastic deformation behavior, and viscoelastic properties. These are also referred to as mechanisms of deformation. As mentioned earlier, they are equally important during compression and decompression; i.e., the application of the compressional load to form the tablet, and the removal of the compressional load to allow tablet ejection. Elastic recovery during this decompression stage can result in tablet capping and lamination.

There are several important things to note. The first is that elastic deformation is a reversible process, but plastic deformation and brittle fracture are not. More importantly, plastic deformation and viscoelastic behavior are kinetic phenomena; time is important, and they can be affected by press speed. In reality, most materials exhibit both plastic and brittle behavior, but specific materials can be classified as "primarily plastic" or "primarily brittle." For example, microcrystalline cellulose deforms primarily by a plastic deformation mechanism; calcium phosphate deforms primarily by a brittle fracture mechanism; lactose is in the middle [8].

Obviously, each material in a formulation can be characterized in this way by use of instrumented press studies and "Heckel" plot analysis in research and development. This approach can be of use to formulators in selecting specific excipients for specific drug entities. However, the characterization and performance of the final formulation are the critical measurements in the scale-up/production compaction operation.

VI. TABLET PRESSES

The equipment used to perform the compaction operation is a tablet press. The small-scale equipment from which one might scale up would include:

Carver Laboratory hydraulic press
Single-stroke Stokes or Manesty model "E" or model "F" presses
Three- to six-station rotary tablet press (e.g., Korsch)

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The most common rotary production tablet presses to which one would scale up the compaction operation include:

Stokes/Pennwalt
Manesty
Fette
Hata
Kilian
Kikusui
Korsch
Courtoy

These rotary tablet presses range from machines with 16–90 or more stations of matched tooling. Specific details for each manufacturer would be best obtained from the supplier's literature.

Some models of these tablet presses are equipped with a *precompression* station. This is an additional set of pressure wheels that can apply force to the material in the die prior to the final (normal) compaction step; i.e., the tablet is compressed twice. When used, the force applied is usually lower than that in the final compaction. A precompression step can densify the material, allow more time for plastic deformation, and allow air to escape rather than being trapped inside the compact.

The original concept was that precompression would allow a more gradual escape of air from the granulation or direct compression mixture. It was believed by some that the entrapment of air in the compact, due to the rapid and forceful compaction, would result in capping and lamination of the tablet. Although this might be a minor consideration, it does not seem to be the most important reason for such tablet defects.

It does seem reasonable that because plastic deformation is a kinetic phenomenon, the extra time occupied by precompression allows the proper bonds to be formed in a timely manner. Another consideration may be that the relaxation of the compact is also provided more time and then a final compaction step occurs.

VII. INSTRUMENTED PRESSES AND SIMULATORS

Much of the information about compaction can be attributed to the early work in tablet press instrumentation and publications in the general area identified as the physics of tablet compression. For the interested reader, a review of the early history of that work has been published elsewhere [2].

The current uses of instrumented presses and simulators can be separated into three distinct areas: research and development, pilot plant (scale-up), and pro-

duction (operations). Although the major focus of this chapter is scale-up and production, the R&D applications will be discussed briefly.

In general, one should be aware that tablet press instrumentation involves the use of strain gauges or piezoelectric transducers to provide a voltage signal proportional to the force applied for the compaction operation. Let us say we can measure forces, such as those applied to the granulation by the punches, that applied to the die wall, that required for tablet ejection, etc. With the use of other transducers we can also measure distance. With the measurement of force and distance, we can calculate work, energy, etc.

The details of instrumentation for tablet presses is thoroughly described in several texts and review papers [1,2,9,10] and will not be repeated here. The concepts, however, are important. The first and most important result of the instrumentation results in a plot of force vs. time (see Fig. 1). This shows the maximum force (or pressure) used for compaction of a tablet; and such plots become even more important on a rotary press, when this measurement can be made on each tablet produced.

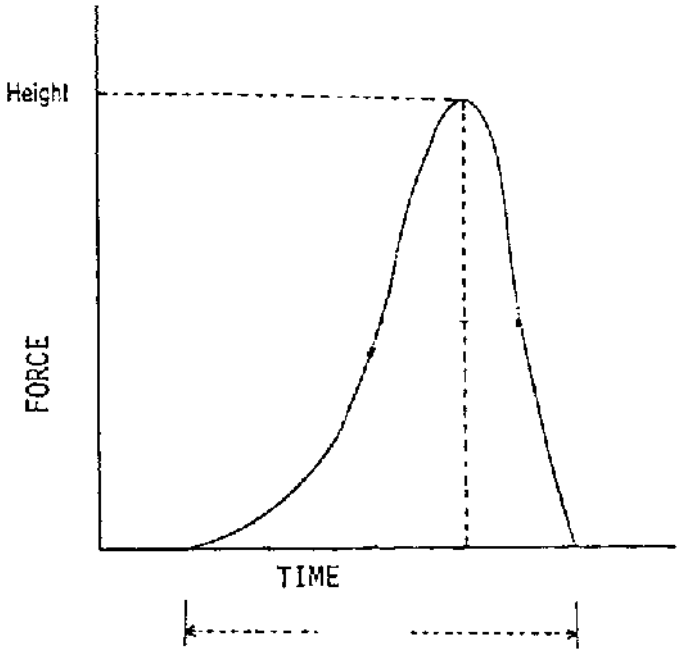

Figure 1 Schematic representation of a compaction force vs. time curve. On a single-stroke tablet press, the time represents approximately one-tenth of the time between tablets. The most common parameter is the compaction force represented by the peak height.

A. Uses in Research and Development

From these simple data on a single-stroke research press, a formulator can begin to generate relationships between tablet properties and the compressional forces used to compact them. Thus, one could plot tablet hardness as a function of compaction force or pressure (see Fig. 2). The same would be true for disintegration time, thickness, a dissolution number, etc. In fact, any dependent variable (tablet property) can be related to the independent variable (compaction force.) It is important to remember that force is the parameter one can control and, therefore, the independent variable.

Powder densification can be followed with measurements of porosity and force by means of the Heckel or Athy/Heckel equation [1]:

$$\log 1/E = K_y P + K_r$$

where:

E is porosity

P is applied pressure

K_y is a material-dependent constant inversely proportional to yield strength

K_r is a constant related to initial repacking

The appropriate calculations, of course, require the measurement of the "true" density of the materials being compacted.

One can analyze the data from this type of work to classify materials with respect to their brittle fracture or plastic deformation tendencies or behavior [1,10]. Examples of Heckel plots are shown in Figure 3. This technique has also been used to follow bead compaction with modifications of the Heckel equation to account for rheological behavior [8].

More recently, Heckel analysis was expanded in an attempt to analyze the various sections of the plot to more precisely differentiate the densification behavior of various materials [11] (see Fig. 4).

The most common analyses in compaction research include:

- Compaction force vs. time curves to obtain a peak force on which to base the tablet property relationships and to measure *functional dwell time* (the time over which the maximum force is applied, most often defined as the time where the compaction force is at 90% of the maximum value)
- Ejection force vs. time curves to observe shape and peak force to evaluate lubrication efficacy
- Tablet porosity vs. force curve to visualize the densification process
- Heckel plots to quantitate the densification process and characterize materials with respect to the deformation mechanism

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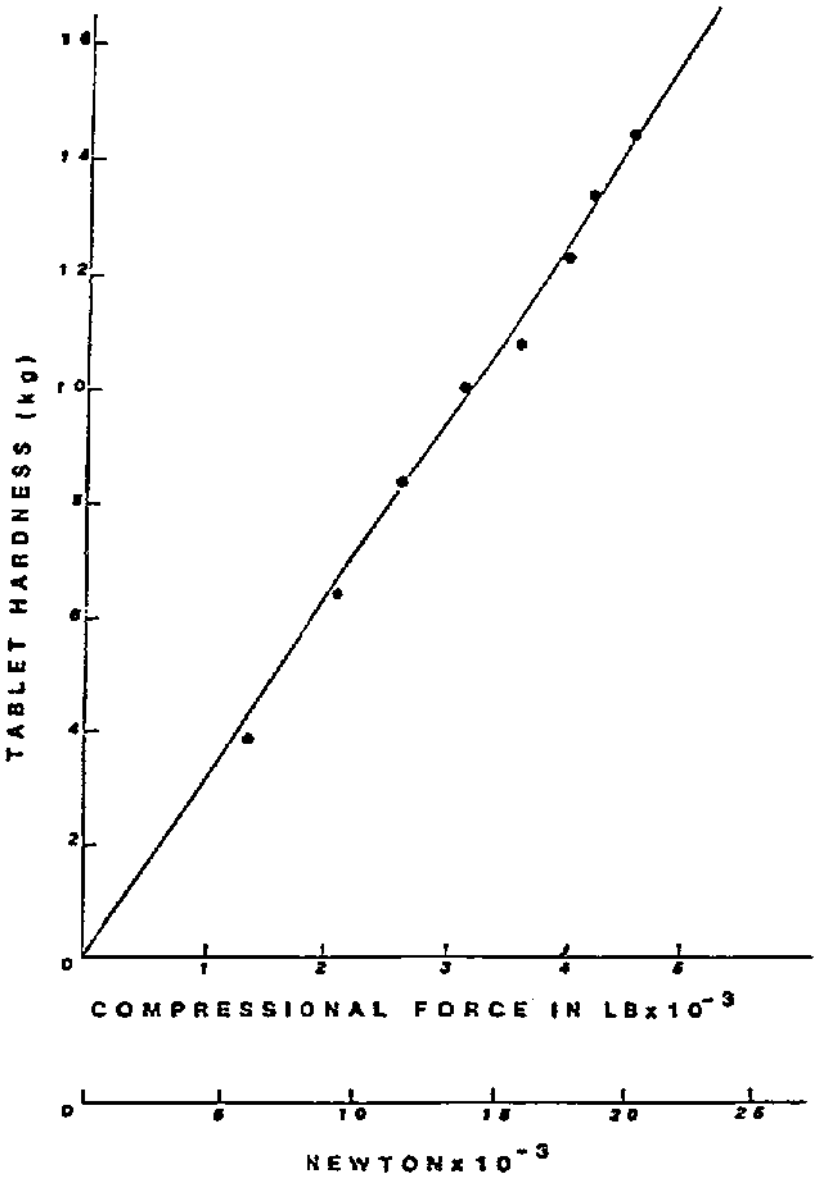

Figure 2 Tablet hardness as a function compaction force for an experimental formulation.

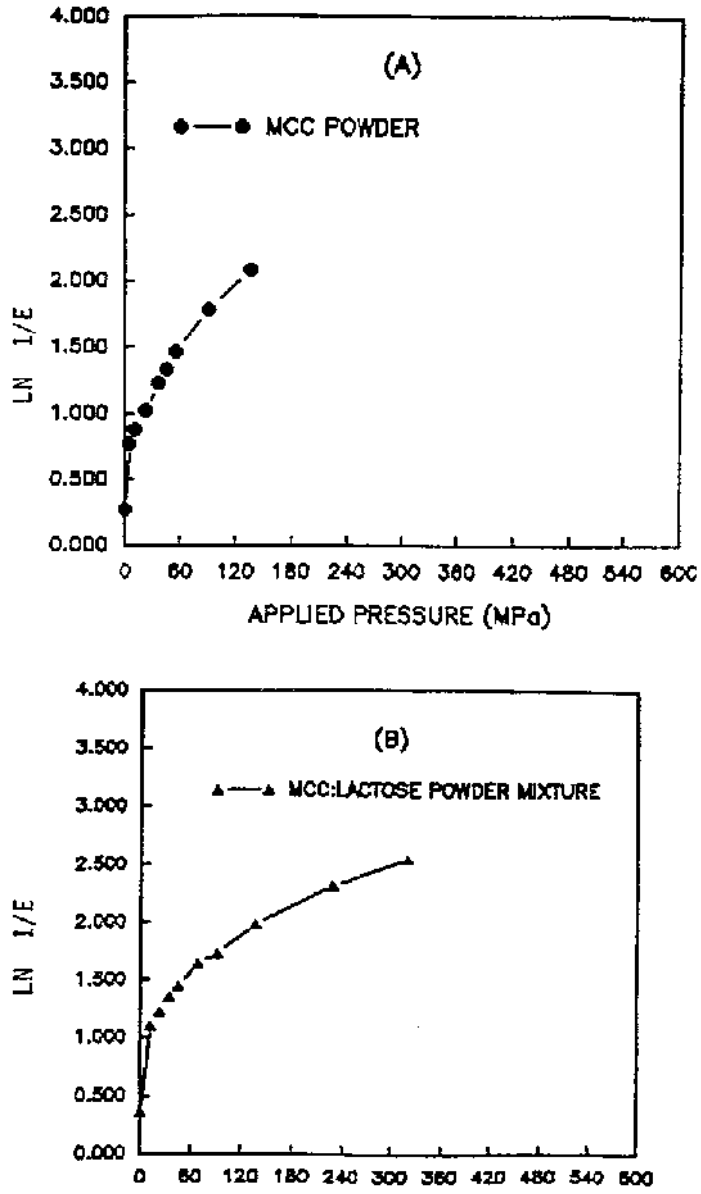

Figure 3 Heckel plots for (A) microcrystalline cellulose and (B) an MCC/lactose mixture.

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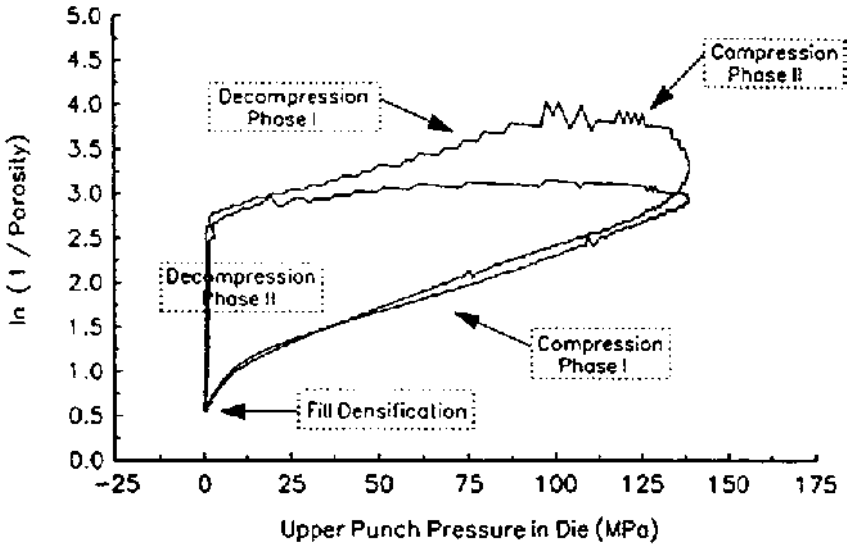

Figure 4 A full-cycle Heckel plot for an experimental material, with densification, compression, and decompression phases noted.

Compaction profiles, which are plots of radial (die wall) pressure vs. axial (compaction) pressure to determine compression and decompression behavior

Force–displacement plots to determine the work of compaction and the energy involved

Some of these measurements can also be performed on *compaction simulators,* which are single-stroke presses specifically designed to evaluate individual materials and/or full formulations [12]. The simulation of short dwell times and of many different profiles for punch movement in real time are the advantages of this type of measurement. Recent work with a compaction simulator has even included a thermodynamic analysis of compaction [13,14].

B. Uses in Production

The major use of the instrumented press in the operations or production area is for tablet weight monitoring and control. Early research in this field was able to show that the measured force of compression was proportional to the mass of material in the die cavity. This, of course, led to systems that could monitor the uniformity of the peak heights measure, send a signal to a servo motor on the press to adjust the weight control if necessary, and finally turn off the press or

divert off-weight tablets if adjustments could not be made in a timely manner (seconds). The fully computerized tablet presses available today perform these and other operations.

Other uses in production might include tooling care and maintenance. It is important to note that because of the way in which the force is set on production presses, the punch lengths must be matched exactly, or the force signal will vary. Therefore, if one observes one station of tooling with a force value different from the others, it probably indicates an incorrect punch length.

C. Uses in Scale-Up

There are several uses of tablet press instrumentation in the scale-up process itself. One of these involves obtaining a sample of the scale-up batch and compacting that sample on the pilot-plant or research instrumented tablet press on which the formulation has been previously evaluated. Similarity of the fingerprint or the various research plots (Heckel, force-displacement, radial vs. axial plots) is evidence that the scale-up batch is similar to the previously evaluated research batch [2].

Larger-scale instrumented equipment, such as the Presster™, can also give an indication of compaction characteristics of a scale-up batch with respect to tablet hardness vs. compaction force measurements [15].

If the tablet presses in production are instrumented and *if* they provide a force reading, then one can perform many of the analyses already discussed to evaluate the scale-up formulation, i.e., compaction force (and/or precompression force) vs. time, ejection force vs. time, or displacement information to provide densification information. It is the author's experience, however, that most production presses are not used in this way, though many in the pilot plant are. Although many production presses are instrumented, the force readings are used only for tablet weight control by monitoring the uniformity of the peak heights; i.e., one does not collect actual force readings or traces. Automatic systems with servo motors then adjust tablet weight (die fill).

The alternative would be to obtain a portion of the formulation, take it back to the instrumented press used in the pilot plant or in R&D, and perform the same evaluation as was performed on the smaller batches. By this technique, one can evaluate the scale-up process for all the other operations and then note any differences in performance on the production press.

VIII. TABLET PROPERTIES

Although there are many tablet properties to be evaluated, the most important to observe during the scale-up process are tablet hardness (or tensile strength) and tablet dissolution. The former could be affected significantly by press speed (if the

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formulation deforms primarily by a plastic deformation mechanism). Both hardness and dissolution are most often a function of compaction force; they are, of course, related to each other, and both must be monitored carefully. With a proper developmental experimental plan or by the use of appropriate experimental design and/or optimization studies in R&D or in the pilot plant, the product development scientist should already know the effects of "force" on tablet hardness and dissolution and the relationship between the two.

For dissolution testing, it is no longer sufficient to show that the product meets specifications—i.e., to use the USP Q-value acceptance table and single-point testing—a profile is required. To determine whether the dissolution profile from the scale-up lot is "the same as" that for the research or clinical or "bio"-batches, one uses the relationship given in the SUPAC document (see Appendix) for immediate-release dosage forms [16]. This equation determines a similarity factor for two products (test and reference). The SUPAC document actually addresses many variations in the scale-up or site transfer of a product, including components and composition, site changes, changes in batch size, and manufacturing changes. Equation (1) determines a similarity factor (f_2) based on the dissolution points on two curves, one for each of two products/batches. R_t and T_t are the percent dissolved at each time point, where at least 12 tablets (individual dosage units) are tested. A similarity factor [an f_2 value] between 50 and 100 indicates that the two profiles are similar.

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{N} \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\} \tag{1}$$

IX. SPECIAL CONSIDERATIONS IN SCALE-UP

It is obvious that most of the effects of scale-up are seen in the unit operations that occur before compressing, especially blending, granulation, milling, and drying. These operations impart the important physical properties to the mixture to be compressed. For example, separation of particle sizes in the hopper would be a function of the choice of excipients or the processing steps to get to the final granulation or direct compression mixture.

There are, however, several special concerns in the scale-up of compaction that relate exclusively to the compaction step and that cannot be determined on a smaller scale. The list might include:

Press speed for materials that compact by plastic deformation
Overmixing of the lubricant by the force feeder
Heat build-up over a long run
Abrasive materials
Tooling care—unmatched sets of tooling

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A. Press Speed

Strain rate sensitivity of (or the effect of press speed on) the formulation is of primary concern in scale-up. Whether the product development work was performed on a single-stroke press or a smaller rotary press, the objective in operations will be to increase efficiency, in this case the tablet output rate and, therefore, the speed of the press. For a material that deforms exclusively by brittle fracture, there will be no concern. Materials that exhibit plastic deformation, which is a kinetic phenomenon, do exhibit strain rate sensitivity, and the effect of press speed will be significant. One must be aware that although specific ingredients (such as calcium phosphate and lactose) may exhibit predominately brittle fracture behavior, almost everything has some plastic deformation component, and for some materials (such as microcrystalline cellulose) plastic deformation is the predominant behavior. The usual parameter indication is that target tablet hardness cannot be achieved at the faster press speed. Slowing the press may be the only option to correct the problem.

B. Lubrication

The effects of lubrication, especially with magnesium stearate, are not only a function of the ingredient level, but also a function of the blending time. It is well known that overmixing causes a spreading of the particles and an increase in the hydrophobicity of this material. The resulting effects on dissolution are well known. Less well known, however, is the effect of this type of overlubrication/overmixing on tablet hardness or tensile strength. Lubricants, and especially magnesium stearate, can coat the surface of other ingredients or granules and, by preventing particle contact and bonding, can result in a softer tablet.

It is the authors' experience that with a formulation compressed without a forced feeder in R&D, the scale-up in a different country, but by gravity feed and without a forced feeder, was perfect. In a second country, however, all production presses operated with forced feeders, and the target tablet hardness was not achieved. It was possible to conclude that press speed was not the cause of the problem; but it was much later (and based on laboratory experiments) that it was possible to conclude that the lubricant was overmixed on the tablet press, resulting in a softer tablet. Fortunately, the drug was very soluble and no dissolution problem resulted, but slower dissolution could be a problem with a drug of low solubility.

C. Batch Size/Length of the Compaction Run

No matter what type of tablet press was used in R&D or in the pilot plant, there is no possible way to experience the phenomenon on a full-size batch and the associated time of the compaction run. One must be aware of the possible build-up of

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heat due to the length of the compaction operation, i.e., the operation of the press. Formulators should be aware of and attentive to the effects of a possible temperature increase on the stability/degradation of the active compound (or any heat-labile ingredient) or the softening of any low-melting ingredients. Abrasive materials in the formula can produce such a heat build-up even without the tablet machine effects.

D. Tooling Care

It is a fundamental assumption for the use of instrumented presses for tablet weight control in production that the sets of tooling on the press are perfectly matched. These systems work on the basis that a low fill wight (low powder mass) in the die cavity results in a low force signal and that a high fill weight results in a high force signal. Although the forces are not recorded, the uniformity of the peak heights is, and weight adjustments are made accordingly.

The force signals, however, can also be affected by a change or variation in the length of the punches. If any one punch is slightly shorter than the others, less force will be applied to the powder mass, and the signal will be low. These weight control systems would then assume that the tablet weight is low. Therefore, tooling maintenance is extremely important in the scale-up operation.

X. OTHER PARAMETERS TO MEASURE DURING SCALE-UP

As already noted, the most important parameters or characteristics to observe during scale-up of the compaction process are tablet hardness (or tensile strength) and tablet dissolution. However, the following might also provide useful information.

A. Tablet Weight Uniformity

Tablet weight uniformity will provide a measure of the efficiency of the powder flow, the force feeder, or the automated weight control system. Weight monitoring by the press operator is usually the weight of a 5- or 10-tablet sample. Uniformity of individual tablets, which after all does relate to dose, will be more informative. The powder flow may not be sufficiently good, even with forced feeders.

B. Tablet Hardness Uniformity

Tablet hardness uniformity will monitor the same parameters, but could also be an indication of matched or unmatched punches on the tablet press. It may also be

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useful to observe the tablet behavior during hardness testing. Sometimes, capping or lamination that does not appear during compaction but does appear during hardness testing may indicate that one is operating in a borderline force area. One can observe this with a plot of hardness or tensile strength vs. force; a parabolic shape is produced [17]. If the hardness is lower at higher forces, it could be an indication of weak bonds of lamination that show up as a softer tablet during the hardness testing. This may be the one case where lower compaction force could produce a harder tablet.

C. Tablet Hardness vs. Dissolution Data

Although this information should have been generated during the development of the formulation, it is often useful to confirm the relationship between these two dependent variables on tablets compacted on the production press during scale-up. Such information becomes invaluable for troubleshooting.

D. Instrumented Press Data

If the tablet presses are instrumented and if they provide force readings or, more importantly, if they provide force vs. time curves, then the following parameters should be measured:

Dwell time (which is most often defined as the time where the compaction force is at 90% of the maximum value)
Compressional force
Ejection force
Displacement

(See Sec. VII.A on Instrumented Presses in Research for discussion.)

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8 (2)
Practical Aspects of Tableting Scale-Up

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The key to scaling up a tableting process is to consider it during the entire development process. From the inception of a development project, the formulation scientist must consider scale-up. It should not be a process removed from development. A formulation scientist should begin a development project with the end in mind. Just as a builder, prior to nailing boards, planks, and plywood together, has a blueprint of what the structure is supposed to look like, a formulator should know what the goals of the delivery system are.

Some questions a formulator needs to address up front are: What are the marketing plans? What are the potential obstacles to uniformity? Is the active raw material physically and chemically consistent? What are the physical plant constraints? Addressing these and other questions in the early stages of development could aid in avoiding many scale-up nightmares. Additionally, the identification of potential scale-up issues forces the formulator to consider commercialization of the drug delivery system. Too often, formulation scientists develop tablet formulations in a bubble, only to be later handed off to some poor process development person who has to make it work.

Although the focus of this chapter is on the scale-up of the tableting process, one cannot ignore the significance of upstream (precompaction) processing. A pragmatic formulator approaches a development project as a computer programmer would approach the development of a program. A programmer defines the input (the independent variables) and output (the dependent variables) *prior to* tackling the program. The formulator should do the same in the early stages of formulation development. Independent variables of a tablet formulation include the active drug substance, clinical data, marketing demands, manu-

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facturing constraints, and sales forecasts. Additional inputs are the location of manufacturing (if known) and available manufacturing techniques. Dependent variables a formulator must consider during early stages of development of a tablet formula include marketing issues such as the color, shape, and size of the tablet, final product specifications (dissolution, etc.), bioavailability, run rates, patient/consumer acceptance, and stability (shelf life). A successful development project is one that delivers the desired output for the given independent variables.

Characterization of the active drug substance early in the development process is paramount in avoiding scale-up issues downstream. Characterization exercises should include determining physical, chemical, and functional attributes. Physical characterization of the drug substance includes measuring particle size, density, surface area, etc. Some chemical characterization should focus on solubility, stability, and reactivity. In tablet formulation development, functionality could play an important role in the successful scale-up. Functional testing should include measuring parameters such as compactabilty and flow. Characterization activities should be performed while considering the defined delivery system output. What is the definition of success for the formulation project? For example, characterization activities carried out for a low-dose tablet will be vastly different than characterization of a compound to be used in a tablet formula that is made up mostly of active ingredients.

It is important that the formulation scientist also define other independent variables (inputs). One additional given input is the drug's clinical characteristics. Formulators inherit clinical requirements, such as dose, route of administration, area of adsorption, and metabolism. The formulation of a tablet and its subsequent scale-up depend on marketing inputs, such as color, flavor, size, shape, and target patient. Manufacturing constraints must also be considered prior to scaling up a tablet formulation. What are the equipment or facility constraints? What are the personnel capabilities? What is the desired manufacturing rate (tied to marketing forecasts)? Regulatory issues are also important to consider during scale-up activities of a tablet process. Understanding one's limitations within the various regulations (SUPAC, etc.) aids the formulator in scaling up a process that the FDA will find equivalent to the one by which the clinical batches were produced. A formulator needs to understand that some flexibility exists in the current regulatory environment when scaling up from a laboratory to a pilot plant and from a pilot plant to manufacturing environments. Clinical batch size versus allowable scale-up batch size is an important relationship to understand early in the development project. Formulation composition and an understanding of what changes to composition can be made will aid the formulator in scale-up. Defining processing equipment operating principles during development and their relationship to the available equipment in the scale-up facility will also aid in the successful scale-up of a tableting process.

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After most of the independent variables have been defined (or characterized), the formulator must consider what the criteria for success are. What are the dependent variables, or output, of the formulation? It's simple: input + formulation = output. The formulator's job is to develop a system that takes all of the project's input into consideration and to produce a product that meets the criteria for success (output). Some output, or dependent, variables include the specifications that the dosage form must meet and the bioavailability. Run rates in manufacturing need to satisfy market demands. Reliability and consistency in manufacturing should be a goal in any process. Another dependent development variable is consumer (or patient) acceptance of the dosage form.

Once the formulation scientist gets a handle on the formulation input (dependent variables) and the formulation output (dependent variables), a set of experiments needs to be designed to determine how to take the given and get the desired. Upon execution of the experiments, the formulator should gather an understanding of how the input relates to the output. For example, if marketing wants a 300-mg tablet and the dose has been set at 0.1 mg, a formulator will take all necessary precautions to ensure dose uniformity. It is obvious that experimentation in the latter case would focus on the preparation of tablets that are 300 mg (output) containing 0.1 mg of drug (input). If, in contrast, marketing desires a 300-mg tablet containing 250 mg of drug, the formulator might shift the focus of the experiments from obtaining dose uniformity to the compactability of the active drug.

After all the preformulation and characterization activities have been executed and formulation excipents rationalized, a formulator needs to begin the building of early tablet prototypes. During the early stages of development, the formulator will decide how the precompressed material will be prepared. If a formulation scientist is developing a formulation for eventual commercialization, he or she will evaluate the early blends in an effort to identify potential downstream (scale-up) processing issues. A direct compression formulation is usually where the formulator begins to evaluate formulation issues. If, during the compression of the formulator's first 100 tablets on a single-punch tablet press, segregation and capping are observed, adjustments obviously need to be made. In this example, one can only imagine what the results would be for a lot scaled up with that formula. Based on the results of the first (DC) attempt, most formulators would evaluate the need to additionally process their formula. Some considerations could be particle size distribution adjustments, wet granulation, addition of compression aids, and roller compaction.

Early data collection of prototype-blend experiments could be an invaluable tool to successful scale-up. Physical characteristics such as particle size distribution, bulk and tapped density, and flowability and functional characteristics (mainly compactability) are key indicators of possible downsteam scale-up problems. If, for example, the active drug substance has a mean particle diameter

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nowhere near that of the excipients, one is begging for segregation upon scale-up. Bulk and tapped density data will aid in determining blender loads. Flowability is an important consideration when transferring a process from the laboratory to a manufacturing environment. Not only does the precompacted blend need to flow out of the blender, but the material may need to be able to quickly (and uniformly) fill the dies of a high-speed tablet press. Compactability characteristics are obviously the most important functional consideration in the production of a tablet.

Compactability, for the purposes of this chapter, is defined as the ability to consolidate the particles of a blend to result in increased apparent density and a unit that has some physical strength. Often called *compressibility,* compactability needs to be characterized and optimized early in the development process. Characterizing compactability requires the collection of data related to many aspects of tableting. Consider how a tablet is formed: (1) A mixture of powders flows into a die cavity; (2) an adjustment in a critically important volume is made; (3) the blend is subjected to a great deal of stress, strain, and shear (hopefully resulting in a consolidated compact); (4) the compact (tablet) must be pushed out of the die cavity; (5) the tablet must be pulled, pushed, or knocked off the surface of the lower punch face; and finally, (6) the tablet must safely travel into a container where it will be stored for further processing. The characterization and optimization of the compactability would therefore include flow measurements, force vs. compactability measurements, ejection force measurements, punch face release measurements, and resulting tablet attrition data collection. The earlier these parameters are defined in the development process, the better the chances are for a successful scale-up.

Flowability is important to the successful scale-up of a tableting process. The rate at which the precompacted blend flows into the hoppers of the tablet press and subsequently into the die cavity could be crucial to dose uniformity. Three measurements are most commonly used to measure flow:

Angle of repose—a blend is poured through a funnel into a pile and the angle at the base of the cone is measured.

Dynamic flow—an instrument is used to measure the time it takes a constant volume of material to flow through a fixed orifice (these instruments usually have mechanical vibrators on them).

Funnel flow—a glass funnel of fixed volume and angle is filled and the time it takes to empty is measured.

The third method of flow measurement enables the formulator to characterize the flow as well. Is the flow a mass flow or a funnel flow? Does it rathole or bridge?

Compactability exercises are probably the single most important set of experiments a formulator carries out early in the development of a tablet formula. Proper execution of compaction studies could avoid a host of potential scale-up

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difficulties. Compaction studies are carried out on various types of tablet presses. The presses are equipped with instrumentation able to measure various forces and an output device able to interpret these forces. The type(s) of forces measured can vary. Some scientists measure the force applied to the blend, while other formulators choose to measure the force transmitted through the blend. These studies are generally carried out by compacting a blend at various levels of force at a constant rate.

Various measurements are made on the resulting tablets. Useful information used to optimize a formula include: force versus hardness, force versus friability, and hardness versus dissolution. One could also compare hardness with thickness and/or friability. Numerous comparisons can be made using the data in an effort to optimize the formulation. Force versus tablet hardness plots are the most common compaction profiles used. Force versus these hardness plots are extremely valuable when designing early tablet prototypes. The guesswork is removed when rationalizing excipients and levels. Several formulations containing various levels of excipients can be compacted at different forces and the hardness of the resulting tablets measured. A formulation scientist can use the data to compare different prototypes. An optimal formula is one that results in the hardest tablet given the lowest amount of force applied (see Fig. 1) while meeting all other success criteria. These measurements should be used for comparison/optimization purposes. The rate at which a tablet is formed needs to be addressed as a part of the scale-up process.

Other force measurements valuable in the development of a tablet formula relate to the ejection of the tablet out of the die. The goal of the formulator should be to optimize compactability (a hard tablet using low force) while minimizing forces related to tablet ejection. If ejection forces are too high, the stress caused can result in capping, lamination, chipping, cracking, and/or breaking. Two predominant forces related to the ejection of a tablet should be examined. The force required to remove the tablet from the die (ejection) and the force it takes to remove the tablet from the lower punch face (knock-off force). When examining and optimizing ejection force, the formulator should focus on minimizing peak height. (For examples of ejection data generated by an instrumented press see Figs. 2 and 3.) Optimizing lubricant levels, thus reducing ejection forces, is often done at the expense of compactability. In general, the excipients (or processes) used to reduce ejection forces inevitably increase the force required for compaction.

The rate of the compaction process is another variable that should be considered throughout development, including scale-up. Typically, the development of a tablet formulation takes place on tablet presses that are relatively slow. The tableting rate is important to consider for several reasons. Blend flow is important to ensure bulk blend transfer into the tablet press (hopper) and consistent die fill. Variation or difficulty in the bulk flow and die fill can contribute to tablet weight variation. As the compaction rate increases, the blended material must be able to

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Figure 1 Force vs. hardness compaction profile.

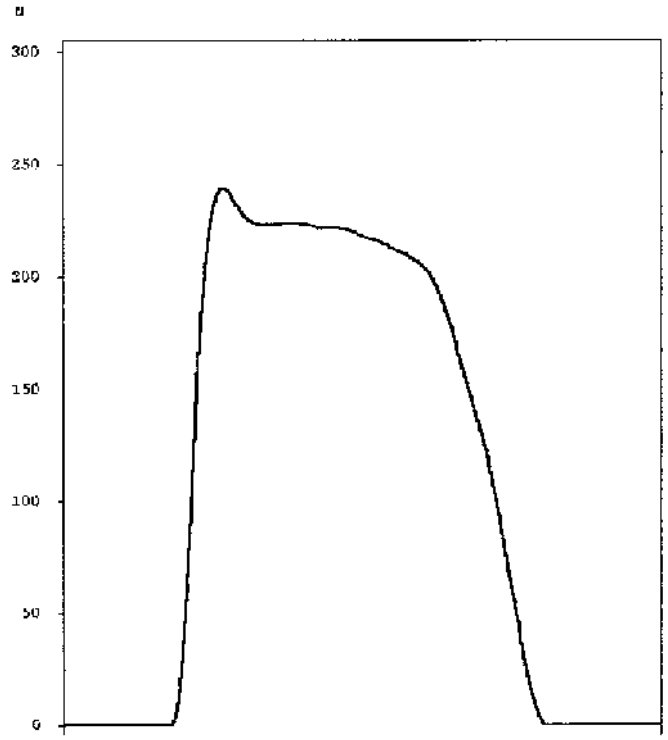

Figure 2 Ejection force curve.

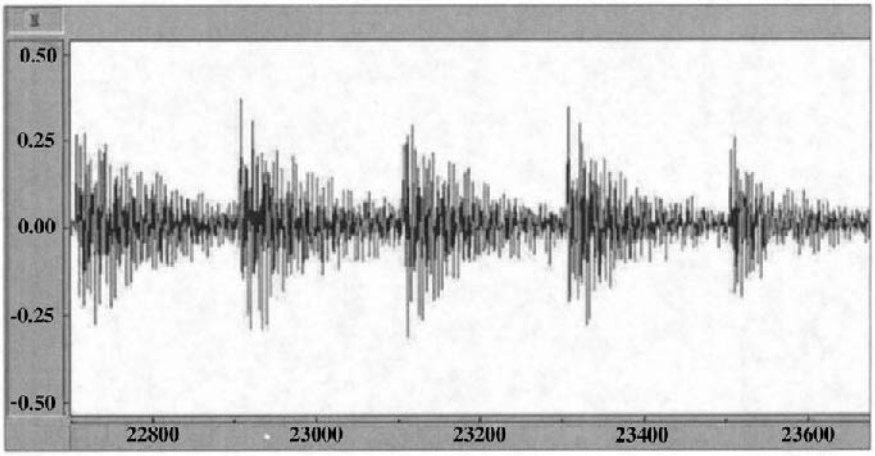

Figure 3 Take-off force trace.

keep up with flow requirements. Optimal blend flow can only be defined upon scale-up. The optimal flow of a blended material depends on dose, tablet size and shape, the type of tablet press being used, and a host of other variables. As the tableting rate increases, formulators often find the need to incorporate die-induced feed frames onto the tablet press being used for the scale-up work. An overzealous feed frame speed can wreck havoc on a blend susceptible to overmixing. Overmixing in a feed frame could lead to a reduction in lubrication effectiveness, increase the hydrophobicity of the blend, and/or a modification of particle size distribution.

In addition to the blend flow/movement characteristics, the tableting rate affects the time that the blend is subjected to compaction forces. The two major elements in the formation of a tablet are the forces applied to the blend and the length of time those forces are applied (time when compression wheel is in contact with the flat portion of punch head is called *dwell time*). Dwell times significantly differ upon scale-up. Dwell times also differ between presses within a manufacturing area. Dwell times on typical development tablet presses run from 0.080 to 0.500 seconds. Production scale presses can go as low as 0.005 seconds per compaction event. The difference in dwell time affects the maximum peak height of a compaction event (see Figs. 4 and 5). In this example, the same blend was subjected to compaction at two different rates. The peak height for the compaction event with a shorter dwell time is usually significantly higher then the peak height resulting from the longer dwell time. The significance of compaction peak height is important in scale-up. Larger peak forces can affect the operation of a high-speed (production-scale) tablet

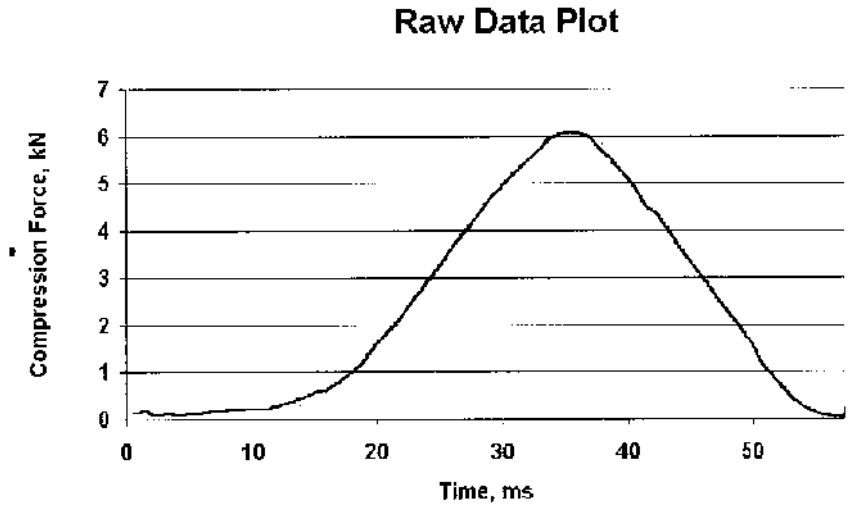

Figure 4 Example of a short dwell time.

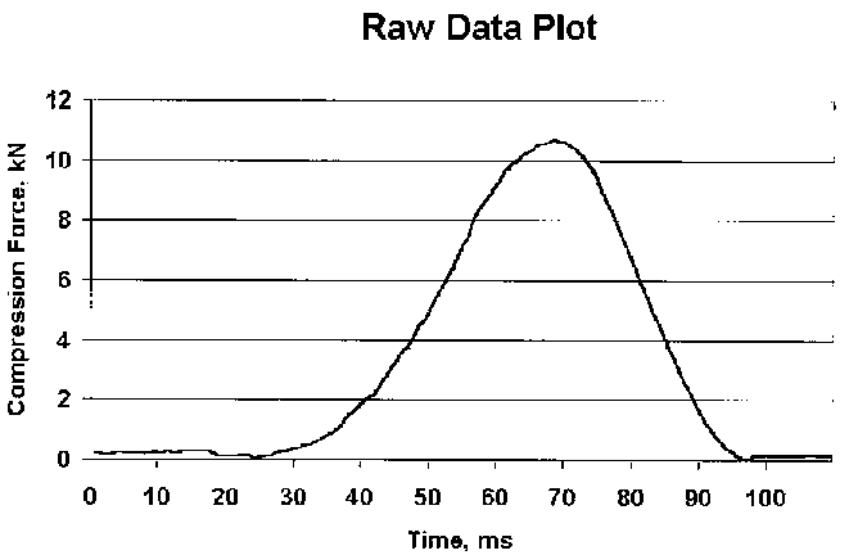

Figure 5 Example of a long dwell time.

press. Tooling, cams, and pressure roll wheels will wear faster as compaction forces increase. The tablet stresses strain and shear also increase as dwell times decrease and compaction force increases. These stresses can cause several scale-up nightmares, such as capping, lamination, and die binding. The most common cure for these scale-up issues is slowing the press down, thus increasing dwell time.

In an effort to overcome the dwell time/scale-up issues, Metropolitan Computer Corporation (MCC) has developed a single-station development tablet press that reproduces the compaction event time of manufacturing-scale tablet presses. The Presster™ (see Fig. 6) can be set up to match the rate, roll wheel configuration, and tooling of any manufacturing-scale tablet press. This enables the formulator to eliminate compaction rate as a variable upon scale-up. It does require that early in development the formulation scientist identify the tablet press that the commercialized product will run on. This is in keeping with the theme of this chapter—begin a development project with the end in mind.

In summary, scale-up of a tablet formulation should not be a process separate from the development of the initial formulation. Scale-up should be a consideration from the onset of the development of the early prototypes. The formulation scientist should begin a project with the end (commercialization) in mind. The task a formulator is assigned is one where the input (independent variables) and output (dependent variables) are clearly defined at the beginning of a development project. The formulator fills the gap between the input and the output. The solid-

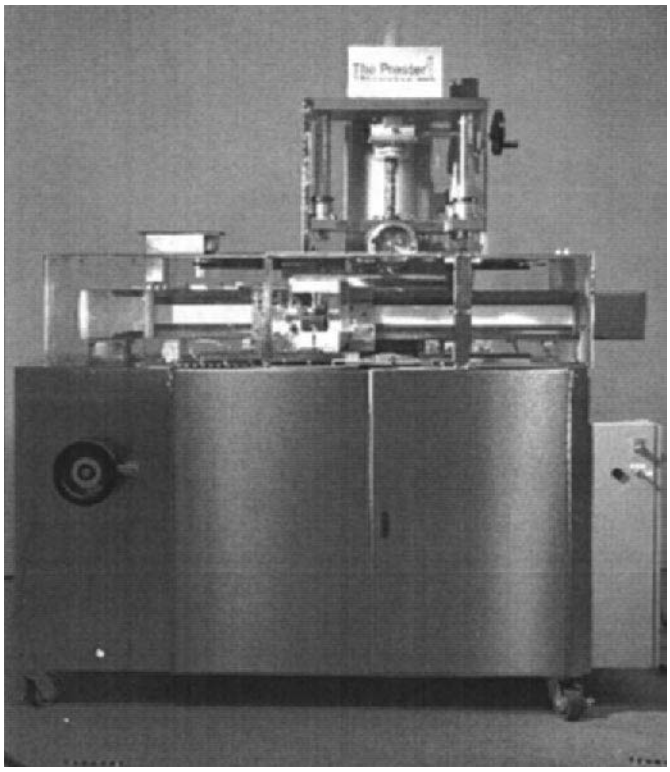

Figure 6 The MCC Presster™.

dose formulation scientist receives reams of information from groups such as pharmacokinetics, toxicology, clinical science, and synthesis, together with a bottle, bucket, or drum of active substance. The formulator ultimately must deliver a dosage form that passes predetermined specifications, can pass a validation exercise, is stable, can be consistently and efficiently manufactured, and is acceptable to the consumer.

I. SCALE-UP CASE STUDIES

A. Example 1: Blend Feed Segregation

1. Formulation/Process Background

This particular formulation was a direct compression formula containing two active ingredients: Active A, 60 mg, and Active B, 4 mg per tablet. The actives made

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up about 50% of the total tablet mass. Active A was a crystalline material with a mean particle diameter of approximately 180 microns. Active B was an amorphous powder with a mean particle diameter of approximately 120 microns. The tablet matrix comprised microcrystalline cellulose, spray-dried lactose, disintegrant, and lubricant.

The process to prepare the blend was relatively straightforward. Active A was milled through a 0.075″-opening conical mill. All the other components were screened through a #20 mesh (840-micron) screen. All materials except the lubricant were blended in a diffusion blender. The lubricant was blended for a short time at the end.

2. Laboratory Work Through Scale-Up

The initial lab batch was prepared using small, pilot-scale equipment. The first batch was 8 kg (prepared in a 16-quart V-blender). No blend testing was performed on the first lab-blend batch. The compaction was performed on a 16-station gravity-feed tablet press. Extensive tablet uniformity testing was carried out on the tablets generated from the initial 8 kg. A total of 120 tablets were assayed for both actives. The tablets tested were from a composite sample taken throughout the compaction process. The uniformity of both active ingredients in the tablets produced from the laboratory batch was excellent. Both active ingredients assayed between 96% and 106% of label strength, with a %RSD of less than 2.

Based on the success of the laboratory batch, an intermediate-scale batch was prepared. The lot size was approximately 65 kg. The blend was prepared in a 5-cubic-foot diffusion blender. Several unit dose samples of the blend were withdrawn from the drum containing the blend discharged from the blender using a single compartment thief. All the unit dose blend samples met acceptance criteria for both actives. This blend was compacted on a 30-station force-fed tablet press. Samples were taken throughout the compaction process. A composite sample was made, and 120 tablets were assayed for dose uniformity. Uniformity of both active ingredients in the tablets was excellent. Both active ingredients assayed between 97% and 105% of label strength, with a %RSD under 2.

Again, based on the success of the intermediate-size batch, a decision was made to prepare a manufacturing-scale batch. The manufacturing lot size was approximately 200 kg. The blend was prepared in a 16-cubic-foot diffusion blender. Using a single-compartment thief, several unit dose samples of the blend were withdrawn from all the drums containing the blend discharged from the blender. All the unit dose blend samples met acceptance criteria for both actives. This blend was compacted on a 30-station force-fed tablet press. Samples were taken throughout the compaction process. A composite sample was made, and 240 tablets were tested for dose uniformity. Uniformity of both active ingredients con-

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tained in the tablets was outside the limits of the acceptance criteria. Both active ingredients varied in assay between 80% and 122% of label strength, with a %RSD of more than 9.

3. Cause of the Issue

After an exhaustive investigation, it was determined that the cause of the nonuniform tablets was segregation in the tote/overhead feeding system used in the manufacturing operation. The laboratory- and intermediate-size batches were hand-scooped into the hopper of the tablet press. The overhead-feed duct acted as a classifier. The differences in cohesion and adhesion of the two actives, coupled with the length and angle of the ductwork, fostered segregation.

4. Addressing the Problem

There were two possible approaches to addressing the segregation issue. The first was to modify the blend (granulation, etc.). The second was to modify the blend feed system. The latter was chosen in an effort to prevent recurrence in other, similar formulations. After the modification of the tablet press overhead-feed system, all subsequent batches passed uniformity testing and eventually a validation exercise.

5. Lessons Learned

Consider the systems between major steps of the process as sources of process influence.

B. Example 2: Cracked Dies

1. Formulation/Process Background

The formulation was a chewable antibiotic for children. The active substance was fluid-bed granulated in a sucrose base. The granulation was blended in a diffusion blender with additional amounts of sucrose, flavors, colors, and other excipients.

2. Laboratory Work Through Scale-Up

Due to the limited availability of the active component, several small (approximately 5-kg) granulations and blends were prepared. All prototype-formulation work was compacted on a singe-station tablet press. The material compacted during the lab-trial work met predetermined acceptance criteria physically and chemically.

Upon compaction scale-up of the formula to a higher-speed rotary tablet press, die cracking was noticed.

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3. Cause of the Issue

The dies cracked due to the inordinate amount of force required to compact the tablet, coupled with a poorly designed tablet shape (kids/fun shapes). As the tablet press speed was increased, the dwell time of the compaction event decreased, thus increasing the amount of peak force required for compaction.

4. Addressing the Problem

Several adjustments were made to the formula and process to improve the compactibility of this product. The moisture specification was adjusted, additional dry binder was added to the formula, and the tooling design was re-engineered.

5. Lessons Learned

Compaction dwell time must be a consideration when scaling up.

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8 (3)
Dimensional Analysis of the Tableting Process

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I. INTRODUCTION

Scale-up of the tableting process in the pharmaceutical industry is still an empirical process. Dimensional analysis, a powerful method that has been successfully used in other applications, can provide a solid scientific basis for tableting scale-up. It is a method for producing dimensionless numbers that completely describe the process. The analysis should be carried out *before* the measurements are made, because dimensionless numbers essentially condense the frame in which the measurements are performed and evaluated. It can be applied even when the equations governing the process are not known.

II. DIMENSIONAL ANALYSIS—RELEVANCE LIST

With the basic dimensions of mass, length, and time denoted as [M], [L], and [T], respectively, the relevance list for the target quantity H [$ML^{-1}T^{-2}$] (mechanical tensile strength of the tablet) included:

Depth of fill, or loading depth of the powder bed h [L]
Final (out-of-die) tablet thickness h_t [L]
Compression roll diameter D_{cr} [L]
Maximum applied compression pressure p_m [$ML^{-1}T^{-2}$]

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Table 1 Core and Residual Matrices

	Core matrix			Residual matrix				
Dimension	κ	h_t	n	H	h	D_{cr}	p_m	τ
Mass [M]	−1	0	0	1	0	0	1	0
Length [L]	1	1	0	−1	1	1	−1	0
Time [T]	2	0	−1	−2	0	0	−2	1

Compression rate n [T^{-1}]
Powder compressibility parameter κ [$M^{-1}LT^2$] = $\Delta V/(\Delta p \cdot V_t)$ (where ΔV and Δp are the changes in tablet volume V and applied pressure p, respectively, and V_t is the final tablet volume)
Geometric dwell time τ [T]

Geometric dwell time is an indicator of a linear speed, sort of a yardstick that allows one to compare speeds of different tablet presses. It is defined here as the time required for a punch to traverse a horizontal distance of 9.5 mm (when the flat portion of the IPT Type B punch head is in contact with the compression wheel).

III. DIMENSIONAL ANALYSIS—DIMENSIONAL MATRIX

The dimensional matrix consists of a (square) core matrix and a residual matrix. Based on our relevance list, the dimensional matrix representing a tableting process can be written as shown in Table 1.

By a simple linear transformation, the core matrix becomes a unity matrix (Table 2).

The dimensionless numbers are formed as fractions, where each physical quantity indicated in the residual matrix represents the numerator, while a product of all quantities of the core matrix (with the exponents indicated in the residual matrix) constitutes the denominator. This standard procedure yielded the following Π set:

$$\{H \cdot \kappa,\ h/h_t,\ D_{cr}/h_t,\ p_m \cdot \kappa,\ n \cdot \tau\}$$

Table 2 Unity Matrix

	Unity matrix			Residual matrix				
Dimension	κ	h_t	n	H	h	D_{cr}	p_m	τ
−[M]	1	0	0	−1	0	0	−1	0
[L] + [M]	0	1	0	0	1	1	0	0
−([T] + 2[M])	0	0	1	0	0	0	0	−1

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Table 3 Tablet Press Parameters

Tablet press	Number of stations	Compression roll diameter D_{cr} (mm)
Manesty Betapress	16	177.8
Fette 2090	36	300

The target dimensionless quantity ($H \cdot \kappa$) can be expressed in terms of all other dimensionless quantities.

IV. EXPERIMENTAL RESULTS

To test the foregoing dimensionless relationship, two powders (Avicel PH101, a ductile, viscoelastic material, and Emcompress, a brittle material, blended with 0.5% magnesium stearate) were compressed on the Presster™, a single-station mechanical replicator of rotary tablet presses. In the first set of experiments, a 16-station Manesty Betapress (a research-scale press) was simulated at two speeds, 60 and 100 rpm. In the second set, a 36-station Fette P2090 (a medium-scale production press) was simulated at two speeds, 55.8 and 70 rpm. It should be noted that 100 rpm of the Betapress corresponds to 55.8 rpm of the Fette 2090 in terms of the linear speed of the turret. Basic parameters for the two tablet presses are presented in Table 3.

A standard IPT Type B tooling was used with a $\frac{3}{8}''$ round flat tool tip. Tablets were made one at a time, and the compression force as well as the upper punch displacement and lower punch displacement were recorded. Tablet weight, thickness, and breaking hardness were measured for each tablet.

The Presster™ is a single-station press that can mimic the load profile of any production press. The Presster™ uses mechanical means to achieve geometric similarity with different tablet presses. Kinematic and dynamic similarities are achieved by matching the speed and force of compression. The process parameters for both press simulations are indicated in Table 4.

Multiple regression of the target quantity ($H \cdot \kappa$) on a combined data set (including data for two materials, two presses, two speed levels for each press, and a

Table 4 Process Parameters

	Measured compression speed (RPM)	Compression force (kN)	
		Avicel	Emcompress
Manesty Betapress	57.7 to 111.6	2.0 to 11.5	5.1 to 26.3
Fette 2090	53.3 to 88.5	4.8 to 6.8	6.9 to 31.1

Table 5 Regression Table ($N = 61$)

	b_i	Standard error of b_i	t (56)	p-level
Intercept	49.7966	2.4245	20.5387	0.0000
$\ln(h/h_t)$	9.0029	0.3925	22.9383	0.0000
$\ln(D_{cr}/h_t)$	−5.7702	0.5174	−11.1502	0.0000
$\ln(p_m \cdot \kappa)$	−5.7195	0.5225	−10.9463	0.0000
$\ln(n \cdot \tau)$	0.7234	0.1193	6.0654	0.0000

Multiple $R = 0.9788$, $F(4,56) = 320.32$, $p < .00000$, Std. error of estimate = 0.28708

range of compression forces) in a log-log domain yielded a multiple regression coefficient of 0.9788. Regression coefficients for each of the dimensionless variables of the Π set were found to be highly significant (p-level of less than 0.00001).

The resulting regression equation was

$$\ln(H\cdot\kappa) = \ln\{a\cdot(h/h_t)^{b_1}\cdot(D_{cr}/h_t)^{b_2}\cdot(p_m\cdot\kappa)^{b_3}\cdot(n\cdot\tau)^{b_4}\}$$

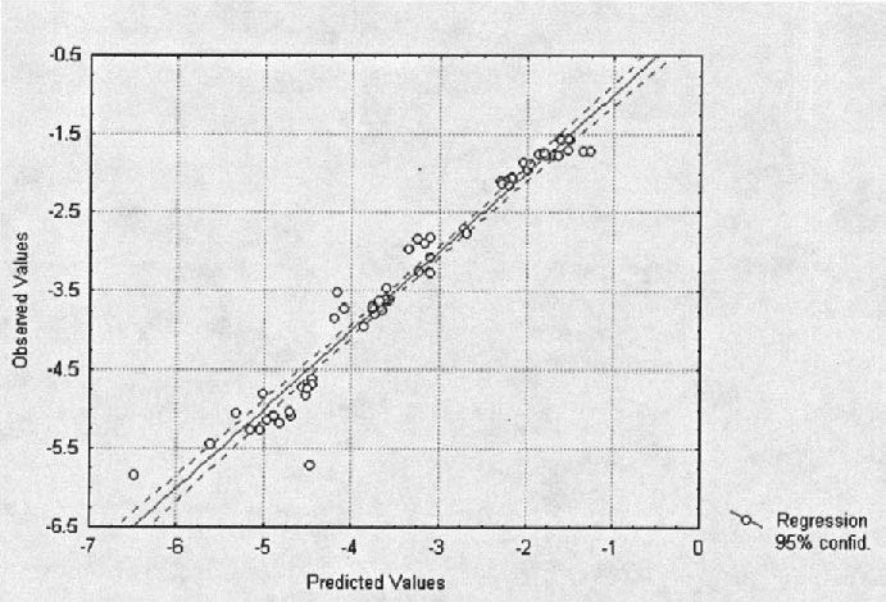

Figure 1 Observed vs. predicted data.

The relevant statistics are summarized in Table 5. The regression plot is presented in Figure 1.

V. CONCLUSION

It was demonstrated that dimensional analysis of the tableting process can produce a scientifically reliable way of predicting tablet properties across the range of materials and with diverse compaction mechanisms. A theoretically sound scale-up method is thus readily available for tableting equipment of different capacity. The method can be readily expanded to include other materials and tablet presses and other target quantities, such as tablet stability (disintegration) and bioavailability (dissolution).

VI. CALCULATIONS AND FORMULAE

Tensile strength H of a tablet was calculated as

$$H = 2C/(p \cdot d \cdot h_t)$$

where

C = crushing force
d = die diameter

Loading depth h was calculated as

$$h = V_0/A$$

where

V_0 = initial powder volume ($V_0 = W \cdot d$)
W = tablet weight
d = bulk density (0.468 g/cc and 0.962 g/cc for Avicel and Emcompress, respectively)
A = punch tip area ($A = p \cdot d^2/4$)

Applied maximum pressure p was calculated as

$$p = F_m/A$$

where

F_m = peak compression force

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Table 6 Powder Compressibility Parameter

Material	Powder compressibility parameter κ (mm^2/N)
Avicel PH101	2.450E-02
Encompress	7.582E-03

The powder compressibility parameter κ was calculated as defined,

$$\kappa = \Delta V/(\Delta p \cdot V_t)$$

where

ΔV = change in tablet volume ($\Delta V = V_0 - V_t$)
V_t = final tablet volume ($V_t = A \cdot h_t$)
Δp = change in compression pressure ($\Delta p = p_m$)

For the purpose of this study, the average powder compressibility parameter κ was calculated as shown in Table 6.

9
Scale-Up of Film Coating

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I. INTRODUCTION

A. Overview of Coating Processes

A comprehensive overview of pharmaceutical coating (materials, formulations, and processes) has been given by Porter and Bruno [1]. It should be noted that there has been a steady transition in the pharmaceutical industry, beginning with sugar coating, moving to film coating, and finally arriving at aqueous film coating. Sugar coating can be characterized as a relatively complex but noncritical process. Complexity stems from the multiplicity of coating formulations used during one process and the sequencing (dosing, distributing, and drying) that must take place for each application of coating liquid; noncriticality is associated with the fact that precise control over process parameters (air volumes, temperatures, spray rates, etc.) is not a prerequisite for success in the process. In contrast, film coating is relatively simple but critical process. In this case, simplicity relates to the need to use fewer (and sometimes only one) coating formulations during the process, which are usually applied in a continuous but controlled manner; criticality is manifest by the need to identify and control a range of key processing factors, especially when applying water-based coating formulations.

Although both sugar coating and film coating are utilized by a significant number of pharmaceutical companies worldwide, the film-coating process is the one most often preferred today. Film coating was formally introduced into the pharmaceutical industry in the middle of the last century. Initially intended to provide a means for more rapidly applying coatings to pharmaceutical tablets, it has readily been adapted for coating other types of products (such as pellets, granules, powders, and capsules). In general terms, film coating is a process whereby a

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polymer-based coating is applied to the substrate such that:

The rate of application of the coating fluid and the drying rate are carefully controlled.
The coating material is uniformly applied to the surface of the substrate.
The quality and functionality of the applied coating are both maximized and reproducible.

Although film coatings are most often applied for their aesthetic qualities, they have a important role to play in improving product stability and robustness, as well as enhancing flavor attributes, facilitating ingestion, and modifying drug release characteristics.

Film-coating formulations encompass those that are expected to allow a drug to be rapidly released from the dosage form, those that may possess special barrier properties (with respect to, for example, moisture or oxygen), and those designed to modify drug release characteristics and facilitate drug targeting. As such, these coating formulations are exemplified by:

Organic solvent–based solutions of polymers [1]
Aqueous solutions or dispersions of polymers [2]
Hot-melt systems [3]
Powder coatings [3]

Despite the apparent variety expressed by these options, aqueous systems hold a dominant position in the pharmaceutical industry at this time. As a consequence, serious constraints are often imposed on the products being coated, the coating formulations used, and the coating processes that are adopted, with the result that scaling up the coating process can present serious challenges.

It is one of the intriguing contradictions of film coating, especially when considering aqueous processes, that, in order to create a more robust product, the initial product has to be designed to survive a process that becomes progressively more stressful the larger the scale of process employed. Such stress is associated with both the environmental conditions within the process and the attritional effects to which the product being coated is subjected. It is often a failure to appreciate these issues that reduces the likelihood of achieving complete success during the scale-up process. It is also worth remembering that process scale-up is not a one-time event; rather, it can be an ongoing process that is driven by the need to increase capacity and cut operating costs throughout the product life cycle. Under these circumstances, the need to modify a less-than-optimal process to accommodate ongoing scale-up issues may face regulatory constraints that prevent total success from being achieved. There is no substitute, therefore, for taking great steps to confirm the robustness of both formulations (core and coating) and coating processes, especially since critical decisions may have been made on the ba-

sis of laboratory-scale trials conducted early on in the development process. More on this subject will be discussed later in this chapter.

1. Film Coating—Equipment Concepts

At the heart of any coating process is the coating vessel, which can take one of two forms:

Coating pans
Fluid-bed coating equipment

In the beginning, film-coating equipment was commonly derived from that used in the sugar-coating process, namely, conventional coating pans. The early days of film coating, however, coincided with the introduction of a fluid bed coating process developed by Dale Wurster [4], and this quickly became adopted for many film-coating operations. The growing demand, however, to find alternatives to the use of organic solvents, together with the introduction of the side-vented coating pan (initially in the form of the Accela-Cota), has resulted in coating pans being preferred for coating tablets, whereas fluid bed processes are more commonly employed for coating multiparticulates [5]. While a veritable plethora of coating equipment is available in the industry today (especially since generic versions of many of the pioneering developments are now available), the basic concepts of panning equipment are shown in Figure 1 and those of fluid bed equipment in Figure 2.

The availability of such a variety of equipment often adds an extra degree of complexity to the scale-up process. Geographical preferences in equipment

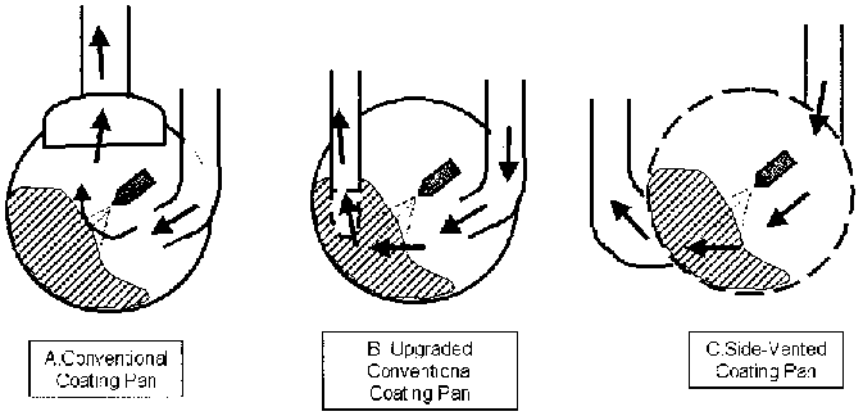

Figure 1 Schematic diagram highlighting the basic concepts of pan-coating equipment.

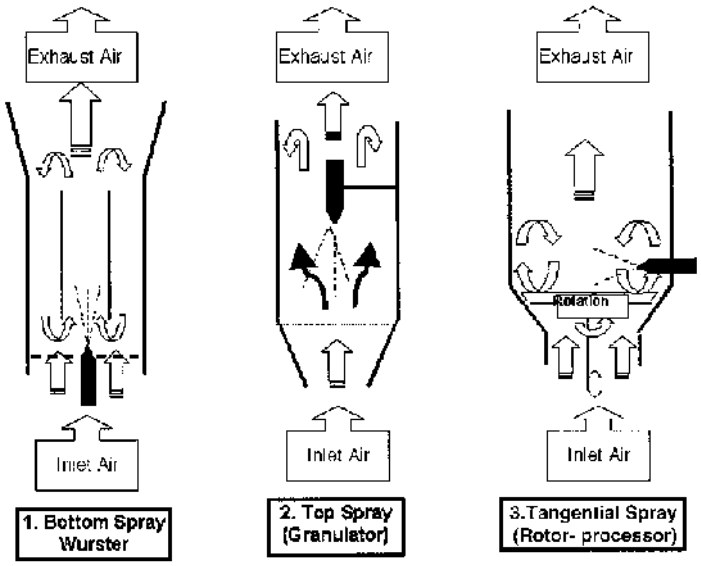

Figure 2 Schematic diagram highlighting the basic concepts of fluid bed coating equipment.

selection (often as the result of a desire to source locally and take advantage of vendor support programs) often means that the manufacturing-scale equipment available may differ from the equipment used during process development, even when the equipment design is essentially based on the "same operating principles."

2. Thermodynamics of the Film-Coating Process

Since the majority of film-coating operations around the world utilize aqueous coating processes, it is often useful to apply thermodynamic models to the process. In this way, the development-scale process can be fundamentally characterized, based on application of the first law of thermodynamics, as suggested by Ebey [6], allowing more accurate predictions for operating the production-scale process in a manner so that the two processes are essentially equivalent.

Ideally, of course, it would be desirable to operate all processes under constant conditions. Such an ideal is often beyond the practical capabilities of many film-coating operations. Application of the concepts proposed by Ebey, however, usually permit predictive processing adjustments to be made in order to allow for natural variation in the coating process. For example, for a process where the

moisture content of the processing air varies from day to day, season to season, etc., it is possible to determine what changes, for example, in spray rates, inlet-air temperatures, or inlet-air volumes are required to maintain the product temperature at the predetermined set point. By way of example, the initial process conditions outlined in Table 1 represent process conditions for an aqueous film-coating process conducted in a laboratory-scale coating pan where the moisture content of the inlet air is such that its dew point is 4.5°C. The modified conditions in the same table exemplify how the process can be adjusted by changing the spray rate to maintain an equivalent process when the moisture content of the inlet air has increased (to where the dew point is now 15.5°C).

Though mathematical tools such as those described by Ebey are useful for predicting adjustments in order to maintain the equivalency of two processes, it must be remembered that these tools are evaluating the macroenvironment within those processes. The changes that may, however, be taking place at the microscopic level (as, for example, that which exists at the precise moment when droplets of coating liquid make contact and begin to interact with the surface of tablets, pellets, etc.) are much more complex and much less predictable. Mathematical models as suggested here, however, still have value in making predictions that can often reduce the actual number of coating trials that need to be performed, even though they cannot be used to predict empirical results, such as coated tablet aesthetics.

Table 1 Example of Application of Thermodynamic Model to Predict Adjustments in Process Conditions When the Inlet-Air Moisture Content Is Increased

Process parameter	Initial process	Modified process
Spray rate (g min^{-1})	75	72
Coating solution solids content (% w/w)	15.0	15.0
Inlet-air temperature (°C)	70	70
Inlet-air dew point (°C)	4.5	15.5
Process-air volume:		
(cfm)	200	200
(m^3h^{-1})	350	350
Exhaust-air temperature (°C)	43	44
Environmental equivalency factor, EE	1.761	1.761

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3. Boundaries of the Film-Coating Process

Unlike the processes described elsewhere in this book, the film-coating process is inherently much more complex, since the list of parameters that contribute to overall success is potentially exhaustive. Thus the complexities of the scale-up process are potentially more challenging. In basic terms, these three components of the film-coating process all contribute, in a very much interactive manner, to the overall success of the process:

The core (ingredients, size, shape, surface chemistry, physical attributes, etc.)
The coating (ingredients, solvents, surface chemistry, rheology, tackiness, etc.)
The coating process (equipment design, process parameters employed, maintenance and calibration programs, etc.)

The inherent complexities of this process are well illustrated by the process operational boundaries highlighted in Figure 3. Although this diagram specifically references tablet coating in a side-vented pan, the concepts are applicable to the film coating of all types of products in a wide variety of coating machines.

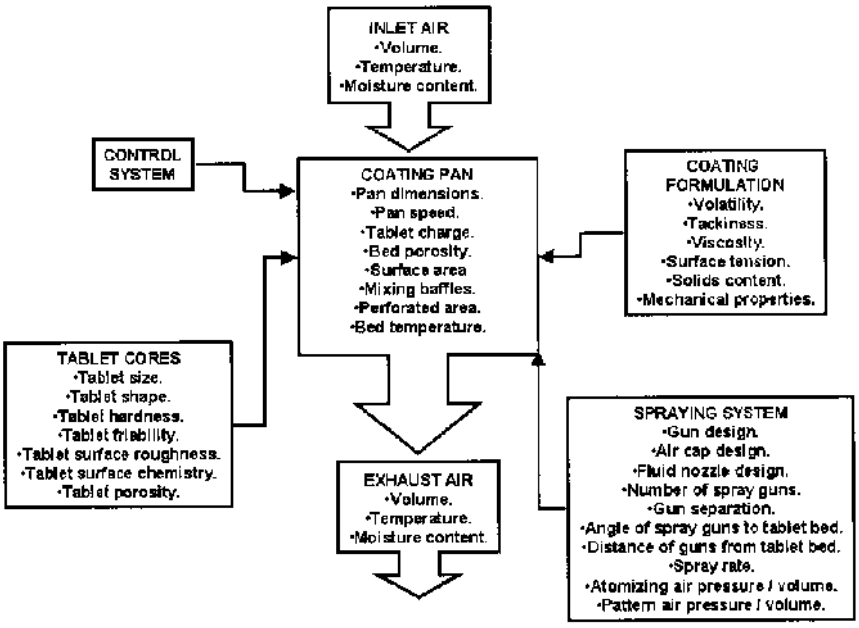

Figure 3 Outline of the operational boundaries of a film-coating process.

II. SCALING UP THE COATING PROCESS

A. General Factors to Consider

The introductory section has provided the reader with some idea of the complexities of pharmaceutical coating processes, especially those relating to the now predominant aqueous film-coating process. These complexities can be transformed into serious challenges that face the scientists and engineers charged with the responsibility for scaling up the coating process. Unlike that associated with many other unit operations, scale-up of the coating process involves much more than just dealing with larger batch sizes and faster throughputs. Application of coatings, often being the penultimate step to packaging, can leave a long-lasting impression in terms of product appearance and product performance (both in terms of functionality and stability). Additionally, once the coating stage is reached, there has already been much investment (time and money) in that batch of product.

In a somewhat simplistic way, scale-up of a coating process typically involves:

Taking a laboratory-scale process (hopefully one that has been appropriately optimized) and transferring the processing technology first to the pilot scale and ultimately to full production scale
Further optimizing the process on the larger scale to take into account issues whose influence could not easily be predicted during earlier process development activities

Irrespective of the type of coating process used, the potential process changes that commonly occur on scale-up include:

Increased batch sizes
Increased attritional effects
Increased spray rates
Increased number of spray guns (or change from a single- to a multiple-head nozzle)
Increased drying air volumes
Increased processing times (per batch)

Many of these parameters are quite predictable, especially when applying some of the thermodynamic concepts described earlier. The increased processing time, which brings with it increased exposure to stressful conditions (both mechanical and as a result of environmental conditions used in the process, especially when that process is aqueous based) is much more unpredictable, and is often the root cause of much angst during the preparation of early commercial batches.

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1. The Robustness Factor

In spite of the issues outlined in the previous section, all too often the amount of time spent on formulation and process design is inconsistent with the impact that is felt when performance in the coating operation fails to meet expectations. More attention in this regard is usually paid when the applied coating has some specialized functionality (such as improving product shelf life or modifying drug release characteristics); however, even when the purpose of the coating is primarily for aesthetics and product identification (in which cases, poor coated product quality is unlikely to impact product efficacy), failure to meet certain visual standards all too often results in batch rejection, leading to:

Discarding the batch (often determined on the basis of balancing recovery costs with the inherent value of the batch)
Reprocessing the batch
Sorting the batch to remove defective material

In each of these cases, there is a certain financial cost associated with potential product loss, reprocessing, and work in process.

Clearly, therefore, there is a strong incentive to ensure that:

The formulations (core and coating) are sufficiently robust to meet the needs of the operation. This requirement is all the more important when viewed in terms of the increased (but often ill-defined) stresses to which the product is subjected on scale-up.
Critical elements of the coating process and their impact on final product quality (in the broadest sense) have been determined and taken into account during process optimization.

While these requirements seem obvious, they are often ignored. Critical decisions with respect to the design of coating formulations and processes are frequently made on the basis of data produced from small-scale processing trials. The consequences of such decisions only become apparent after product approval, thus resulting in the fact that the changes required to rectify matters are often very much constrained by regulatory issues (although these may be diminished to a degree as a result of the issue of the SUPAC Guidances).

One of the elements of film coating that attracts much attention at technical symposia is that dealing with troubleshooting. This very fact is a clear indication of how poorly the matters described here are considered. Although it is certainly important to understand the issues that can potentially lead to problems and to explore recovery options, the very idea that troubleshooting needs to be considered is clearly an admission of failure during critical stages of product and process development. The photographs shown in Figure 4 provide typical examples of problems that crop up all too often under the troubleshooting banner and usually relate to some aspect of the coating process employed.

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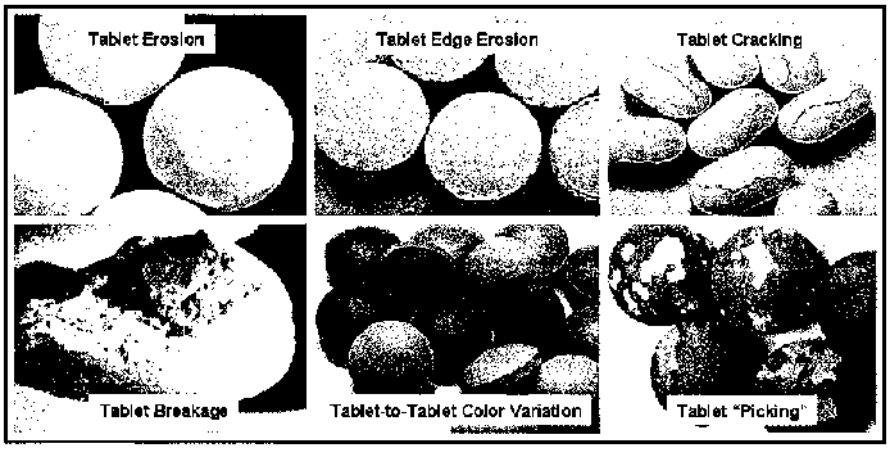

Figure 4 Common examples of film-coating problems that trigger troubleshooting exercises.

2. Opportunities for Process Optimization and Use of Expert Systems

A lot of the data developed during product and process development are often empirically derived and, as such, reflect the relative experience and preferences of those responsible for that development process. Although application of such experience can be of tremendous value, it is not unusual to find that each new product that is being developed, or process refinement being employed, has inherent idiosyncrasies that reduce the relevance of prior experience. In order to create a "robust" product and process, personal bias has to be removed, and, instead, decisions must be made based on scientific validity. All too often, the phrase "we have fully optimized the product and process" is used to describe a situation where decisions have been made on the basis of an iterative process where process (and formulation) variables have been studied in a "trial and error" manner, changing one parameter at a time. This process, often called one of "successive approximation," is followed until an acceptable process has been achieved. The problems associated with employing such techniques include:

A truly optimal process (or product) is rarely achieved.
A comprehensive database that relates to the critical features of that process is rarely obtained,
Subsequent decisions that demand further process modifications (for example, on the basis of meeting operational requirements to improve process productivity or reduce process costs) often confound the "optimization" process.

The answer to these concerns involves the employment, during the development process, of techniques that utilize a design of experiments (DOE) approach. The application of such techniques has been well documented in the published literature. For example, Porter et al. [7], in examining a side-vented pan process, were able to produce unambiguous quantitative results that defined how, inter alia, uniformity of distribution of the coating and coating process efficiency could be maximized while meeting other objectives with respect to coated product quality (for example, gloss, smoothness, and residual moisture content). Turkoglu and Sakr [8], in studying the application of a modified-release coating to pellets in a rotary fluidized-bed process, determined that coating temperature and atomizing air pressure were key factors that influenced drug release from the pellets when applying an aqueous ethylcellulose dispersion. Finally, Rodriguez et al. [9] employed similar techniques when studying the thermodynamics of an aqueous film-coating process performed in a GS Coating Systems pan.

Ultimately, the real advantage of utilizing a DOE approach during process development and optimization is that:

All critical process parameters can be identified in a way that removes personal bias.
A truly optimized process can be developed that has a sufficiently sound scientific basis to satisfy queries from regulatory agencies.
Further process refinements, particularly during scale-up, can be made in a much more predictable manner when faced with the need to meet specific operational constraints.

Clearly then, adopting a formal, scientifically valid approach to designing and optimizing a particular coating process provides a good foundation ultimately for scaling up that process. That having been said, in these days of globalization, the scale-up process can involve technology transfer from one department to another that may be geographically remote from one another. In such a situation, the department on the receiving end of the transfer process may be in a technical void with respect to critical knowledge about that process. Under these circumstances, ready access to such technical information (on a 24-hour basis) is often of paramount importance if success in the scale-up process is to be achieved and maintained. Considering such knowledge may reside with only a few key people, the challenge is thus how to provide the necessary access.

Conventional wisdom is to prepare exhaustive technical reports, either in hard copy or electronic form, that can be distributed as need requires. In the present environment, however, instant access to information, utilizing a user-friendly approach, is often demanded. One such approach that is gaining more attention in the pharmaceutical industry involves the application of *expert systems.*

Fundamentally, these systems consist essentially of a computer program that makes decisions or recommendations based on knowledge gained from experts in the field. Such programs are usually customized to fit a given situation and

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can utilize tools such as artificial neural networks, rule-based systems, and decision trees. The application of expert systems to pharmaceutical processes (including film coating) has been described by Rowe [10], and the commercial availability of such systems has been demonstrated [11].

So far, the discussion has centered on providing a description of the basis for typical film-coating processes, outlining some of the critical issues that need to be considered when contemplating process scale-up, and identifying some useful tools that may be employed to facilitate that process. Clearly there is no substitute for careful preparation, and the benefits of doing so can best be illustrated by reference to case studies that exemplify scale-up studies that have been successfully concluded. In this regard, the case studies that will be discussed involve scaling up a process that includes:

Coating of tablets in a pan process
Coating pellets in a fluid bed process

B. Scaling Up a Pan-Coating Process

1. Introduction

It should be quite clear now that time and money spent designing a robust process (where all of the critical process factors have been defined and their impact well documented) has the potential to save time and money later on, especially during the time leading up to and immediately after product launch. Designing an optimal process also has great benefit in the training of process operators so that they become well informed about the critical constraints of that process.

If a particular process is going to be used for a range of products that have similar characteristics, then time spent optimizing that process provides benefit many times over. There will, however, be times when a particular product has special needs that will mean that a well-optimized process may have to be further refined to meet those needs. Such a requirement is particularly evident when a coating process that has been designed for the application of conventional coatings (where aesthetics may be high on the list of attributes defining product quality) is now required to be adapted for the application of highly functional coatings, such as modified-release coatings (in which case, drug release characteristics will assume a much greater degree of importance).

Some key attributes of coated products and coating processes that may well be used to set objectives for optimizing a coating process are shown in Table 2. In many cases, the attributes as listed are very subjective and thus must be defined in clearly measurable terms if they are to be used as the basis for process optimization. Additionally, meeting defined objectives may equally be dependent on the existence of certain coating and tablet formulation attributes as well. Nonetheless, although the information listed in Table 2 is not meant to be all-inclusive, it does provide an idea of the types of response that could be used as a basis for optimizing a coating process.

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Table 2 Coated Product Attributes and Coating Process Characteristics That May Be Used as Objectives to Develop an Optimal Process

Coated tablet attributes		Coating process characteristics
Aesthetic	Functional	
1. High gloss	1. Drug release characteristics meet target requirements	1. High (and reproducible) process coating efficiency
2. Smooth coating	2. Coated product meets stability requirements	2. High uniformity of distribution (on a weight basis) of coating from tablet to tablet
3. Good color uniformity	3. Effective taste masking is achieved (if required)	3. High productivity
4. Absence of edge chipping	4. Coated tablet meets target strength requirements	
5. Absence of film cracking		
6. Absence of logo bridging		
7. Absence of twinning		
8. Absence of picking		

When optimizing a coating process, however, a major challenge that must be faced involves selecting the appropriate process variables that must be examined. Reference to the operating boundaries of a typical coating process shown in Figure 3 clearly indicates that the list of potential variables to be studied is quite extensive. In order to create a manageable design of experiments program, the list of variables to be studied should not typically exceed four or five; otherwise the number of coating trials to be undertaken becomes prohibitive. Thus attention should be focused only on those variables that have a critical role to play. Reducing the number of variables to a manageable level can be accomplished in a number of ways, including:

Fixing as constants those variables that are not open to change (for example, selecting a particular type of coating pan, spray gun, mixing baffle design, pan loading, etc.).

Applying a preliminary screening technique, where a larger number of variables can be studied in a much more superficial manner. This approach enables the critical variables to be identified and then used as the basis for a more comprehensive evaluation.

Earlier reference was made to published articles that described the use of optimization techniques for coating processes. In particular, the one presented by Porter et al. [7] provides a useful example of how aesthetic, functional, and processing issues can be dealt with. The key elements of the study that formed the basis for this article are listed in Table 3; typical results obtained in this study are summarized in Table 4. From these data, it is possible to optimize the coating pro-

Table 3 Process Parameters Examined in a Study Designed to Optimize a Coating Process Based on the Use of a 24″ Laboratory Side-Vented Coating Pan

Coating process variable	Variable range setting
A. Fixed operating parameters	
1. Pan loading (kg)	15.0
2. Drying air (cfm)	Inlet: 250; exhaust: 300
3. Coating system	Opadry II
4. Quantity of coating applied (% w/w)	3.0 (theoretical)
5. Pattern air pressure	
(psi)	30.0
(bar)	2.1
B. Variable operating parameters	
1. Solids content of coating suspension (% w/w)	10–20
2. Inlet-air temperature (°C)	60–90
3. Spray rate (g min^{-1})	35–75
4. Atomizing air pressure	
(psi)	22–60
(bar)	1.5–4.1
5. Pan speed (rpm)	8–20
6. Number of spray guns used	1 or 2

Table 4 Typical Results Obtained in Optimization Study

Response measured	Response units	Response ranges
Uniformity of distribution of coating material	% RSD	11.88–59.59
Coating process efficiency	%	26.23–99.37
Roughness value of applied coating[a]	R_z, μm	7.76–15.90
Gloss value of applied coating[b]	G_u at 60° angle	2.60–3.78
Final moisture content of coated tablet[c]	% w/w	0.10–5.33
Exhaust temperature of coating process	°C	32.8–57.3

[a] The higher the value, the rougher the coating.
[b] The higher the value, the glossier the tablets.
[c] Initial uncoated tablet moisture content was 3.0% w/w.

cess with respect to:

Aesthetic qualities (gloss and coating smoothness) of the final coated tablet
Potential impact on final tablet stability (as this relates to product temperatures experienced in the process and residual coated tablet moisture content)
Process efficiencies (with respect to actual vs. theoretical amount of coating applied, and uniformity of distribution of the coating)

An important fact to be recognized, however, is that an extensive database relating to the coating process in question has been established, and key process variables (including their interactive effects) have been identified, providing a sound platform from which to begin the scale-up process.

2. Predicting Scale-Up Issues

Once an appropriate laboratory-scale process has been established, many of the key elements of the process should have been determined. Some operating parameters (such as inlet-air temperature, coating formulation to be used, and solids content of the coating solution/suspension) can be directly translated to the larger-scale process. Others, however, will have to change, and these include:

Drying-air volume
Pan speed
Pan loading
Number of spray guns to be used
Gun-to-tablet-bed distance
Spray rate
Spray gun dynamics

a. Drying-Air Volume. Drying-air volume, although potentially variable, is often selected based either on the recommendations of the vendor of the equipment to be used or on the basis of the optimum conditions designed for the air-handling system that has been installed. The supply- and exhaust-air fan speeds should be set, based on the equipment used, to meet the negative pressure pan settings that are usually recommended. Once the appropriate drying-air volume has been established, this setting becomes a driver for other key processing variables, such as spray rate (see later discussion).

b. Pan Speed. Selecting appropriate pan speeds often becomes more of a challenge than is really necessary. Clearly tablet motion, a factor influenced greatly by pan speed, can be a major issue when it comes to potential tablet breakage, edge wear, and surface erosion. On the other hand, according to data established by Porter et al. [7], the uniformity of distribution of the applied coating is also greatly influenced by pan speed, with the higher pan speeds being better in

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this regard. Consequently, there is a great incentive to design tablet cores so that they can withstand high pan speeds in order to allow coating uniformity to be fully maximized.

Typically, those pan speeds that are selected on scale-up are often lower than are truly optimal, in recognition of the fact that attritional effects do increase with increasing scale of process. Nonetheless, a good rule of thumb, based on pan speeds used on the laboratory scale and dimensions of the laboratory-scale equipment, is to calculate the linear velocity of the tablets in the coating pan and then to determine the pan speed on the larger scale that will give an equivalent linear velocity. In this way, tablet dwell time in the spray zone on the larger scale will be equivalent to that achieved on the smaller scale, and full benefit can be taken of the optimization strategies used on the smaller scale to maximize uniformity of distribution of the coating. An example of how pan speed can be determined on scale-up is shown Table 5.

c. Pan Loading. In general, defining appropriate pan loading should not be a troublesome issue. A coating pan of given dimensions is designed to hold a certain charge of tablets. Unfortunately, pan loadings are usually defined in terms of *volume* fill, rather than by weight. Thus, the optimum pan loading by weight will vary from product to product depending on the *apparent density* (which takes into account the mass/volume ratio of an individual tablet as well as the shape and size of that tablet) of that product. Even allowing for such product variation, calculating optimal pan loadings should not be a serious challenge. The difficulty

Table 5 Estimating Pan Speed on Scale-Up

Parameter	Pan size			
Pan diameter	24 in. (60 cm)	36 in. (90 cm)	48 in. (120 cm)	60 in. (150 cm)
Typical pan rotational speed ranges (rpm)	5–20	3–17	2–15	2–11
Pan circumference	75 in. (190 cm)	115 in. (290 cm)	150 in. (380 cm)	190 in. (480 cm)
Peripheral pan speed at 10 rpm	12.5 in. sec^{-1} (31.8 cm sec^{-1})	19.2 in. sec^{-1} (48.8 cm sec^{-1})	25.0 in. sec^{-1} (63.5 cm sec^{-1})	31.5 in. sec^{-1} (80.0 cm sec^{-1})
Projected pan rotational speed at a peripheral speed of 12.5 in sec^{-1} (31.8 cm sec^{-1})[a]	10	6.5	5.0	4.0

[a] This example is based on the rotational speed of 10 rpm used in a laboratory-scale coating pan.

arises, however, for these reasons:

On the laboratory scale, it is not too difficult to ensure that a pan is appropriately loaded. Even when only a very small amount of product is available, this problem can be dealt with by bulking up active tablets with placebos to make a full charge.

On the production scale, pan loading often has nothing to do with the ideal loading for the pan, but rather with the total batch weight of the compressed tablets and how evenly these can be divided into a whole number of pan loads. For example, if the total batch weight is 500 kg and these tablets are to be coated in a pan that optimally holds 120 kg per run, then the instructions will call for *five* pan loads of 100 kg each to be coated. The result is that each coating run will have each pan underloaded by about 16%.

In the example shown, a 16% underloading may not seem to be too much of a problem, but potentially critical issues that may arise (especially if the degree to which the pan is underloaded is even greater than the amount shown in the example) include:

The possibility that, in a side-vented coating pan, there may not be enough tablets in the pan to ensure that the exhaust-air plenum is completely covered (in which case, drying air will take the path of least resistance and flow directly toward the air plenum rather than passing through the tablet bed). With some designs of coating pan, this potential problem may be obviated by the placement of a sliding damper in the exhaust-air plenum so that the exposed part can be sealed off.

The potential that the side walls of the coating pan, or even baffles, become more exposed to the spray, causing coating liquid to build up on exposed metal surfaces, often with the results that tablets will stick to these surfaces. Again, with some foresight, changing the gun-to-bed distances, gun spacing, or, indeed, the number of guns used can minimize this problem. These solutions are likely to be utilized if, for a particular product, the pan loadings are relatively constant. In situations where compression batch weights frequently vary, then such corrective measures are less likely to be employed.

The likelihood that when the pan is significantly underloaded, as baffles move through the tablet bed as the pan rotates, the surface of the tablet bed moves sufficiently to change the gun-to-bed distance. This situation, as will be seen later, could potentially change the characteristics of the spray droplets that are impinging on the surfaces of the tablets.

As baffles become more exposed and as pan speeds are constantly adjusted to keep the tablets in motion (more of a challenge in an underloaded pan), there is increased risk that tablets will become damaged.

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Thus during product and process development, even though compression batch weights are often defined in terms of the capacities of blenders, granulators, dryers, etc., there is sufficient justification, when the product is to be coated, to keep in mind the capacities of the coating pans that will be used.

d. Number of Spray Guns to be Used. In any film-coating process, it is critical to ensure that the spray zone is optimized with respect to these key criteria:

- Making sure that the full width of the tablet bed is covered so that few, if any, tablets on the surface pass through the spray zone without receiving some coating
- Setting up each gun (in terms of atomizing and pattern air) so that maximum coverage is achieved without compromising the quality (in terms of droplet size, size distribution, droplet density, and relative "wetness") of the atomized coating liquid
- Avoiding overspray on to the pan side walls

This being the case, a major decision that has to be faced is how many spray guns should be used. The answer may well depend on the type of spray guns available. As will be seen in later discussion, some spray guns have greater capabilities than others in achieving broader coverage without compromising spray quality.

Sight should not be lost of the possibility that, on scale-up, the type of spray guns available on the production-sized equipment may be different that those used on the lab scale. This situation may arise because:

- The spray guns used on the laboratory scale are not capable of achieving the spray rates required or of maintaining effective atomization at those higher spray rates on the larger scale.
- Scale-up may involve transfer to a manufacturing site that is geographically remote from that where process development was undertaken, and preference may have been shown for locally sourced spray guns.

Unfortunately, scant attention is often paid to the need to minimize the number of changes that take place on scale-up, and this may be especially true in the case of spray-gun selection, where, all too often, one type of spray gun is assumed to be very much equivalent to another. Again, as will be seen later, such equivalency may be far from true.

Concluding, therefore, that the main objective is to maximize bed coverage, issues that greatly influence the choice in number of spray guns used will be those as shown in Figure 5, where broader coverage per gun may well reduce the number of guns required, while more restricted coverage, often chosen in attempts to produce better coated tablet quality (in terms of coating gloss and smoothness), will necessitate the use of a larger number of guns. The data listed in Table 6 illustrate how spray pattern can influence coated tablet quality, with round spray

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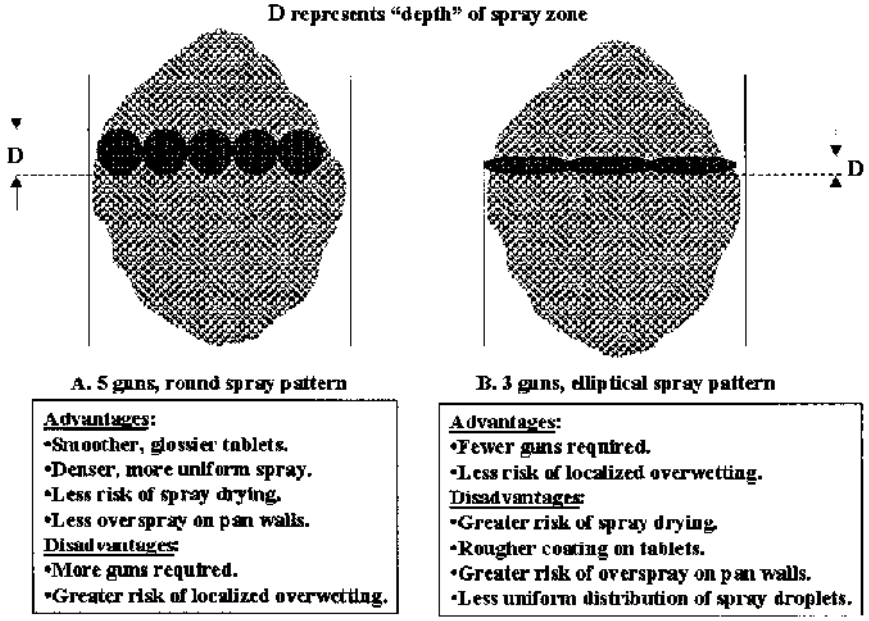

Figure 5 Influence of typical spray patterns on the number of spray guns used.

patterns tending to produce smoother coated tablets, although with the increased risk that localized overwetting can occur, resulting in greater likelihood of sticking and picking. Clearly, the main objective is to avoid problems like those shown in Figure 6, where ineffective bed coverage leads to increased opportunities for tablets to pass through the spray zone without receiving any coating.

Table 6 Influence of Spray Pattern Used on Tablet Quality

Polymer concentration (% w/w)	Atomizing air pressure	Spray pattern shape	Mean coating roughness, R_a (μm)	% Tablets showing defects (picking or sticking)
9	40 psi (2.8 bar)	Elliptical	2.72	24.0
		Round	1.68	26.0
9	60 psi (4.1 bar)	Elliptical	2.53	4.5
		Round	1.44	35.0
9	80 psi (5.5 bar)	Elliptical	2.29	2.5
		Round	1.29	35.0
12	60 psi (4.1 bar)	Elliptical	3.51	2.0
		Round	2.07	9.0

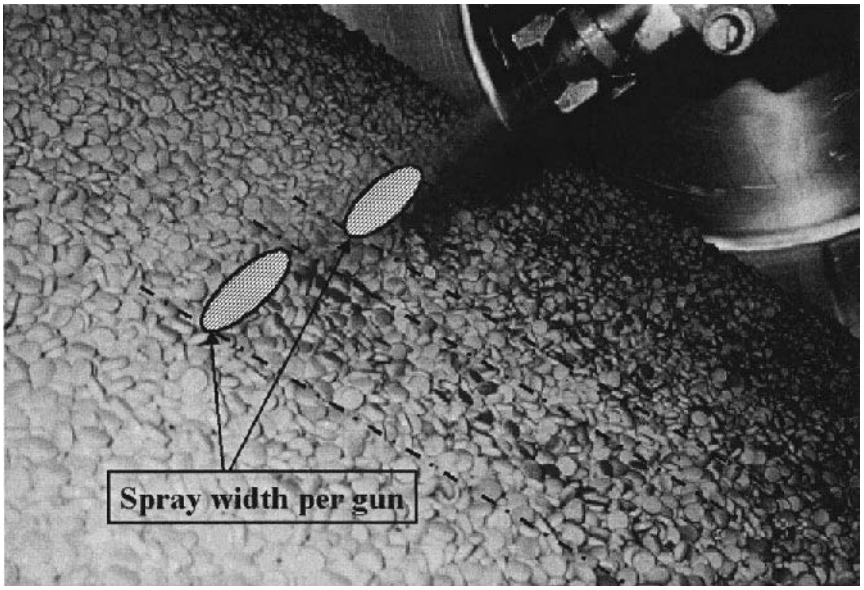

Figure 6 Example of how using too few spray guns leads to poor bed coverage.

e. Gun-to-Tablet-Bed Distance. There are very few examples of where a truly scientific approach is taken to establish appropriate positioning of spray guns inside coating pans (unlike with fluid bed coating machines, where gun location is more often predetermined). Typically, with the help of rudimentary positioning tools, such as a ruler, the operator is often left to set up gun position by eye. It is quite surprising that this feature of equipment setup often receives scant attention, considering that gun positioning needs to be optimized to:

Ensure that optimal and reproducible bed coverage is achieved.
Facilitate broad coverage while providing maximum surface drying time (before tablets on the surface of the bed "fold under" and get mixed into the tablet mass)
Achieve reproducible (from run-to-run) spray droplet characteristics as they arrive at the tablet surface (see later discussion)

It is also interesting to note that spray-gun-to-tablet-bed distances are often different in production-scale equipment than they are in equipment used in the laboratory. Fundamentally, if this parameter has been optimized appropriately during process development, then there is no reason not to believe that these distances should be the same, irrespective of the scale of the process used. Nonethe-

less, the rationale for the existence of differences includes:

On the laboratory scale, because of geometric constraints, there is often very little opportunity to optimize the gun-to-bed distance, and thus this parameter takes on a fixed setting often defined by personal preference. Once a move is made to the production scale, there is more opportunity to reconsider gun positioning (although logic does not always prevail).

On the production scale, only a suboptimal number of guns may be available, with the result that the guns are moved further back to ensure that appropriate bed coverage is achieved. This requirement may also be dictated by use of different types of spray guns on the larger scale that also necessitates repositioning to gain good bed coverage.

The spray rate per gun on the production scale can be substantially higher, requiring that the guns be moved further away to prevent localized overwetting.

Clearly, therefore, greater attention should be paid to how spray guns are set up. In reality, unless spray gun positioning is optimized during process development, the same type of guns are to be used in both the laboratory and the manufacturing plant, and the spray rate per gun can be maintained (within reasonable ranges) in both cases, it is futile to expect to be able to fix gun-to-bed distances no matter the scale of process used. Even so, greater consideration should be given to achieving these ideals.

Pragmatically, therefore, it is quite normal to find that gun-to-bed distances will be 50–60% greater on the production scale than those used on the typical laboratory scale (for a 24-in.), or 60-cm-, diameter coating pan holding 10–15 kg of tablets).

f. Spray Rate. Assuming there are no major climatic differences to be faced during technology transfer, then predicting typical spray rates to be adopted during scale-up is a relatively simple task. As a simple guideline, calculations should be based on the relative airflows used for each scale of process, as shown in Eq. (1):

$$S_2 = (S_1 \times V_2)/V_1 \tag{1}$$

where:

S_1 = spray rate used on the scale used in process development

V_1 = air volume used on the scale used in process development

V_2 = air volume used on the larger-scale process

S_2 = prediction for the spray rate to be used

If substantial changes in other parameters are expected (environmental humidity, processing temperatures as a result of heater capabilities, etc.), then better predictions can be made using the thermodynamic principles outlined in Sec. I.A.2.

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For a side-vented pan-coating process, the processing data shown in Table 7 exemplify some spray rates that may well be used during process scale-up. It is interesting to note from these data that the drying- (and exhaust-) air volumes used in the production-scale Hi-Coaters are somewhat lower than those seen in an equivalent scale Accela-Cota or, indeed, as might be predicted from studies conducted in a laboratory-scale Hi-Coater. These differences reflect design considerations that suggest that, in the Hi-Coater, incoming air has essentially no place to go except out through the exhaust plenum and thus must pass through the coating pan (and, thus, the tablet bed). In other types of side-vented coating pans, particularly those that are completely perforated, incoming air is often introduced into a cabinet that surrounds the outside of the coating pan itself and that must pass through the perforated section of the pan in order to gain access to the inside the pan (and thus effectively dry the tablets). As a consequence, fully perforated pans are often operated with higher drying-air volumes. These different requirements do not pose any problems unless a pharmaceutical manufacturer decides to switch from one type of coating pan to another and contracts with an independent vendor to provide the air handling equipment. In this situation, it is critical that recommended specifications (from the coating pan vendor) be obtained in order to ensure that the independent contractor provides an appropriately sized system.

These idiosyncrasies, in terms of air flow requirements, do complicate matters, however, when scaling up from one type of coating pan to another.

Table 7 Example of Operating Parameter Ranges Used When Scaling Up an Aqueous Film-Coating Process

	Pan type (and size or model)					
	Accela-Cota			Hi-Coater		
Parameter	24″	48″	60″	HCT 60	HC 130	HC 170
Inlet-air volume[a]:						
(a) cfm	250	1800	3800	260	900	1300
(b) $m^3\ hr^{-1}$	440	3200	6700	450	1600	2300
Exhaust-air volume[a]:						
(a) cfm	300	2000	4000	280	1300	2100
(b) $m^3\ hr^{-1}$	525	3500	7000	500	2300	3700
Inlet temperature (°C)	60–80	60–80	60–80	60–80	60–80	60–80
Exhaust temperature (°C)	40–45	40–45	40–45	40–45	40–45	40–45
Spray rate ($g\ min^{-1}$)	40–70	250–500	500–1000	40–70	300–600	500–900
Pan speed (rpm)	12–14	4–7	3–6	12–14	4–7	3–6

[a] These are nominal air volumes, since actual values may be different depending on the installation and on whether the coating pan vendor or an independent supplier supplied the air handling equipment.

These complications arise when applying the simple predictions [based on Eq. (1)] for spray rates. If the scale-up process involves switching from a laboratory-scale fully perforated pan to a production-scale Hi-Coater, there is a risk that the predicted spray rates will be understated. For the sake of the calculation, a useful rule of thumb is to *double* the value for the actual air volume that will be employed in the larger-scale Hi-Coater and to use that value solely for the purposes of the calculation.

g. Spray Gun Dynamics. Earlier in this section, frequent reference was made to the importance of establishing spraying conditions that are consistent from the development scale right up to that used in the manufacturing plant. Similarly, mention was also made of the scant attention typically paid to spraying dynamics and the lack of a strong understanding of what actually happens when droplets of coating fluid emerge from a nozzle, move toward the tablet bed, and impinge upon the surfaces of tablets.

All too often, an overly simplistic view is taken of the role that spray gun design (namely, brand of gun and features of the fluid nozzles and air caps used) can play in achieving good, reproducible coated tablet quality. The fact that spray gun design may differ (from laboratory to production setting) is often considered to have little relevance, and accommodations for such differences are routinely made based on prior experience and, often, instinct, without benefit of reference to scientific data. A commonly held assumption, therefore, is that guns made by one manufacturer are essentially the same in terms of gun performance as those from another and that differences that exist are purely in the features presented and, ultimately, the cost.

Quality attributes of film-coated tablets that can be associated with spray gun performance include:

Appearance:
- Coating gloss
- Coating roughness
- Existence of defects ("picking," edge chipping/edgewear, filling in of logos)
- Color uniformity

Functional:
- Uniformity of distribution of coating
- Coating porosity (which influences film permeability)
- Solvent (water) penetration into the tablet cores and, hence, product stability

Clearly, there is thus a great incentive to gain a better understanding of those factors that influence gun performance as well as those differences that exist between guns supplied from different manufacturers.

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In a recent presentation, Cunningham [12] has described some of the factors that can influence spray gun performance and has compared the performance of spray guns from different vendors. As can be seen from the results shown in Figure 7 (where the performance of a Schlick spray gun is compared to a Spraying Systems spray gun), the influence of gun-to-bed distance and coating suspension solids content on mean droplet size is quite different for each type of spray gun. In both cases, droplet size tends to increase the further away from the nozzle one goes (probably due to droplet collisions, causing size enlargement). The influence of coating suspension solids content on mean droplet size is much more pronounced, however, in the case of the Schlick gun (producing results in the range of approximately 25–275 μm, compared to the Spraying Systems gun, which yields droplet sizes in the range of 30–60 μm under the same conditions).

These results clearly have implications for situations where the type of gun may be changed on scale-up but also where gun-to-bed distance may also be changed in the same process. Comparing the data shown in Figure 8, the differences are even more pronounced when observing the influences of spray rate and atomizing air pressure on mean droplet size. Since these two parameters are commonly increased during the scale-up process, it can clearly be seen that little change would occur when using a Schlick gun, but the change would, indeed, be substantial if a Spraying Systems VAU gun were used.

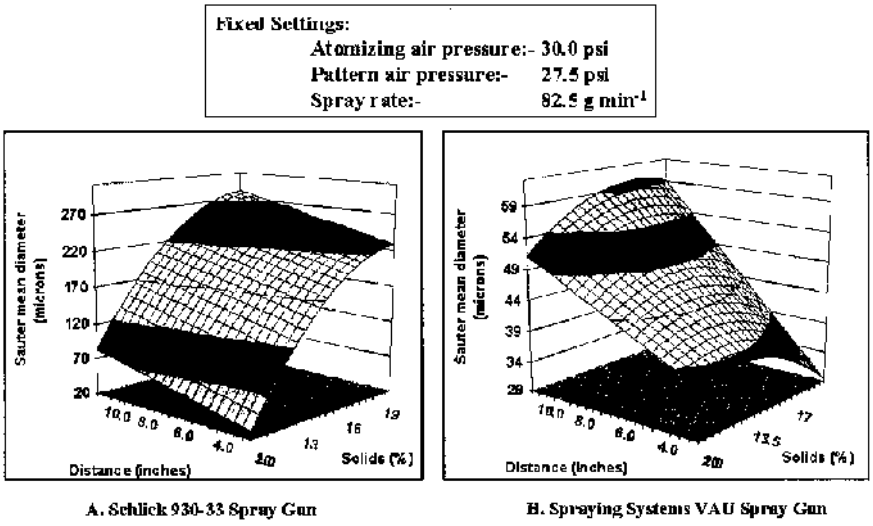

Figure 7 Example of how the type of spray gun used, gun-to-bed distance, and solids content of the coating fluid can influence the size of droplets generated.

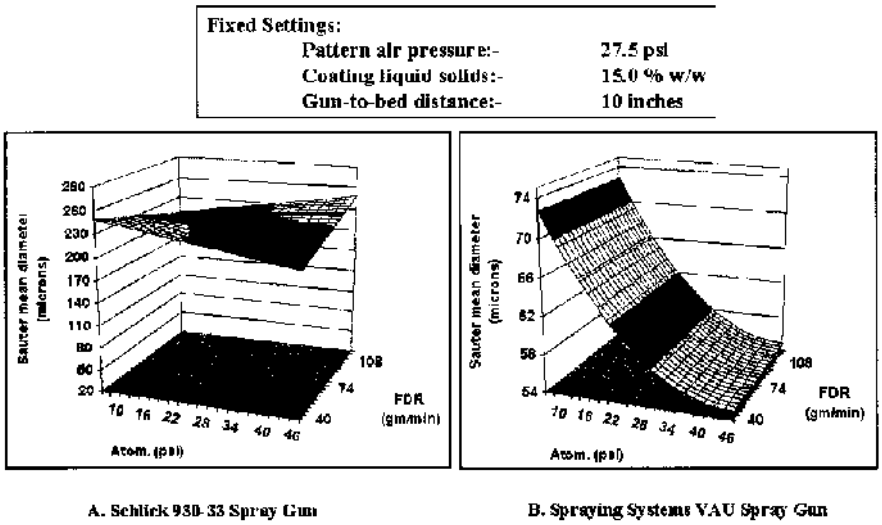

Figure 8 Example of how the type of spray gun used, atomizing air pressure, and spray rate can influence the size of droplets generated.

An argument might be made that, when coating tablets, such changes in mean droplet may be of no consequence, since the ranges of droplet sizes achieved are still quite small when compared to that of the tablets being coated. This viewpoint is overly simplistic, since the size of droplets formed can have an influence on coating smoothness and gloss as well an impact on how rapidly the liquid dries during flight from the spray nozzle to the tablet surface.

Further comparisons between these two types of spray guns indicate that there are differences in droplet velocity produced (see Fig. 9) as well as in the breadth of coverage on the surface of the tablet be (see Fig. 10). Droplet velocity, especially for those droplets arriving at the tablet surface, can potentially influence:

Wetting (velocity at impact can influence the advancing contact angle formed between the tablet surface and the droplet and the degree to which the droplet spreads immediately after contact) and, ultimately, film adhesion

Overspray, where the velocity of impact may cause droplets to be reflected from the tablet surface

The breadth of coverage can influence the number of spray guns that will be needed, and the likelihood that overspray onto the side walls of the pan will occur. Clearly the results shown in Figure 10 suggest that fewer spray guns of the Schlick type will be required to give equivalent coverage to that obtained when using Spraying Systems guns.

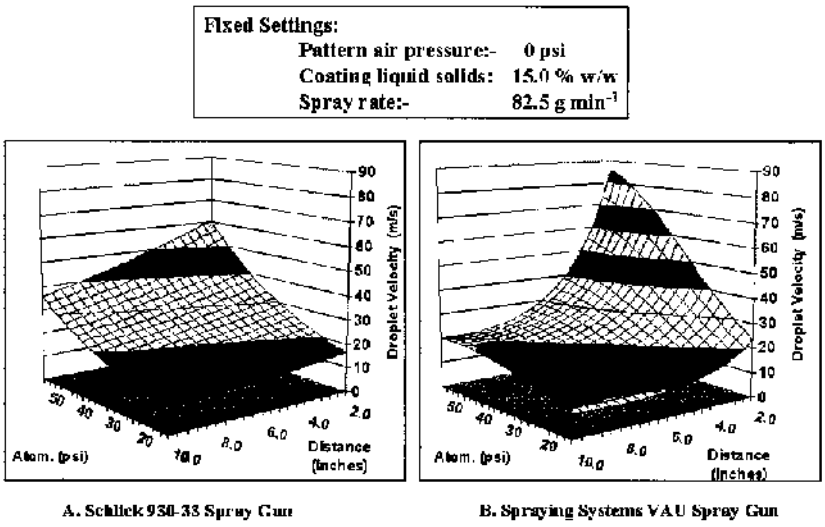

Figure 9 Example of how the type of spray gun used, atomizing air pressure, and gun-to-bed distance can influence droplet velocity.

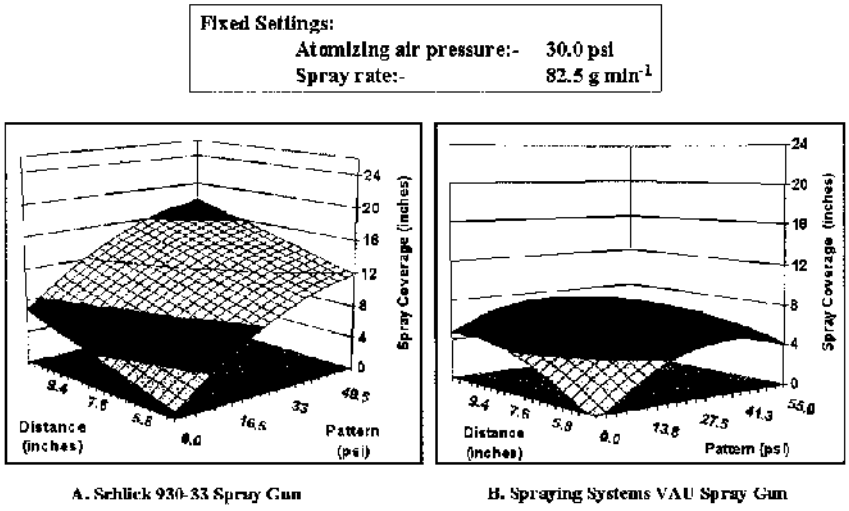

Figure 10 Example of how the type of spray gun used, gun-to-bed distance, and pattern air pressure can influence bed coverage.

In summary, the results shown in Figures 7–10, though only representing data for two distinct types of spray guns, provide clear warning of the potential problems that can occur if, during the scale-up process, commonly seen differences in spray gun performance are ignored. Appreciation for this situation is of paramount importance when one considers that there is a very real possibility that the types of spray guns used may be changed, especially if scale-up involves technology transfer from a development site to a manufacturing one that is geographically remote, quite a common occurrence in these days of globalization.

3. Scale-Up of Pan-Coating Processes: A Case Study

From the foregoing discussion, there are clearly many issues to be confronted when scaling up the pan-coating process. Evidently, the more definitive the data that are developed early on, the less likely that major problems will occur later on, especially problems that could inevitably delay a product launch and cost much in the way of lost revenues, particularly when dealing with a potentially "blockbuster" drug product.

This case study will summarize the development of a pan-coating process designed for the application of an enteric coating to a tablet product, provide insight into some of the early process optimization studies that were undertaken, and show how these ultimately facilitated the development of production-scale manufacturing processes.

a. Initial Process Development. Early development studies were carried out using a laboratory-scale 24″ Accela-Cota and employing a statistical design of experiments technique in which the operational variables were as shown in Table 8. Although several response variables were examined in this study, the principal issues concerned themselves with providing good functional enteric performance. Recognizing that enteric products are often potentially known for their lack of robustness (manifested as inherent brittleness of the coating, which is likely to cause enteric failures during subsequent handling, such as emptying the coating pan,

Table 8 Ranges of Process Variables Used During Optimization of the Enteric Film-Coating Process

Parameter studied	Ranges examined
Solids content of coating suspension (based on Sureteric® YAE-6-18108) (% w/w)	10–25
Inlet-air temperature (°C)	50–70
Spray rate (g min^{-1})	50–90
Quantity of coating applied (% w/w)	5–10
Atomizing air pressure (psi)	25–55
Atomizing air pressure (bar)	1.75–3.75

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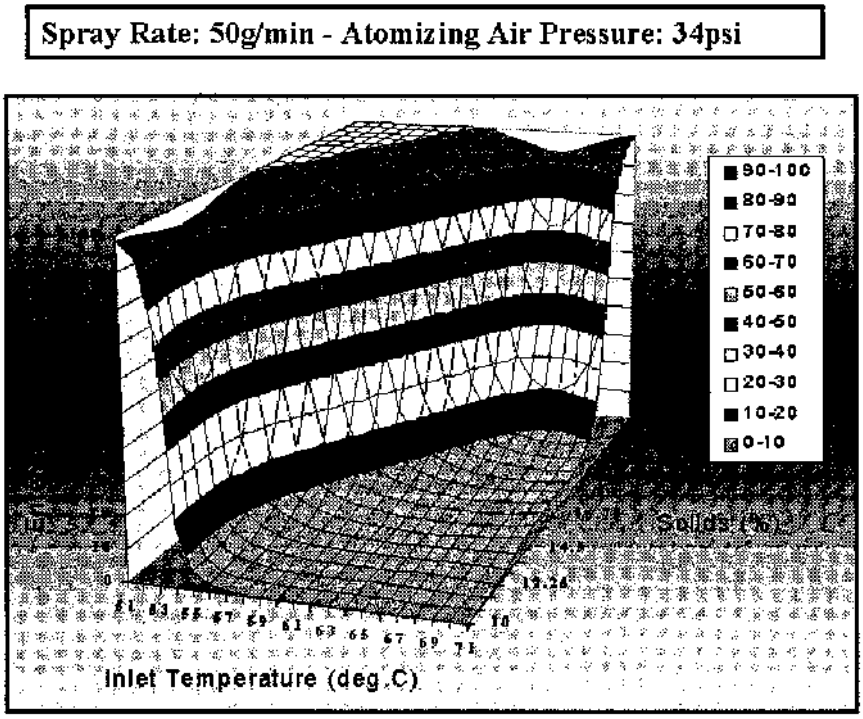

Figure 11 Influence of inlet-air temperature and solids content of the coating suspension on enteric test performance of enteric-coated tablets.

printing, and packaging), an extra challenge was imposed in the form of a *stress test* (see later discussion) to confirm appropriate robustness of the final dosage form. The two criteria used to measure enteric performance, therefore, were:

Enteric test (ET): One hundred tablets were exposed to artificial gastric juice (0.1 N hydrochloric acid solution) for two hours using a modified disintegration tester. Performance was expressed in terms of *percent failure,* which was represented by the percentage of tablets showing any sign of enteric failure (such as premature disintegration, swelling, or even slight softening).

Stressed enteric test (SET): Essentially the same test as the enteric test, but in this case the 100 tablets were placed in a friability tester for four minutes at 25 rpm prior to being submitted for the enteric disintegration test in artificial gastric juice.

From this initial study, and referring to the data shown in Figure 11, it is evident that good functional enteric performance can be achieved when the coating

process is operated under conditions where:

The inlet-air temperature is greater than 60°C
The coating suspension solids content is in the range of 10–15% w/w.

The data represented by the stressed enteric results (SET), however, tell a slightly different story (see Fig. 12A). Clearly, the process operating ranges where acceptable performance can be achieved are quite limited. However, if the level of applied enteric coating is fixed at a minimum of 10% w/w and the coating suspension solids content is reduced to 15% w/w, then the process operating ranges become quite broad (see Fig. 12B).

b. Scaling Up the Optimized Enteric-Coating Process. Based on the results described in the previous section, an optimized coating procedure was designed and used as a platform for scaling up the enteric-coating process. Details of this optimized laboratory process, as well as the conditions used in the scale-up study, are shown in Table 9. In addition, the results for the enteric tests performed on tablets coated in these coating trials are shown in Table 10. The fact that these results clearly meet (and in most cases, surpass) the specifications designated for the enteric testing of aspirin tablets provides sufficient confirmation for the validity of the optimization and scale-up procedures used in this case study.

C. Scaling Up Fluid Bed Coating Processes

1. Introduction

Fluid bed coating processes, although applicable for coating the full range of pharmaceutical product types, are more likely to be reserved for the coating of multiparticulates, usually with some kind of functional coating (taste masking, enteric, sustained release). The nature of the substrate and the purpose of the applied coating clearly provide additional challenges during both initial process development and the scale-up process. This situation is made even more complex by the fact that with the current preference for aqueous coating formulations, such highly functional coatings often demand the use of latex or polymer dispersion coating systems. These systems have certain idiosyncrasies in terms of film formation that place extra demands when optimizing the coating process in order to ensure that stable, reproducible applied coatings are obtained.

Much has been said in the discussion so far as it relates to scaling-up the pan-coating processes. Philosophically, many of the issues already described are equally applicable to the fluid bed process. There are, however, some important differences that must be appreciated during the development of fluid bed coating processes. For the most part, although there is a plethora of pan-coating equipment currently available and each brand has its specific characteristics and features, the operating principles are essentially the same for most types of equipment that are in common usage in the pharmaceutical industry today. In contrast, when it comes

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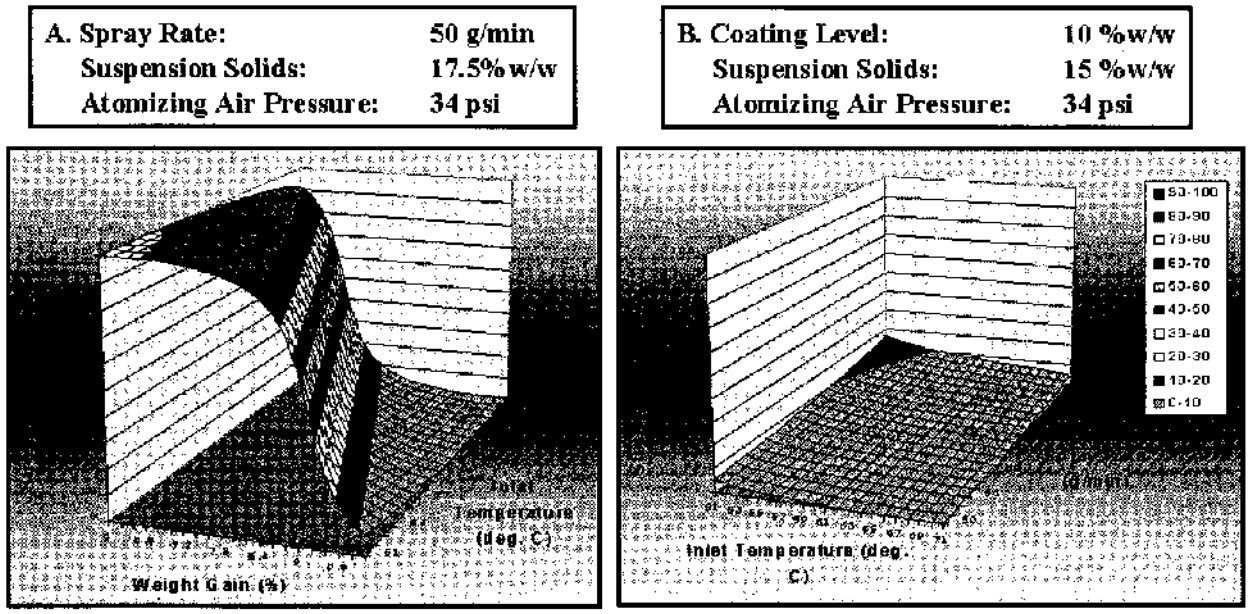

Figure 12 Example of how process conditions can influence the enteric performance of tablets that have been submitted to a stress test prior to undertaking the enteric test.

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Table 9 Coating Process Details Used in Scaling Up an Aqueous Enteric-Coating Process Using an Accela-Cota Process

	Coating process conditions for scale indicated		
Process parameter	24″ Accela-Cota	48″ Accela-Cota	60″ Accela-Cota
Inlet-air volume:			
(cfm)	250	1800–2000	2300–2700
($m^3\ hr^{-1}$)	425	3100–3400	3900–4600
Exhaust-air volume:			
(cfm)	300	1900–2100	2400–2800
($m^3\ hr^{-1}$)	500	3200–3600	4100–4800
Inlet-air temperature (°C)	75–84	70–80	70–80
Exhaust-air temperature (°C)	38–41	40–45	40–45
Spray rate (g min^{-1})	60–70	400–500	650–700
Number of spray guns (Binks 605; fluid nozzle 66SS; air cap 66SH)	2	3	5
Gun-tablet-bed distance:			
(inches)	5–7	8–12	10–12
(cm)	12–18	20–30	25–30
Atomizing air pressure:			
(psi)	35–40	60–80	50–70
(bar)	2.4–2.7	4.1–5.5	3.5–4.8
Pan loading (kg) of aspirin 325 mg tablets	12.0	135	300
Tablet bed prewarm temperature (°C)	45–50	45–48	45–48
Pan speed (rpm)	14	6	4
Enteric-coating suspension solids content (% w/w)	15.0	15.0	15.0
Quantity of coating applied (% w/w)[a]	10.0	10.0	10.0
Coating process time (hr)[a]	2.00	3.00–3.75	4.75–5.10

[a] This only refers to the enteric-coating layer; in addition, a subcoating [based on Opadry] applied to a level of 2.0% w/w, and a colored top coating [based on Opadry II] applied to a level of 3.0% w/w were also used.

to fluid bed coating, there are three distinct processing concepts commonly used, as illustrated in Figure 2. To summarize, these are:

The *top-spray* process, which is a manifestation of the fluid bed granulation process that has long been used in the pharmaceutical industry

The *bottom-spray* process, commonly called the *Wurster* process and the only one specifically designed as a coating process

Table 10 Enteric Test Results for Aspirin (325 mg) Tablets Coated in Scale-Up Processing Studies

	Disintegration test			Dissolution test	
	% Failures in 0.1 N HCl solution				
Batch size (kg)	Enteric test (ET)	Stressed enteric test (SET)	Disintegration time in buffer, pH = 6.8	% Drug released after 2 hours in 0.1 N HCl ([a])	% Drug released after 90 min in buffer pH = 6.8 ([a])
12	0	0	8:05 ± 0:32	0	104.5
135	0	0	7:04 ± 0:52	0	91.5
300	0	0	6:32 ± 1:00	0	105.2

[a] Compendial specification calls for: <10% dissolved in 0.1 N HCl after 2 hours and >80% dissolved in buffer, pH = 6.8, after 90 minutes.

The *tangential-spray,* or *rotor,* process, originally designed as a granulator for producing spheronized granulates

Each of these processing concepts, which can all be supplied by each of the major vendors of fluid bed coating equipment, has special characteristics that makes it suitable for certain tasks, as shown in Table 11. Although the concepts

Table 11 Features and Uses of the Three Concepts for Fluid Bed Film Coating

Process	Advantages	Disadvantages	Uses
Top spray	Larger batches Easy nozzle access Relatively simple setup Good mixing	Limited batch weight flexibility Limited weight gains Greater risk of spray drying	*Application of:* Aqueous coatings Taste mask coatings Hot-melt coatings
Bottom spray	Moderate batch sizes Uniform distribution of coatings Wide range of applications	Poor nozzle access during coating Requires tallest expansion chamber	*Application of:* Aqueous coatings Taste mask coatings Modified-release coatings Drug-layer coatings
Tangential spray	Relatively easy setup Easy nozzle access Shortest processing chamber Fast spray rates Wide batch weight flexibility	High mechanical stress on product being coated	*Application of:* Drug layer coatings Modified-release coatings

outlined in this table represent those that are frequently used in the industry today, some specialized fluid bed processes, the operating principles of which fall outside those of the three listed, are also worthy of note. Examples would be the "Kugelcoater" (which is manufactured by BWI Manesty in Europe), and the "Precision Coater" (manufactured by GEA).

In contrast to pan-coating processes, some characteristics of fluid bed processes that may feature strongly in the scale-up process include the facts that:

Nozzle positions (with the possible exception of the top-spray process) are somewhat fixed, and the distances between the nozzle tips and product being coated are often quite small and unlikely to change on scale-up.

Spray patterns are always round, and thus pattern air is not a factor in the atomizing process or in defining the spray characteristics.

Although fluid bed machines have optimal operating capacities, they often have much more flexibility in accommodating a range of batch sizes within a given process, especially those based on the tangential-spray concept. Although there is a certain minimum requirement in order to facilitate appropriate fluidization of the product, this flexibility is often a requirement when one considers that the amount of coating material that is often applied may range from 1 to 50% (and even broader if one includes the drug-layering process). Such extremes are rarely required in typical pan-coating operations.

Nozzle (atomizing) air can contribute significantly to product movement and can also be a source of a significant increase in product attrition.

Drying air is also the main source of "power" for creating product movement. Thus the needs of the drying process and that required to create motion are interdependent, adding complexity in terms of meeting (and optimizing) the requirements of each. For example, when a significant amount of coating material is being applied, the batch mass will increase, requiring more air volume to maintain motion; at the same time, the requirements for drying remain little changed.

2. Predicting Scale-Up Issues

As with pan coating, the key to successfully scaling up the fluid bed process involves the design of a completely optimized laboratory-scale process on which key decisions can be based. As discussed earlier, Turkoglu and Sakr [8] have provided an appropriately relevant example of how such an optimized fluid bed process (in this case, a tangential-spray process) may be designed.

It is not unexpected to assume that certain features of the process will again remain unchanged throughout the scale-up process. These features include:

Product and coating formulations

Solids content of the coating liquid

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Inlet-air and product temperatures (although these may be adjusted to accommodate other limitations that may arise, such as uncontrollable changes in drying-air humidity and limitations on heater capacity)

Key processing parameters on which much attention will have to be focused include primarily:

Batch size
Drying-/fluidizing air volumes
Spray nozzle dynamics
Spray/evaporation rate

The photographs shown in Figure 13 provide a useful example of the kinds of equipment changes that can take place when scaling up a fluid bed process. In this case, reference is made to the Wurster process, which possesses some useful characteristics. Once the pilot scale (in this case, the 18″ Wurster process) is reached, larger machines are based on multiples of the 18″ concept, thus somewhat simplifying further scale-up. Thus, with this type of process, many of the challenges occur when scaling up from the laboratory to pilot scale, rather than from pilot to full production scale.

a. Considerations for Batch Size. Mention was made earlier in this chapter, and much has been said in pharmaceutical publications, about the batch-size flexibility that is often associated with the fluid bed process. It is perhaps more appropriate, however, to talk in terms of the flexibility of such equipment to accommodate ranges in starting batch weight. Any fluid bed process that is involved in a coating application will always have an optimum batch fill weight that, as with pan-coating processes, will be defined by the interior volume of that particular machine. Each will also have an upper capacity limit that is defined by the operating needs of that process.

It is critical, during initial process development, to give serious consideration to the amount of material that will be applied (especially for processes involving drug layering or those involved with the application of modified-release coatings to fine particle products, where required coating levels in excess of 50% are not uncommon). Key factors to be established are:

What are the minimum and maximum limits for batch capacity in a particular machine?
How much coating material is to be applied?

Answering these questions provides suitable guidelines for deciding on which particular type of process is appropriate. Selection of the wrong process may require that, part way through processing, the batch may have to be divided in order to allow the full process to be completed. Such a necessity is more likely when using the bottom-spray (Wurster) process and least likely when using the tangential-

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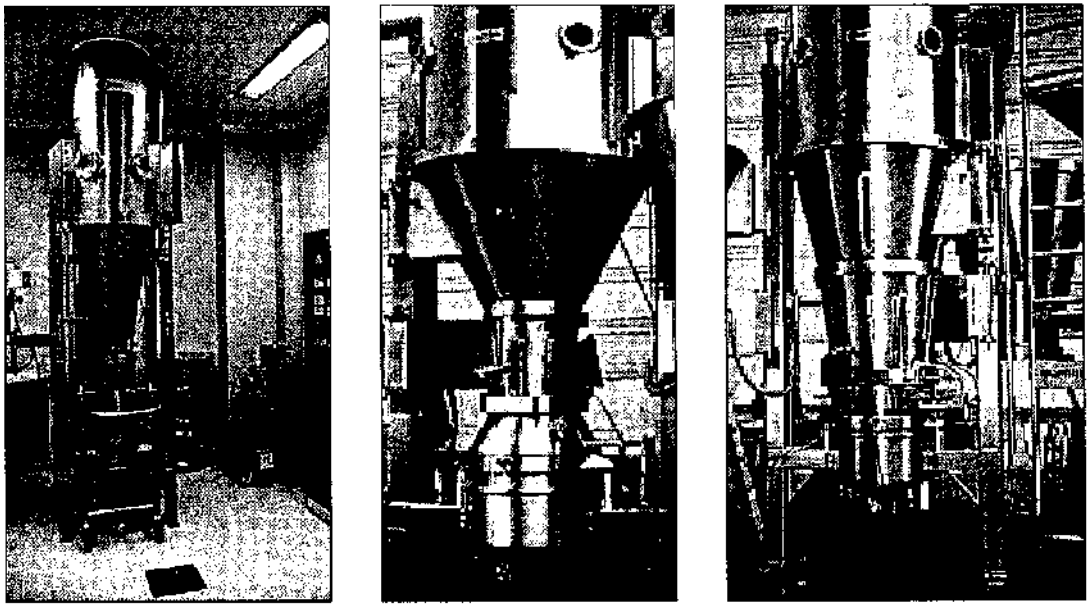

A. 7" Wurster		B. 18" Wurster		C. 32" Wurster	
Typical batch load:	4.0kg	Typical batch load:	40.0kg	Typical batch load:	180.0kg
Number of spray guns:	one	Number of spray guns:	one	Number of spray guns:	three
Number of partitions:	one	Number of partitions:	one	Number of partitions:	three
Partition diameter:	89mm	Partition diameter:	219mm	Partition diameter:	219mm

Figure 13 Photographs illustrating equipment used during the scale-up of the Wurster process.

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spray process. Dividing batches in this manner is rarely troublesome on the laboratory scale but becomes much more of a issue when going to large, production-scale processes, which is something that may prove to be a potentially costly oversight during the initial stages of process development. Since batch size constraints may be more significant in the Wurster process, this processing concept will be used primarily as the basis for further discussion on the subject of defining appropriate batch sizes.

For fluid bed processes, a useful limit to consider is *working capacity,* which essentially refers to the final batch weight. In the case of the Wurster process, this term refers to the volume *outside* the inner partitions. The minimum starting batch size for the Wurster process is usually approximately 40% of its working capacity. This loading is essentially a guideline, since a critical element of this process is to ensure that there will ultimately be enough material in the *up-bed* region [that is, that region inside the partition(s) when the process is in operation] to capture all of the material that is being sprayed, thereby avoiding low process coating efficiencies as a result of either material that will be deposited on the side walls of the inner partition(s) or material that is not captured by the product being coated and that passes all the way up into the filter system. Using the 40% guideline is only suitable when the amount of coating (or drug to be layered) is substantial. When the coating level is low (less than 10% w/w), then the starting batch weight should be more in the range of 60–70% of working capacity.

For the Wurster process, calculating batch volume on scale-up can be calculated using Eq. (2):

$$B = \frac{\pi r_1^2 L - n(\pi r_2^2 L)}{1000} \tag{2}$$

where:

B = batch volume, or working capacity (liters)

r_2 = radius of the product (Wurster) chamber (cm)

r_2 = radius of each inner partition (cm)

n = number of inner partitions

L = length of each inner partition (cm)

If the batch volume is multiplied by the bulk density of the product to be coated, then the batch load, by weight, can be determined.

Although these examples are more specific to the Wurster process, similar guidelines can be applied to the top-spray process, in which case the definition for working capacity will be different. When dealing with the tangential-spray process, the quantity of product that is sufficient to ensure that the spray nozzles are completely immersed when the product is in motion will define the minimum starting batch weight.

b. Drying/Fluidizing Air Volumes. As stated earlier, unlike the case of a coating pan, the air that passes through a fluid bed machine serves two purposes: drying and imparting motion. The key objectives in each case need not be mutually inclusive. Keeping the product moving in an appropriate manner and maintaining the volume of air required to do that may well depend on:

The mass of material inside the machine. This requirement is confounded by the fact that as more coating is applied, the mass increases, as does the requirement for fluidizing air.

The tackiness of the coating being applied. Tacky coatings can increase both the "drag" on coated particles and also the potential for agglomeration to occur. In either case, an increase in fluidizing air may well be required to offset these two problems. Tackiness is often associated with the nature of the polymer(s) used in the coating system, the presence of other additives (such as plasticizers), excessive levels of residual solvents present as a result of ineffective drying, and, especially, with the use of latex coating systems. When ineffective drying is the cause of tackiness, an increase in air volume may well be a suitable remedy. When this problem is caused by the other factors, an increase in air flow may act as a double-edged sword: Increasing air flow, by improving motion, may well alleviate the problem; however, increased air flow, by increasing the level of heat in the product, may well result in increased tackiness.

In each of these scenarios, though a change in air flow will presumably improve product movement, unless spray rates (or process temperatures) are changed appropriately, the associated increase in drying capacity may well be detrimental to the process.

In general terms, the top- and tangential-spray processes may be less demanding in their requirements with respect to air flow. In the former, the fluidization pattern is quite random; in the latter, much of the burden for creating motion falls on the spinning disk so that the incoming air is required only to:

Create lift at the walls of the processing chamber
Prevent product from dropping below the spinning disk
Facilitate drying

Again, it is the Wurster process that presents the greatest challenge in optimizing air flows, where it is desirable to ensure that product rapidly accelerates up through the inner partition while maintaining a smooth, even flow in the down-bed (and essentially maintaining product in the down-bed in a near-weightless condition). Considering the range in particle sizes of the products that may be coated in this process, some accommodation can be made in terms of specific product requirements by changing the orifice plate [which determines the relative amounts of air passing upward through the region of the inner partition(s) and also that meeting the downward-moving product in the down-bed region of the pro-

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cessing chamber] at the bottom of the processing chamber as well as the relative height of the inner partition.

When scaling up the fluid bed process, a major requirement is to produce fluidization behavior on the larger machines equivalent to that used on the scale that provided the basis for process development. To achieve this goal and to minimize attritional effects, the same air velocities for each scale of equipment are required. Thus the overall increase in air volume required during scale-up will be related to the increase in area of the perforated base plate and, in the case of the Wurster process, the open area of the partition plate immediately beneath each of the inner partitions. Such calculations are simplified when scaling up from an 18″ pilot-scale machine to, say, a 32″ machine, since the latter represents a three-multiple of the former and thus would require a threefold increase in air flow.

c. Spray Nozzle Dynamics. Spray nozzle dynamics often prove to be a more challenging subject when dealing with fluid bed processes, because:

- Often the product being coated is a multiparticulate ranging in size from approximately 50 μm up to about 2–3 mm in size.
- In order to coat each particle in a discrete manner and avoid agglomeration, the coating fluid must often be atomized more finely and in a more controlled manner than in the case where tablets are coated in a typical pan process.
- In order to maintain fineness of atomization at the higher spray rates typically required in the larger-scale processes, atomizing air pressures may often have to be increased to levels where atomization air velocity can seriously increase product attrition.
- In order to meet the atomization constraints required, it is almost always necessary to change the model of spray gun used in order to achieve the effective levels of atomization at the increased spray rates required during the scale-up process.

With the possible exception of the top-spray process, the issue of nozzle-to-bed differences becomes a nonissue in the fluid bed process, since this distance is extremely small and, to all intents and purposes, fixed. Indeed, the close proximity between the nozzle and the product being coated can be problematic in some cases, since the velocity gradient created between the fluidizing air and the atomizing air can cause product to be drawn into the wettest part of the spray, increasing the chances of localized overwetting and agglomeration.

With the substantial interest in use of aqueous coating systems, an added burden is placed on the atomizing process. This burden results from the relatively high viscosities and surface tensions of aqueous systems. Fortunately, in applications using modified-release coatings, aqueous versions of such coating systems are typically in the form of latexes, or polymer dispersions, which have relatively low viscosities for the solids content of the coating system, and the presence of

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surfactants (as dispersion stabilizers) facilitates a reduction in what would otherwise be high surface tension values.

The data displayed in Figure 14 clearly indicate the dilemma with which one is faced when trying to achieve an increase in spray rate for a given type of nozzle. In the examples shown, the Schlick 970 series gun is typical of what is used on the laboratory scale, whereas the 940 series gun is more suitable for pilot- and production-scale operations. Clearly, the 940 series gun has serious limitations when scaling up to full production requirements, since if, for example, it is desirable to achieve a mean droplet size of 15 μm, this objective can be achieved (by increasing the atomizing air pressure as spray rate is increased) as long as the required spray rate does not exceed 250 mL min^{-1}. For all practical purposes, 6 bar represents a practical upper limit for atomizing air pressure in this type of coating process in order to prevent serious product damage due to attrition. Under these circumstances, if effective atomization cannot be achieved, use of specialized nozzle setups, such as those employed in the Glatt HS system, offers a potential solution. These types of nozzle allow higher spray rates to be achieved (see Fig. 15), since:

The higher atomizing air velocities produce smaller droplets, even at high spray rates.

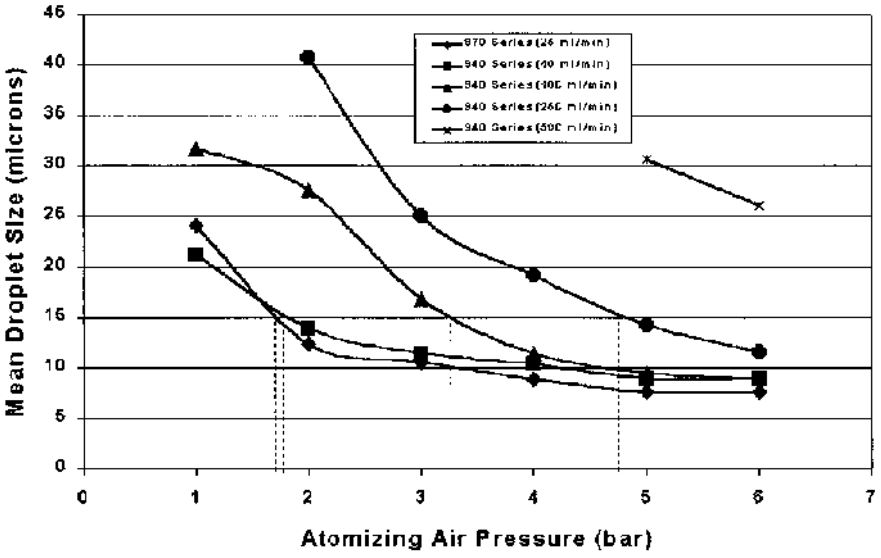

Figure 14 Influence of spray nozzle type and atomizing air pressure on the mean droplet size of water sprayed from guns used in a Wurster process.

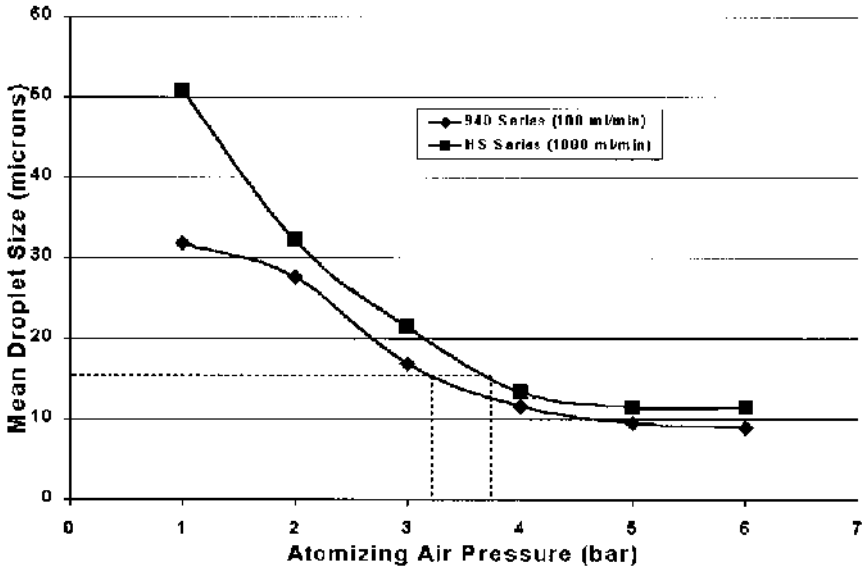

Figure 15 Example showing how a highly specialized nozzle (HS nozzle) can achieve equivalent atomization at high spray rates to that obtained in a more conventional nozzle when used at lower spray rates.

A special nozzle surround keeps product further away from the nozzle tip, thus preventing that product from being drawn into the "wet" area of the spray zone, and also limits the attritional effects that normally accompany the use of high atomizing air pressures and velocities.

d. Spray/Evaporation Rate. As described when discussing scaling up the spray application rates used in pan-coating operations, application of simple models [as represented by Eq. (1)] can prove to be extremely useful also for fluid bed processes. Further refinements, in terms of fully optimizing the process in this regard, can be achieved by applying appropriate thermodynamic principles. Jones [13] has provided a good example of how such an approach can be applied to a fluid bed coating process.

The spray rate that can be achieved in a given process is related to the volume of air that passes through the machine and to the temperature and humidity of that air. Clearly, therefore, spray rate will be governed to some extent by the rate at which the solvent (aqueous or otherwise) can be removed. Spray rate will also be influenced by:

The behavior of the coating fluid.
The inherent tackiness of the coating, especially during the critical time immediately after deposition onto the surface of the substrate.

The rate at which the product being coated moves through the spray zone. Generally, the faster that product moves through the spray zone, the lower is the "dwell time," the less coating that is captured during that time, resulting in a faster dry time for the coating. As the rate at which the applied coating dries (so that particle-to-particle contact no longer carries the risk of interparticulate adhesion, resulting in agglomeration) has a direct influence on the ultimate spray rate that can be achieved, rapid particle movement through the spray zone increases the potential to spray faster.

e. Summary of Scale-Up Issues. Scaling up the fluid bed process clearly faces many hurdles that are both similar and, at the same time, different to those faced with pan-coating processes. Additional complexity stems from the nature of the substrate that is likely to be coated in the fluid bed process as well as from the fact that, very often, the applied coating has a very important role to play in drug delivery.

That said, the task should not be overcomplicated, and many good instances exist to illustrate successful conclusions to such efforts. For example, the data shown in Table 12 illustrate the scaling up of the Wurster process in which an aqueous latex coating has been applied to drug-loaded pellets in order to prepare a modified-release product. It is appropriate to point out that since the 32″ Wurster essentially comprises three 18″ Wurster units, the air flow used in the former represents approximately a threefold increase over that of the latter, with the result that the spray rate is scaled up by the same factor. This situation illustrates the relative simplicity of scaling up from the pilot-scale unit.

The functional characteristics (in terms of drug release) for the pellets coated in this particular study are shown in Figure 16. Statistical comparison of these data (using the f_2 factor) confirm that these drug release profiles are essen-

Table 12 Coating Process Conditions Used in the Scaling Up of the Wurster Process for Application of an Aqueous Latex Coating to Drug-Loaded Pellets

	Process parameter settings		
Process parameter	7″ Wurster	18″ Wurster	32″ Wurster
Inlet temperature (°C)	70	70	64
Inlet dew point (°C)	20	15	11
Product temperature (°C)	34	34	33
Fluidizing air volume ($m^3\ hr^{-1}$)	270	1225	3740
Atomizing air pressure (bar)	2.0	2.0	3.0
Spray rate ($g\ min^{-1}$)	50	300	850
Exit air RH (%)	85.4	73.7	64.5
Yield (5%)	99.0	96.7	98.4

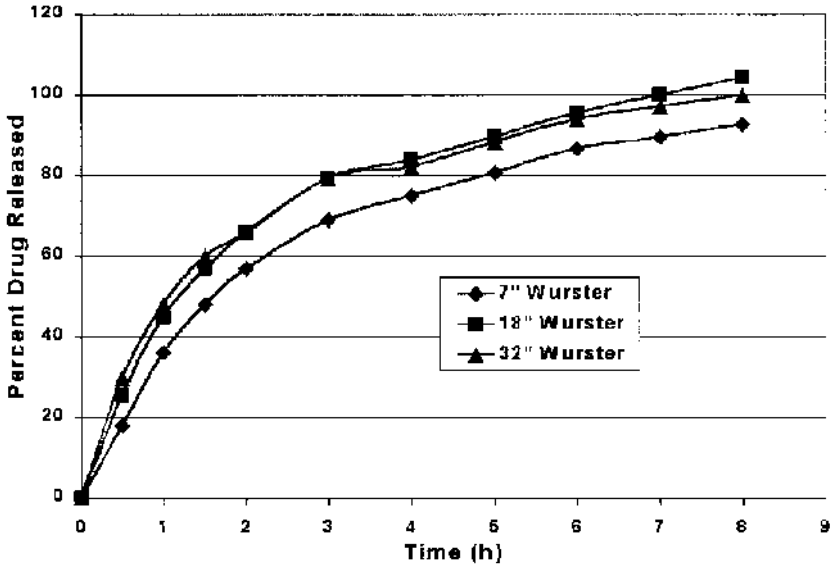

Figure 16 Comparison of drug release characteristics of pellets coated with an aqueous ethylcellulose dispersion using a laboratory-, pilot-, and production-scale Wurster process.

tially equivalent, although the best comparison, as is evident by simple visual inspection, is illustrated by the results for the coating trials performed on the pilot and production scales. This observation should not be all that surprising, since the processing conditions used in both these cases showed closer agreement.

3. Scale-Up of Fluid Bed Coating Processes: A Case Study

Effective product and process optimization play a prominent role in any successful scale-up study. As an illustration, this case study summarizes the initial development and subsequent scale-up of a Wurster process designed to facilitate the application of an aqueous ethylcellulose dispersion to drug-loaded pellets. At the same time, it was intended to deal, up front, with some of the idiosyncrasies of such a coating system that often influence the functionality of the final dosage form.

a. Initial Process Development. A preliminary study was established to examine the potential influence of processing parameters on some critical performance attributes of the final product, especially those associated with ultimate drug release rate and the reproducibility of the same.

Making certain assumptions about formulation issues (with regard to both the substrate being coated and the coating system being applied), the ultimate influence of the applied coating on drug release rate can be reduced to two

key elements:

The thickness of the coating applied
The structure of that coating

Having fixed the amount of coating to be applied and controlling the surface area to be covered by selection of a specific size fraction of pellets to be coated, the one significant processing factor that can affect coating thickness is the relative coating efficiency achieved (that is, the actual quantity of coating deposited relative to the theoretical amount applied). At the same time, coating structure will be influenced by:

The effectiveness of coalescence of the latex coating
The incidences of defects such as "pick marks" or "cracks"

Consequently, in this study, the critical factors that were examined during process development involved establishing the influence of process conditions on:

Coating process efficiency
Coalescence of the film coating (determined by means of assessing drug release characteristics before and after imposition of a "curing" step)
Evaluating the impact of processing conditions on film structure (by means of visual analysis using scanning electron microscopy)

Initial process development and ultimate process optimization were conducted as described by Vesey and Porter [14]. Basically, the study was performed

Table 13 Process Variables Used in the Development and Optimization of a Coating Process Designed for the Application of a Modified-Release Film Coating to Drug-Loaded Pellets

Process variable	Variable ranges evaluated
Solids content of aqueous ethylcellulose dispersion (% w/w)	10.0–25.0
Inlet-air temperature (°C)[a]	50–70
Spray rate (g min^{-1})	15–45
Atomizing air pressure (bar)	1–3
Oven curing time at 60°C (hr)	0 or 24

[a] The fluidizing-air volume was adjusted during each run to maintain a constant fluidization pattern; the volume of air required to achieve this was recorded in each case.

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Table 14 Summary of Ranges Obtained for Response Variables Studied

Response variable	Variable ranges
Product temperature (°C)	22–58
Process air flow ($m^3\ hr^{-1}$)[a]	61–142
Coating process efficiency (%)	79.1–97.9
T_{50}, before curing (min)	75–340
T_{50}, after curing (min)	90–320
f_2 value	56.6–95.6

[a] These ranges were used simply to maintain equivalent fluidization patterns for each coating run.

in a Glatt GPCG-3 unit fitted with a Wurster insert. The process variables that were evaluated are as shown in Table 13.

In order to assess the influence of process conditions on the coalescence efficiency of the latex coating, dissolution profiles (for samples from each coating run) were compared before and after being subjected to a curing step. Statistical analysis was undertaken using the f_2 fit factor, which is based on a logarithmic transformation of the sum of the squared error when comparing two dissolution profiles. The ultimate fit factor, expressed in terms of numerical values between 0 and 100, suggests that statistically equivalent dissolution profiles are achieved when the numeric values exceed 50.

A summary of the response variables obtained in this preliminary study are shown in Table 14, and the order ranking for the influence of process variables on the critical responses associated with coating process efficiency and drug release are provided in Table 15. As can be seen from the summary provided in Table 14, there is clearly an influence of the processing conditions used on ultimate drug release characteristics. On further examination, it was concluded that the major causes of the magnitude of differences in drug release characteristics were primarily due to:

- Variation in coating process efficiency, which resulted in a significant variation in the actual amount of coating applied.
- Overwetting that occurred for the coating runs where product temperature fell substantially below those typically observed (38–42°C) for this type of process. Such overwetting induced a significant degree of drug leaching, as confirmed using elemental analysis employed during the application of scanning electron microscopy.

On the basis of the results obtained, an optimized procedure was designed that was intended both to maximize the coating process efficiencies and to ensure that the f_2 fit factor values were in excess of 70.

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b. Scaling Up the Optimized Process. Using the optimized coating process as a basis, procedures were developed that enabled the process to be scaled up from the 3-kg laboratory scale to a 70-kg pilot scale and ultimately to a 200-kg production scale. The details of the coating process conditions that were designed for each of these processes are shown in Table 16. As is readily evident from the table, the objectives set for coating process efficiencies were easily met. Data representing drug release characteristics are illustrated in Figure 17, with clear indication that the equivalent coating process profiles were obtained for each scale of process. With respect to ensuring good coalescence of the latex coating, the f_2 fit factor values were 73.3, 70.6, and 75.4 (for the drug release characteristics obtained before and after implementation of an oven-curing step) for the laboratory, pilot, and production coating processes respectively, confirming that the objectives set in this area were also attained. Hence, once again the value of taking a systematic, sound scientific approach (and one that excludes personal bias) to process development as the basis for scale-up strategies has been confirmed.

Table 15 Rank Order Summary of Process Variables Influencing Coating Process Efficiencies and Drug Release Characteristics (T_{50})

Coating process efficiency		Drug release (T_{50}) before curing		Drug release (T_{50}) after curing	
Variable	Ranking	Variable	Ranking	Variable	Ranking
Inlet temperature	17%	Spray rate	40%	Spray rate	38%
Spray rate × atomizing air pressure	17%	Coating suspended solids	28%	Inlet temperature × spray rate	21%
Coating suspension solids	17%	Inlet temperature	20%	Coating suspension solids	19%
Inlet temperature × spray rate	17%	Atomizing air pressure	12%	Inlet temperature	13%
Spray rate × coating suspension solids	11%			(Coating suspension solids)^2	9%
Atomizing air pressure	11%				
(Atomizing air pressure)^2	10%				

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Table 16 Details of Coating Procedures Used in Scaling Up the Wurster Process

Process parameter used	Coating process conditions		
	Glatt GPCG-3	Glatt GPCG-60	Glatt GPCG-200
Batch size (kg)	3	70	200
Fluidizing-air volume (cfm)	83–107	800–900	N/A[a]
($m^3\ hr^{-1}$)	140–180	1360–1530	
Inlet-air temperature (°C)	64–67	60–66	72–75
Exhaust-air temperature (°C)	40–45	39–41	47–51
Product temperature (°C)	41–47	40–46	43–46
Atomizing-air pressure (bar)	1.5	2.0	2.0
Number of nozzles used	One (Schlick 970, 1.2-mm orifice)	One (HS, 1.5-mm orifice)	Three (Schlick 940, 1.5-mm orifice)
Solids content of coating dispersion[b] (% w/w)	15.0	15.0	15.0
Theoretical quantity of coating applied (% w/w)	10.0	10.0	10.0
Spray rate ($g\ min^{-1}$)	25–28	210–306	500–650
Coating process efficiency (%)	99.3	99.6	99.6

[a] Machine did not have a device monitoring air flow; fluidizing air was adjusted to maintain a fluidization pattern equivalent to those used on other scales.
[b] Surelease E-7-19010.

III. ALTERNATIVE CONSIDERATIONS TO SCALING UP COATING PROCESSES

Up to this point, the issue of process scale-up has been dealt with in terms of technology transfer from a small- to intermediate- to full production-scale processes. In each case, the coating process is a batch process that gets progressively larger. During the last decade of the 20th century, new processing concepts were introduced that potentially facilitate a paradigm shift as far as pharmaceutical coating process technologies are concerned and also in terms of how the issue of scale-up may be dealt with.

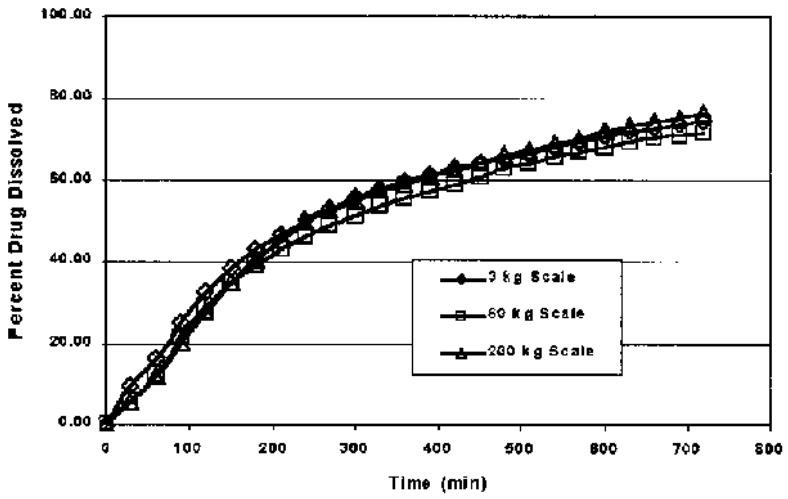

Figure 17 Drug release characteristics of pellets coated on various scales of the Wurster process when the laboratory-scale process, used as the basis for scale-up, has been fully optimized.

One approach, fundamentally based on existing processing concepts, involves the adoption of continuous processing technologies. Another introduces a totally different approach to the application of film coatings and, in doing so, totally changes and essentially eliminates most issues as they relate to preparing larger and larger batches of coated products.

A. Continuous Coating Processes Based on Existing Film-Coating Technologies

The concept of continuous processing, in terms of oral solid dosage forms, is not new to the pharmaceutical industry. Indeed, the tableting process is a continuous one. Some companies will also lay claim to having introduced continuous coating processes decades ago. But in each case, these processes have been fundamentally batch/continuous processes where material handling times (involved with unloading and loading the coating vessel between batches) has simply been reduced to a minimum.

The present concept of continuous coating is one in which uncoated product is constantly fed in at one end and completely coated product comes out at the other end. Processes of this type had their origins in other industries (especially the food and agriculture, where batch sizes are routinely much larger than those dealt with in the pharmaceutical industry).

Mancoff [15] and Pentecost [16] have both described continuous film-coating processes that have been designed primarily for pharmaceutical applications. The fundamental basis of such processes is as shown in the schematic outline described in Figure 18. The inherent advantages exhibited by these processes are that:

Dwell time in the coating vessel is short (approximately 5–15 minutes).
Throughput, on a continuous basis, is typically 500–2000 kg hr^{-1}.
The bed depth is much shallower than typically seen in a more conventional pan.
Coating uniformity is significantly improved, and typically, when applying a colored coating, a 2.0% weight gain in the continuous pan provides equivalent coverage to that which can be achieved with a 3.0–4.0% weight gain in a more conventional batch process.
Stress on the product being coated is substantially reduced as a result of the shorter residence times (in the process) and the shallower bed depths used.

To date, use of such continuous processes has been restricted primarily to the manufacture of large-volume products, an application for which continuous processes potentially have a major advantage. Nonetheless, continuous coating processes provide a potentially viable alternative for the scale-up of any film-coating process, where many of the tasks potentially become much simpler, since they would always be the same irrespective of whether the production batch size is 250 kg or 5000 kg. Simplification arises from reducing or eliminating tasks that would

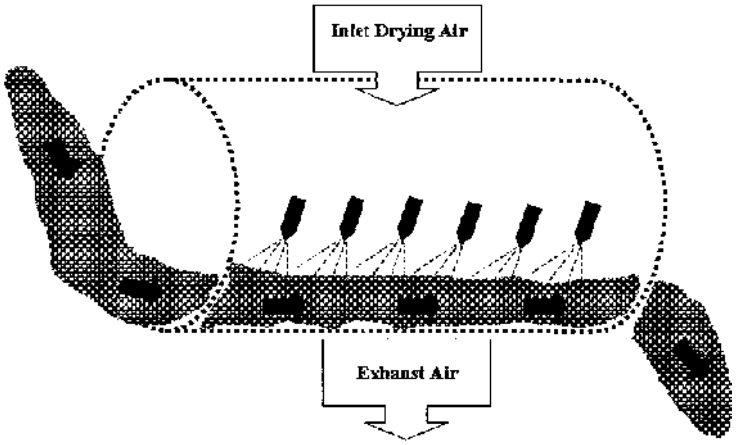

Figure 18 Schematic diagram of a continuous pan-coating process.

otherwise involve:

Deciding appropriate pan loadings
Defining the appropriate number of spray guns to be used
Determining spray application rates
Determining air flow volumes
Defining appropriate gun-to-bed distances

As they currently exist, continuous processes do have their limitations, which include the facts that:

Material produced during start-up and shutdown of the process may have to be either scrapped or reworked, since it is likely to have received less than the targeted levels of coating as a result of reduced exposure to the spray application process.

Laboratory-scale continuous processes are essentially nonexistent, thus making process development on the laboratory scale more challenging, since processes have to be developed on the basis of a small-batch process and then transferred to a continuous process.

The quantity of coating that can be applied in one pass is limited to about a 2.0% weight gain, thus providing a challenge when applying modified-release coatings, where weight gains on the order of 2–10% may be required (unless the use of multiple passes is acceptable). This disadvantage can be offset to some extent when the sprayable solids content of the coating liquid can be increased beyond typical levels of 10–15% w/w. For example, spraying a latex coating at 30% w/w solids would facilitate an increase in the amount of coating deposited to about 4–5%.

It is likely, however, that future developments in this area will allow the advantages of this type of process to be fully realized while addressing and eliminating current disadvantages.

In order to assess what the potential advantages of the continuous process might be, as an alternative to more traditional ones in the scale-up process, it is necessary to determine what the potential throughout rates might be for the continuous process. There are two elements to making such a determination, one based on the thermodynamic limitations of the process, the other on geometric limitations. Throughout (T_{Th}), in kg hr^{-1}, based on thermodynamic limitations is essentially given by:

$$T_{Th} = \frac{(SR) \times (SC)}{W} \times 0.06 \tag{3}$$

where:

SR = spray rate (g min^{-1})

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SC = the solids content of the coating system (expressed as a decimal fraction, where, for example, 10% becomes 0.10)

W = weight gain to be achieved (again expressed as a decimal fraction)

Throughput (T_{geom}), in kg hr^{-1}, based on geometric limitations, is given by:

$$T_{geom} = \frac{(A) \times (L) \times (\rho)}{r} \times 0.06 \quad (4)$$

where:

A = cross-sectional area of the tablet bed (cm^2)

L = length of the pan (cm)

ρ = bulk density of the tablets (g cm^{-3})

r = tablet residence time in the process (min)

There is a link between the two calculations in terms of residence time, *r,* which is influenced by thermodynamic factors.

B. Continuous Processes Based on Electrostatic Powder Deposition

Discussion to this point has focused on processes involving:

Spraying of liquid coating systems
"Solidifying" the coating through a solvent removal (drying) process
Coating tablets en masse
Using constant tablet motion, together with other appropriate mixing devices, to facilitate uniform distribution of the coating.

These fundamentals provide the basis for many of the difficulties that are encountered as the process is scaled up.

A more recently introduced concept, described by Staniforth et al. [17] involves the use of electrophotographic principles (essentially those used in the photocopying process) as a basis for the application of dry powder coatings to pharmaceutical tablets. This concept is illustrated in Figure 19. Although representing an early prototype, the essential principles of the process are clearly outlined. The salient features of this process are:

It is continuous.
Tablets are handled and coated individually, irrespective of whether the batch size is one tablet or 1 million tablets.
Tablets are coated first on one side and then on the other, thus allowing different coatings (in terms of color, functionality, or both) to be deposited on each side.

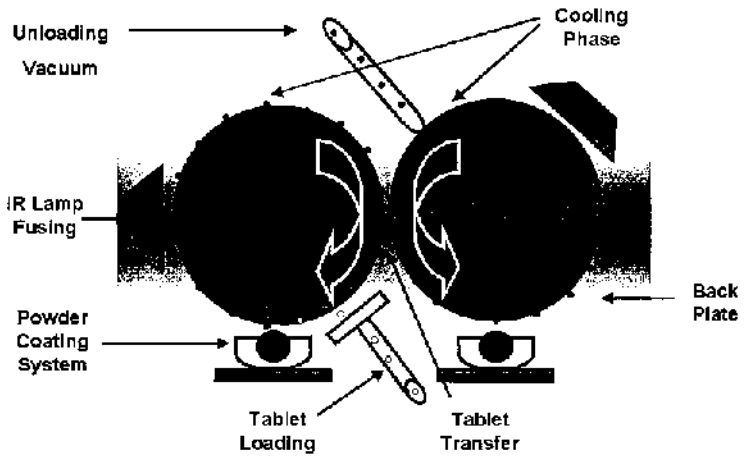

Figure 19 Schematic diagram of a continuous electrostatic powder coating process.

The coating zone is defined by the needs of an individual tablet, and the quantity of coating applied is controlled by the magnitude of the electrical field that is created and the electrostatic properties of the powder that is to be deposited.

Deposition of the coating is much more precise than is typically achieved using current spray application processes, leading to substantial improvements in coating uniformity both from tablet to tablet and across the surface of each individual tablet.

Heat fusion takes the place of solvent removal as the means of creating a dry, continuous coating.

Absence of both a drying step and direct tablet-to-tablet contact essentially eliminates those stress factors that are an ever-present feature of the scale-up of more traditional coating processes.

Considering the processing fundamentals of this dry process, almost all of the issues associated with the scale-up of more traditional film-coating processes are eliminated, and the key objective is to feed tablets directly from the tablet press into the electrostatic coating operation and thence on to packaging. Thus once the process is defined in terms of coating one tablet, it is replicated an appropriate number of times in order to coat all of the tablets in the batch.

IV. SCALE-UP OF COATING PROCESSES: OVERALL SUMMARY

The characteristics of pharmaceutical coating processes sets them apart form most, if not all, other pharmaceutical unit operations, not only in terms of issues

that need to be understood during process development, but also when it comes to scaling up those processes. This is especially true when dealing with the number of process variables that have to be considered. If coating processes are subdivided into pan and fluid bed processes, then for those specific types of processes that are routinely employed in the pharmaceutical industry today, it is valid to summarize these processes as belonging to two or three fundamental operating principles. Even if this simplistic view, however, is taken, process scale-up is much more complex than just considering it a case of geometric enlargement.

Spraying of coating liquids, ensuring that effective and consistent drying takes place, achieving appropriate uniformity of distribution of the coating, and enabling final coating structure and functionality to remain consistent with the intended purpose of that coating are all events that must well defined if successful process scale-up is to be accomplished. Coming to grips with the multiplicity of parameters that commonly define such a process is clearly facilitated when employing statistical techniques exemplified by the design of experiments approach. Technology transfer on a global scale is equally well facilitated by access to expert systems that capture all of the relevant process and formulation events that have been used to define the final coated dosage form. Finally, in the long run, the best approach to troubleshooting such a complex process to avoid trouble altogether.

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10

Engineering Aspects of Process Scale-Up and Pilot Plant Design

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I. INTRODUCTION

This chapter deals with the design of a pilot plant facility. Although this chapter discusses many aspects of pilot plant scale-up considerations, it is not meant as a treatise on process scale-up. Many other authors in this book discuss this subject more thoroughly. All discussions on process scale-up in this chapter are presented to serve as examples of the thought process that must be considered when engaged in the design of a facility.

Although all types of manufacturing processes will be discussed throughout this chapter, solid-dose manufacturing will be used as the primary example. We will go through the design of a solid-dose manufacturing facility and take it through the different stages of the process.

There are four general steps in the design of a pilot plant: planning, design, construction, and qualification. We will discuss the first two in detail by breaking them up further into more specific areas of consideration. There is also a brief overview of the last two phases of the project.

During the planning phase, a series of basic questions must be answered. What is the ultimate goal for the facility? What type of production will the facility be used for? What quantities of materials will be typically manufactured? To answer these questions and the many more that come up, a team must be assembled. This team should be made up of professionals in the field that are qualified and empowered to ask questions and make decisions that will ultimately lead to the successful completion of the facility.

During the design phase, the process flow must be mapped out thoroughly.

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Decisions on room qualifications and controls must be made. The utilities and process equipment must be described. In this section of the chapter, we will describe a typical process for solid-dose manufacturing and use it as an example. This illustration will allow us to view a specific design and watch it take form. Security issues must also be addressed during the design of the facility. Will there be controlled substances in the facility?

During the construction phase of the project, we will make decisions on coordination options and permit requirements. We will discuss the various options available for the tracking of the project to ensure timelines are kept. Additionally, it is at this time when staffing requirements must be finalized. And a consideration of protocols, production records, and quality assurance documentation must be formalized.

Finally, during the qualification of the facility, all systems are tested, calibrated, and cleaned. The mechanical and service infrastructure must be qualified. The operational qualification will involve practice runs. All documentation must be finalized. This includes standard operating procedures, batch records, and equipment logs.

II. PHASE 1—PLANNING

As discussed earlier, all phases can be broken down into more specific areas. In this chapter the planning phase is broken down into process characterization, manufacturing projections, and manufacturing philosophy. However, before any activity begins, a team that will spearhead the project must be assembled. This team should be comprised of individuals experienced in the following fields, process engineering, process development, project management, and operations management. Additional team members may include professionals in regulatory affairs, purchasing, and quality assurance. Upper management should empower this team to make critical decisions and move ahead in a timely manner. Open and frequent communication is vital for this team. Frequent meetings should be scheduled to monitor progress and react to any problems that may arise.

A. Project Management

Good project management is a key to completing this project on schedule. During the first meetings of the team, clear goals must be set. The paths towards these goals must be mapped out and critical steps identified. A baseline schedule should be clearly described. As part of the project management setup phase, all resources should be identified, both those within the organization as well as those that need to be contracted out. Because, at this stage, process requirements have not been assessed, the project management schedule should be in broad terms, allowing for

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different types of processes to be built into the facility design. Later on in the design phase a review of the project is conducted to focus the activities on more specific tasks.

B. Process Characterization

How does the team characterize the process for which the pilot plant is to be manufactured? The first question that needs to be answered is "What is the ultimate goal for the facility?" Is it to support development for solid dosage forms, liquid products, or biologically derived products? Or does it have to serve multiple functions? The answer to this question will allow us to focus and generate more accurate plans. Until later on in the design phase, this process characterization should be kept broad and not very detailed. Included in the evaluation should be the ancillary service equipment and support services, such as electrical and air handling requirements.

C. Solid Dosage Forms

Solid dosage forms include tablets and capsules. The manufacturing of solid dosage forms involves extensive powder handling. The powder must be blended for uniformity and converted into the dosage form either through compression or encapsulation. Typical requirements include weighing, blending, mixing/granulation areas, compression/encapsulation areas, and coating areas.

D. Liquids and Ointments

Liquids and ointments include syrups, elixirs, solutions, creams, and ointments. Typically, they require extensive mixing and bottle filling capacities. Purified water is essential for the manufacture of these products as well as on-site packaging capabilities (filling).

E. Biologically Derived Products

Biologically derived products include fermentation products and genetically engineered materials. These products typically require sterile manufacturing areas. They require extensive air handling equipment and environmental controls. Sterilization/sanitation must be easily carried out.

F. Manufacturing Projections

Preliminary manufacturing projections are critical at this stage of planning. What type of batches will be manufactured at this facility? A pilot plant can, by design,

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serve a wide array of batch sizes and purposes. It can be used to manufacture small development batches of one kilogram or less. And it can serve to manufacture large scale-up batches of as much as 120 kg. To cover this broad range of batch sizes, many different sizes of equipment must be available.

G. Types of Products to Be Manufactured

As already described, there are a variety of reasons for the manufacture of batches in the pilot plant facility. First, the batch may be manufacture as a development batch. In other words, it could be the first attempt at manufacturing a product. This type of experimental manufacturing could be the result of a design of experiments analysis. These experiments are usually carried out at very small sizes, possibly 1 kg or less. However, many of these batches could be made as part of one experiment. For these batches it is important that the equipment can easily be used for many runs in as little time as possible. It is also important that manpower requirements remain as low as possible for manufacturing these small-scale batches as well as for the cleaning the equipment.

Another type of batch to be manufactured could be larger-scale development batches. These batches are typically 5–20 kg kilograms in size and are used for a variety of reasons. They could be used for clinical studies, analytical development, process development, stability testing, and formulation optimization, among other purposes. For many of these types of batches, it is important that current good manufacturing practices (cGMP) are followed. It may also be critical at this time that the process used for manufacturing is one that can be duplicated, albeit on a larger scale, on the factory floor. If batches are to be used for stability studies, special consideration must be given to the packaging capabilities of this facility.

H. Full-Scale Scenarios

Larger-scale batches may also be planned for this facility. Many pilot plants can manufacture 120 kg or more of material. These batches may be used as prevalidation batches, scale-up batches, as well as full-scale production batches. For successful manufacture of these types of batches, the equipment must be of the same operating principle as that found in the manufacturing facility. Maintenance of the pilot plant must be exactly as that of the full-scale manufacturing facility. In fact, they should share documentation, batch records, SOPs, logbooks, etc. Additionally, quality assurance (QA) must play a significant role in a pilot plant with these capabilities. Quality assurance must maintain a presence during the manufacturing of the batches. They will ultimately be responsible for the release of the product for either clinical studies or commercialization. The requirements of QA must be accounted for in the design of the facility. These include testing areas, proper

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product containment areas (quarantine), work-in-process (WIP) areas as well as released material areas. Additionally, consideration must be given for the handling of larger quantities of materials. Overhead feeding systems may be incorporated into the design of the facility. Perhaps in situ cleaning capabilities (clean in place) may also be investigated.

For the manufacture of products that will be used for human consumption, either by clinical studies or through marketing, a facility must be operated under Good Manufacturing Practices (cGMP). The Code of Federal Regulations, Section 21, part 211, describes the conditions required for maintaining cGMP compliance. Compliance of cGMP guidelines is enforced by the Food and Drug Administration (FDA). Compliance to these guidelines must be built into the design of the facility.

In our example of a solid dosage pilot facility, we have decided that our plant will be used for a variety of batches. We will develop novel formulations and prepare samples for marketing evaluation, we will support manufacturing, and we will occasionally manufacture a full-scale production batch as required by the market demands.

I. Manufacturing Philosophy

Once the manufacturing projection questions have been answered, a manufacturing philosophy must be decided on. This includes deciding on documentation requirements, special materials handling, controlled substance security, cleaning validation criteria, and equipment and facility qualification requirements. Now that we know what types of batches are to be manufactured, we can be more detailed in the description of the requirements of the facility. These requirements may be based on internal as well as regulatory requirements. In fact, if a full-scale facility is already in place, this step can be completed fairly easily and quickly. Many of the policies and systems may be transferred directly into the pilot facility. And others may be transferred with only slight modifications.

J. Documentation Requirements

Documentation requirements are predicated on the types of batches to be manufactured at the pilot facility. For the development of novel formulations, laboratory notebooks are the primary source of documentation. Room and equipment logbooks should be maintained. Personnel training records and SOPs must also be maintained. Once the facility is used for the larger-scale batches described earlier, what was recommended now becomes required. Manufacturing runs need to be documented accurately, preferably in batch records. Logbooks should maintain an accurate record of the product history in rooms and equipment. At this level of manufacturing, it is also important that personnel training records be kept. These

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should document the employees training in general safety issues, cGMP issues, equipment operation, and material handling. All documentation should be catalogued and easily accessible for review by either internal quality functions or by external auditing groups, such as customers or the FDA.

K. Special Materials Handling

Now that we know what types of batches will be manufactured, we can think about special materials handling. Although the design team can not be 100% sure what types of raw materials will be introduced into the facility, it can make provisions for special handling. What types of materials require special handling? First, let's answer the question "Why does a material need special handling?" Special handling may be needed to protect the user from detrimental effects from exposure to the compound. Secondly, the compound may need special handling to protect it against the environment.

In the first case, the operator may be working with toxic materials. Toxicity may be expressed either acutely or chronically. Each of these types of materials has different types of controls, which are required for the protection of the user. For toxic products, there are a variety of levels of controls that may be enacted. Many of these controls can be separated from the design of the facility itself, for example, portable respirators and gowns. Others may need to be incorporated into the design. For highly toxic products, we may need to supply the operator with a source of clean air.

There are many cases where the compound needs to be protected from the environment. Some material may be sensitive to light, in which case we may need to control the wavelength of the light during certain operations. Other materials may be sensitive to moisture, in which case controls of temperature and humidity are essential.

In general, however, the question of how much control to design into the facility needs to be answered. It is possible to design a facility without many of the special materials handling scenarios addressed and allow for a case-by-case analysis later on during the actual handling.

L. Controlled Substance Security

Similar to special material handling is the issue of controlled substance security. If it is decided to allow for this type of material handling, special considerations need to be made for legal issues involved. Security areas must be built into the design if these special classes of materials are to be handled. In 1970, the Controlled Substances Act (CSA), Title II of the Comprehensive Drug Abuse Prevention and Control Act, was enacted into law. This law deals with the regulation of narcotics, stimulants, depressants, hallucinogens, and anabolic steroids. All of these com-

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pounds are categorized into five schedules. The criteria used to categorize each drug are the drug's medicinal value, harmfulness, and potential for abuse or addiction. Schedule I is the most highly regulated one, while schedule V is the least controlled. Facilities that are to manufacture these controlled substances need to register with the Drug Enforcement Agency under section 823 of the CSA. Once licensed, the facility must maintain strict documentation of all controlled substance activities, such as purchasing, storage, manufacturing, distribution, and destruction. Additionally, areas of secure storage must be designed and maintained.

M. Cleaning Validation Criteria

Although we will deal with cleaning issues later in this chapter, it is necessary to consider the issues involved with cleaning validation in the planning part of the process. If the facility is to be operated under cGMP guidelines, a master plan for cleaning validation must be set in place. Of particular concern is ensuring that the cleaning procedures to be used are appropriate and effective. To fully evaluate a cleaning protocol's efficiency, we must consider the types of materials the facility will be exposed to. Along with the master plan for cleaning validation, feasibility of clean-in-place (CIP) systems should be evaluated. Many of the tanks used in the manufacture of liquids and ointments as well as biological products are available with these CIP systems incorporated into their design. Additionally, the facility must be designed to allow for thorough cleaning of the rooms as well as the equipment. Floor drains should be included. The floors and walls should be made of materials that are easy to clean, water and chemical resistant, and impervious.

N. Equipment and Facility Qualification Requirements

As part of the planning part of the project, an evaluation of the cleaning requirements for both the equipment and the facility must be done. An overall plan must be outlined for the evaluation of the success of the team. This success may be measured by the results of the equipment and facility qualification. What criteria will we use to qualify our construction and installation? The answer to this question will allow us to tailor our activities so that we can remain focused on the task at hand.

III. PHASE 2—DESIGN

Now that we have completed the planning phase, we can move into the design phase. As described earlier, the design phase is when the process flow is mapped out in detail. The utilities and process equipment required are described and in-

corporated into the plan. In this section we will first discuss the facilities. More specifically, we will go through a process flow for a solid-dosage pilot plant. Then the room classifications will be mapped out. In other words, we will decide on dedicated areas, multifunctional areas, and common areas. Secondly, the utility requirements will be discussed. What will our requirements for electricity, steam, water, communications, and air be? The process equipment will be described; scale-up factors and operating plans will also be analyzed. And finally, requirements for physical and analytical testing will be evaluated.

A. Facilities

Now that we have decided what types of batches will be manufactured in the pilot plant, we need to map out the process. In a solid dosage form facility there are a few process flows that can be followed. Some processes that can be used are dry blending, wet granulation, and dry granulation (see Fig. 1). Either compaction into

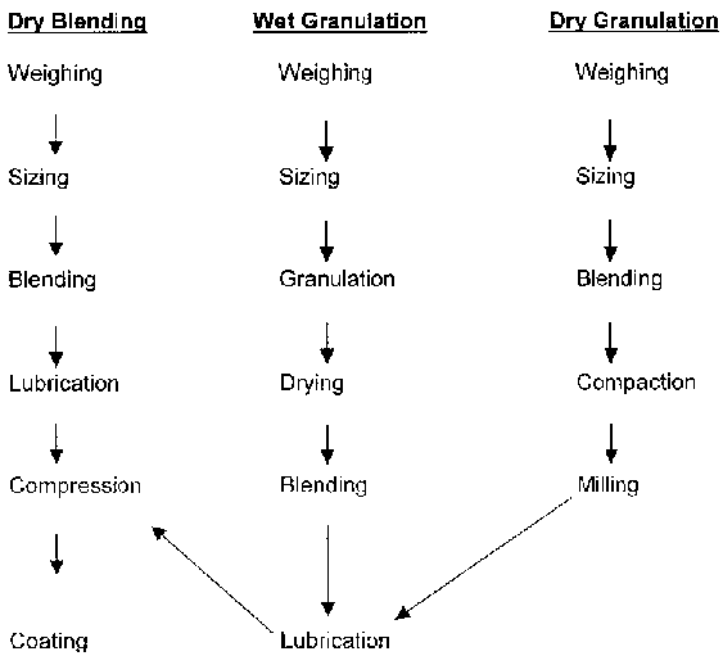

Figure 1 Process flow diagram.

tablet form or encapsulation then converts the resulting material into a dosage form. And lastly, for a variety of reasons, the tablets can be coated and imprinted. Because our facility will not be a full-scale production facility primarily, we will not use automated material handling. The design team must allow for easy and efficient material flow. However, automation may not allow us to manufacture small batches. It may also interfere with our ability to stay flexible throughout the manufacturing process, as is required by the nature of the manufacture of experimental batches.

B. Sizing

Sizing allows us to control the particle size of the incoming raw material. It serves the purpose of aiding in material flow and efficiency of blending. Additionally, through the control of the particle size of the raw material, the effect of lot-to-lot variability can be reduced. Typically for small-scale batches, sizing can be done in the blending room. However, as we increase the batch size, we may find it necessary to isolate sizing. During sizing, significant quantities of dust may be generated. It is important that dust control systems be built in the design of the room.

C. Blending

For the production of acceptable dosage forms, the powder must be uniform in its content of the drug substance as well as in its content of the excipients. Blending may be achieved in many different types of equipment. These different types of equipment may use different principles of mixing. A review of the blending equipment is presented shortly. For small-scale batches, blenders may be loaded with material by hand. However, as the batch size is increased, more automated ways of loading should be looked at. Typically, there is dust generated only during loading and during discharge. For larger-scale production, positioning of the blenders should allow for direct discharge into containers for transfer to the next unit operation.

D. Wet Granulation

Wet granulation can be used to improve the flow of the material to be processed. Additionally, it is used to improve the uniformity of the material. It may also be used to increase the density of the materials to allow for better processing downstream. Wet granulation processes require the handling of solutions. Typically, there is minimal dust generation. Additionally, processes involve the use of alcohol or water. Facilities should include drying capabilities either built into the granulators or as a separate functional area. Utilities required include electricity, compressed air, and steam.

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E. Compaction

Compaction, also known as compression, is the operation by which the blend is compressed into a tablet. For high-volume operations, an overhead feeding system is usually used. There is some dust generation in this process. Typical utilities required are compressed air and electrical service.

F. Coating

Tablet coating is done for a variety of reasons. The tablet core may contain an active substance that imparts undesirable organoleptic qualities to the tablet. The active moiety of the tablet may be unstable to specific environmental conditions and may need protection. The core may need to be coated to meet marketing requirements. The coating may be needed to impart enteric properties or sustained-release characteristics to the active release profile. Typical coating processes require a solvent, organic or aqueous. Utilities required include compressed air, steam, and electrical service. Provisions should be made for air handling. The exhaust system used must be capable of handling the solvent used in this process.

G. Room Classification

As part of the design of the facility, we may determine the appropriateness of using dedicated areas, multifunctional areas, as well as common areas. For large clinical and production batches, all unit operations are usually maintained in dedicated areas. This helps minimize the possibilities of cross-contamination as well as allow for many different products to be manufactured simultaneously. For the small-scale experimental batches, multifunctional areas may be used. For example, sizing and blending may be done in one room. Common areas may also be incorporated into the facility. Typical uses for these areas include work-in-process areas and in-process testing areas.

H. Space and Security

When allocating the areas for production, attention must be given to the space requirements of the equipment—not only the footprint of the equipment, but also the working area. This includes the ancillary equipment, i.e., controls, materials in-process, as well as operator working areas. In other words, there should be enough space for the operator to bring in the material to be processed, operate the machinery, and record the process in a batch record.

Security issues include the control of DEA scheduled compounds. For the less controlled substances, locked cages provide sufficient security; however, the

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more controlled substances require the use of vaults for storing raw material, in-process as well as finished goods. Additionally, processing rooms may require locking when a controlled substance is in process.

I. Utilities

Now that we have determined what processes the facility will be used for, we can finalize utility requirements. The following utilities are required for our solid-dose facility: heating, ventilation, and air conditioning (HVAC), hot and cold water, steam, electrical service, compressed air, vacuum systems, dust collection, chillers, effluent stream, and purified water. For the more specialized processes or special material handling, we may need specialized gases and breathing air. Purified water is one of the more difficult utilities to maintain the quality of. From a source of potable water, a series of treatments must be performed to control microbiological quality. Typical treatment options include carbon filters, reverse osmosis, and UV radiation.

Heating, ventilation, and air conditioning (HVAC) is a very expensive utility. However, it is essential and serves a variety of purposes. Not only is it important to maintain constant temperature and humidity, it is also important to balance the pressure in the processing areas to minimize cross-contamination opportunities. Dust collection, as mentioned earlier, is very important when handling powders. The dust generated during some processes may be toxic and may pose an explosion hazard. This system is typically very closely associated with the HVAC system.

Compressed air is required for the operation of some of the processing equipment we have described earlier. Typically, this service is supplied by an in-house compressor unit equipped with a filtration unit.

J. Process Equipment

We have already briefly discussed the manufacturing process. We will now discuss the equipment used in the unit operations for our solid-dose pilot plant. The following is presented to serve as an example of what the design team considers when involved in the design of a solid-dose pilot facility. Because we are designing a facility to be used to make small-scale batches using processes that will eventually be transferred to a large-scale manufacturing facility, in this section we will briefly discuss scale-up issues with each of the processes discussed. The following section discusses equipment operating principles. For the sake of clarity, these classifications are as designated by the Manufacturing Equipment Addendum of the Guidance for Industry document describing SUPAC-IR/MR: Immediate-Release and Modified-Release Solid Dosage Forms published January 1999.

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K. Sizing

In solid-dose manufacturing, sizing plays a key role in helping ensure that uniformity is achieved. There are two ways in which sizing is performed, through particle size reduction and through particle separation. Particle size reduction is performed through one of the following mechanisms: impact, attrition, compression, and cutting. The operating equipment includes the following: fluid energy mills, impact milling, cutting, compression milling, screening, tumble milling.

In general, considerations for the scale-up of a sizing operation are just a few. Of course, our main interest is in maintaining the same particle size distribution as in the small-scale process. A major factor, assuming that equivalent screen sizes are used, is the feed rate of the material into the equipment. As the feed rate is increased, so is residence time within the chamber of the equipment. This results in a finer distribution. To successfully mimic large-scale conditions, we may want to design an overhead feeding mechanism into our sizing equipment.

L. Blending

There are two main operating principles for blending: diffusion blending and convection blending. Diffusion blenders are very common in solid-dose manufacturing. They include the V-blender, double-cone blenders, slant-cone blenders, and bin blenders. Scale-up considerations for processes involving these types of blenders include time of blending, blender loading, and size of blender. Mathematical relationships can be established between blending time and diameter of rotation.

Convection mixers use a different principle for blending. These mixers have an impeller. This class includes ribbon blenders, orbiting screw blenders, vertical and horizontal high-intensity mixers, as well as diffusion blenders with an intensifier bar. Scale-up considerations are similar to those for the tumble blenders.

M. Granulation

There is a variety of operating principles for granulation processes. These include dry granulation, wet high-shear granulation, wet low-shear granulation, and fluid-bed granulation. Dry granulation is accomplished through either slugging or roller compaction. Wet high-shear granulation equipment uses high-energy impellers during the addition of the granulation solvent. These can be either vertically or horizontally driven. Wet low-shear granulators can use either a rotating impeller, reciprocal kneading, or a screw-type mechanism to induce the granulation.

Fluid-bed granulation is accomplished by fluidizing the material to be granulated in a chamber while spraying the granulation solution into the fluidized powder. Scale-up of granulation processes is very complex and has been covered

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extensively in previous chapters. The successful scale-up of a granulation process can be measured by the compaction properties of the resulting material as well as by the drug uniformity found in the blend and finished product.

N. Compaction

Compaction, also known as *tableting,* involves the compression of the blend into a unit dose. The mechanism for this type of processing has remained unchanged for quite some time. The main components of the compression cycle are: pressure rolls, weight adjustment cam, ejection cam, and feed frame. The main considerations when scaling up is compression speed. Compression speed effects dwell time and feed rate. As you go from a small development compression machine to a high-speed production machine, the powder is processed much more rapidly.

O. Encapsulation

There are three main systems for filling capsules with powder: gravity, tamping, and dosator. Typically for small-scale batches, gravity systems are adequate. However, as speed of processing becomes an issue, force filling becomes more important. For consideration when scaling up is the ability of the powder to fill at the higher speeds required. Also important is the flow of the material from the hopper into the mechanism of the encapsulator.

P. Coating

Coating is accomplished by atomizing the coating material into a fine mist that is then sprayed onto a rotating bed of tablets on a perforated pan. Throughout this process, there is a fine balance between the process air coming into the system and the process air leaving the system. Additionally, special attention is paid to the degree of atomization of the solution as well as to the rate of application of the solution. The main issues for consideration of scaling up in a coating process are: the tablet loading of the coating pan, the spray rate of the coating solution, the quantity of solution required, as well as the volume of air used during coating. As mentioned earlier, coating systems require extensive air handling utilities. They require very strict temperature and humidity controls.

Q. In-Process Testing

In-process testing is especially critical, if the material being produced is to be used for human consumption. The types of in-process testing requirements will vary with the process. However, following is a brief description of the types of the in-process testing requirements of a solid-dose manufacturing process.

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During the screening step, an in-process particle size analysis may be done. This may give us an indication of the control of the sizing operation. After the completion of blending, samples are taken for blend uniformity analysis. If the process includes wet granulation, a sample is taken for moisture content determination. If the granulation process used any organic solvents, then a sample must be taken to test for residual solvents. Throughout the compaction process, samples must be taken regularly for measurement of weight, hardness, thickness, and friability. Similarly, during the encapsulation process, samples are taken regularly for weight determination.

During the design of the facility, provisions must be made for the areas for in-process testing to be carried out. Much of the testing may be done in common areas, i.e., tablet and capsule testing. However, some must be done in specialized areas, i.e., uniformity testing.

IV. CONCLUSION

At this point in the project, we are ready to begin the construction phase. At which point, the project management function becomes paramount in importance. All tasks must be identified and tracked properly. Coordination of this phase can be kept in-house or be turned over to contractors. It is important that if the bulk of this phase is contracted out, strict goals are identified so that the progress of the project can be tracked closely. It is also at this point that we will need to obtain building permits, emission permits, drug licenses, as well as controlled drug licenses.

Upon the conclusion of the construction phase, qualification of the facility, utilities, and equipment is carried out. Protocols outlining the acceptance criteria need to be written and approved. These protocols set standards required for the acceptance of the facility and equipment as completed.

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A Collaborative Search for Efficient Methods of Ensuring Unchanged Product Quality and Performance During Scale-Up of Immediate-Release Solid Oral Dosage Forms

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I. BACKGROUND

Quality and performance attributes of pharmaceutical products are a function of several formulation and manufacturing factors. To develop drug products with optimal performance characteristics (for use in clinical testing), certain physical, chemical, and biological attributes of a drug are characterized in preformulation and preclinical programs. The effects of manufacturing factors on product quality and performance are evaluated during product development. These important steps are essential for minimizing the likelihood that product quality problems will confound the pivotal safety and efficacy databases. Generally, after establishment of an acceptable safety and efficacy profile of a drug (using a high-quality clinical trial product), the manufacturing processes are scaled up to provided sufficient volume of product to meet market needs. Manufacturing process and formulation changes needed for scale-up should not adversely affect the safety or efficacy of a product.

Two fundamental product quality questions posed during drug development are:

How do we build quality into products that are tested in the clinic to establish safety and efficacy?

How do we utilize product development and clinical data/experience to establish appropriate specifications for the "to-be-marketed" product?

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These questions are at the core of the basic principles of quality assurance. These principles may be stated as follows [1]:

1. Quality, safety, and effectiveness must be designed and built into the product.
2. Quality cannot be inspected or tested into the finished product.
3. Each step of the manufacturing process must be controlled to maximize the probability that the finished product meets all quality and design specifications.

In Figure 1, the two fundamental product quality questions are positioned within the well-recognized stages or phases of the drug development process. During product development, a set of formulation and manufacturing factors and their target values or acceptable ranges are identified, generally through extensive experimentation, and manufacturing processes validated to ensure acceptable and reproducible quality and performance. Product specifications are developed to confirm product quality and focus on attributes that impact product performance. Specifications establish a set of criteria to which a product should conform to be considered acceptable for its intended use; regulatory authorities require these as conditions of approval [2]. Unchanged product quality and performance, batch to batch, is assured via adherence to Current Good Manufacturing Practices (CGMPs), conformance with established raw material specifications, in-process controls, and finished-product specifications. It is through careful design and validation of both the process and process controls that a manufacturer establishes a high degree of confidence that all manufactured units from successive lots will be

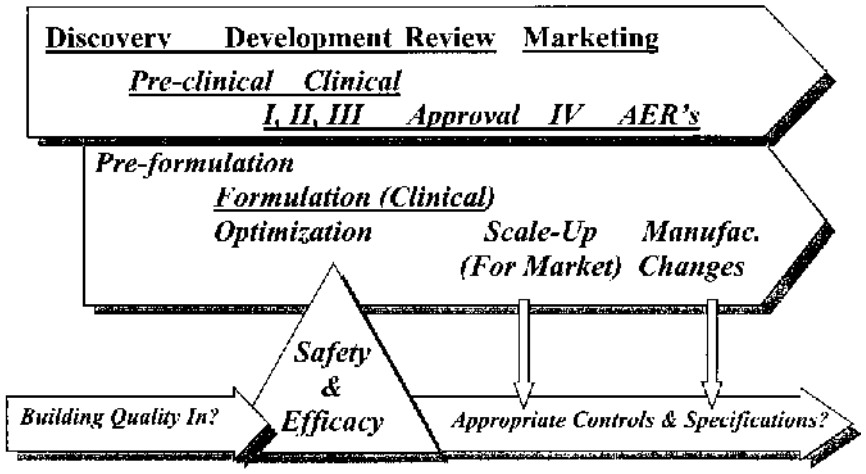

Figure 1 Connecting-the-dots: Discovery–development–marketing.

acceptable [1]. Data generated during these various stages of drug development provide information and knowledge about the safety and efficacy of a drug candidate. These data are then reviewed by regulatory agencies to ensure an acceptable benefit-to-risk profile prior to granting approval for marketing. Additional testing sometimes is necessary after approval (Phase IV). Postmarketing surveillance and compliance programs are utilized to monitor product quality and performance (e.g., adverse event reports, AERs) after regulatory approval.

Manufacturing changes have the potential for altering the safety and efficacy profile of a product. A demonstration of bioequivalence and acceptable stability of postchange product is therefore needed to qualify significant manufacturing changes. Bioequivalence assessments and chemistry requirements are also used, in place of clinical safety and efficacy evaluation, for approval of generic drug products and postapproval changes to these products. Maintaining and documenting consistent quality and performance in the presence of change is a challenge to both industry and regulatory agencies. Ideally, product quality and performance specifications are developed and validated based on a mechanistic understanding on how formulation and manufacturing factors affect product performance. However, in some instances both scientific and resource (time) challenges may not permit development of a mechanistic framework for quality/performance specifications. In the absence of a clear understanding on how manufacturing changes impact product performance, changes are discouraged or extensive testing recommended by regulatory agencies. Under these conditions significant resources may have to be expended to qualify even minor changes, and the introduction of new and/or more efficient manufacturing technology may be hindered.

II. INTRODUCTION

Since the late 1980s, several scientific workshops and symposia have been held on topics of manufacturing changes and approaches for ensuring unchanged product quality and performance. These public debate opportunities initiated the process of building scientific consensus on how critical formulation and manufacturing variables should be identified, optimized, and controlled. These proceedings have provided tangible results [3,4]; an excellent example is the Food and Drug Administration's (FDA) Scale-Up and Post Approval Changes guidance document for immediate-release solid oral dosage forms (SUPAC-IR) [5]. (For this and other SUPAC documents, see Appendices.) This plus other similar results provided a stage for building enduring collaborative relationships between industry, academia, and the FDA for the worthy purpose of enhancing the scientific foundations of regulatory policies related to product quality. The Product Quality Research Institute, Inc. (PQRI) is an ensuing vehicle for this collabor-ation [6]. It is a virtual research institute founded in 1999 by several

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pharmaceutical trades and professional associations and the Center for Drug Evaluation and Research (CDER) FDA. The American Association of Pharmaceutical Scientists (AAPS) administers it. The United States Pharmacopoeia (USP) recently joined this institute.

The SUPAC-IR guidance document is generally regarded as a significant initial milestone on the path to building scientific consensus on approaches for qualifying manufacturing changes. It also provides a benchmark to chart the progress of future collaborative projects being developed on this topic in the PQRI. These projects propose to further improve the scientific foundations of industrial practices and regulatory policies related to conventional or immediate-release (IR) solid oral dosage forms. Initial focus on IR products was based on their market prevalence, long (~100 years) manufacturing history, and the recognition of scientific and technical advances in the establishment of causal links between critical manufacturing variables and product performance.

For the past several years, scientific debates within the pharmaceutical community on the topic of manufacturing changes have centered on the question of additional tests and reporting requirements needed to document unchanged quality and performance. The SUPAC approach focused this debate on the definitions of *significant changes* and what constitutes *sufficient characterization.*

In PQRI, this debate served as a focal point for discussions, and for this purpose it was framed as: "Adherence to CGMP's plus conformance with appropriate process controls and product specifications are sufficient to qualify manufacturing changes to IR products." The counterargument in this debate is that the primary objectives of in-process controls and product specifications are to ensure that validated processes remains under control to yield products that conform with established specifications and that, when significant changes occur, specifications may not provide sufficient characterization to ensure unchanged performance. The PQRI programs offer a means for transforming these debates into opportunities for enhancing the science of minimize risks of unacceptable deviations in product performance when manufacturing changes are implemented.

Clearly, significant progress has been made during the past four decades in moving the practice of pharmaceutical product development from art to science. The debate on manufacturing changes could also have been farmed as an art vs. science debate. The term *art* as used in this discussion stands for "the power of performing certain actions, especially as acquired by experience, study, or observation" [7]. It is distinguished from the term *science,* which "signifies accumulated and *accepted knowledge* that has been systematized and formulated with reference to the discovery of general thruths or the operation of general laws" [7]. Acceptance of established knowledge by several scientific disciplines and the public is often a prerequisite for its application in public policy decisions, especially when such decisions can have a broad and significant impact on public health.

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The objective of this chapter is to illustrate some key elements of the scientific debate on the value of established specifications for qualifying manufacturing changes. For this purpose an example of the scale-up of a capsule product and the associated formulation and equipment changes was selected and evaluated within the framework of current regulatory recommendations. Many pharmaceutical scientists may consider adherence to CGMPs plus conformance with product specifications sufficient to qualify changes encountered in this example as opposed to the current regulatory recommendations of additional bioequivalence and stability testing and the prior-approval supplement process.

III. MANUFACTURING CHANGES

Manufacturing changes are often necessary for reasons such as scale-up, introduction of new manufacturing technology, and company mergers. In these situations formulation and manufacturing process conditions are identified that allow the product to satisfy established specification for the prechange product and the modified process validated in accordance with CGMPs. For accomplishing this task, several changes in manufacturing equipment, processing conditions, and/or formulation may be necessary due to the multifactorial nature of the pharmaceutical products. This scenario and certain elements of the SUPAC debate are examined using a scale-up example selected from the literature [8]. The information used in this chapter was derived from the literature and other public sources.

Manufacturing changes: Scale-up of a developmental product using encapsulation equipment of different design.

Development product: Capsule product containing *x* mg of drug *y* ("freely water soluble") and 1% magnesium stearate was developed using a Zanasi LZ-64 capsule-filling machine. Initial development experiments identified a causal link between blend time and dissolution rate. Capsules prepared with powders blended for 5 minutes exhibited a more rapid dissolution rate (~95% dissolved in 10 minutes) compared to powders blended for 40 minutes (~90% dissolved in 45 minutes). A 10-kg lot was blended for 15 minutes in a V-blender. Under these conditions the resulting capsules conformed to an in vitro dissolution acceptance criteria of Q75% in 45 minutes (in 900 mL water at 37°C, USP Basket 100 rpm).

Scale-up product: Initial trial for scale-up utilized a batch size of 570 kg, a Hoflinger & Karg GFK-1500 capsule-filling machine (H&K), and a V-blender, with the mixing time set to 15 minutes. Capsules resulting from this batch did not conform to the dissolution specification (only about 40% dissolved in 45 minutes). To rule out "overblending" with magnesium stearate, a blend time of 5 minutes in the V-blender was uti-

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lized and another batch manufactured. This step failed to resolve the observed dissolution problem, suggesting that "overblending" may not be occurring in the V-blender. Further analysis of the problem indicated that during encapsulation on the H&K machine, powder was being sheared (during the tamping steps, not during the auger-feeding process), resulting in an unacceptable dissolution rate. Using a shear simulation approach, the optimal level of magnesium stearate of 0.3% was identified for the H&K machine, which satisfied encapsulation (e.g., content uniformity) and dissolution criteria. The full production batch (1100 kg) was produced on the H&K machine using 0.3% magnesium stearate and a blend time of 15 minutes.

Formulation attributes for optimal encapsulation on machines of different design can vary. Changing Zanasi to H&K may require a reduction in the amount of magnesium stearate, even for a formulation without a pronounced drug–lubricant–mixing interaction. With respect to formulation requirements for the Zanasi and H&K machines, the following observations have been made [9]:

1. Powder flow requirements vary with equipment design. To maintain a low weight variation, optimum values of Carr's index (CI) is in the 25 to 35 range for Zanasi and $18 < CI < 30$ for H&K. (*Note:* Carr's Index is calculated from the loose bulk density (LBD) and tapped bulk density (TBD) of powders. $CI = 100[(TBD - LBD)/TBD]$
2. *Zanasi:* Powders with high Cl (>30) produce stronger plugs with lower weight variation; for powders with a low Cl (<20), higher compression forces may be needed (150–200 N) to improve powder retention in dosator tube.
   H&K: Formulations with high Cl (>30) tend to flood near the ejection station.
3. Based on plug ejection forces, a relatively lower level of lubricant (about $\frac{1}{2}$) is sufficient for H&K machines as compared to Zanasi.

A recent survey of capsule formulation practices in industry reported that a majority of companies (64%) use equipment of the same design and operating principles for development/pilot and production batches, and about 18% develop pilot formulations on equipment of different design from the production machines. The choice of encapsulation equipment design, dosing disc vs. dosator type machines, is about equally divided, with about 18% of companies using both types of machines; i.e., about 40% of companies use only one type (design) of machine [9]. In today's global economy, developing capsule formulations that can be encapsulated using equipment of different design can be advantageous. The survey estimated that only about 18% of companies use both types of machines (both dosator and dosing disc types) in their facilities, suggesting that many current for-

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mulations may not be tailored for equipment of different design. With the increasing number of mergers and the consolidation of manufacturing operations, plus a trend for outsourcing certain manufacturing operations, it could be anticipated that the selected example represents a class of SUPAC that may be relevant for a number of companies. The other critical aspect of this case deals with changes in the amount of magnesium stearate, the most widely used excipient in tablet and capsule formulations. Therefore, information developed in this analysis should be useful beyond this particular case study.

IV. REGULATORY RECOMMENDATIONS ON MANUFACTURING CHANGES

A. A Note on Regulatory Recommendations

It is important to note that the FDA guidance documents reflect that agency's current thinking on a given issue. These documents do not create or confer any rights for or on any person and do not operate to bind the FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both. These guidance documents assist in clarifying regulatory decisions and thereby eliminate or reduce unanticipated decisions.

The SUPAC-IR guidance was issued in November 1995 to provide recommendations on tests and filing documentation to sponsors of new and abbreviated drug applications on the following types of postapproval changes in the manufacture of immediate-release oral solid products: (1) components and composition, (2) site of manufacture, (3) scale-up/scale-down of manufacture, and/or (4) manufacturing process and equipment. The guidance defines: levels of change, recommended chemistry, manufacturing, and controls tests for each level of change, in vitro dissolution tests and/or in vivo bioequivalence tests for each level of change, and documentation that should support the change. Prior to SUPAC-IR, all postapproval changes were considered together and generally required extensive stability and bioequivalence documentation. SUPAC-IR changed this by creating a multitiered system for both stability and bioequivalence documentation that was based on the estimated likelihood that a specific manufacturing change would adversely affect product performance.

The Food and Drug Administration Modernization Act (1997), section 116, amended the Food, Drug, and Cosmetic Act by adding section 506A (21 U.S.C. 356a), which provides requirements for making and reporting manufacturing changes to an approved application and for distributing a drug product made with such changes. The Center for Drug Evaluation and Research (CDER) of the FDA issued a new guidance to provide recommendations on postapproval changes in accordance with section 506A [10]. Note that this guidance supercedes the SU-

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PAC-IR on recommendations for reporting categories. Another guidance was issued recently that discusses waiver of in vivo bioequivalence studies for IR products during both pre- and postapproval phases [11].

The discussion to follow examines the SUPAC-IR guidance recommendations for the manufacturing changes encountered in the selected example. Although this guidance did not provide recommendations on multiple related changes, the new guidance [10] does address this issue as follows:

> For multiple related changes where the recommended reporting categories for the individual changes differ, CDER recommends that the filing be in accordance with the most restrictive of those recommended for the individual changes. When the multiple related changes all have the same recommended reporting category, CDER recommends that the filing be in accordance with the reporting category for the individual changes.

After identifying the regulatory recommendation, a brief scientific/regulatory risk analysis is conducted within the framework of the two fundamental product quality questions posed earlier.

B. Batch Size (10 kg to 1100 kg)

Changes in batch size are categorized in two levels. The Level 1 change in batch size is up to and including 10 times the size of the pilot or bio batch that is accomplished using equipment of the *same design and operating principles* and without changing its manufacturing procedures and formulation. Changes in batch size beyond 10 times the size of pilot batch is accomplished using equipment of the same design and operating principles, and its manufacturing procedures and formulation are considered Level 2 change.

The SUPAC-IR guidance suggests that a pilot-scale batch be, at minimum, one-tenth that of full production scale or 100,000 dose units (tablets or capsules), whichever is larger. If the dose of drug *Y* was 100 mg, a 10-kg batch will, in theory, produce 100,000 units but will not meet the $\frac{1}{10}$ production-scale criteria. The origin of the $\frac{1}{10}$ production-scale criterion was intended primarily to ensure that the pilot batch was manufactured by a procedure fully representative of and simulating that used for full manufacturing scale (e.g., heat and mass transfer efficiency).

If the development formulation were considered a pilot batch, then increasing batch size from 10 kg to 1100 kg using equipment of the same design and operating principles (see later) would be considered a Level 2 change. Additional tests recommended include stability (three months' accelerated stability and long-term stability data on one batch) and multipoint dissolution profile comparison in the application or compendial medium (Case B).

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C. Manufacturing (Equipment and Process) Changes

In the SUPAC-IR guidance, changes in equipment and/or process are considered separately under the section on manufacturing changes. Three levels of process changes are defined. Level 1 is limited to changes in processing times and operating speeds within application/validation ranges, Level 2 is when these changes are outside of application/validation ranges, and Level 3 is for change in process (unit operation), such as wet granulation to direct compression.

Two change levels are defined for equipment changes. Level 1 for changes to alternative equipment of the *same* design and operating principles (same or different capacity) and Level 2 for equipment of *different* design and different operating principles. A companion guidance document is provided that describes and classifies pharmaceutical equipment on the basis of operating principles and design [12]. The operating principle is used to define an equipment class, and equipment design is used to create a subclass. For example, a change from one type of diffusion mixer (such as a V-blender from manufacturer A) to another diffusion mixer (a V-blender from manufacturer B) generally would not represent a change in operating principle. However, a change from a V-blender to a ribbon blender demonstrates a change in the operating principle from diffusion blending to convection blending.

For equipment changes, this guidance [12] provides the following recommendations:

> Applicants should carefully consider and evaluate on a case-by-case basis changes in equipment that are in the same class but different subclass. In many situations, this type of change in equipment would be considered similar. For example, within the Blending and Mixing section, under the Diffusion Mixers Class, a change from a V-blender (subclass) to a Bin tumbler (subclass) represents a change within a class and between subclasses. Provided the manufacturing process with the new equipment is validated, this change would likely not need a preapproval supplement. The applicant should have available at the time of the change the scientific data and rationale used to make this determination. This information is subject to FDA review at its discretion. It is up to the applicant to determine the filing requirement.

1. Equipment and Process Change (V-Blender, Capacity)

Change in V-blender capacity (Level 1 Equipment Change) may be qualified by conforming to CGMPs, application/compendial release requirements, and a commitment to place one batch of postapproval product on long-term stability. In this example, the mixing time was 15 minutes for both pre- and postchange products. *Note:* A more appropriate control for this unit operation might be the number of revolutions, not time.

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2. Equipment Change (Encapsulation Machine, Zanasi LZ64 to Hoflinger & Karg GFK-1500)

The operating principle *encapsulation* is the division of material into a hard gelatin capsules. Encapsulator subclasses are distinguished from one another primarily by the method used for introducing material into the capsule. Encapsulators can deliver materials with a rotating auger, vacuum, vibration of perforated plate, tamping into a bored disk (dosing disk), or cylindrical tubes fitted with pistons (dosator).

The Zanasi LZ64 fills capsules by dipping a dosator into powder bed and compacting the powder bed into cylindrical plugs. The Hoflinger & Karg GFK-1500 delivers the powder from a feed hopper onto a dosing disk by means of a vertical auger. The powder falls into cavities in the dosing disk and is successively forced by a set of tamping pins to form cylindrical plugs that are then inserted into bodies of capsule shell [8].

This change (Zanasi to H&K) represents a change in subclass. A conservative approach would be to classify this as a Level 2 equipment change. If so classified, SUPAC-IR guidance recommends the following additional tests:

Stability testing: Recommendation based on the availability of a significant body of information on the stability of the drug product that is "likely to exist after five years of commercial experience for new molecular entities, or three years of commercial experience for new dosage forms."

Significant body of information available: One batch with three months' accelerated stability data reported in supplement; one batch on long-term stability data reported in annual report.

Significant body of information not available: Up to three batches with three months accelerated stability data reported in supplement; up to three batches on long-term stability data reported in annual report.

Dissolution documentation: Case C dissolution profile. Multipoint dissolution profiles performed in water, 0.1N HCl, and USP buffer media at pH 4.5, 6.5, and 7.5 (five separate profiles) for the proposed and currently accepted formulations. Adequate sampling should be performed at 15, 30, 45, 60, and 120 minutes until either 90% of drug from the drug product is dissolved or an asymptote is reached. A surfactant may be used with appropriate justification.

D. Composition Change (Magnesium Stearate 1% to 0.3%)

Changes in the qualitative or quantitative formulation, including inactive ingredients, as provided in the approved application, are considered major changes

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and should be filed in a prior-approval supplement, unless exempted by regulation or guidance (Food, Drug, and Cosmetic Act; 506A(c)(2)(A)). With respect to magnesium stearate in IR products, SUPAC-IR guidance recommends a quantitative change to the following extent: 0.25% be considered Level 1, and changes within 0.5% are considered Level 2. In this example, the target amount of magnesium stearate was 1%, which was changed to 0.3% (i.e., −0.7%), which exceeds the recommended range for Level 2. Therefore, this change may be considered Level 3, with the following recommended additional tests:

Stability tests:
Significant body of information available: One batch with three months' accelerated stability data reported in supplement; one batch on long-term stability data reported in annual report.
Significant body of information not available: Up to three batches with three months' accelerated stability data reported in supplement; one batch on long-term stability data reported in annual report.
Dissolution documentation: Case B dissolution profile.
In vivo bioequivalence documentation: Full bioequivalence study.

E. Multiple Related Changes

For multiple related changes where the recommended reporting categories for the individual changes differ, the new guidance [10] recommends that the filing be in accordance with the most restrictive of those recommended for individual changes. For the selected example this appears to be Level 3 component and composition change category (earlier). Based on this change level, to justify changes in the selected example, an in vivo bioequivalence study along with stability (accelerated and long-term) studies are recommended. The filing mechanism recommended is the prior-approval supplement. Note that a waiver of in vivo bioequivalence study may be justified if the drug in this example exhibits high solubility, high permeability, and wide therapeutic index; and both the pre- and postchange products exhibit rapid dissolution in vitro [11].

The selected example [8] represents a relatively straightforward formulation development project with a well-recognized interaction between drug, excipient, and process conditions that, when not managed properly, can have an adverse impact on product quality (content uniformity and dissolution). It offers a means to exemplify; (1) the relationship between the two product quality questions stated in the introductory section, and (2) challenges and debates associated with the development of regulatory policy for addressing manufacturing changes to products that are multifactorial in their design.

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V. PERSPECTIVES ON ENSURING UNCHANGED QUALITY AND PERFORMANCE

Pharmaceutical products must demonstrate and maintain established public standards for attributes that relate to their safety or effectiveness. In the United States these attributes are expressed as *identity* (e.g., chemical structure), *strength* (e.g., assay, content uniformity), *quality* (e.g., combination of certain physical, chemical, and biological attributes), *purity* (e.g., limits on impurities and degradation products), and *potency* (e.g., biological activity, bioavailability, bioequivalence) [10]. Public standards serve as one of several mechanisms for minimizing the risk of product-related injuries. In principle these standards should reflect the current state of scientific understanding and ensure and promote the development of high-quality products.

A. Building Quality into Products

During the development of a pharmaceutical product, the impact of several factors (e.g., formulation, process, packaging, and storage conditions) on product quality and performance should be characterized and optimized. Preformulation programs evolved in the late 1950s; prior to this the general emphasis in product development was on producing elegant dosage forms based on organoleptic considerations [13]. The goals of modern preformulation programs are to develop analytical methods and (1) to characterize the necessary physical, chemical, and permeability attributes of a new drug substance, (2) to determine the degradation mechanisms and establish its kinetic rate profile, and (3) to establish compatibility with the excipient to be used in a formulation. In the discussion to follow it is assumed that the selected formulation was developed following sufficient preformulation characterization to ensure compatibility between the formulation ingredients. Also note that the concept of "building quality in" during the product development phase is equally relevant for postapproval changes.

The selected formulation example is a binary powder mixture (drug Y and magnesium stearate) that is encapsulated in hard gelatin capsules [8]. In this formulation, magnesium stearate (a hydrophobic lubricant) is included to assist in the manufacturability of the product (i.e., ensure content uniformity and uninterrupted machine operations). Suboptimal levels can bring about content uniformity problems. However, physical interaction between drug particles, hydrophobic lubricants, and processing conditions (e.g., shear forces exerted on the powder during mixing and encapsulation processes) can decrease the wettability of drug particles and retard dissolution. This phenomenon was recognized over 30 years ago and has since been investigated extensively; these research efforts have provided mechanistic explanations and also proposed formulation strategies to overcome adverse effects of this interaction on drug dissolution [14–31].

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To implement change in capsule filling equipment in this case, several change management strategies could be adopted: (a) reduce shear on the powder by adjusting the pin settings on the H&K machine, (b) optimize (reduce) the level of magnesium stearate to satisfy the content uniformity and dissolution acceptance criteria, and (c) change the formulation to facilitate plug formation and/or minimize undesirable effects of magnesium stearate (e.g., addition of a wetting agent such as sodium lauryl sulfate). Use of a less hydrophobic lubricant is also an option [18,20], but this approach is seldom practiced (see up coming Fig. 2). The selection of a change management strategy is likely to be based on a number of technical and economic factors. An important consideration for this decision should be an understanding of the impact on product performance and the risk of product failure (i.e., failure to meet established dissolution and other specifications) during routine production. It is postulated that the risk of product failure during routine manufacturing is likely to be in the order (a) > (b) > (c).

The first strategy, adjustments of pin settings, was rejected by the authors because they concluded that this strategy would only reduce, not eliminate, the problem and that this strategy may be appropriate for a formulation that is less sensitive to the effect of shearing [8]. This decision was in line with the concept of "building quality in." It is rationalized later why this equipment adjustment strategy for the selected example was postulated to be a *high-risk* practice. Although this discussion is focused on the adverse impact on dissolution due to shear observed during the encapsulation process, this could also have occurred during the mixing process if a V-blender equipped with a high-speed intensifier bar was used [20].

Even if machine adjustments could have been made, to reduce this dissolution problem to an undetectable level for a given lot of magnesium stearate there would exist a (significant) chance of product failure with different lots of magnesium stearate. Additional control strategies may also be needed to ensure that machines were set correctly and that the settings did not change during a production run. The physical properties of magnesium stearate from different commercial sources as well as lot–lot variations from a single source can be problematic [32]. If this strategy were adopted, would the risk of failure become apparent during process validation? Perhaps, if different lots of magnesium stearate were used during process validation and (predictive) functionality tests developed/adopted to qualify vendors and lots. The final step in process validation, i.e., the demonstration of repeatability, is predicated on quality being "built into" products. If this were not so, one would expect to encounter problems during routine manufacturing, when some differences in compendial materials may be unavoidable. This may be a reason why Harwood and Molnar [33] characterized process validations as a "well-rehearsed demonstration that manufacturing formula can work three successive times," and that "validation exercise precedes a trouble-free time period in the manufacturing area only to be followed by many hours (possibly days

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or weeks) of troubleshooting and experimental work after a batch or two of product fails to meet specifications. This becomes a never-ending task."

A survey of formulation practices, conducted in 1993, provides some insight on how variability associated with magnesium stearate is currently being managed [34]. In this survey, when asked whether their company specified an exclusive source and type of magnesium stearate, 80% of respondents said yes. Others indicated that they utilized a functionality test (particle size testing and/or bulk density test) or simply relied on compendial standards [34]. The USP/NF monograph on magnesium stearate does not include tests for its lubricant functionality [35].

In spite of the problems associated with magnesium stearate, 54 of 58 formulators identified magnesium stearate as their first choice [34]. This popularity was also evident in a spur-of-the-moment survey of the FDA's Inactive Ingredient Guide, conducted by this author, of excipients used in formulations of capsule dosage forms (see Fig. 2; note that gelatin and other materials, such as colors, were not included in this figure and that titanium dioxide is probably a component of both the gelatin shell and the encapsulated material). This popularity suggests that that lot–lot variability and other problems associated with magnesium stearate variability are being successfully managed by industry.

The other two possible strategies rely on adjusting or changing the formula. Reducing the amount of magnesium stearate from 1% to 0.3% was determined to be optimum and adopted by the authors [8]. Another option could have been to include a wetting agent to make this formulation insensitive to equipment and pro-

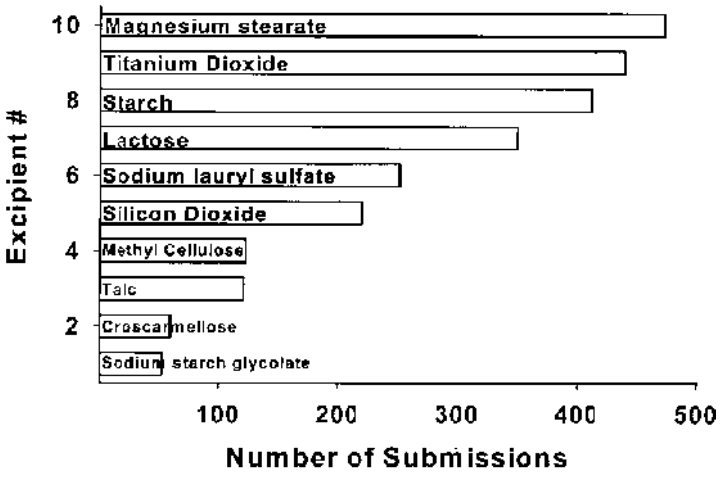

Figure 2 Common excipients in oral capsules.

cessing conditions. The latter approach may be preferred if drug Y was poorly soluble. From Figure 2 it appears that about half the submissions on oral capsule formulation to the FDA utilize a wetting agent (sodium lauryl sulfate), suggesting that the lubricant plus wetting agent combination is a fairly common formulation design strategy.

In an FDA-sponsored study it was found that the impact of magnesium stearate on drug dissolution and the bioavailability of piroxicam (a low-solubility drug) from capsule formulations (encapsulated on Zanasi LZ-64) containing a wetting agent was negligible. Sodium lauryl sulfate level and piroxicam particle size were the most important main effects affecting dissolution. Lubricant levels (range studied 0.5–1.5%) and lubricant blending times (2–18 minutes in a V-blender) either were not significant or were among the lowest-ranking factors affecting dissolution. Changes in equipment, e.g., Zanasi to H&K, were not evaluated in this study [36].

B. Do Specifications Ensure Unchanged Product Performance?

The desired goal of a manufacturing change-management system is generally to maintain an unchanged safety and efficacy profile of a product. Two primary attributes utilized for most drug products are bioequivalence and unchanged stability profile or expiration date (shelf life).

1. Bioavailability and Bioequivalence

In the selected example, critical formulation factors with respect to dissolution (and bioequivalence) are the ones that affect the ability of the dissolution medium to gain access to the drug particle surface (wettability) and drug particle size/surface area (ignoring dissolution of the gelatin shell). The criticality of these factors is likely to be a function of drug properties such as its aqueous solubility. These critical factors are controlled by establishing standard operating procedures (SOPs), in-process controls for blending and encapsulation operations, specifications for drug (and possibly magnesium stearate) particle size (not discussed in this chapter), content uniformity, and dissolution (which also serves as a functionality test for drug–lubricant-blending interaction). Information derived from several biopharmaceutical and pharmacokinetic studies conducted during drug development are generally utilized to justify a proposed dissolution specification (also see decision tree #7 in Ref. 2). The one-point dissolution test acceptance criterion, in this case Q75% in 45 minutes, is designed to guard against poor dissolution. By reducing the amount of magnesium stearate, the likelihood of slow dissolution is further reduced. Based on this developmental experience, one could argue that conformance with established controls and specifications should be suf-

ficient to ensure bioequivalence between pre- and postchange product, especially since the drug is freely soluble in water.

In the discussion so far it was assumed that the dissolution specification developed for this formulation of drug Y, Q75% in 45 minutes (in 900 mL water at 37°C, USP Basket 100 rpm), was appropriate for ensuring bioequivalence between different lots of clinical products as well as the scaled-up formulation. In many cases dissolution specifications are based only on observed variability information of different lots of a product used in clinical trials. Information on critical formulation variables is generally not developed or provided for regulatory review. Therefore, the value of dissolution specifications established in this manner is unknown for managing changes. If the postchange product were not characterized in vivo, can we assume with confidence that the specifications developed or justified using data obtained on prechange product lots would ensure bioequivalence of postchange product?

Since in this study in vitro dissolution served as the response or objective function for optimizing the level of magnesium stearate, it would appear that the authors of Ref. 8 had a high degree of confidence in this method. The dissolution test method and acceptance criterion in the selected example is fairly common. Its in vivo relevance is assumed by many with a fair degree of confidence, as exemplified by the following perspective expressed in the USP [35]:

1. There is no known medically significant bioinequivalence problem with articles where 75% of an article is dissolved in water or acid at 37°C in 45 minutes in the official basket or paddle apparatus operated at the usual speed, that is, USP First Case.
2. A majority of monographs have such requirements.
3. USP First Case performance is recognized as a reliable formulation objective in the United States and bears attention worldwide for product development where in vivo bioavailability testing is not readily available.
4. It obviates wasteful biostudies.
5. Medically significant cases of bioinequivalence rest mainly on four causal factors: inappropriate particle size of an active ingredient; *magnesium stearate in excess as a lubricant-glidant;* coatings, especially shellac; and inadequate disintegrant. *Each of these factors is reactive to dissolution testing.*

These generalizations appear to be based primarily on accumulated experiences, and it is difficult to define the term *medically significant bioinequivalence.* Critical analyses of data supporting such generalizations are needed to establish multidisciplinary consensus. Current regulatory policies and practices are designed to ensure the introduction of bioequivalent products on the U.S. market. For most IR products of a drug with demonstrated bioequivalence, the same dissolution specification generally gets adopted in the USP. However, conformance only to the same dissolution specification may not ensure bioequivalence [37].

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The rate and extent of absorption of drug Y will be a function of its solubility, intestinal permeability, and stability in the gastrointestinal fluids and dissolution rate. Differences in the absorption of two pharmaceutically equivalent products should then primarily be a function of their in vivo dissolution rate differences, assuming the excipients used do not alter bioavailability [38]. Therefore, the key question here is: Does an in vitro dissolution test emulate in vivo drug dissolution?

To further explore some complexities associated with decisions on the value of dissolution tests, it is postulated that for the selected formulation, in vitro dissolution is *likely* to be a more sensitive tool for studying formulation differences than in vivo bioequivalence studies. The following arguments can be made to support this postulate.

(1) For most IR products (and especially those of water-soluble drugs), dissolution in vivo is *not* likely to be rate-determining step and/or
(2) The surface tension of in vitro dissolution media without added surfactants is significantly greater than what is likely to be observed for human gastric and intestinal fluids [39].

In the absence of an established in vitro–in vivo correlation (IVIVC) or association it is difficult to substantiate the assumptions inherent in these arguments. And IVIVCs for IR formulations (such as Level A or C) are rare (since dissolution in vivo is often not the rate-determining step). But when such correlations are reported (e.g., for poorly soluble drugs), these tend to be formulation specific; i.e., an established IVIVC may not accurately predict the performance of a product with significant changes or differences in formulation [37]. In this case study, the risk of bioinequivalence is present due to an increased potential for a higher rate of in vivo dissolution/absorption as a result of reduced magnesium stearate level. If a relative bioavailability study comparing the prechange product to a simple aqueous solution of drug Y was conducted during drug development and the two found to be bioequivalent, these data could support the first argument [40].

The second argument is appealing form a mechanistic perspective. If this argument can be substantiated, it would provide additional support for the postulate stated earlier, now restated as follows: Demonstration of similar in vitro dissolution of the scaled-up product on an H&K machine would minimize the risk of bioinequivalence. Lowering the surface tension of the dissolution medium (water; 72 dynes/cm) by about 50% (to the approximate surface tension of gastric fluid) should enhance the dissolution rate. If drug Y were lithium carbonate (low-solubility drug), an experiment that was conducted in 1974 [19] provides useful insight on this issue. In this experiment it was found that a 50% reduction in the surface tension of dissolution medium, by the addition of 0.02% sodium lauryl sulfate to the medium, had no effect on the dissolution rate. However, increasing the amount of sodium lauryl sulfate to 0.5% (i.e., greater than

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the critical micelle concentration) did have a pronounced effect on the dissolution rate of lithium carbonate. This partially supports the postulate stated earlier, but raises other questions, such as the similarity (e.g., solubilization mechanism) of sodium lauryl sulfate to biological surfactants. Questions related to in vivo relevance (or similarity) of the hydrodynamic conditions in the dissolution vessel are also raised.

In the study with lithium carbonate capsule formulations [19] it was observed that the addition of 0.002% sodium lauryl sulfate in the capsule formulation was more effective in improving dissolution than when dissolution medium contained very large quantities of sodium lauryl sulfate. With respect to this drug–lubricant-mixing interaction, it has been suggested that the (sodium lauryl sulfate) surfactant affects drug dissolution by interacting with magnesium stearate during the mixing process [31], presumably by reducing drug–lubricant bonds or by creating hydrophilic channels in the hydrophobic lubricant film formed on drug particles during (prolonged) mixing. A higher impact of a small amount of surfactant incorporated within a dosage form on the fluid microenvironment (due to high local concentrations) surrounding the particles undergoing dissolution is also a possible explanation. Also note that it has been reported that the hydrophobic nature of different batches of magnesium stearate can vary depending on the presence of water-soluble, surface-active impurities such as sodium stearate. Batches containing a very low concentration of these impurities have been shown to retard drug dissolution to a greater extent than when using batches that contain higher levels of impurities [41]. Inferences that may be drawn from these observations—incorporating a wetting agent in a formulation with drug–lubricant-mixing interaction: (a) reduces the adverse effect of this interaction on drug dissolution (i.e., reduces lot–lot variability and the likelihood that a product will fail to meet specifications) and (b) reduces the dependency of the in vitro dissolution rate on the composition (presence or absence of a surfactant) of the dissolution medium. Does the latter inference help to reduce the concern with respect to the appropriateness of the dissolution medium (and hydrodynamics)?

In the piroxicam capsules study discussed earlier [36], the sodium lauryl sulfate level (formulation studied in vivo contained 0, 0.5, 1.0% for slow-, medium-, and fast-dissolving products, respectively) and drug particle size were the most important main factors affecting dissolution (in USP apparatus *T,* 50 rpm, 900 mL of simulated gastric fluid without enzymes). Products with a dissolution of 66 (slow), 80 (medium), and 95% (fast) in 45 minutes were bioequivalent. In vitro dissolution tests were more sensitive to formulation differences, suggesting that these formulation differences did not influence the in vivo dissolution/absorption processes and/or the differences could not be observed in vivo because physiologic factors, such as gastric emptying, contributed to the observed variability in blood levels (also note that piroxicam exhibits a relatively long elimination half-life).

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Reported in vitro dissolution failures due to cross-linking of gelatin shells that did not result in bioinequivalence [42,45] serve as another set of examples, although based on a different mechanism, that suggests that significant in vitro differences do not necessarily translate to in vivo differences.

A high degree of sensitivity of in vitro dissolution tests to formulation differences raises questions about the appropriate acceptance criteria—how similar should two in vitro dissolution profiles be to be considered similar? The SUPAC-IR introduced to the regulatory decision-making process a metric referred to as "f2" [43] for profile comparison. Application of this criterion to the examples cited in this report (e.g., piroxicam formulations) would have resulted in a recommendation for the in vivo bioequivalence study.

2. Expiration Date or Shelf Life

Stability is an essential quality attribute of a drug product that can also have a significant clinical consequence. The time during which a batch may be expected to remain within specifications depends not only on the rate of physical, chemical, or microbiological changes, but also on the initial average value for the batch. During drug development, stability studies are conducted to establish an expiration-dating period that would be applicable to all future batches of the product manufactured under similar circumstances. This approach assumes that an inference drawn from these studies extends to all future batches. Therefore, tested batches should be representative of the population of future production batches. Generally, an expiration date is determined based on the statistical analysis of observed long-term stability data under the storage conditions recommended in the labeling [44].

For the selected example one could argue that the likelihood of observing a change in the expiration date of this product following changes is minimal, since, (a) there was a quantitative change only in the level of magnesium stearate, and (b) the manufacturing process is dry and did not involve heat transfer. In the postapproval phase further support for this risk estimate can be derived from the knowledge of the acceptable stability profile of the prechange product. The SUPAC-IR guidance recognizes this link by utilizing the "significant body of information" approach. Causal links between preformulation characterization (including compatibility evaluation) and product stability would be another source of information, which could be brought to bear on such decisions. This approach is not currently utilized in SUPAC-IR guidance but probably is being practiced in industry when go/no-go decisions are made to implement certain changes.

The drug dissolution profiles from capsules have been documented to change with time due to changes in the gelatin capsule shell properties, interaction between gelatin and an encapsulated ingredient such as anionic compounds (e.g., substituted benzoic and sulfonic acid dyes), and compounds with keto groups. The

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moisture content of a hard gelatin capsule (and its performance) may change depending on the sorption isotherms of the fill material. The disintegration time of plugs filled in capsule and/or drug particle size or morphic form may also change with time [45].

A significant fraction of observed stability problems involve physical changes in the product without accompanying chemical changes (e.g., dissolution failures). A survey of market withdrawals for the year 1998 identified 154 recalls (all categories), the lowest number in 12 years [46]. For solid oral dosage forms (including modified-release), the product quality problems that led to these recalls are listed in Table 1. For several years, failing to meet dissolution specifications has occupied a prominent spot on this list. In 1997, 26 recalls were due to dissolution failures. The recall information is provided only to bring attention to the issue of ensuring stability, including physical (dissolution) stability. This report does not intend to suggest or discuss the root cause for these recalls, it only suggests that the current scientific understanding of time-dependent physical changes in pharmaceutical dosage forms is limited.

When one takes into account the large number of solid oral products on the market, these recall numbers represent a very small fraction; however, recalls are undesirable and further efforts are needed to prevent them. Accelerated tests have been very useful in predicting chemical changes, but their value for predicting physical changes (e.g., dissolution shelf life) under ambient conditions is difficult to ascertain. With respect to physical stability, data obtained under accelerated conditions are useful for assessing the "ruggedness" of the product and its ability to withstand the varied climatic conditions during shipping and storage [47]. To ensure an unchanged stability profile and expiration date following manufacturing changes, in addition to accelerated stability testing an

Table 1 Product Quality Problems That Led to Recall of Solid Oral Dosage Forms in 1998

Problem	Number of recalls
Potency/content uniformity	15
Dissolution	8 (4 cap.)
Other specifications	3
Contamination (microbial and other)	5
Noncompliance with NDA/monograph requirements	5
Manufacturing/testing method deficiencies	1

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evaluation of long-term stability data under the storage conditions recommended in the labeling is necessary.

C. "Connecting-the-Dots": Art–Science–Regulatory Policies

The uncertainties or lack of scientific consensus presented in the previous section contribute to the conservative structures of regulatory recommendations (e.g., multimedia dissolution profile comparisons and in vivo bioequivalence studies). Regulatory decisions are essentially risk management decisions. When developing regulatory recommendations on manufacturing changes, one needs to: (a) estimate the risk of adverse effects on quality and performance—the likelihood of occurrence and the severity of the consequences; (b) identify optimal regulatory approaches (additional tests and reporting mechanisms) to mitigate an unacceptable level of risk; and (c) ensure that regulatory recommendations are acceptable to society (i.e., consistent with its statutes).

The risk of bioinequivalence between pre- and postchange products is due to (a) the potential for a different (higher) rate of in vivo dissolution between pre- and postchange products due to a lower amount of magnesium stearate in the latter and and/or (b) a reliance on the in vitro dissolution test (similar dissolution) to ensure unchanged bioavailability. The former risk factor is complex; it essentially manifests as a physical interaction between drug, lubricant, and processing conditions. Drug attributes (e.g., solubility, particle size), the physical and chemical attributes of magnesium stearate (surface area, level of impurities such as sodium stearate, etc.), the mechanism and duration of shearing during processing are all likely to modulate this risk factor. Published reports on this topic are predominantly in vitro studies, with very few linkages to in vivo evaluations.

To mitigate the risks associated with the use of dissolution tests, the BCS was adopted in the SUPAC-IR guidance and more recently its regulatory applications expanded in the BCS-based biowaiver guidance [11]. This new guidance document provides a means for justifying biowaivers for *rapidly dissolving* products (85% in 30 minutes in 900 mL of 0.1 N HCl, 4.5 pH and 6.8 pH media, in USP I or II) of *highly soluble* (highest dose strength soluble in 250 mL in pH 1–7.5 range) and *highly permeable* (extent of absorption equal to or greater than 90%) drugs [11]. Such waivers are not recommended for drugs with a narrow therapeutic range (NTR). The high-permeability plus high-solubility attributes are utilized to minimize risk of bioinequivalence due to solubility- or permeability-limited absorption processes. Low-permeability drugs exhibit incomplete absorption from the small intestine, and therefore the small intestinal residence time of these drugs (dissolved) is considered critical. Relatively minor differences in the time needed for complete in vivo dissolution of low-permeability drugs can potentially reduce the time available for their absorption during small intestinal transit. The rapid dis-

solution (in three different pH conditions) and built-in profile similarity criteria are to ensure that dissolution in vivo is not likely to be rate limiting and that minimal differences in product disintegration time (to minimize the likelihood of differences in gastric emptying) are observed between the pre- and postchange products. It could be argued that rapid dissolution in fluid representing gastric fluid pH should be sufficient, since it is unlikely that rapidly dissolving products will be exposed in solid form to a pH of 6.8, reflecting the lower portion of the small intestine. The multimedia dissolution is recommended to account for the observed physiologic (and pathologic) variability in gastric fluid pH and gastric emptying process. Since the time of drug administration (during bioequivalence studies and use by patients) is not synchronized (and should not be for practical reasons) with the gastric motility pattern, gastric emptying in some subjects could occur almost immediately after administration. In such cases dissolution would occur in the small intestine following emptying. If one of the two products being compared exhibits a different dissolution rate (compared to the other product) in intestinal pH, then the effect of variable gastric emptying on in vivo dissolution may not be a truly random phenomenon. This may increase the likelihood of bioinequivalence when only a single in vitro dissolution condition (e.g., 0.1 N HCl) is used to compare two products. The multimedia dissolution criteria are intended to minimize this possibility. The permeability attribute of drugs plays a significant role in the request for biowaivers. In addition to the reasons stated earlier, permeability contributes to the development of "sink condition" for in vivo drug dissolution. Drug dissolution in vitro in a relatively large volume, 900 mL, is likely to be a better emulation of the in vivo dissolution process of a highly permeable drug. High permeability also reduces the probability that the excipient will affect bioavailability due to an effect on gastrointestinal membranes and/or motility [48].

In the previous section it was postulated that reduction in the magnesium stearate level and inclusion of sodium lauryl sulfate were preferred strategies over machine adjustment (pin settings on H&K) to implement the desired equipment changes in the selected example. The BCS-based biowaiver guidance makes it possible to adopt such strategies without the need for in vivo bioequivalence studies. However, in vivo bioequivalence evaluation is currently recommended for: (a) drugs that are not highly soluble or permeable, (b) drugs considered to have a NTR, and (c) drug products that do not conform to the rapid dissolution criteria. If a company decides to add sodium lauryl sulfate to counteract the effects of drug–lubricant-processing interaction for their capsule product of a low-permeability or low-solubility drug, they would need to conduct an in vivo bioequivalence study to qualify this change. From Figure 2 it is apparent that a large number (~50%) of marketed capsule products contain sodium lauryl sulfate. This information suggests that this excipient (in amounts used in tablets and capsules) is not likely to alter intestinal permeability. However, the in vivo evidence supporting this assumption is scattered among different submissions and is currently not considered sufficient for broad generalization.

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To further expand the use of dissolution tests for ensuring bioequivalence, two major concerns will need to be addressed: (a) the impact of excipients on bioavailability, and (b) the ability of dissolution tests to emulate critical in vivo dissolution processes as these relate to differences in the two formulations. For the latter, an evaluation of failed bioequivalence studies would be a good starting point. It was estimated from NDA submissions that about 20–30% of in vivo bioequivalence studies fail to demonstrate bioequivalence for products that conform to established dissolution specifications. Of these only a fraction appear to be truly bioinequivalent products that require reformulation. A pattern that seems to repeat in some of these failures is a combination of pH (dissolution medium), drug ionization behavior (pKa in a 3–6 range), and certain product attributes (particle size and disintegration time differences). For example, similar or even identical dissolution in 0.1 N HCl (USP I or II, usual rpm settings) may not ensure bioequivalence for two IR drug products of a weak base differing in particle size, disintegration time, and/or amount of dicalcium phosphate in a formulation (changes commonly encountered when a manufacturing process is changed from wet granulation to direct compression) [48].

In 1997, the SUPAC approach was estimated to provided substantial cost savings to industry. These savings were realized primarily from (a) revenues from previously unmarketable stability test batches, (b) more rapid implementation of site changes (reduced overhead expenses for maintaining two sites), and (c) reduced stability testing costs. With long regulatory lead times, stability batches often become "short-dated"; i.e., the remaining shelf life is not sufficient for the batches to be marketable. One company estimated that it saved $4 million from being able to sell stability batches of a product that otherwise would have been lost [49]. Moving away from a prior approval process for low-risk manufacturing changes can provide significant cost savings for industry and allow the FDA to focus its limited resources on high-risk issues and practices. An opportunity that has not yet been realized is the establishment of causal links between preformulation information and stability (shelf life). Such causal links will provide a means for identifying risk factors for stability and allow further development of risk-based regulatory testing and reporting recommendations. Recently the FDA/CDER presented its initial thoughts on a Risk-Based Chemistry Review program [50] that intends to further down-regulate chemistry requirements for postapproval changes. The risk-based review, the planned revision of SUPAC-IR, and PQRI projects are all designed to enhance the scientific basis of regulatory polices while reducing regulatory burden on industry.

VI. CONCLUSION

The different perspectives presented in this chapter were inspired by many discussions and debates (e.g., at the FDA, PQRI, the University of Maryland, and nu-

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merous national and international workshops) the author was privileged to participate in over the last five years. An attempt was made to define and focus these debates by selecting a real-life example of scale-up and pharmaceutical literature utilized to examine the scientific basis underlying some of these arguments. This analysis served to reinforce (at least for the author) that these debates are indeed art vs. science debates. It is hoped that consensus on this understanding within the pharmaceutical community will provide a shared vision and strategies (industry, academia, and regulatory authorities) for moving the science of product development forward.

In the last three decades the science and practice of biopharmaceutics has evolved from a mostly empirical study of factors that affect drug absorption to a more rigorous mechanistic study of drug absorption at the cellular level. This new understanding is providing novel opportunities in every aspect of the drug development process, such as;

1. In the drug discovery process, increased emphasis is being placed on the biopharmaceutical attributes of new chemical entities to identify the most promising candidates for development, and new tools are being developed for the rapid assessment of such attributes.
2. In product development, new strategies are being utilized for improving oral drug absorption.
3. In clinical practice, the likely impact of drug–drug and drug–food interactions on bioavailability can now be anticipated with some confidence.
4. In regulatory assessment of bioavailability/bioequivalence, increased emphasis is being directed toward in vitro methods.

The characterization of the biopharmaceutical attributes of a drug substance early in the drug development process provides valuable information for: (a) design and development of products with optimal bioavailability, (b) development of meaningful in vitro dissolution test specifications (methods and acceptance criteria) for quality assurance, and (c) development of in vitro tests for ensuring bioequivalence when changes in product formulation are necessary. The Biopharmaceutics Classification System (BCS) serves as an example of how preformulation information can be utilized not only for product development but also for bioequivalence assessment. This approach offers significant opportunities for "building quality in" and thereby reducing unnecessary testing in humans. A similar approach for stability, i.e., for predicting and/or ensuring shelf life (chemical, physical, and microbiological), will be very valuable.

The SUPAC and other related regulatory guidance documents have, for the first time, provided an opportunity to reduce the regulatory constraints based on the pharmaceutical sciences. The FDA's participation in PQRI reflects its desire to enhance the scientific basis of its policies, thus creating numerous regulatory opportunities. It is hoped that the pharmaceutical community will recognize these

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opportunities and work together to overcome the many challenges that exist—pharmaceutical dosage forms are complex multifactorial systems, and data underlying a publicly available pharmaceutical knowledge base have been derived from traditional trial-and-error and one-factor-at-a-time experiments. Estimating the limits of generalization of, and strategies for filling gaps in, this accumulated knowledge may be difficult without additional prospective experimentation and/or sharing of proprietary data in a suitably blinded manner to ensure their confidentiality.

With the focus on combinatorial chemistry and high-throughput screening in drug discovery, it is likely that product development activities (have?) may become "rate-limiting" in the drug development process. This challenge could be considered as an industrial opportunity for developing new (predictive) product development systems that can improve the efficiency of the process for identifying optimally performing formulations and process conditions. The regulatory opportunity provides a means for reducing regulatory burden and hence is also an industrial opportunity. The economic and public benefits that will be derived form these opportunities can potentially pave the way for additional public and private support for research in this area. Both regulatory and industrial opportunities can turn in to academic opportunities. PQRI provides a win–win–win opportunity for the public, industry, and the agency.

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The opinions expressed in this chapter are those of the author and do not necessarily reflect the views or policies of the FDA.

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Appendix A

Guidance for Industry[1]—Immediate Release Solid Oral Dosage Forms

Scale-Up and Postapproval Changes: Chemisty, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation

I. PURPOSE OF GUIDANCE

This guidance provides recommendations to sponsors of new drug applications (NDA's), abbreviated new drug applications (ANDA's), and abbreviated antibiotic applications (AADA's) who intend, during the postapproval period, to change: 1) the components or composition; 2) the site of manufacture; 3) the scale-up/scale-down of manufacture; and/or 4) the manufacturing (process and equipment) of an immediate release oral formulation.

This guidance is the result of: 1) a workshop on the scale-up of immediate release drug products conducted by the American Association of Pharmaceutical Scientists in conjunction with the United States Pharmacopoeial

[1] This guidance has been prepared by the Immediate Release Scale-up and Post Approval Change (SUPAC) Expert Working Group of the Chemistry Manufacturing Controls Coordinating Committee (CMC CC) of the Center for Drug Evaluation and Research at the Food and Drug Administration. This guidance is an informal communication under 21 CFR 10.90(b)(9) that reflects the best judgment of CDER employees at this time. It does not create or confer any rights, privileges or benefits for or on any person, nor does it operate to bind or obligate FDA in any way. For additional copies of this guidance contact the Consumer Affairs Branch (formerly the Executive Secretariat Staff), HFD-8, Center for Drug Evaluation and Research, 7500 Standish Place, Rockville, MD 20855 (Phone: 301-594-1012). An electronic version of this guidance is also available via Internet by connecting to the CDER file transfer protocol (FTP) server (CDVS2.CDER.FDA.GOV).

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Convention and the Food and Drug Administration (FDA); 2) research conducted by the University of Maryland at Baltimore on the chemistry, manufacturing and controls of immediate release drug products under the FDA/University of Maryland Manufacturing Research Contract; 3) the drug categorization research conducted at the University of Michigan and the University of Uppsala on the permeability of drug substances; and 4) the Scale- Up and Post Approval Changes (SUPAC) Task Force which was established by the Center for Drug Evaluation and Research (CDER) Chemistry, Manufacturing and Controls Coordinating Committee to develop guidance on scale-up and other postapproval changes.

The guidance defines: 1) levels of change; 2) recommended chemistry, manufacturing, and controls tests for each level of change; 3) in vitro dissolution tests and/or in vivo bioequivalence tests for each level of change; and 4) documentation that should support the change. For those changes filed in a "changes being effected supplement" [21 CFR 314.70(c)], the FDA may, after a review of the supplemental information, decide that the changes are not approvable. This guidance thus sets forth application information that should be provided to CDER to assure continuing product quality and performance characteristics of an immediate release solid oral dose formulation for specified postapproval changes. This guidance does not comment on or otherwise affect compliance/inspection documentation that has been defined by CDER's Office of Compliance or FDA's Office of Regulatory Affairs. This guidance does not affect any postapproval changes other than the ones specified. For changes not addressed in this guidance, or for multiple changes submitted at one time or over a short period of time, or where the number of batches needed for stability testing is not specified, sponsors should contact the appropriate CDER review division or consult other CDER guidances/guidelines to obtain information about tests and application documentation.

21 CFR 314.70(a) provides that applicants may make changes to an approved application in accordance with a guideline, notice, or regulation published in the FEDERAL REGISTER that provides for a less burdensome notification of the change (for example, by notification at the time a supplement is submitted or in the next annual report). This guidance permits less burdensome notice of certain postapproval changes within the meaning of § 314.70(a).

For postapproval changes for immediate release dosage forms that affect components and composition, scale-up, site change, and manufacturing process or equipment changes, this guidance supersedes the recommendations in section 4.G of the Office of Generic Drugs Policy and Procedure Guide 22–90 (September 11, 1990). For all other dosage forms and changes, this guidance does not affect the recommendations in Guide 22–90.

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II. DEFINITION OF TERMS[2]

A. Batch

A specific quantity of a drug or other material produced according to a single manufacturing order during the same cycle of manufacture and intended to have uniform character and quality, within specified limits [21 CFR 210.3(b)(2)].

B. Contiguous Campus

Continuous or unbroken site or a set of buildings in adjacent city blocks.

C. Dissolution Testing

Case A: Dissolution of Q = 85% in 15 minutes in 900 milliliters (mL) of 0.1N hydrochloride (HCl), using the United States Pharmacopeia (USP) <711> Apparatus 1 at 100 revolutions per minute (rpm) or Apparatus 2 at 50 rpm.

Case B: Multi-point dissolution profile in the application/compendial medium at 15, 30, 45, 60, and 120 minutes or until an asymptote is reached for the proposed and currently accepted formulation.

Case C: Multi-point dissolution profiles performed in water, 0.1N HCl, and USP buffer media at pH 4.5, 6.5, and 7.5 (five separate profiles) for the proposed and currently accepted formulations. Adequate sampling should be performed at 15, 30, 45, 60, and 120 minutes until either 90% of drug from the drug product is dissolved or an asymptote is reached. A surfactant may be used with appropriate justification.

D. Drug Product

A drug product is a finished dosage form (e.g., tablet, capsule, or solution) that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients [21 CFR 314.3(b)]. A solid oral dosage form includes tablets, chewable tablets, capsules, and soft gelatin capsules.

E. Drug Substance

An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of a dis-

[2] See Workshop Report: Scale-up of Immediate Release Oral Solid Dosage Forms, *Pharmaceutical Research*, 10 (2): 313–316, Skelly et al; and Federal Register. Vol. 59, No. 183, Thursday, September 22, 1994, pages 48754–59.

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ease, or to affect the structure of any function of the human body, but does not include intermediates used in the synthesis of such ingredient [21 CFR 314.3(b)].

F. Equipment

Automated or non-automated, mechanical or non-mechanical equipment used to produce the drug product, including equipment used to package the drug product.

G. Formulation

A listing of the ingredients and composition of the dosage form.

H. Justification

Reports containing scientific data and expert professional judgment to substantiate decisions.

I. New Drug Substance

Any substance that, when used in the manufacture, processing, or packing of a drug, causes that drug to be a new drug, but does not include intermediates used in the synthesis of such substance [21 CFR 310.3(g)].

J. Operating Principle

Rules or concepts governing the operation of the system.

K. Pilot Scale

The manufacture of either drug substance or drug product by a procedure fully representative of and simulating that used for full manufacturing scale.

For solid oral dosage forms this is generally taken to be, at a minimum, one-tenth that of full production, or 100,000 tablets or capsules, whichever is larger (see the FEDERAL REGISTER of Thursday, September 22, 1994, 59 FR 48754-59).

L. Process

A series of operations and/or actions used to produce a desired result.

M. Ranges

The extent to which or the limits between which acceptable variation exists.

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N. Same

Agreeing in kind, amount; unchanged in character or condition.

O. Scale-Up

The process of increasing the batch size.

P. Scale-Down

The process of decreasing the batch size.

Q. Similar

Having a general likeness.

R. Significant Body of Information

A significant body of information on the stability of the drug product is likely to exist after five years of commercial experience for new molecular entities, or three years of commercial experience for new dosage forms.

S. Validation

Establishing through documented evidence a high degree of assurance that a specific process will consistently produce a product that meets its predetermined specifications and quality attributes. A validated manufacturing process is one that has been proven to do what it purports or is represented to do. The proof of validation is obtained through collection and evaluation of data, preferably beginning from the process development phase and continuing through the production phase. Validation necessarily includes process qualification (the qualification of materials, equipment, systems, buildings, and personnel), but it also includes the control of the entire processes for repeated batches or run*s*.

III. COMPONENTS AND COMPOSITION

This section of the guidance focuses on changes in excipients in the drug product. Changes in the amount of drug substance are not addressed by this guidance. Changes in components or composition that have the effect of adding a new excipient or deleting an excipient are defined at Level 3 (defined below), except as described below.

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A. Level 1 Changes

1. Definition of Level

Level 1 changes are those that are unlikely to have any detectable impact on formulation quality and performance.

Examples:

a. Deletion or partial deletion of an ingredient intended to affect the color or flavor of the drug product; or change in the ingredient of the printing ink to another approved ingredient.
b. Changes in excipients, expressed as percentage (w/w) of total formulation, less than or equal to the following percent ranges:

Excipient	Percent excipient (w/w) out of total target dosage form weight
Filler	±5
Disintegrant	
Starch	±3
Other	±1
Binder	±0.5
Lubricant	
Calcium (Ca) or Magnesium (Mg) Stearate	±0.25
Other	±1
Glidant	
Talc	±1
Other	±0.1
Film Coat	±1

These percentages are based on the assumption that the drug substance in the product is formulated to 100% of label/potency. The total additive effect of all excipient changes should not be more than 5%. (Example: In a product consisting of active ingredient A, lactose, microcrystalline cellulose and magnesium stearate, the lactose and microcrystalline cellulose should not vary by more than an absolute total of 5% (e.g. lactose increases 2.5% and microcrystalline cellulose decreases by 2.5%) relative to the target dosage form weight if it is to stay within the Level 1 range).

The components (active and excipients) in the formulation should have numerical targets which represent the nominal composition of the drug product on which any future changes in the composition of the product are to be based. Allowable changes in the composition should be based on the approved target composition and not on previous Level 1 changes in the composition.

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2. Test Documentation

a. Chemistry Documentation
   Application/compendial release requirements and stability testing.
   Stability testing: one batch on long-term stability data reported in annual report.
b. Dissolution Documentation
   None beyond application/compendial requirements.
c. In Vivo Bioequivalence Documentation
   None.

3. Filing Documentation

Annual report (all information including long-term stability data).

B. Level 2 Changes

1. Definition of Level

Level 2 changes are those that could have a significant impact on formulation quality and performance. Tests and filing documentation for a Level 2 change vary depending on three factors: therapeutic range, solubility, and permeability. Therapeutic range is defined as either narrow or non-narrow. A list of narrow therapeutic range drugs is provided in Appendix A. Drug solubility and drug permeability are defined as either low or high. Solubility is calculated based on the minimum concentration of drug, milligram/milliliter (mg/mL), in the largest dosage strength, determined in the physiological pH range (pH 1 to 8) and temperature (37 + 0.5 C). High solubility drugs are those with a dose/solubility volume of less than or equal to 250 mL. (Example: Compound A has as its lowest solubility at 37 + 0.5 C, 1.0 mg/mL at pH 7, and is available in 100 mg, 200 mg and 400 mg strengths. This drug would be considered a low solubility drug as its dose/solubility volume is greater than 250 mL (400 mg/1.0 mg/mL=400 mL). Permeability (P, centimeter per second) is defined as the effective human jejunal wall permeability of a drug and includes an apparent resistance to mass transport to the intestinal membrane. High permeability drugs are generally those with an extent of absorption greater than 90% in the absence of documented instability in the gastrointestinal tract, or those whose permeability attributes have been determined experimentally).

Examples:

a. Change in the technical grade of an excipient. (Example: Avicel PH102 vs. Avicel PH200.)
b. Changes in excipients, expressed as percent (w/w) of total formulation, greater than those listed above for a Level 1 change but less than or

equal to the following percent ranges (which represent a two fold increase over Level 1 changes):

Excipient	Percent excipient (w/w) out of total target dosage form weight
Filler	±10
Disintegrant	
Starch	±6
Other	±2.10
Binder	±1
Lubricant	
Ca or Mg Stearate	±0.5
Other	±2
Glidant	
Talc	±2
Other	±0.2
Film Coat	±2

These percentages are based on the assumption that the drug substance in the drug product is formulated to 100% of label/potency. The total additive effect of all excipient changes should not change by more than 10%.

The components (active and excipients) in the formulation should have numerical targets that represent the nominal composition of the product on which any future changes in the composition of the product are to be based. Allowable changes in the composition should be based on the approved target composition and not on the composition based on previous Level 1 or Level 2 changes.

2. Test Documentation

a. Chemistry Documentation. Application/compendial release requirements and batch records.

Stability testing: 1 batch with 3 months accelerated stability data in supplement and 1 batch on long-term stability.

b. Dissolution Documentation.

Case A: High Permeability, High Solubility Drugs
Dissolution of 85% in 15 minutes in 900 mL of 0.1N HCl. If a drug product fails to meet this criterion, the applicant should perform the tests described for Case B or C (below).

Case B: Low Permeability, High Solubility Drugs
Multi-point dissolution profile should be performed in the

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application/compendial medium at 15, 30, 45, 60 and 120 minutes or until an asymptote is reached. The dissolution profile of the proposed and currently used product formulations should be similar.

Case C: High Permeability, Low Solubility Drugs
Multi-point dissolution profiles should be performed in water, 0.1 N HCl, and USP buffer media at pH 4.5, 6.5, and 7.5 (five separate profiles) for the proposed and currently accepted formulations. Adequate sampling should be performed at 15, 30, 45, 60, and 120 minutes until either 90% of drug from the drug product is dissolved or an asymptote is reached. A surfactant may be used, but only with appropriate justification. The dissolution profile of the proposed and currently used product formulations should be similar.

c. In Vivo Bioequivalence Documentation. None: if the situation does not meet the description in Case A, Case B or Case C, refer to Level 3 changes.

3. Filing Documentation

Prior approval supplement (all information including accelerated stability data); annual report (long-term stability data).

C. Level 3 Changes

1. Definition of Level

Level 3 changes are those that are likely to have a significant impact on formulation quality and performance. Tests and filing documentation vary depending on the following three factors: therapeutic range, solubility, and permeability.

Examples:

a. Any qualitative and quantitative excipient changes to a narrow therapeutic drug beyond the ranges noted in Section III.A.1.b.
b. All other drugs not meeting the dissolution criteria under Section III.B.2.b.
c. Changes in the excipient ranges of low solubility, low permeability drugs beyond those listed in Section III.A.1.b.
d. Changes in the excipient ranges of all drugs beyond those listed in Section III.B.1.b.

2. Test Documentation

a. Chemistry Documentation. Application/compendial release requirements and batch records.

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SIGNIFICANT BODY OF INFORMATION AVAILABLE. One batch with three months accelerated stability data reported in supplement; one batch on long-term stability data reported in annual report.

SIGNIFICANT BODY OF INFORMATION NOT AVAILABLE. Up to three batches with three months accelerated stability data reported in supplement; one batch on long-term stability data reported in annual report.

b. Dissolution Documentation. Case B dissolution profile as described in Section III.B.2.b.

c. In Vivo Bioequivalence Documentation. Full bioequivalence study. The bioequivalence study may be waived with an acceptable *in vivo/in vitro* correlation has been verified.

3. Filing Documentation

Prior approval supplement (all information including accelerated stability data); annual report (long-term stability data).

IV. SITE CHANGES

Site changes consist of changes in location of the site of manufacture for both company-owned and contract manufacturing facilities and do not include any scale-up changes, changes in manufacturing (including process and/or equipment), or changes in components or composition. Scale-up is addressed in Section V of this guidance. New manufacturing locations should have a satisfactory current Good Manufacturing Practice (CGMP) inspection.

A. Level 1 Changes

1. Definition of Level

Level 1 changes consist of site changes within a single facility where the same equipment, standard operating procedures (SOP's), environmental conditions (e.g., temperature and humidity) and controls, and personnel common to both manufacturing sites are used, and where no changes are made to the manufacturing batch records, except for administrative information and the location of the facility. Common is defined as employees already working on the campus who have suitable experience with the manufacturing process.

2. Test Documentation

a. Chemistry Documentation. None beyond application/compendial release requirements.

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b. Dissolution Documentation. None beyond application/compendial release requirements.

c. In Vivo Bioequivalence Documentation. None.

3. Filing Documentation

Annual report.

B. Level 2 Changes

1. Definition of Level

Level 2 changes consist of site changes within a contiguous campus, or between facilities in adjacent city blocks, where the same equipment, SOP's, environmental conditions (e.g., temperature and humidity) and controls, and personnel common to both manufacturing sites are used, and where no changes are made to the manufacturing batch records, except for administrative information and the location of the facility.

2. Test Documentation

a. Chemistry Documentation. Location of new site and updated batch records. None beyond application/compendial release requirements. One batch on long-term stability data reported in annual report.

b. Dissolution Documentation. None beyond application/compendial release requirements.

c. In Vivo Bioequivalence Documentation. None.

3. Filing Documentation

Changes being effected supplement; annual report (long-term stability test data).

C. Level 3 Changes

1. Definition of Level

Level 3 changes consist of a change in manufacturing site to a different campus. A different campus is defined as one that is not on the same original contiguous site or where the facilities are not in adjacent city blocks. To qualify as a Level 3 change, the same equipment, SOP's, environmental conditions, and controls should be used in the manufacturing process at the new site, and no changes may be made to the manufacturing batch records except for administrative information, location and language translation, where needed.

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2. Test Documentation

a. Chemistry Documentation. Location of new site and updated batch records. Application/compendial release requirements

Stability:

SIGNIFICANT BODY OF DATA AVAILABLE. One batch with three months accelerated stability data reported in supplement; one batch on long-term stability data reported in annual report.

SIGNIFICANT BODY OF DATA NOT AVAILABLE. Up to three batches with three months accelerated stability data reported in supplement; up to three batches on long- term stability data reported in annual report.

b. Dissolution Documentation.

Case B: Multi-point dissolution profile should be performed in the application/compendial medium at 15, 30, 45, 60 and 120 minutes or until an asymptote is reached. The dissolution profile of the drug product at the current and proposed site should be similar.

c. In Vivo Bioequivalence Documentation. None.

3. Filing Documentation

Changes being effected supplement; annual report (long-term stability data).

V. CHANGES IN BATCH SIZE (SCALE-UP/SCALE-DOWN)

Postapproval changes in the size of a batch from the pivotal/pilot scale biobatch material to larger or smaller production batches call for submission of additional information in the application. Scale-down below 100,000 dosage units is not covered by this guidance. All scale-up changes should be properly validated and, where needed, inspected by appropriate agency personnel.

A. Level 1 Changes

1. Definition of Level

Change in batch size, up to and including a factor of 10 times the size of the pilot/biobatch, where: 1) the equipment used to produce the test batch(es) is of the same design and operating principles; 2) the batch(es) is (are) manufactured in full compliance with CGMP's; and 3) the same standard operating

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procedures (SOP's) and controls, as well as the same formulation and manufacturing procedures, are used on the test batch(es) and on the full-scale production batch(es).

2. Test Documentation

a. Chemistry Documentation. Application/compendial release requirements. Notification of change and submission of updated batch records in annual report.

One batch on long-term stability reported in annual report.

b. Dissolution Documentation. None beyond application/compendial release requirements.

c. In Vivo Bioequivalence. None.

3. Filing Documentation

Annual report (long-term stability data).

B. Level 2 Changes

1. Definition of Level

Changes in batch size beyond a factor of ten times the size of the pilot/biobatch, where: 1) the equipment used to produce the test batch(es) is of the same design and operating principles; 2) the batch(es) is (are) manufactured in full compliance with CGMP'S; and 3) the same SOP's and controls as well as the same formulation and manufacturing procedures are used on the test batch(es) and on the full-scale production batch(es).

2. Test Documentation

a. Chemistry Documentation. Application/compendial release requirements. Notification of change and submission of updated batch records. Stability testing: One batch with three months accelerated stability data and one batch on long-term stability.

b. Dissolution Documentation. Case B testing.

c. In Vivo Bioequivalence. None.

d. Filing Documentation. Changes being effected supplement; annual report (long-term stability data).

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VI. MANUFACTURING

Manufacturing changes may affect both equipment used in the manufacturing process and the process itself.

A. Equipment

1. Level 1 Changes

a. Definition of Change. This category consists of: 1) change from non-automated or non-mechanical equipment to automated or mechanical equipment to move ingredients; and 2) change to alternative equipment of the same design and operating principles of the same or of a different capacity.

b. Test Documentation.

i. Chemistry Documentation
Application/compendial release requirements. Notification of change and submission of updated batch records.
Stability testing: One batch on long-term stability.

ii. Dissolution Documentation
None beyond application/compendial release requirements.

iii. *In Vivo* Bioequivalence Documentation
None.

c. Filing Documentation. Annual report (long-term stability data).

2. Level 2 Changes

a. Definition of Level. Change in equipment to a different design and different operating principles.

b. Test Documentation.

i. Chemistry Documentation
Application/compendial release requirements.
Notification of change and submission of updated batch records.

Stability testing:

SIGNIFICANT BODY OF DATA AVAILABLE. One batch with three months accelerated stability data reported in supplement; one batch on long-term stability data reported in annual report.

SIGNIFICANT BODY OF DATA NOT AVAILABLE. Up to three batches with three months accelerated stability data reported in supplement; up to three batches on long-term stability data reported in annual report.

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ii. Dissolution Documentation
Case C dissolution profile.
iii. In Vivo Bioequivalence Documentation
None.

c. Filing Documentation. Prior approval supplement with justification for change; annual report (long-term stability data).

B. Process

1. Level 1 Changes

a. Definition of Level. This category includes process changes including changes such as mixing times and operating speeds within application/validation ranges.

b. Test Documentation.

i. Chemistry Documentation
None beyond application/compendial release requirements.
ii. Dissolution Documentation
None beyond application/compendial release requirements.
iii. In Vivo Bioequivalence Documentation
None.

c. Filing Documentation. Annual report.

2. Level 2 Changes

a. Definition of Level. This category includes process changes including changes such as mixing times and operating speeds outside of application/validation ranges.

b. Test Documentation.

i. Chemistry Documentation
Application/compendial release requirements. Notification of change and submission of updated batch records.
Stability testing: One batch on long-term stability.
ii. Dissolution Documentation
Case B dissolution profile.
iii. In Vivo Bioequivalence Documentation
None.

c. Filing Documentation. Changes being effected supplement; annual report (long-term stability data).

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3. Level 3 Changes

a. Definition of Level. This category includes change in the type of process used in the manufacture of the product, such as a change from wet granulation to direct compression of dry powder.

b. Test Documentation.

i. Chemistry Documentation
Application/compendial release requirements. Notification of change and submission of updated batch records.

Stability testing:

SIGNIFICANT BODY OF DATA AVAILABLE. One batch with three months accelerated stability data reported in supplement; one batch on long-term stability data reported in annual report.

SIGNIFICANT BODY OF DATA NOT AVAILABLE. Up to three batches with three months accelerated stability data reported in supplement; up to three batches on long-term stability data reported in annual report.

ii. Dissolution Documentation
Case B dissolution.

iii. In Vivo Bioequivalence Documentation
In vivo bioequivalence study. The bioequivalence study may be waived if a suitable in vivo/in vitro correlation has been verified.

c. Filing Documentation. Prior approval supplement with justification; annual report (long-term stability data).

VII. *IN VITRO* DISSOLUTION

See current United States Pharmacopeia/National Formulary, section <711>, for general dissolution specifications. All profiles should be conducted on at least 12 individual dosage units.

Dissolution profiles may be compared using the following equation that defines a similarity factor (f_2):

$$f_2 = 50 \text{ LOG } \{[1 + 1/n \, \Sigma_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \times 100\}^2$$

where R and T are the percent dissolved at each time point. An f_2 value between 50 and 100 suggests the two dissolution profiles are similar.

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VIII. IN VIVO BIOEQUIVALENCE STUDIES

Below is a general outline of an in vivo bioequivalence study. It is intended as a guide and the design of the actual study may vary depending on the drug and dosage form.

A. Objective

To compare the rate and extent of absorption of the drug product for which the manufacture has been changed, as defined in this guidance, to the drug product manufactured prior to the change.

B. Design

The study design should be a single dose, two-treatment, two-period crossover with adequate washout period between the two phases of the study. Equal numbers of subjects should be randomly assigned to each of the two dosing sequences.

C. Selection of Subjects

The number of subjects enrolled in the bioequivalence study should be determined statistically to account for the intrasubject variability and to meet the current bioequivalence interval.

D. Procedure

Each subject should receive the following two treatments:

Treatment 1: Product manufactured with the proposed change.
Treatment 2: Product manufactured prior to the proposed change.

Following an overnight fast of at least 10 hours, subjects should receive either Treatments 1 or 2 above with 240 mL water. Food should not be allowed until 4 hours after dosing. Water may be allowed after the first hour. Subjects should be served standardized meals beginning at 4 hours during the study.

E. Restrictions

Prior to and during each study phase, water may be allowed ad libitum except for 1 hour before and after drug administration. The subject should be served standardized meals and beverages at specified times. No alcohol or xanthine- or caffeine-containing foods and beverages should be consumed for 48 hours prior to each study period and until after the last blood sample is collected.

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F. Blood Sampling

Blood samples should be collected in sufficient volume for analysis of parent drug and active metabolite(s), if any. The sampling times should be such that it should be able to capture the C and T during the $_{max\ max}$ absorption period. Sampling should be carried out for at least three terminal elimination half-lives for both parent drug and active metabolite(s). Whole blood, plasma or serum, whichever is appropriate for the analytes, should be harvested promptly and samples should be frozen at −20 C or −70 C to maintain sample stability.

G. Analytical Method

The assay methodology selected should ensure specificity, accuracy, interday and intraday precision, linearity of standard curves, and adequate sensitivity, recovery, and stability of the samples under the storage and handling conditions associated with the analytical method.

H. Pharmacokinetic Analysis

From the plasma drug concentration-time data, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, C_{max}, T_{max}, K_{el} and $t_{1/2}$ should be estimated.

I. Statistical Analysis

Analysis of variance appropriate for a crossover design on the pharmacokinetic parameters using the general linear models procedures of SAS or an equivalent program should be performed, with examination of period, sequence and treatment effects. The 90% confidence intervals for the estimates of the difference between the test and reference least squares means for the pharmacokinetic parameters ($AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, C_{max} should be calculated, using the two one-sided t-test procedure).

REFERENCES

A. Code of Federal Regulations 210.3(b)(2) and (10), 310.3(b) and (g), and 320.1(a) and (e).
B. FDA/University of Maryland Manufacturing Research Contract Summary.
C. Federal Register. Vol. 59, No. 183, Thursday, September 22, 1994, pages 48754–59.
D. "Guideline for Industry: Stability Testing of New Drug Substances and Products," U.S. Department of Health and Human Services, Food and Drug Administration, September 1994.

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E. "Guideline for Submitting Documentation for the Manufacture of and Controls for Drug Products," U.S. Department of Health and Human Services, Food and Drug Administration, February 1987.
F. Policy and Procedure Guide #22–90: "Interim Policy on Exceptions to the Batch-Size and Production Condition Requirements for Non-Antibiotic, Solid, Oral-Dosage Form Drug Products Supporting Proposed ANDA's", U.S. Department of Health and Human Services, Center for Drug Evaluation and Research, Office of Generic Drugs, September 13, 1990.
G. Workshop Report: Scale up of Immediate Release Oral Solid Dosage Forms, *Pharmaceutical Research*, 10 (2): 313–16, Skelly et al.

NARROW THERAPEUTIC RANGE DRUGS

Aminophylline Tablets, ER Tablets
Carbamazepine Tablets, Oral Suspension
Clindamycin Hydrochloride Capsules
Clonidine Hydrochloride Tablets
Clonidine Transdermal Patches
Dyphylline Tablets
Ethinyl Estradiol/Progestin Oral Contraceptive Tablets
Guanethidine Sulfate Tablets
Isoetharine Mesylate Inhalation Aerosol
Isoproterenol Sulfate Tablets
Lithium Carbonate Capsules, Tablets, ER Tablets
Metaproterenol Sulfate Tablets
Minoxidil Tablets
Oxtriphylline Tablets, DR Tablets, ER Tablets
Phenytoin, Sodium Capsules (Prompt or Extended), Oral Suspension
Prazosin Hydrochloride Capsules
Primidone Tablets, Oral Suspension
Procainamide Hydrochloride, Capsules, Tablets, ER Tablets
Quinidine Sulfate Capsules, Tablets, ER Tablets
Quinidine Gluconate Tablets, ER Tablets
Theophylline Capsules, ER Capsules, Tablets, ER Tablets
Valproic Acid Capsules, Syrup
Divalproex, Sodium DR Capsules, DR Tablets
Warfarin, Sodium Tablets
ER - Extended Release
DR - Delayed Release

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Appendix B

Guidance for Industry[1]— SUPAC-MR: Modified Release Solid Oral Dosage Forms

Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation

I. INTRODUCTION

This guidance provides recommendations to pharmaceutical sponsors of new drug applications (NDAs), abbreviated new drug applications (ANDAs), and abbreviated antibiotic drug applications (AADAs) who intend to change (1) the components or composition, (2) the site of manufacture, (3) the scale-up/scale-down of manufacture, and/or (4) the manufacturing (process and equipment) of a modified release solid oral dosage form during the postapproval period. The guidance defines (1) levels of change, (2) recommended chemistry, manufacturing, and controls (CMC) tests for each level of change, (3) recommended in vitro dissolution tests and/or in vivo bioequivalence tests for each level of

[1] This guidance has been prepared by the Scale-up and Postapproval Change Modified Release (SUPAC-MR) Working Group operating under the direction of the Chemistry Manufacturing Controls Coordinating Committee (CMC CC) and the Biopharmaceutics Coordinating Committee (BCC) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA). This guidance represents the Agency's current thinking on modified release solid oral dosage forms scale-up and postapproval changes. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirement of the applicable statute, regulations, or both.

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change; and (4) documentation that should support the change. This guidance specifies application information that should be provided to the Center for Drug Evaluation and Research (CDER) to ensure continuing product quality and performance characteristics of a modified release solid oral dose formulation for specified postapproval changes.

This guidance does not comment on or otherwise affect compliance/inspection documentation that has been defined by CDER's Office of Compliance or FDA's Office of Regulatory Affairs. This guidance does not affect any postapproval changes other than the ones specified. For those changes filed in a Changes Being Effected (CBE) supplement (21 CFR 314.70(c)), the FDA may, after a review of the supplemental information, decide that the changes are not approvable. For changes not addressed in this guidance, or for multiple changes submitted at one time or over a short period of time, sponsors should contact the appropriate CDER review division or consult other CDER guidances to obtain information about tests and application documentation. FDA regulations at 21 CFR 314.70(a) provide that applicants may make changes to an approved application in accordance with a guidance, notice, or regulation published in the *Federal Register* that provides for a less burdensome notification of the change (for example, by notification at the time a supplement is submitted or in the next annual report). This guidance permits less burdensome notice of certain postapproval changes within the meaning of § 314.70(a). For postapproval changes for modified release solid oral dosage forms that affect components and composition, scale-up/scale-down, site change, and manufacturing process or equipment changes, this guidance supersedes the recommendations in section 4.G of the Office of Generic Drugs (OGD) Policy and Procedure Guide 22–90 (September 11, 1990). For all other dosage forms and changes, this guidance does not affect the recommendations in Guide 22–90.

II. GENERAL STABILITY CONSIDERATIONS

The effect SUPAC-type changes have on the stability of the drug product should be evaluated. For general guidance on conducting stability studies, applicants are referred to the FDA *Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics (02/87)*. For SUPAC submissions, the following points also should be considered:

- In most cases (except those involving scale up), stability data from pilot scale batches will be acceptable to support the proposed change.
- Where stability data show a trend toward potency loss or degradant increase under accelerated conditions, it is recommended that historical accelerated stability data from a representative prechange batch be sub-

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mitted for comparison. It is also recommended that under these circumstances, all available long-term data on test batches from ongoing studies be provided in the supplement. Submission of historical accelerated and available long-term data would facilitate review and approval of the supplement.

- A commitment should be included to conduct long-term stability studies through the expiration dating period, according to the approved protocol, on the first or first three (see text for details) production batches and to report the results in the annual reports.

III. COMPONENTS AND COMPOSITION—NONRELEASE CONTROLLING EXCIPIENT

This section of the guidance focuses on changes in nonrelease controlling excipients in the drug product. For modified release solid oral dosage forms, consideration should be given as to whether the excipient is critical or not critical to drug release. The sponsor should provide appropriate justifications for claiming any excipient(s) as a nonrelease controlling excipient in the formulation of the modified release solid oral dosage form. The functionality of each excipient should be identified. Changes in the amount of the drug substance are not addressed by this guidance. Changes in components or composition that have the effect of adding a new excipient or deleting an excipient are defined at level 3 (defined below), except as described below in Section III.A.1.a. Waiver of bioequivalence testing for a change in composition which involves only a different color, flavor or preservative may be permissible as described in 21 CFR 320.22(d)(4).

A. Level 1 Change

1. Definition of Level

Level 1 changes are those that are unlikely to have any detectable impact on formulation quality and performance.

Examples:

a. Deletion or partial deletion of an ingredient intended to affect the color or flavor of the drug product; or change in the ingredient of the printing ink to another approved ingredient.
b. Changes in nonrelease controlling excipients, expressed as percentage (w/w) of total formulation, less than or equal to the following percent ranges:

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Nonrelease controlling excipient	Percent excipient (w/w) out of total target dosage from weight
Filler	±5
Disintegrant	
Starch	±3
Other	±1
Binder	±0.5
Lubricant	
Ca or Mg Stearate	±0.25
Other	±1
Glidant	
Talc	±1
Other	±0.1
Film Coat	±1

These percentages are based on the assumption that the drug substance in the product is formulated to 100% of label/potency. The total additive effect of all nonrelease controlling excipient changes should not be more than 5%.[2] The total weight of the dosage form should still be within the original approved application range.

The components (active and excipients) in the formulation should have numerical targets that represent the nominal composition of the drug product on which any future changes in the composition of the product are to be based. Allowable changes in the composition should be based on the original approved target composition and not on previous level 1 changes in the composition. For products approved with only a range for excipients, the target value may be assumed to be the midpoint of the original approved application range.

2. Test Documentation

a. Chemistry Documentation. Application/compendial product release requirements.

Stability: First production batch on long-term stability data reported in annual report.

b. Dissolution Documentation. None beyond application/compendial requirements.

c. Bioequivalence Documentation. None.

[2] Example: In a product consisting of active ingredient A, lactose, microcrystalline cellulose, and magnesium stearate, the lactose and microcrystalline cellulose should not vary by more than an absolute total of 5% (e.g., lactose increases by 2.5% and microcrystalline cellulose decreases by 2.5%) relative to the target dosage form weight if it is to stay within the level 1 range.

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3. Filing Documentation

Annual report (all information including long-term stability data).

B. Level 2 Change

1. Definition of Level

Level 2 changes are those that could have a significant impact on formulation quality and performance.

Examples:

a. A change in the technical grade and/or specifications of a nonrelease controlling excipient[3]
b. Changes in nonrelease controlling excipients, expressed as percentage (w/w) of total formulation, greater than those listed above for a level 1 change, but less than or equal to the following percent ranges (which represent a two-fold increase over level 1 changes):

Nonrelease controlling excipient	Percent excipient (w/w) out of total target dosage from weight
Filler	±10
Disintegrant	
Starch	±6
Other	±2
Binder	±1
Lubricant	
Ca or Mg Stearate	±0.5
Other	±2
Glidant	
Talc	±2
Other	±0.2
Film Coat	±2

These percentages are based on the assumption that the drug substance in the drug product is formulated to 100% of label/potency. The total additive effect of all nonrelease controlling excipient changes should not change by more than 10%. The total weight of the dosage form could still be within or outside the original approved application range.

[3] Example: Avicel PH102 vs. Avicel PH200.

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The components (active and excipients) in the formulation should have numerical targets that represent the nominal composition of the product on which any future changes in the composition of the product are to be based. Allowable changes in the composition are based on the original approved target composition and not on the composition based on previous level 1 or level 2 changes. For products approved with only a range for excipients, the target value may be assumed to be the midpoint of the original approved application range.

2. Test Documentation

a. Chemistry Documentation. Application/compendial product release requirements and updated executed batch records.

Stability: One batch with three months accelerated stability data reported in prior approval supplement and long-term stability data of first production batch reported in annual report.

b. Dissolution Documentation. Extended release: In addition to application/compendial release requirements, multipoint dissolution profiles should be obtained in three other media, for example, in water, 0.1N HCl, and USP buffer media at pH 4.5, and 6.8 for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example, at 1, 2, and 4 hours and every two hours thereafter until either 80% of the drug from the drug product is released or an asymptote is reached. A surfactant may be used with appropriate justification.

Delayed release: In addition to application/compendial release requirements, dissolution tests should be performed in 0.1 N HCl for 2 hours (acid stage) followed by testing in USP buffer media, in the range of pH 4.5–7.5 (buffer stage) under standard (application/compendial) test conditions and two additional agitation speeds using the application/ compendial test apparatus (three additional test conditions). If the application/compendial test apparatus is the rotating basket method (Apparatus 1), a rotation speed of 50, 100, and 150 rpm may be used, and if the application/compendial test apparatus is the rotating paddle method (Apparatus 2), a rotation speed of 50, 75, and 100 rpm may be used. Multipoint dissolution profiles should be obtained during the buffer stage of testing. Adequate sampling should be performed, for example, at 15, 30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug from the drug product is released or an asymptote is reached. The above dissolution testing should be performed using the changed drug product and the biobatch or marketed batch (unchanged drug product).

All modified release solid oral dosage forms: In the presence of an established in vitro/in vivo correlation (6), only application/compendial dissolution testing need be performed (i.e., only in vitro release data by the correlating method

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need to be submitted). The dissolution profiles of the changed drug product and the biobatch or marketed batch (unchanged drug product) should be similar. The sponsor should apply appropriate statistical testing with justifications (e.g., the f equation) for comparing 2 dissolution profiles (5). Similarity testing for the two dissolution profiles (i.e., for the unchanged drug product and the changed drug product) obtained in each individual medium is appropriate.

c. Bioequivalence Documentation. None.

3. Filing Documentation

Prior approval supplement (all information including accelerated stability data); annual report (long-term stability data).

C. Level 3 Change

1. Definition of Level

Level 3 changes are those that are likely to have a significant impact on formulation quality and performance.

Example:

a. Changes in the nonrelease controlling excipient range beyond those listed in Section III.B.1.b. The total weight of the dosage form may be within or outside the approved original application range.

2. Test Documentation

a. Chemistry Documentation. Application/compendial product release requirements and updated executed batch records.

Stability: Significant body of information available: One batch with three months' accelerated stability data reported in prior approval supplement and long-term stability data of first three production batches reported in annual report..

Significant body of information not available: Three batches with three months' accelerated stability data reported in prior approval supplement and long-term stability data of first three production batches reported in annual report.

b. Dissolution Documentation. Extended release: In addition to application/compendial release requirements, a multipoint dissolution profile should be obtained using the application/compendial test conditions for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example, at 1, 2, and 4 hours and every two hours thereafter, until either 80% of the drug from the drug product is released or an asymptote is reached.

Delayed release: In addition to application/compendial release requirements, a multipoint dissolution profile should be obtained during the buffer stage

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of testing using the application/compendial test conditions for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example at 15, 30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug from the drug product is released or an asymptote is reached.

c. Bioequivalence Documentation. A single-dose bioequivalence study (3). The bioequivalence study may be waived in the presence of an established in vitro/in vivo correlation (6).

3. Filing Documentation

Prior approval supplement (all information including accelerated stability data); annual report (long-term stability data).

IV. COMPONENTS AND COMPOSITION—RELEASE CONTROLLING EXCIPIENT

This section of the guidance focuses on changes in release controlling excipients in the drug product. For modified release solid oral dosage forms, consideration should be given as to whether or not the excipient is critical to drug release. The sponsor should provide appropriate justifications (i.e., mechanism of drug release and manufacturing process) for claiming any excipient(s) as a release controlling excipient in the formulation of the modified release solid oral dosage form. The functionality of each excipient should be identified. Changes in the amount of the drug substance are not addressed by this guidance. Changes exceeding the ranges defined in each of the levels below may be allowed if considered to be within normal batch-to-batch variation and contained within an approved original application. In such situations, sponsors should contact the appropriate CDER review division for further guidance.

A. Level 1 Change

1. Definition of Level

Level 1 changes are those that are unlikely to have any detectable impact on formulation quality and performance.

Example:

a. Changes in the release controlling excipient(s), expressed as percentage (w/w) of total release controlling excipient(s) in the formulation less than or equal to 5% w/w of total release controlling excipient content in the modified release solid oral dosage form.

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The drug substance in the product is formulated to 100% of label/potency. The total additive effect of all release controlling excipient changes should not be more than 5% w/w of the total release controlling excipients in the original approved formulation.[4] The total weight of the dosage form should still be within the 4 approved original application range.

The components (active and excipients) in the formulation should have numerical targets that represent the nominal composition of the product on which any future changes in the composition of the product are to be based. Allowable changes in the composition should be based on the original approved target composition and not on previous level 1 changes in the composition. For products approved with only a range for excipients, the target value may be assumed to be the midpoint of the original approved application range.

2. Test Documentation

a. Chemistry Documentation. Application/compendial product release requirements.

Stability: First production batch on long-term stability data reported in annual report.

b. Dissolution Documentation. None beyond application/compendial requirements.

c. Bioequivalence Documentation. None.

3. Filing Documentation

Annual report (all information including long-term stability data).

B. Level 2 Change

1. Definition of Level

Level 2 changes are those that could have a significant impact on formulation quality and performance. Test documentation for a level 2 change would vary de-

[4] Example: In a product consisting of active ingredient A, ethylcellulose and a plasticizer, the ethylcellulose and plasticizer content should not vary by more than an absolute total of 5% w/w of the total release controlling excipients (e.g., ethylcellulose content increases by 2.5% and plasticizer content increases by 2.5%) relative to the original approved total release controlling excipient content weight in the modified release solid oral dosage form if it is to stay within the given range allowed for level 1.

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pending on whether the product could be considered to have a narrow therapeutic range.[5]

Examples:

a. Change in the technical grade and/or specifications of the release controlling excipient(s).[6]
b. Changes in the release controlling excipient(s), expressed as percentage (w/w) of total release controlling excipient(s) in the formulation, greater than those listed above for a level 1 change, but less than or equal to 10% w/w of total release controlling excipient content in the modified release solid oral dosage form.

The drug substance in the drug product is formulated to 100% of label/potency. The total additive effect of all release controlling excipient changes should not be more than 10% w/w of the total release controlling excipient(s) in the original approved formulation. The total weight of the dosage form could still be within or outside the approved original application range.

The components (active and excipients) in the formulation should have numerical targets that represent the nominal composition of the product on which any future changes in the composition of the product are to be based. Allowable changes in the composition are based on the original approved target composition and not on the composition based on previous level 1 or level 2 changes. For products approved with only a range for excipients, the target value may be assumed to be the midpoint of the original approved application range.

2. Test Documentation

a. Chemistry Documentation. Application/compendial product release requirements and updated executed batch records.

Stability:

- Nonnarrow therapeutic range drugs: One batch with three months' accelerated stability data reported in prior approval supplement and long-term stability data of first production batch reported in annual report.

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[5] At present, there is no official CDER list of narrow therapeutic range drugs. A list was developed earlier in a preliminary attempt to identify drugs where there was greater concern that deviation from the specifications and potential changes in bioavailability could raise clinical issues. This preliminary list was not based solely on 21 CFR 320.33(c) which is contained in a section of the regulations related to criteria and evidence to assess actual or potential bioequivalence problems, nor does it accurately reflect the Agency's opinion on narrow therapeutic range drugs. Currently, the issue of narrow therapeutic range drugs is under discussion within CDER. If unsure about the classification of a drug as a narrow therapeutic range drug, sponsors should contact the appropriate CDER review division.

[6] Example: Eudragit RS-100 vs. Eudragit RL-100.

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- Narrow therapeutic range drugs: Three batches with three months' accelerated stability data reported in prior approval supplement and long-term stability data of first three production batches reported in annual report.

b. Dissolution Documentation.

- Nonnarrow therapeutic range drugs

Extended release: In addition to application/compendial release requirements, multipoint dissolution profiles should be obtained in three other media, for example, in water, 0.1N HCl, and USP buffer media at pH 4.5, and 6.8 for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example, at 1, 2, and 4 hours and every two hours thereafter until either 80% of the drug from the drug product is released or an asymptote is reached. A surfactant may be used with appropriate justification.

Delayed release: In addition to application/compendial release requirements, dissolution tests should be performed in 0.1 N HCl for 2 hours (acid stage) followed by testing in USP buffer media in the range of pH 4.5–7.5 (buffer stage) under standard (application/compendial) test conditions and two additional agitation speeds using the application/compendial test apparatus (three additional test conditions). If the application/compendial test apparatus is the rotating basket method (Apparatus 1), a rotation speed of 50, 100, and 150 rpm may be used, and if the application/compendial test apparatus is the rotating paddle method (Apparatus 2), a rotation speed of 50, 75, and 100 rpm may be used. Multipoint dissolution profiles should be obtained during the buffer stage of testing. Adequate sampling should be performed, for example, at 15, 30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug from the drug product is released or an asymptote is reached. The above dissolution testing should be performed using the changed drug product and the biobatch or marketed batch (unchanged drug product).

All modified release solid oral dosage forms: In the presence of an established in vitro/in vivo correlation (6), only application/compendial dissolution testing should be performed (i.e., only in vitro release data by the correlating method should be submitted). The dissolution profiles of the changed drug product and the biobatch or marketed batch (unchanged drug product) should be similar. The sponsor should apply appropriate statistical testing with justifications (e.g., the f equation) for comparing dissolution profiles (5). Similarity testing for the two dissolution profiles (i.e., for the unchanged drug product and the changed drug product) obtained in each individual medium is appropriate.

- Narrow therapeutic range drugs

Extended release: In addition to application/compendial release requirements, a multipoint dissolution profile should be obtained in application/compen-

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dial medium for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example at 1, 2, and 4 hours and every two hours thereafter until either 80% of the drug from the drug product is released or an asymptote is reached.

Delayed release: In addition to application/compendial release requirements, a multipoint dissolution profile should be obtained during the buffer stage of testing using the application/compendial medium for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example, at 15, 30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug from the drug product is released or an asymptote is reached.

c. Bioequivalence Documentation.

- Nonnarrow therapeutic range drugs: None.
- Narrow therapeutic range drugs: A single-dose bioequivalence study (3). The bioequivalence study may be waived in the presence of an established in vitro/in vivo correlation (6). Changes in release controlling excipients in the formulation should be within the range of release controlling excipients of the established correlation.

3. Filing Documentation

Prior approval supplement (all information including accelerated stability data); annual report (long-term stability data).

C. Level 3 Change

1. Definition of Level

Level 3 changes are those that are likely to have a significant impact on formulation quality and performance affecting all therapeutic ranges of the drug.

Examples:

a. Addition or deletion of release controlling excipient(s) (e.g., release controlling polymer/plasticizer).
b. Changes in the release controlling excipient(s), expressed as percentage (w/w) of total release controlling excipient(s) in the formulation, greater than those listed above for a level 2 change (i.e., greater than 10% w/w of total release controlling excipient content in the modified release solid oral dosage form). Total weight of the dosage form may be within or outside the original approved application range.

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2. Test Documentation

a. Chemistry Documentation. Application/compendial product release requirements and updated executed batch records.

Stability: Three batches with three months' accelerated stability data reported in prior approval supplement and long-term stability data of first three production batches reported in annual report.

b. Dissolution Documentation. Extended release: In addition to application/compendial release requirements, a multipoint dissolution profile should be obtained using application/compendial test conditions for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example at 1, 2, and 4 hours and every two hours thereafter until either 80% of the drug from the drug product is released or an asymptote is reached.

Delayed release: In addition to application/compendial release requirements, a multipoint dissolution profile should be obtained during the buffer stage of testing using the application/compendial test conditions for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example at 15, 30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug from the drug product is released or an asymptote is reached.

c. Bioequivalence Documentation. A single-dose bioequivalence study (3). The bioequivalence study may be waived in the presence of an established in vitro/in vivo correlation (6). Changes in release controlling excipients in the formulation should be within the range of release controlling excipients of the established correlation.

3. Filing Documentation

Prior approval supplement (all information including accelerated stability data); annual report (long-term stability data).

V. SITE CHANGES

Site changes consist of changes in location of the site of manufacture, packaging operations, and/or analytical testing laboratory for both company-owned and contract manufacturing facilities. They do not include any scale-up changes, changes in manufacturing (including process and/or equipment), or changes in components or composition. New manufacturing locations should have had a satisfactory current good manufacturing practice (cGMP) inspection.

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A stand-alone packaging operations site change, using container(s)/closure(s) in the approved application, may be submitted as a Changes Being Effected supplement. The facility should also have a current and satisfactory cGMP compliance profile with the FDA for the type of packaging operation in question before submitting the supplement. If the facility has not received a satisfactory cGMP inspection for the type of packaging operation in question, a prior approval supplement is recommended. The supplement should contain a written certification from the packaging facility stating that it is in conformance with cGMPs. It should also contain a commitment to place the first production batch of the product, and annual batches thereafter, on long-term stability studies using the approved protocol in the application and to submit the resulting data in annual reports. Where the product is available in more than one strength, size, or container/closure system, one lot of each combination should be placed on long-term stability studies. Bracketing or matrixing is allowed only if it has been approved previously by the FDA. Any changes to an approved stability protocol should have a supplemental approval prior to the initiation of the stability study.

A stand-alone analytical testing laboratory site change may be submitted as a Changes Being Effected supplement if the new facility has a current and satisfactory cGMP compliance profile with the FDA for the type of testing operation in question. The supplement should contain a commitment to use the same test methods employed in the approved application, written certification from the testing laboratory stating that they are in conformance with cGMPs, and a full description of the testing to be performed by the testing lab. If the facility has not received a satisfactory cGMP inspection for the type of testing involved, a prior approval supplement is recommended.

A. Level 1 Change

1. Definition of Level

Level 1 changes consist of site changes within a single facility where the same equipment, standard operating procedures (SOPs), environmental conditions (e.g., temperature and humidity) and controls, and personnel common to both[7] manufacturing sites are used and where no changes are made to the executed batch records, except for administrative information and the location of the facility.

2. Test Documentation

a. Chemistry Documentation. None beyond application/compendial product release requirements.

[7] *Common* is defined as employees already working on the campus who have suitable experience with the manufacturing process.

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b. Dissolution Documentation. None beyond application/compendial release requirements.

c. Bioequivalence Documentation. None.

3. Filing Documentation

Annual report.

B. Level 2 Change

1. Definition of Level

Level 2 changes consist of site changes within a contiguous campus, or between facilities in adjacent city blocks, where the same equipment, SOPs, environmental conditions (e.g., temperature and humidity) and controls, and personnel common[7] to both manufacturing sites are used and where no changes are made to the executed batch records, except for administrative information and the location of the facility.

2. Test Documentation

a. Chemistry Documentation. Notification of location of new site and updated executed batch records. None beyond application/compendial product release requirements. Stability: One batch with three months accelerated stability data reported in Changes Being Effected supplement and long-term stability data of first production batch reported in annual report.

b. Dissolution Documentation. Extended release: In addition to application/compendial release requirements, multipoint dissolution profiles should be obtained in three other media, for example, in water, 0.1N HCl, and USP buffer media at pH 4.5, and 6.8 for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example at 1, 2, and 4 hours and every two hours thereafter until either 80% of the drug from the drug product is released or an asymptote is reached. A surfactant may be used with appropriate justification. Delayed release: In addition to application/compendial release requirements, dissolution tests should be performed in 0.1 N HCl for 2 hours (acid stage) followed by testing in USP buffer media, in the range of pH 4.5–7.5 (buffer stage) under standard (application/compendial) test conditions and two additional agitation speeds using the application/ compendial test apparatus (three additional test conditions). If the application/compendial test apparatus is the rotating basket method (Apparatus 1), a rotation speed of 50, 100, and 150 rpm may be used, and if the application/compendial test apparatus is the rotating paddle method (Apparatus 2), a rotation speed of 50, 75, and 100 rpm may be used.

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Multipoint dissolution profiles should be obtained during the buffer stage of testing. Adequate sampling should be performed, for example, at 15, 30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug from the drug product is released or an asymptote is reached. The above dissolution testing should be performed using the changed drug product and the biobatch or marketed batch (unchanged drug product).

All modified release solid oral dosage forms: In the presence of an established in vitro/in vivo correlation (6), only application/compendial dissolution testing should be performed (i.e., only in vitro release data by the correlating method should be submitted). The dissolution profiles of the changed drug product and the biobatch or marketed batch (unchanged drug product) should be similar. The sponsor should apply appropriate statistical testing with justifications (e.g., the f equation) for comparing 2 dissolution profiles (5). Similarity testing for the two dissolution profiles (i.e., for the unchanged drug product and the changed drug product) obtained in each individual medium is appropriate.

c. Bioequivalence Documentation. None.

3. Filing Documentation

Changes Being Effected supplement (all information including accelerated stability data); annual report (long-term stability data).

C. Level 3 Change

1. Definition of Level

Level 3 changes consist of a change in manufacturing site to a different campus. A different campus is defined as one that is not on the same original contiguous site or where the facilities are not in adjacent city blocks. To qualify as a level 3 change, the same equipment, SOPs, environmental conditions, and controls should be used in the manufacturing process at the new site, and no changes may be made to the executed batch records except for administrative information, location and language translation, where needed.

2. Test Documentation

a. Chemistry Documentation. Notification of location of new site and updated executed batch records. Application/compendial product release requirements.

Stability: Significant body of information available: One batch with three months' accelerated stability data reported in prior approval supplement and long-term stability data of first three production batches reported in annual report.

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Significant body of information not available: Three batches with three months' accelerated stability data reported in prior approval supplement and long-term stability data of first three production batches reported in annual report.

b. Dissolution Documentation. Extended release: In addition to application/compendial release requirements, a multipoint dissolution profile should be obtained using application/compendial test conditions for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example at 1, 2, and 4 hours and every two hours thereafter until either 80% of the drug from the drug product is released or an asymptote is reached.

Delayed release: In addition to application/compendial release requirements, a multipoint dissolution profile should be obtained during the buffer stage of testing using the application/compendial test conditions for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example, at 15, 30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug from the drug product is released or an asymptote is reached.

c. Bioequivalence Documentation. A single-dose bioequivalence study (3). The bioequivalence study may be waived in the presence of an established in vitro/in vivo correlation (6).

3. Filing Documentation

Prior approval supplement (all information including accelerated stability test data); annual report (long-term stability data).

VI. CHANGES IN BATCH SIZE (SCALE-UP/SCALE-DOWN)

Postapproval changes in the size of a batch from the pivotal/pilot scale biobatch material to larger or smaller production batches call for submission of additional information to the application. Scale-down below 100,000 dosage units is not covered by this guidance. Adjustments in parameters such as mixing times and speeds may be made to tailor the process to the characteristics of larger or smaller scale equipment. All scale-up changes should be properly validated and, where needed, inspected by appropriate Agency personnel.

A. Level 1 Change

1. Definition of Level

Change in batch size, up to and including a factor of ten times the size of the pilot/biobatch, where (1) the equipment used to produce the test batch(es) may

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vary in capacity, but are of the same design and operating principles; (2) the batch(es) is manufactured in full compliance with cGMPs; and (3) the same standard operating procedures (SOPs) and controls, as well as the same formulation and manufacturing procedures, are used on the test batch(es) and on the full-scale production batch(es).

2. Test Documentation

a. Chemistry Documentation. Application/compendial product release requirements. Notification of change and submission of updated executed batch records in annual report. Stability: First production batch on long-term stability data reported in annual report.

b. Dissolution Documentation. None beyond application/compendial release requirements.

c. Bioequivalence Documentation. None.

3. Filing Documentation

Annual report (all information including long-term stability data).

B. Level 2 Change

1. Definition of Level

Changes in batch size beyond a factor of ten times the size of the pilot/biobatch where (1) the equipment used to produce the test batch(es) is of the same design and operating principles; (2) the batch(es) is manufactured in full compliance with cGMPs; and (3) the same SOPs and controls as well as the same formulation and manufacturing procedures are used on the test batch(es) and on the full-scale production batch(es).

2. Test Documentation

a. Chemistry Documentation. Application/compendial product release requirements. Notification of change and submission of updated batch records.

Stability: One batch with three months' accelerated stability data reported in Changes Being Effected supplement and long-term stability data of first production batch reported in annual report.

b. Dissolution Documentation. Extended release: In addition to application/compendial release requirements, multipoint dissolution profiles should be obtained in three other media, for example, in water, 0.1N HCl, and USP buffer media at pH 4.5, and 6.8 for the changed drug product and the biobatch or mar-

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keted batch (unchanged drug product). Adequate sampling should be performed, for example, at 1, 2, and 4 hours, and every two hours thereafter until either 80% of the drug from the drug product is released or an asymptote is reached. A surfactant may be used with appropriate justification.

Delayed release: In addition to application/compendial release requirements, dissolution tests should be performed in 0.1 N HCl for 2 hours (acid stage) followed by testing in USP buffer media in the range of pH 4.5–7.5 (buffer stage) under standard (application/compendial) test conditions and two additional agitation speeds using the application/ compendial test apparatus (three additional test conditions). If the application/compendial test apparatus is the rotating basket method (Apparatus 1), a rotation speed of 50, 100, and 150 rpm may be used, and if the application/compendial test apparatus is the rotating paddle method (Apparatus 2), a rotation speed of 50, 75, and 100 rpm may be used. Multipoint dissolution profiles should be obtained during the buffer stage of testing. Adequate sampling should be performed, for example, at 15, 30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug from the drug product is released or an asymptote is reached. The above dissolution testing should be performed using the changed drug product and the biobatch or marketed batch (unchanged drug product).

All modified release solid oral dosage forms: In the presence of an established in vitro/in vivo correlation (6), only application/compendial dissolution testing should be performed (i.e., only in vitro release data by the correlating method should be submitted). The dissolution profiles of the changed drug product and the biobatch or marketed batch (unchanged drug product) should be similar. The sponsor should apply appropriate statistical testing with justifications (e.g., the f equation) for comparing 2 dissolution profiles (5). Similarity testing for the two dissolution profiles (i.e., for the unchanged drug product and the changed drug product) obtained in each individual medium is appropriate.

c. Bioequivalence Documentation. None.

3. Filing Documentation

Changes Being Effected supplement (all information including accelerated stability data); annual report (long-term stability data).

VII. MANUFACTURING EQUIPMENT CHANGES

Manufacturing changes may involve the equipment used in the manufacturing process (critical manufacturing variable). If a manufacturer wishes to use manufacturing equipment that is not identical in every respect to the original manufacturing equipment used in the approved application, appropriate validation studies

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should be conducted to demonstrate that the new equipment is similar to the original equipment. For modified release solid oral dosage forms, consideration should be given as to whether or not the change in manufacturing equipment is critical to drug release (critical equipment variable).

A. Level 1 Change

1. Definition of Level

This category consists of (1) change from nonautomated or nonmechanical equipment to automated or mechanical equipment to move ingredients and (2) change to alternative equipment of the same design and operating principles of the same or of a different capacity.

2. Test Documentation

a. Chemistry Documentation. Application/compendial product release requirements. Notification of change and submission of updated executed batch records.

Stability: First production batch on long-term stability data reported in annual report.

b. Dissolution Documentation. None beyond application/compendial release requirements.

c. Bioequivalence Documentation. None.

3. Filing Documentation

Annual report (all information including long-term stability data).

B. Level 2 Change

1. Definition of Level

Change in equipment to a different design and different operating principles.

2. Test Documentation

a. Chemistry Documentation. Application/compendial product release requirements. Notification of change and submission of updated executed batch records.

Stability:

Significant body of information available: One batch with three months' accelerated stability data reported in prior approval supplement and long-term stability data of first three production batches reported in annual report.

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Significant body of information not available: Three batches with three months' accelerated stability data reported in prior approval supplement and long-term stability data of first three production batches reported in annual report.

b. Dissolution Documentation. Extended release: In addition to application/compendial release requirements, multipoint dissolution profiles should be obtained in three other media, for example, in water, 0.1N HCl, and USP buffer media at pH 4.5, and 6.8 for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example, at 1, 2, and 4 hours and every two hours thereafter until either 80% of the drug from the drug product is released or an asymptote is reached. A surfactant may be used with appropriate justification.

Delayed release: In addition to application/compendial release requirements, dissolution tests should be performed in 0.1 N HCl for 2 hours (acid stage) followed by testing in USP buffer media, in the range of pH 4.5–7.5 (buffer stage) under standard (application/compendial) test conditions and two additional agitation speeds using the application/ compendial test apparatus (three additional test conditions). If the application/compendial test apparatus is the rotating basket method (Apparatus 1), a rotation speed of 50, 100, and 150 rpm may be used, and if the application/compendial test apparatus is the rotating paddle method (Apparatus 2), a rotation speed of 50, 75, and 100 rpm may be used. Multipoint dissolution profiles should be obtained during the buffer stage of testing. Adequate sampling should be performed, for example, at 15, 30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug from the drug product is released or an asymptote is reached. The above dissolution testing should be performed using the changed drug product and the biobatch or marketed batch (unchanged drug product).

All modified release solid oral dosage forms: In the presence of an established in vitro/in vivo correlation (6), only application/compendial dissolution testing should be performed (i.e., only in vitro release data by the correlating method should be submitted). The dissolution profiles of the changed drug product and the biobatch or marketed batch (unchanged drug product) should be similar. The sponsor should apply appropriate statistical testing with justifications (e.g., the f equation) for comparing 2 dissolution profiles (5). Similarity testing for the two dissolution profiles (i.e., for the unchanged drug product and the changed drug product) obtained in each individual medium is appropriate.

c. Bioequivalence Documentation. None.

3. Filing Documentation

Prior approval supplement with justification for change (all information including accelerated stability data); annual report (long-term stability data).

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VIII. MANUFACTURING PROCESS CHANGES

Manufacturing changes may involve the manufacturing process itself (critical manufacturing variable). If a manufacturer wishes to use a manufacturing process that is not identical in every respect to the original manufacturing process used in the approved application, appropriate validation studies should be conducted to demonstrate that the new process is similar to the original process. For modified release solid oral dosage forms, consideration should be given as to whether or not the change in manufacturing process is critical to drug release (critical processing variable). For purposes of categorizing the level of changes, process change may be considered only to affect a release controlling excipient when both types of excipients (i.e., nonrelease and release controlling) are present during the unit operation undergoing a change.

A. Level 1 Change

1. Definition of Level

Process changes involving adjustment of equipment operating conditions such as mixing times and operating speeds within original approved application ranges affecting the nonrelease controlling and/or release controlling excipient(s). The sponsor should provide appropriate justifications for claiming any excipient(s) as a nonrelease controlling or a release controlling excipient in the formulation of the modified release solid oral dosage form.

2. Test Documentation

a. Chemistry Documentation. None beyond application/compendial product release requirements. Notification of the change and submission of the updated executed batch records.

b. Dissolution Documentation. None beyond application/compendial release requirements.

c. Bioequivalence Documentation. None.

3. Filing Documentation

Annual report.

B. Level 2 Change

1. Definition of Level

This category includes process changes involving adjustment of equipment operating conditions such as mixing times and operating speeds outside of original approved application ranges.

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2. Test Documentation

a. Chemistry Documentation. Application/compendial product release requirements. Notification of change and submission of updated executed batch records. Stability: One batch with three months' accelerated stability data reported in Changes Being Effected supplement and long-term stability data of first production batch reported in annual report.

b. Dissolution Documentation. Extended release: In addition to application/compendial release requirements, multipoint dissolution profiles should be obtained in three other media, for example, in water, 0.1N HCl, and USP buffer media at pH 4.5, and 6.8 for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example at 1, 2, and 4 hours and every two hours thereafter until either 80% of the drug from the drug product is released or an asymptote is reached. A surfactant may be used with appropriate justification.

Delayed release: In addition to application/compendial release requirements, dissolution tests should be performed in 0.1 N HCl for 2 hours (acid stage) followed by testing in USP buffer media, in the range of pH 4.5–7.5 (buffer stage) under standard (application/compendial) test conditions and two additional agitation speeds using the application/ compendial test apparatus (three additional test conditions). If the application/compendial test apparatus is the rotating basket method (Apparatus 1), a rotation speed of 50, 100, and 150 rpm may be used, and if the application/compendial test apparatus is the rotating paddle method (Apparatus 2), a rotation speed of 50, 75, and 100 rpm may be used. Multipoint dissolution profiles should be obtained during the buffer stage of testing. Adequate sampling should be performed, for example, at 15, 30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug from the drug product is released or an asymptote is reached. The above dissolution testing should be performed using the changed drug product and the biobatch or marketed batch (unchanged drug product).

All modified release solid oral dosage forms: In the presence of an established in vitro/in vivo correlation (6), only application/compendial dissolution testing should be performed (i.e., only in vitro release data by the correlating method should be submitted). The dissolution profiles of the changed drug product and the biobatch or marketed batch (unchanged drug product) should be similar. The sponsor should apply appropriate statistical testing with justifications (e.g., the f equation) for comparing 2 dissolution profiles (5). Similarity testing for the two dissolution profiles (i.e., for the unchanged drug product and the changed drug product) obtained in each individual medium is appropriate.

c. Bioequivalence Documentation. None.

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3. Filing Documentation

Changes Being Effected supplement (all information including accelerated stability data); annual report (long-term stability data).

C. Level 3 Change

1. Definition of Level

This category includes change in the type of process used in the manufacture of the product, such as a change from wet granulation to direct compression of dry powder.

2. Test Documentation

a. Chemistry Documentation. Application/compendial product release requirements. Notification of change and submission of updated executed batch records.

Stability: Three batches with three months' accelerated stability data reported in prior approval supplement and long-term stability data of first three production batches reported in annual report.

b. Dissolution Documentation. Extended release: In addition to application/compendial release requirements, a multipoint dissolution profile should be obtained using application/compendial test conditions for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example at 1, 2, and 4 hours and every two hours thereafter until either 80% of the drug from the drug product is released or an asymptote is reached.

Delayed release: In addition to application/compendial release requirements, a multipoint dissolution profile should be obtained during the buffer stage of testing using the application/compendial test conditions for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example at 15, 30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug from the drug product is released or an asymptote is reached.

c. Bioequivalence Documentation. A single-dose bioequivalence study (3). The bioequivalence study may be waived in the presence of an established in vitro/in vivo correlation (6).

3. Filing Documentation

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GLOSSARY OF TERMS

The following terms and their definitions (9) are being provided to assist the reader in using this guidance document.

Batch: A specific quantity of a drug or other material produced according to a single manufacturing order during the same cycle of manufacture and intended to have uniform character and quality, within specified limits (21 CFR 210.3(b)(2)).
Batch Formula (Composition): A complete list of the ingredients and their amounts to be used for the manufacture of a representative batch of the drug product. All ingredients should be included in the batch formula whether or not they remain in the finished product (1).
Biobatch: The lot of drug product formulated for purposes of pharmacokinetic evaluation in a bioavailability/bioequivalency study. For modified release solid oral, this batch should be 10% or greater than the proposed commercial production batch or at least 100,000 units, whichever is greater.
Bioequivalence Studies for Modified Release Drug Product: Refer to the OGD Guidance (3). The bioequivalence study should be conducted using the reference listed drug (RLD) product and/or the innovator drug product as the reference and the test product should be the product (generic or innovator) which has undergone postapproval change.
Contiguous Campus: Continuous or unbroken site or a set of buildings in adjacent city blocks.
Critical Equipment Variable: A specific design, operating principle, or automation of equipment that can affect a specific performance variable critical to the ultimate and predictable performance of the dosage form and its drug.
Critical Manufacturing Variable: Includes those manufacturing materials (critical composition variable), methods, equipment, and processes that significantly affect drug release, from the formulation (e.g., coating thickness, particle size, crystal form, excipient type, concentrations and distribution, and tablet hardness).
Critical Processing Variable: A specific step, unit process, or condition of a unit process that can affect a specific performance variable critical to the ultimate and predictable performance of the dosage form and its drug.
Delayed Release: Release of a drug (or drugs) at a time other than immediately following oral administration.
Dissolution Testing: Extended release: Dissolution testing should be conducted on 12 individual dosage units for the changed drug product and the biobatch or marketed batch (unchanged drug product). The potential for pH dependence of drug release from a modified release drug product is well recognized. Multipoint dissolution profiles should be obtained using discriminating agitation speed and medium. A surfactant may be used with appropriate justification. Early

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sampling times of 1, 2, and 4 hours should be included in the sampling schedule to provide assurance against premature release of the drug (dose dumping) from the formulation. Differing sampling times should be justified to prevent premature drug release. See current USP 23 NF 18, sections <711> and <724>, for general dissolution requirements. The general dissolution conditions to be followed are shown below:

1. Apparatus: USP 23 Apparatus 1 (rotating basket)
   USP 23 Apparatus 2 (rotating paddle)
   USP 23 Apparatus 3 (reciprocating cylinder) *
   USP 23 Apparatus 4 (flow-through cell) *
   USP 23 Apparatus 7 (reciprocating disk) *
2. Rotation Speed: 50, 100, and 150 rpm (basket)
   50, 75 and 100 rpm (paddle)
3. Temperature: 37 ± 0.5 C°
4. Units To Be Tested: 12
5. Dissolution Volume: 500–1000 mL
6. Dissolution Medium: Aqueous media of various pH.
7. Sampling Schedule: Adequate sampling should be performed, for example at 1, 2, and 4 hours, and every two hours thereafter until either 80% of the drug is released or an asymptote is reached.
8. Tolerances: As established.
9. Content Uniformity: Content uniformity testing of the proposed product lot should be performed as described in USP 23.
   When using USP 23 Apparatus 3 (reciprocating cylinder), USP 23 Apparatus 4 (flow- * through cell), or USP 23 Apparatus 7 (reciprocating disk) the above dissolution testing conditions should be modified accordingly.

Delayed release: For enteric coated drug products, drug release procedures described in USP 23 NF 18, sections <711> and <724> should be followed. When the guidance refers to dissolution testing in addition to application/compendial release requirements, the dissolution test should be performed in 0.1N HCl for 2 hours (acid stage) followed by testing in USP buffer media, in the range of pH 4.5–7.5 (buffer stage) under standard (application/compendial) test conditions and increased agitation speeds using the application/ compendial test apparatus. For the rotating basket method (Apparatus 1), a rotation speed of 50, 100, and 150 rpm may be used and for the rotating paddle method (Apparatus 2), a rotation speed of 50, 75, and 100 rpm may be studied. Multipoint dissolution profiles should be obtained during the buffer stage of testing. Adequate sampling should be performed, for example, at 15, 30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug is released or an asymptote is reached. The above dissolution testing

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should be performed using the changed drug product and the biobatch or marketed batch (unchanged drug product).

Drug Product: A drug product is a finished dosage form (e.g., tablet and capsule) that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients (21 CFR 314.3(b)). A solid oral dosage form includes but is not limited to tablets, chewable tablets, enteric coated tablets, capsules, caplets, encapsulated beads, and gelcaps.

Drug Substance: An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of a disease, or to affect the structure of any function of the human body, but does not include intermediates used in the synthesis of such ingredient (21 CFR 314.3(b)).

Enteric Coated: Intended to delay the release of the drug (or drugs) until the dosage form has passed through the stomach. Enteric coated products are delayed release dosage forms.

Equipment: Automated or nonautomated, mechanical or nonmechanical equipment used to produce the drug product, including equipment used to package the drug product.

Extended Release: Extended release products are formulated to make the drug available over an extended period after ingestion. This allows a reduction in dosing frequency compared to a drug presented as a conventional dosage form (e.g., as a solution or an immediate release dosage form).

Formulation: A listing of the ingredients and composition of the dosage form.

Immediate Release: Allows the drug to dissolve in the gastrointestinal contents, with no intention of delaying or prolonging the dissolution or absorption of the drug.

In Vitro Dissolution Profile Comparison: Model Independent Approach Using Similarity Factor: Dissolution profiles may be compared using the following equation that defines a similarity factor (f_2):

$$f_2 = 50 \text{ LOG } \{[1+1/n \textstyle\sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \times 100\}$$

where LOG = logarithm to base 10, n = number of sampling time points, $\sum$ = summation over all time points, R_t = dissolution at time point t of the reference (unchanged drug product, i.e., pre- change batch), T_t = dissolution at time point t of the test (changed drug product, i.e., post-change batch) (5 and 8).

For comparison of multipoint dissolution profiles obtained in multiple media, similarity testing should be performed using pairwise dissolution profiles (i.e., for the unchanged and changed product) obtained in each individual medium. It is recommended that only one point past the plateau of the profiles be used in calculating the f_2 value. A correction for a lag time prior to similarity testing should not be performed unless justified.

An f value between 50 and 100 suggests the two dissolution profiles are similar. Also, the $_2$ average difference at any dissolution sampling time point

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should not be greater than 15% between the changed drug product and the biobatch or marketed batch (unchanged drug product) dissolution profiles. An appropriate reference for this comparison should represent an average dissolution profile derived from at least three consecutive recent batches of the unchanged drug product (biobatch or marketed batch). Finally, the dissolution data obtained under the application/compendial dissolution testing conditions (media, agitation, etc.), on both the changed drug product and the biobatch or marketed batch (unchanged drug product) should be within the application/compendial specifications.

An f_2 value less than 50 does not necessarily indicate lack of similarity. If the sponsor is of the opinion that the differences observed related to this calculation of f_2 are typical for the drug product involved in this SUPAC situation, an appropriate justification can be submitted, but only as part of a prior approval supplement. This justification should include additional data to support the claim of similarity, as well as supporting statistical analysis (e.g. 90% confidence interval analysis). If this justification is not found acceptable, the potential effect of the proposed change on the differences in dissolution on bioavailability should be determined.

Dissolution profiles can also be compared using other model independent or model dependent methods (5).

In Vitro–In Vivo Correlation: A predictive mathematical model describing the relationship between an in vitro property of an oral dosage form (usually the rate or extent of drug dissolution or release) and a relevant in vivo response (e.g., plasma drug concentration or amount of drug absorbed).

For modified release dosage forms, changes in release controlling excipients in the formulation should be within the range of release controlling excipients of the established correlation. In the presence of an established in vitro/in vivo correlation (6), only application/ compendial dissolution testing need be performed. Also, an established in vitro/in vivo correlation can be used for any level of changes described in this guidance.

Justification: Reports containing scientific data and expert professional judgment to substantiate decisions.

Lot: A batch or a specific identified portion of a batch, having uniform character and quality within specified limits or, in the case of a drug product produced by continuous process, a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits (21 CFR 210.3(b)(10)).

Modified Release Dosage Forms: Dosage forms whose drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as a solution or an immediate release dosage form. Modified release solid oral dosage forms include both delayed and extended release drug products.

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Nonrelease Controlling Excipient (Non-Critical Composition Variable: An excipient in the final dosage form whose primary function does not include modifying the duration of release of the active drug substance from the dosage form.
Operating Principles: Rules or concepts governing the operation of the system.
Pilot Scale: The manufacture of either drug substance or drug product by a procedure fully representative of and simulating that used for full manufacturing scale. For solid oral dosage forms this is generally taken to be, at a minimum, one tenth that of full production, or 100,000 tablets or capsules, whichever is larger (4).
Process: A series of operations, actions and controls used to manufacture a drug product.
Ranges: The extent to which or the limits between which acceptable variation exists.
Release Controlling Excipient (Critical Composition Variable): An excipient in the final dosage form whose primary function is to modify the duration of release of the active drug substance from the dosage form.
Release Mechanism: The process by which the drug substance is released from the dosage form. Typically the definition contains the energy source or pictorially describes the way the drug is released.
Representative: Corresponding to or replacing some other species or the like; exemplifying a group or kind; typical.
Same: Agreeing in kind, amount; unchanged in character or condition.
Satisfactory Current Good Manufacturing Practice (cGMP) Inspection: A satisfactory cGMP inspection is one during which (1) no objectionable conditions or practices were found during an inspection or (2) objectionable conditions were found, however, corrective action is left to the firm to take voluntarily and the objectionable conditions do not justify further administrative or regulatory actions.
Scale-up: The process of increasing the batch size.
Scale-down: The process of decreasing the batch size.
Significant Body of Information:

- Immediate Release Solid Oral Dosage Forms: A significant body of information on the stability of the drug product is likely to exist after five years of commercial experience for new molecular entities, or three years of commercial experience for new dosage forms.
- Modified Release Solid Oral Dosage Forms: A significant body of information should include, for "Modified Release Solid Oral Dosage Forms," a product-specific body of information. This product-specific body of information is likely to exist after five years of commercial experience for the original modified release solid oral drug product, or three years of commercial experience for any subsequent modified release solid oral drug product utilizing similar drug release mechanism.

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Similar: Having a general likeness.
Technical Grade: Technical grades of excipients may differ in (1) specifications and/or functionality, (2) impurities, and (3) impurity profiles.
Validation: Establishing through documented evidence a high degree of assurance that a specific process will consistently produce a product that meets its predetermined specifications and quality attributes. A validated manufacturing process is one that has been proven to do what it purports or is represented to do. The proof of validation is obtained through collection and evaluation of data, preferably beginning from the process development phase and continuing through into the production phase. Validation necessarily includes process qualification (the qualification of materials, equipment, systems, buildings, and personnel), but it also includes the control of entire processes for repeated batches or runs.

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A-1 Extended Release Solid Oral Dosage Forms Non-release Controlling Components and Composition

Level	Classification	Therapeutic range	Test documentation	Filing documentation
I	-Complete or partial deletion of color/ flavor -Change in inks, imprints -Up to SUPAC- IR level 1 excipient ranges -No other changes	All drugs	-Stability -Application/ compendial requirements -No biostudy	-Annual report
II	-Change in technical grade and/ or specifications -Higher than SUPAC- IR level 1 but less than level 2 excipient ranges -No other changes	All drugs	-Notification & updated batch record -Stability -Application/ compendial requirements plus multi-point dissolution profiles in three other media (e. g., water, 0.1N HCL, and USP buffer media at pH 4.5 and 6.8) until >= 80% of drug released or an asymptote is reached[1] -Apply some statistical test (f2 test) for comparing dissolution profiles[2] -No biostudy	-Prior approval supplement
III	-Higher than SUPAC- IR level 2 excipient ranges	All drugs	-Updated batch record -Stability -Application/ compendial (profile) requirements -Biostudy or IVIVC[1]	-Prior approval supplement

[1] In the presence of an established in vitro/in vivo correlation only application/ compendial dissolution testing should be performed.

[2] In the absence of an established in vitro/in vivo correlation.

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A-2 Extended Release Solid Oral Dosage Forms Release Controlling Components and Composition

Level	Classification	Therapeutic range	Test documentation	Filing documentation
I	-<= 5% w/ w change based on total release controlling excipient (e.g., controlled release polymer, plasticizer) content -No other changes	All drugs	-Stability -Application/ compendial requirements -No biostudy	-Annual report
II	-Change in technical grade and/ or specifications -<= 10% w/ w change based on total release controlling excipient (e.g., controlled release polymer, plasticizer) content -No other changes	Non- narrow	-Notification & updated batch record -Stability -Application/ compendial requirements plus multi- point dissolution profiles in three other media (e.g., water, 0.1N HCL, and USP buffer media at pH 4.5 and 6.8) until >= 80% of drug released or an asymptote is reached[1] -Apply some statistical test (F2 test) for comparing dissolution profiles[2] -No biostudy	-Prior approval supplement
		Narrow	-Updated batch record -Stability -Application/ compendial (profile) requirements -Biostudy or IVIVC[1]	-Prior approval supplement
III	-> 10% w/ w change based on all drugs total release controlling excipient (e.g., controlled release polymer, plasticizer) content	All drugs	-Updated batch record -Stability -Application/ compendial (profile) requirements -Biostudy or IVIVC[1]	-Prior approval supplement

[1] In the presence of an established in vitro/in vivo correlation only application/ compendial dissolution testing should be performed.
[2] In the absence of an established in vitro/in vivo correlation.

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A-3 Extended Release Solid Oral Dosage Forms Site Change

Level	Classification	Therapeutic range	Test documentation	Filing documentation
I	-Single facility -Common personnel -No other changes	All drugs	-Application/ compendial requirements -No biostudy	-Annual report
II	-Same contiguous campus -Common personnel -No other changes	All drugs	-Identification and description of site change, and updated batch record -Notification of site change -Stability -Application/ compendial requirements plus multi-point dissolution profiles in three other media (e.g., water, 0.1N HCL, and USP buffer media at pH 4.5 and 6.8) until >= 80% of drug released or an asymptote is reached[1] -Apply some statistical test (F2 test) for comparing dissolution profiles[2] -No biostudy	-Changes being effected supplement
III	-Different campus -Different personnel	All drugs	-Notification of site change -Updated batch record -Stability -Application/ compendial (profile) requirements -Biostudy or IVIVC[1]	-Prior approval supplement

[1] In the presence of an established in vitro/in vivo correlation only application/ compendial dissolution testing should be performed.

[2] In the absence of an established in vitro/in vivo correlation.

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A-4 Extended Release Solid Oral Dosage Forms Scale-up/ Scale-down

Level	Classification	Change	Test documentation	Filing documentation
I	-Scale- up of bio-batch(s) or pivotal clinical batch(s) -No other changes	<= 10X (All drugs)	-Updated batch record -Stability -Application/ compendial requirements -No biostudy	-Annual report
II	-Scale- up of bio-batch(s) or pivotal clinical batch(s) -No other changes	> 10X (All drugs)	-Updated batch record -Stability -Application/ compendial requirements plus multi-point dissolution profiles in three other media (e.g., water, 0.1N HCL, and USP buffer media at pH 4.5 and 6.8) until >= 80% of drug released or an asymptote is reached[1] -Apply some statistical test (F2 test) for comparing dissolution profiles[2] -No biostudy	-Changes being effected supplement

[1] In the presence of an established in vitro/in vivo correlation only application/ compendial dissolution testing should be performed.
[2] In the absence of an established in vitro/in vivo correlation.

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A-5 Extended Release Solid Oral Dosage Forms Manufacturing—Equipment

Level	Classification	Change	Test documentation	Filing documentation
I	-Equipment changes -No other changes (all drugs)	-Alternate equipment of same design and principle -Automated equipment	-Updated batch record -Stability -Application/ compendial requirements -No biostudy	-Annual report
II	-Equipment changes -No other changes (All drugs)	-Change to equipment of a different design and operating principle	-Updated batch record -Stability -Application/ compendial requirements plus multi-point dissolution profiles in three other media (e.g., water, 0.1N HCL, and USP buffer media at pH 4.5 and 6.8) until >= 80% of drug released or an asymptote is reached[1] -Apply some statistical test (F2 test) for comparing dissolution profiles[2] -No biostudy	-Prior approval supplement

[1] In the presence of an established in vitro/in vivo correlation only application/ compendial dissolution testing should be performed.
[2] In the absence of an established in vitro/in vivo correlation.

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A-6 Extended Release Solid Oral Dosage Forms Manufacturing—Processing

Level	Classification	Change	Test documentation	Filing documentation
I	-Processing changes affecting the non- release controlling excipients and/ or the release conrolling excipients -No other changes	-Adjustment of equipment operating conditions (e.g. mixing times, operating speeds, etc.) -Within approved application ranges	-Updated batch record -Application/ compendial requirements -No biostudy	-Annual report
II	-Processing changes affecting the non- release controlling excipients and/ or the release controlling excipients -No other changes	-Adjustment of equipment operating conditions (e.g. mixing times, operating speeds, etc.) -Beyond approved application ranges	-Updated batch record -Stability -Application/ compendial requirements plus multi-point dissolution profiles in three other media (e.g., water, 0.1N HCL, and USP buffer media at pH 4.5 and 6.8) until >= 80% of drug released or an asymptote is reached[1] -Apply some statistical test (F2 test) for comparing dissolution profiles[2] -No biostudy	-Changes being effected supplement
III	-processing changes affecting the non- release controlling excipients and/ or the release controlling excipients	-Change in the type of process used (e.g. from wet granulation to direct compression)	-Updated batch record -Stability -Application/ compendial (profile) requirements -Biostudy or IVIVC[1]	-Prior approval supplement

[1] In the presence of an established in vitro/in vivo correlation only application/ compendial dissolution testing should be performed.

[2] In the absence of an established in vitro/in vivo correlation.

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B-1 Delayed Release Solid Oral Dosage Forms Non-release Controlling Components and Composition

Level	Classification	Therapeutic range	Test documentation	Filing documentation
I	-Complete or partial deletion of color/ flavor -Change in inks, imprints -Up to SUPAC- IR level 1 excipient ranges -No other changes	All drugs	-Stability -Application/ compendial requirements -No biostudy	-Annual report
II	-Change in technical grade and/ or specifications -Higher than SUPAC- IR level 1 but less than level 2 excipient ranges -No other changes	All drugs	-Notification & updated batch record -Stability -Application/ compendial requirements plus multi-point dissolution profiles in additional buffer stage testing (e.g., USP buffer media at pH 4.5–7.5) under standard and increased agitation conditions until >= 80% of drug released or an asymptote is reached[1] -Apply some statistical test (F2 test) for comparing dissolution profiles[2] -No biostudy	-Prior approval supplement
III	-Higher than SUPAC- IR level 2 excipient ranges	All drugs	-Updated batch record -Stability -Application/ compendial (profile) requirements -Biostudy or IVIVC[1]	-Prior approval supplement

[1] In the presence of an established in vitro/in vivo correlation only application/ compendial dissolution testing should be performed.

[2] In the absence of an established in vitro/in vivo correlation.

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B-2 Delayed Release Solid Oral Dosage Forms Release Controlling Components and Composition

Level	Classification	Therapeutic range	Test documentation	Filing documentation
I	-<= 5% w/ w change based on total release controlling excipient (e.g., controlled release polymer, plasticizer) content -No other changes	All drugs	-Stability -Application/ compendial requirements -No biostudy	-Annual report
II	-Change in technical grade and/ or specifications -<= 10% w/ w change based on total release controlling excipient (e.g., controlled release polymer, plasticizer) content -No other changes	Non-narrow	-Notification & updated batch record -Stability -Application/ compendial requirements plus multi- point dissolution profiles in additional buffer stage testing (e.g., USP buffer media at pH 4.5–7.5) under standard and increased agitation conditions until >= 80% of drug released or an asymptote is reached[1] -Apply some statistical test (F2 test) for comparing dissolution profiles[2] -No biostudy	-Prior approval supplement
		Narrow	-Updated batch record -Stability -Application/ compendial (profile) requirements -Biostudy or IVIVC[1]	-Prior approval supplement
III	->10% w/ w change based on total release controlling excipient (e. g., controlled release polymer, plasticizer) content	All drugs	-Updated batch record & stability -Application/ compendial (profile) requirements -Biostudy or IVIVC[1]	-Prior approval supplement

[1] In the presence of an established in vitro/in vivo correlation only application/ compendial dissolution testing should be performed.

[2] In the absence of an established in vitro/in vivo correlation.

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B-3 Delayed Release Solid Oral Dosage Forms Site Change

Level	Classification	Therapeutic range	Test documentation	Filing documentation
I	-Single facility -Common personnel -No other changes	All drugs	-Application/ compendial requirements -No biostudy	-Annual report
II	-Same contiguous campus -Common personnel -No other changes	All drugs	-Identification and description of site change, and updated batch record -Notification of site change -Stability -Application/ compendial requirements plus multi- point dissolution profiles in additional buffer stage testing (e.g., USP buffer media at pH 4.5–7.5) under standard and increased agitation conditions until >= 80% of drug released or an asymptote is reached[1] -Apply some statistical test (F2 test) for comparing dissolution profiles[2] -No biostudy	-Changes being effected supplement
III	-Different campus -Different personnel	All drugs	-Notification of site change -Updated batch record stability -Application/ compendial (profile) requirements -Biostudy or IVIVC[1]	-Prior approval supplement

[1] In the presence of an established in vitro/in vivo correlation only application/ compendial dissolution testing should be performed.

[2] In the absence of an established in vitro/in vivo correlation.

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B-4 Delayed Release Solid Oral Dosage Forms Scale-up/ Scale-down

Level	Classification	Change	Test documentation	Filing documentation
I	-Scale- up of bio-batch(s) or pivotal clinical batch(s) -No other changes	<= 10X (All drugs)	-Updated batch record -Stability -Application/ compendial requirements -No biostudy	-Annual report
II	-Scale- up of bio-batch(s) or pivotal clinical batch(s) -No other changes	> 10X (All drugs)	-Updated batch record -Stability -Application/ compendial requirements plus multi-point dissolution profiles in additional buffer stage testing (e.g., USP buffer media at pH 4.5–7.5) under standard and increased agitation conditions until >= 80% of drug released or an asymptote is reached[1] -Apply some statistical test (F2 test) for comparing dissolution profiles[2] -No biostudy	-Changes being effected supplement

[1] In the presence of an established in vitro/in vivo correlation only application/ compendial dissolution testing should be performed.

[2] In the absence of an established in vitro/in vivo correlation.

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B-5 Delayed Release Solid Oral Dosage Forms Manufacturing—Equipment

Level	Classification	Change	Test documentation	Filing documentation
I	-Equipment changes -No other changes (All drugs)	-Alternate equipment of same design and principle -Automated equipment	-Updated batch record -Stability -Application/ compendial requirements -No biostudy	-Annual report
II	-Equipment changes -No other changes (All drugs)	-Change to equipment of a different design and operating principle	-Updated batch record -Stability -Application/ compendial requirements plus multi-point dissolution profiles in additional buffer stage testing (e.g., USP buffer media at pH 4.5–7.5) under standard and increased agitation conditions until >= 80% of drug released or an asymptote is reached[1] -Apply some statistical test (F2 test) for comparing dissolution profiles[2] -No biostudy	-Prior approval supplement

[1] In the presence of an established in vitro/in vivo correlation only application/ compendial dissolution testing should be performed.
[2] In the absence of an established in vitro/in vivo correlation.

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B-6 Delayed Release Solid Oral Dosage Forms Manufacturing—Processing

Level	Classification	Change	Test documentation	Filing documentation
I	-Processing changes affecting the non- release controlling excipients and/ or the release conrolling excipients -No other changes	-Adjustment of equipment operating conditions (e.g., mixing times, operating speeds, etc.) -Within approved application ranges	-Updated batch record -Application/ compendial requirements -No biostudy	-Annual report
II	-Processing changes affecting the non- release controlling excipients and/ or the release controlling excipients -No other changes	-Adjustment of equipment operating conditions (e.g., mixing times, operating speeds, etc.) -Beyond approved application ranges	-Updated batch record -Stability -Application/ compendial requirements plus multi-point dissolution profiles in additional buffer stage testing (e.g., USP buffer media at pH 4.5–7.5) under standard and increased agitation conditions until >= 80% of drug released or an asymptote is reached[1] -Apply some statistical test (F2 test) for comparing dissolution profiles[2] -No biostudy	-Changes being effected supplement
III	-Processing changes affecting the non- release controlling excipients and/ or the release controlling excipients	-Change in the type of process used (e.g., from wet granulation to direct compression)	-Updated batch record -Stability -Application/ compendial (profile) requirements -Biostudy or IVIVC[1]	-Prior approval supplement

[1] In the presence of an established in vitro/in vivo correlation only application/ compendial dissolution testing should be performed.

[2] In the absence of an established in vitro/in vivo correlation.

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Appendix C

Guidance for Industry[1]— SUPAC-IR/MR: Immediate Release and Modified Release Solid Oral Dosage Forms

Manufacturing Equipment Addendum

I. INTRODUCTION

The purpose of this guidance is to provide recommendations to pharmaceutical manufacturers using the Center for Drug Evaluation and Research's *Guidance for Industry: Immediate Release Solid Oral Dosage Forms—Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (SUPAC-IR), which published in November 1995, and *Guidance for Industry: SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentatio*n, which published in October 1997. This document was developed by the U.S. Food and Drug Administration (FDA) with the assistance of the International Society of Pharmaceutical Engineering (ISPE). This docu-

[1] This guidance has been prepared by the Immediate Release Scale-up and Post Approval Change (SUPAC) Expert Working Group of the Chemistry Manufacturing Controls Coordinating Committee (CMC CC) of the Center for Drug Evaluation and Research at the Food and Drug Administration. This guidance is an informal communication under 21 CFR 10.90(b)(9) that reflects the best judgment of CDER employees at this time. It does not create or confer any rights, privileges or benefits for or on any person, nor does it operate to bind or obligate FDA in any way. For additional copies of this guidance contact the Consumer Affairs Branch (formerly the Executive Secretariat Staff), HFD-8, Center for Drug Evaluation and Research, 7500 Standish Place, Rockville, MD 20855 (Phone: 301-594-1012). An electronic version of this guidance is also available via Internet by connecting to the CDER file transfer protocol (FTP) server (CDVS2.CDER.FDA.GOV).

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ment extends and supersedes the Manufacturing Equipment Addendum published in October 1997 that covered only immediate release solid oral dosage forms. The scope of this document is limited to only changes of equipment. If changes in components and composition, site, scale, or process occur in addition to the equipment change, then this should be considered a multiple change under SUPAC-IR and SUPAC-MR. For modified release solid oral dosage forms, consideration should be given as to whether or not the change in manufacturing equipment is critical to drug release (critical equipment variable).

The document should be used in conjunction with the SUPAC-IR and SUPAC-MR guidance documents in determining what documentation should be submitted to FDA regarding equipment changes made in accordance with the recommendations in these guidance documents. The SUPAC guidance documents define (1) levels of change; (2) recommended chemistry, manufacturing, and controls tests for each level of change; (3) in vitro dissolution tests and/or in vivo bioequivalence tests for each level of change; and (4) documentation that should support the change for new drug applications (NDAs) and abbreviated new drug applications (ANDAs). This document is only an aid and, in some cases, specific equipment may not be listed. It does, however, include a representative list of equipment commonly used in the industry. The guidance does not address equipment that has been modified by a pharmaceutical manufacturer to fit its specific needs. If questions arise in using this guidance document please contact the appropriate reviewing office at CDER.

Although this guidance does not discuss validation, any equipment changes should be validated in accordance with current good manufacturing practices (cGMPs) and the resulting data will be subject to examination by field investigators during routine GMP inspections. The information is presented in broad categories of unit operation (blending and mixing, drying, particle size reduction/separation, granulation, unit dosage, coating and printing, soft gelatin capsule encapsulation). Definitions and classification are provided. For each operation, a table is presented that categorizes equipment by class (operating principle) and subclass (design characteristic). Examples are given within the subclasses.

Equipment within the same class and subclass would be considered to have the same design and operating principle under SUPAC-IR and SUPAC-MR. Therefore, for example, a change from one type of diffusion mixer (e.g, V-blender from manufacturer A) to another diffusion mixer (e.g., V-blender from manufacturer B) generally would not represent a change in operating principle and would, therefore, be considered to be the same under either SUPAC-IR or SUPAC-MR.

A change from equipment in one class to equipment in a different class would usually be considered a change in design and operating principle. For example, a change from a V-blender to a ribbon blender demonstrates a change in the operating principle from diffusion blending to convection blending and would be considered to be different under either SUPAC-IR or SUPAC-MR.

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Applicants should carefully consider and evaluate on a case-by-case basis changes in equipment that are in the same class, but different subclass. In many situations, this type of change in equipment would be considered similar. For example, within the Blending and Mixing section, under the Diffusion Mixers Class, a change from a V-blender (sub-class) to a Bin tumbler (sub-class) represents a change within a class and between sub-classes. Provided the manufacturing process with the new equipment is validated, this change would likely not need a preapproval supplement. The applicant should have available at the time of the change the scientific data and rationale used to make this determination. This information is subject to FDA review at its discretion. It is up to the applicant to determine the filing requirement.

This guidance will be updated as needed to reflect the introduction and discontinuation of specific types of manufacturing equipment. Manufacturers of equipment are encouraged to help keep the document current by communicating changes to the Agency and by making suggestions regarding what equipment should be considered to be within the same class or subclass. The submitted information will be reviewed by FDA and incorporated in an updated guidance document as appropriate.

II. PARTICLE SIZE REDUCTION/SEPARATION

A. Definitions

1. Unit Operations

a. Particle Size Reduction. The mechanical process of breaking particles into smaller pieces via one or more particle size reduction mechanisms. The mechanical process used generally is referred to as milling.

i. Particle - Refers to either a discrete particle or a grouping of particles, generally known as an agglomerate.

ii. Particle Size Reduction Mechanisms

- Impact - Particle size reduction by applying an instantaneous force perpendicular to the particle/agglomerate surface. The force can result from particle-to-particle or particle-to-mill surface collision.
- Attrition - Particle size reduction by applying a force in a direction parallel to the particle surface.
- Compression - Particle size reduction by applying a force slowly (as compared to Impact) to the particle surface in a direction toward the center of the particle.
- Cutting - Particle size reduction by applying a shearing force to a material.

b. Particle Separation. Particle size classification according to particle size alone.

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Table 1 Unit Operation—Particle Size Reduction

Class	Subclass	Examples
Fluid Energy Mills	Tangential Jet	Alpine (Hosokawa) Fluid Energy Aljet Jetpharma Sturtevant
	Loop/Oval	Fluid Energy Aljet
	Opposed Jet	Garlock
	Opposed Jet with Dynamic Classifier Alpine (Hosokawa)	Fluid Energy Aljet
	Fluidized Bed	None Identified
	Fixed Target	None Identified
	Moving Target	None Identified
Impact Mills	Hammer Air Swept	Alpine (Hosokawa) Bepex (Hosokawa) Sturtevant
	Hammer Conventional	Alpine (Hosokawa) Fitzpatrick Fluid Air Mikro (Hosokawa) Rietz (Hosokawa) Stokes-Merrill
	Pin/Disc	Alpine (Hosokawa) Kemutec Sturtevant
	Cage	Stedman
Cutting Mills	None Identified	Alpine (Hosokawa) Fitzpatrick Urschel
Compression Mills	None Identified	MCA International
Screening Mills	Rotating Impeller	Bepex (Hosokawa) Fitzpatrick Fluid Air Jetpharma Kemutec Quadro Stokes-Merrill Zanchetta (Romaco)
	Rotating Screen	Glatt
	Oscillating Bar	Bepex (Hosokawa) Frewitt Jackson-Crockatt Stokes-Merrill Vector
Tumbling Mills	Ball Media	US Stoneware
	Rod Media	None Identified
	Vibrating	Sweco

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2. Operating Principles

a. Fluid Energy Milling. Particles are reduced in size as a result of high-speed particle-to-particle impact and/or attrition; also known as micronizing.

b. Impact Milling. Particles are reduced in size by high-speed mechanical impact or impact with other particles; also known as milling, pulverizing, or comminuting.

c. Cutting. Particles are reduced in size by mechanical shearing.

d. Compression Milling. Particles are reduced in sized by compression stress and shear between two surfaces.

e. Screening. Particles are reduced in size by mechanically induced attrition through a screen. This process commonly is referred to as milling or deagglomeration.

f. Tumble Milling. Particles are reduced in size by attrition utilizing grinding media.

g. Separating. Particles are segregated based upon particle size alone and without any significant particle size reduction. This process commonly is referred to as screening or bolting.

B. Equipment Classifications

1. Fluid Energy Mills

Fluid energy mill subclasses have no moving parts and primarily are distinguished from one another by the configuration and/or shape of their chambers, nozzles, and classifiers.

- Tangential Jet
- Loop/Oval
- Opposed Jet
- Opposed Jet with Dynamic Classifier
- Fluidized Bed
- Fixed Target
- Moving Target

2. Impact Mills

Impact mill subclasses primarily are distinguished from one another by the configuration of the grinding heads, chamber grinding liners (if any), and classifiers.

- Hammer Air Swept
- Hammer Conventional

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- Pin/Disc
- Cage

3. Cutting Mills

Although cutting mills may differ from one another in whether the knives are movable or fixed and in the classifier configuration, no cutting mill subclasses have been identified.

4. Compression Mills

Although compression mills may differ from one another in whether one or both surfaces are moving, no compression mill subclasses have been identified.

5. Screening Mills

Screening mill subclasses primarily are distinguished from one another by the rotating element.

- Rotating Impeller
- Rotating Screen
- Oscillating Bar

6. Tumbling Mills

Tumbling mill subclasses primarily are distinguished from one another by the grinding media used and by whether the mill is vibrated.

- Ball Media
- Rod Media
- Vibrating.

Table 2 Unit Operation—Separation

Class	Subclass	Examples
Separators	Vibratory/Shaker	Allgaier
		McLanahan
		Rotex
		Russell Finex
		Sweco
		VortiSiv
	Centrifugal	AZO
		Kason
		Kemutec
		Sweco

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7. Separators

Separator subclasses primarily are distinguished from one another by the mechanical means used to induce particle movement.

- Vibratory/Shaker
- Centrifugal

III. BLENDING AND MIXING

A. Definitions

1. Unit Operations

Blending and Mixing: The reorientation of particles relative to one another in order to achieve uniformity.

2. Operating Principles

a. Diffusion Blending (Tumble). Particles are reoriented in relation to one another when they are placed in random motion and interparticular friction is reduced as the result of bed expansion (usually within a rotating container); also known as tumble blending.

b. Convection Mixing. Particles are reoriented in relation to one another as a result of mechanical movement; also known as paddle or plow mixing.

c. Pneumatic Mixing. Particles are reoriented in relation to one another as a result of the expansion of a powder bed by gas.

B. Equipment Classifications

1. Diffusion Mixers (Tumble)

Diffusion mixer subclasses primarily are distinguished by geometric shape and the positioning of the axis of rotation.

- V-blenders
- Double Cone Blenders
- Slant Cone Blenders
- Cube Blenders
- Bin Blenders
- Horizontal/Vertical/Drum Blenders
- Static Continuous Blenders
- Dynamic Continuous Blenders

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Table 3 Unit Operation—Blending and Mixing

Class	Subclass	Examples
Diffusion Mixers (Tumble)	V-Blenders	Aaron
		Paul O. Abbe
		Gemco
		Jaygo
		Kemutec
		Lleal
		Lowe
		O'Hara
		Patterson-Kelley
		Pneuvac
		Zanchetta (Romaco)
	Double Cone Blenders	Aaron
		Paul O. Abbe
		Gemco
		Jaygo
		Kemutec
		Lleal
		Lowe
		MO Industries
		Patterson- Kelley
		Pneuvac
		ServoLift
		Zanchetta (Romaco)
	Slant Cone Blenders	Gemco
		Lleal
		Patterson-Kelley
	Cube Blenders	Lightnin
		ServoLift
		Zanchetta (Romaco)
	Bin Blenders	Paul O. Abbe
		L. B. Bohle
		Cora International
		CONSEP
		Creative Design & Machine
		Custom Metal Craft
		GEI-Gallay (GEI International/Patriot)
		Gemco
		Glatt
		Jenike & Johanson
		Kemutec
		Matcon, USA

Table 3 Continued.

Class	Subclass	Examples
		Scholl (MO Industries)
		ServoLift
		Tote Systems
		Zanchetta (Romaco)
	Horizontal/Vertical/Drum Blenders	Munson Mill Machinery
	Static Continuous Blenders	Ross
	Dynamic Continuous Blenders	Patterson-Kelley
Convection Mixers	Ribbon Blenders	Aaron
		Paul O. Abbe
		Automatic Industry Machines
		Azo-Ruberg
		Custom Metal Craft
		Jaygo
		Kemutec
		Lowe
		Pneuvac
		Ross
		Vrieco-Nauta (Hosokawa)
	Orbiting Screw Blenders	Aaron
		Jaygo
		Littleford Day
		Ross
		Vrieco-Nauta (Hosokawa)
	Planetary Blenders	Aaron
		Aeschbach
		AMF
		GEI-Collette (GEI International)
		Hobart
		Jaygo
		Littleford Day
		Ross
		Vrieco
	Forberg Blenders	Paul O. Abbe
		Dynamic Air
	Horizontal Double Arm Blenders	Aaron
		Paul O. Abbe
		Custom Metal Craft
		Dynamic Air

(Continued)

Table 3 Continued.

Class	Subclass	Examples
		Jaygo
		Kemutec
		Littleford Day
		Ross
		Sigma
		Teledyne Readco
	Horizontal High Intensity Mixers (Side Driven)	Littleford Day
		Lodige
		Processall
	Vertical High Intensity Mixers (Top or Bottom Driven)	Aeromatic-Fielder (GEA-Niro)
		APV
		Baker-Perkins
		L.B. Bohle
		Dierks & Shone
		Diosna (Fluid Air)
		GEI-Collette (GEI International)
		Key International
		Littleford Day
		Lodige
		Powrex (Glatt)
		Processall
		Werner & Pfeiderer
		Zanchetta (Romaco)
	Diffusion Mixers (Tumble) with Intensifier/Agitator	Paul O. Abbe
		Gemco
		Patterson-Kelley
Pneumatic Mixers	None Identified	Dynamic Air
		Reimelt.

2. Convection Mixers

Convection blender subclasses primarily are distinguished by vessel shape ad impeller geometry:

- Ribbon Blenders
- Orbiting Screw Blenders
- Planetary Blenders
- Forberg Blenders
- Horizontal Double Arm Blenders

- Horizontal High Intensity Mixers
- Vertical High Intensity Mixers
- Diffusion Mixers (Tumble) with Intensifier/Agitator

3. Pneumatic Mixers

Although pneumatic mixers may differ from one another in vessel geometry, air nozzle type, and air nozzle configuration, no pneumatic mixer subclasses have been identified.

IV. GRANULATION

A. Definitions

1. Unit Operations

Granulation: The process of creating granules. The powder morphology is modified through the use of either a liquid that causes particles to bind through capillary forces or dry compaction forces. The process will result in one or more of the following powder properties: enhanced flow; increased compressibility; densification; alteration of physical appearance to more spherical, uniform, or larger particles; and/or enhanced hydrophilic surface properties.

2. Operating Principles

a. Dry Granulation. Dry powder densification and/or agglomeration by direct physical compaction.

b. Wet High-Shear Granulation. Powder densification and/or agglomeration by the incorporation of a granulation fluid into the powder with high-power-per-unit mass, through rotating high-shear forces.

c. Wet Low-Shear Granulation. Powder densification and/or agglomeration by the incorporation of a granulation fluid into the powder with low-power-per-unit mass, through rotating low-shear forces.

d. Low-Shear Tumble Granulation. Powder densification and/or agglomeration by the incorporation of a granulation fluid into the powder with low-power-per-unit mass, through rotation of the container vessel and/or intensifier bar.

e. Extrusion Granulation. Plasticization of solids or wetted mass of solids and granulation fluid with linear shear through a sized orifice using a pressure gradient.

f. Rotary Granulation. Spheronization, agglomeration, and/or densification of a wetted or non-wetted powder or extruded material. This is accom-

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Table 4 Unit Operation—Granulation

Class	Subclass	Examples
Dry Granulator	Slugging	*Various*
	Roller Compaction	Alexanderwerk
		Bepex (Hosokawa)
		Fitzpatrick
		Freund
		Vector
Wet High-Shear Granulator	Horizontal (Side Driven)	Littleford Day
		Lodige
		Processall
	Vertical (Top or Bottom Driven)	Aeromatic-Fielder (GEA-Niro)
		APV
		Baker-Perkins
		L.B. Bohle
		Dierks & Shone
		Diosna (Fluid Air)
		GEI-Collette (GEI International)
		Key International
		Littleford Day
		Lodige
		Powrex (Glatt)
		Processall
		Werner & Pfeiderer
		Zanchetta (Romaco)
Wet Low-Shear Granulator	Planetary	Aaron
		Aeschbach
		AMF
		GEI-Collette (GEI International)
		Hobart
		Jaygo
		Littleford Day
		Ross
		Vrieco
	Kneading	Aaron
		Paul O. Abbe
		Custom Metal Craft
		Dynamic Air
		Jaygo
		Kemutec
		Littleford Day

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Table 4 Continued.

Class	Subclass	Examples
		Processall
		Ross
		Sigma
		Teledyne Readco
	Screw	Vrieco-Nauta (Hosokawa)
Low-Shear Tumble Granulator	Slant Cone, or Double Cone, or V-Blender	Paul O. Abbe
		Gemco
		Patterson-Kelley
Extrusion Granulator	Radial or Basket	Alexanderwerk
		GEA Niro
		LCI
		Luwa
		Ross
	Axial	Bepex (Hosokawa)
		Gabler
		LCI
	Ram	LCI
	Roller, Gear, or Pelletizer	Alexanderwerk
		Bepex (Hosokawa)
Rotary Granulator	Open	Freund (Vector)
		GEA Niro
		LCI
		Luwa
	Closed	Aeromatic-Fielder (GEA Niro)
		Glatt
		LCI
		Processall
		Vector
Fluid Bed Granulator	None Identified	Aeromatic-Fielder (GEA Niro)
		APV
		BWI Hüttlin (Thomas Engineering)
		Diosna
		Fitzpatrick
		Fluid Air
		Glatt
		Heinen
		Vector
Spray Dry Granulator	None Identified	Allgaier
		GEA Niro
		Glatt
		Heinen

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plished by centrifugal or rotational forces from a central rotating disk, rotating walls, or both. The process may include the incorporation and/or drying of a granulation fluid.

g. Fluid Bed Granulation. Powder densification and/or agglomeration with little or no shear by direct granulation fluid atomization and impingement on solids, while suspended by a controlled gas stream, with simultaneous drying.

h. Spray Dry Granulation. A pumpable granulating liquid containing solids (in solution or suspension) is atomized in a drying chamber and rapidly dried by a controlled gas stream, producing a dry powder.

B. Equipment Classification

1. Dry Granulator

Dry granulator subclasses primarily are distinguished by the densification force application mechanism.

- Slugging
- Roller Compaction

2. Wet High-Shear Granulator

Wet high-shear granulator subclasses primarily are distinguished by the geometric positioning of the primary impellers; impellers can be top, bottom, or side driven.

- Vertical (Top or Bottom Driven)
- Horizontal (Side Driven)

3. Wet Low-Shear Granulator

Wet low-shear granulator subclasses primarily are distinguished by the geometry and design of the shear inducing components; shear can be induced by rotating impeller, reciprocal kneading action, or convection screw action.

- Planetary
- Kneading
- Screw

4. Low-Shear Tumble Granulator

Although low-shear tumble granulators may differ from one another in vessel geometry and type of dispersion or intensifier bar, no low-shear tumble granulator subclasses have been identified.

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5. Extrusion Granulator

Extrusion granulator subclasses primarily are distinguished by the orientation of extrusion surfaces and driving pressure production mechanism.

- Radial or Basket
- Axial
- Ram
- Roller, Gear, or Pelletizer

6. Rotary Granulator

Rotary granulator subclasses primarily are distinguished by their structural architecture. They have either open top architecture, such as a vertical centrifugal spheronizer, or closed top architecture, such as a closed top fluid bed dryer.

- Open
- Closed

7. Fluid Bed Granulator

Although fluid bed granulators may differ from one another in geometry, operating pressures, and other conditions, no fluid bed granulator subclasses have been identified.

8. Spray Dry Granulator

Although spray dry granulators may differ from one another in geometry, operating pressures, and other conditions, no spray dry granulator subclasses have been identified.

Note: If a single piece of equipment is capable of performing multiple discrete unit operations (mixing, granulating, drying), the unit was evaluated solely for its ability to granulate. If multifunctional units were incapable of discrete steps (fluid bed granulator/drier), the unit was evaluated as an integrated unit.

V. DRYING

A. Definitions

1. Unit Operation

Drying: The removal of a liquid from a solid by evaporation.

2. Operating Principles

a. Direct Heating, Static Solids Bed. Heat transfer is accomplished by direct contact between the wet solids and hot gases. The vaporized liquid is car-

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Table 5 Unit Operation—Drying

Class	Subclass	Examples
Direct Heating, Static Solids Bed	Tray and Truck	Colton Despatch Gruenberg Hot Pack Lydon O'Hara Proctor & Schwartz Trent
	Belt	Despatch Proctor & Schwartz
Direct Heating, Moving Solids Bed	Rotating Tray	Krauss Maffei Wyssmont
	Horizontal Vibrating Conveyor	Carrier Witte
Direct Heating, Fluidized Solids Bed (Fluid Bed Dryer)	None Identified	Aeromatic-Fielder (GEA-Niro) APV BWI Hüttlin (Thomas Engineering) Diosna Fitzpatrick Fluid Air Glatt Heinen Vector
Direct Heating, Dilute Solids Bed, Spray Dryer	None Identified	Allgaier APV BWI Hüttlin (Thomas Engineering) GEA-Niro Glatt
Direct Heating, Dilute Solids Bed, Flash Dryer	None Identified	Allgaier APV GEA-Niro Micron (Hosokawa)
Indirect Conduction, Moving Solids Bed	Paddle	Bepex (Hosokawa) Jaygo Littleford Day Processall
	Rotary (Tumble)	Paul O. Abbe Gemco Glatt

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Table 5 Continued.

Class	Subclass	Examples
		Littleford Day
		Patterson-Kelley
		Processall
		Zanchetta (Romaco)
	Agitation	L. B. Bohle
		Diosna
		GEI-Collette (GEI International)
		Krauss-Maffei
		Processall
		Vrieco-Nauta (Hosokawa)
		Zanchetta (Romaco)
Indirect Conduction, Static Solids Bed	None Identified	Hull
Indirect Conduction, Lyophilization	None Identified	Amsco
		Hull
		Serail
		Stokes
Gas Stripping	None Identified	Aeromatic-Fielder (GEA-Niro)
		L.B. Bohle
		Diosna (Fluid Air)
		GEI-Collette (GEI International)
		Processall
		Zanchetta (Romaco)
Indirect Radiant Heating, Moving Solids Bed (Microwave Dryer)	None Identified	Aeromatic-Fielder (GEA-Niro)
		L. B. Bohle
		Diosna
		GEI-Collette (GEI International)

ried away by the drying gases. There is no relative motion among solid particles. The solids bed exists as a dense bed, with the particles resting upon one another.

b. Direct Heating, Moving Solids Bed. Heat transfer is accomplished by direct contact between the wet solids and hot gases. The vaporized liquid is carried away by the drying gases. Solids motion is achieved by either mechanical agitation or gravity force, which slightly expands the bed enough to flow one particle over another.

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c. Direct Heating, Fluidized Solids Bed. Heat transfer is accomplished by direct contact between the wet solids and hot gases. The vaporized liquid is carried away by the drying gases. The solids are in an expanded condition, with the particles supported by drag forces caused by the gas phase. The solids and gases intermix and behave like a boiling liquid. This process commonly is referred to as fluid bed drying.

d. Direct Heating, Dilute Solids Bed, Spray Drying. Heat transfer is accomplished by direct contact between a highly dispersed liquid and hot gases. The feed liquid may be a solution, slurry, emulsion, gel or paste, provided it is pumpable and capable of being atomized. The fluid is dispersed as fine droplets into a moving stream of hot gases, where they evaporate rapidly before reaching the wall of the drying chamber. The vaporized liquid is carried away by the drying gases. The solids are fully expanded and so widely separated that they exert essentially no influence on one another.

e. Direct Heating, Dilute Solids Bed, Flash Drying. Heat transfer is accomplished by direct contact between wet solids and hot gases. The solid mass is suspended in a finely divided state in a high-velocity and high-temperature gas stream. The vaporized liquid is carried away by the drying gases.

f. Indirect Conduction, Moving Solids Bed. Heat transfer to the wet solid is through a retaining wall. The vaporized liquid is removed independently from the heating medium. Solids motion is achieved by either mechanical agitation or gravity force, which slightly expands the bed enough to flow one particle over another.

g. Indirect Conduction, Static Solids Bed. Heat transfer to the wet solid is through a retaining wall. The vaporized liquid is removed independently from the heating medium. There is no relative motion among solid particles. The solids bed exists as a dense bed, with the particles resting upon one another.

h. Indirect Conduction, Lyophilization. Drying in which the water vapor sublimes from the product after freezing.

i. Gas Stripping. Heat transfer is a combination of direct and indirect heating. The solids motion is achieved by agitation and the bed is partially fluidized.

j. Indirect Radiant, Moving Solids Bed. Heat transfer is accomplished with varying wavelengths of energy. Vaporized liquid is removed independently from the solids bed. The solids motion is achieved by mechanical agitation, which slightly expands the bed enough to flow one particle over one another. This process commonly is referred to as microwave drying.

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B. Equipment Classifications

1. Direct Heating, Static Solids Bed

Static solids bed subclasses primarily are distinguished by the method of moving the solids into the dryer.

- Tray and Truck
- Belt

2. Direct Heating, Moving Solids Bed

Moving solids bed subclasses primarily are distinguished by the method or technology for moving the solids bed.

- Rotating Tray
- Horizontal Vibrating Conveyor

3. Direct Heating, Fluidized Solids Bed (Fluid Bed Dryer)

Although fluid bed dryers may differ from one another in geometry, operating pressures, and other conditions, no fluidized solids bed dryer subclasses have been identified.

4. Direct Heating, Dilute Solids Bed, Spray Dryer

Although spray dryers may differ from one another in geometry, operating pressures, and other conditions, no spray dryer subclasses have been identified.

5. Direct Heating, Dilute Solids Bed, Flash Dryer

Although flash dryers may differ from one another in geometry, operating pressures, and other conditions, no flash dryer subclasses have been identified.

6. Indirect Conduction Heating, Moving Solids Bed

Moving solids bed subclasses primarily are distinguished by the method or technology for moving the solids bed.

- Paddle
- Rotary (Tumble)
- Agitation

7. Indirect Conduction Heating, Static Solids Beds

No indirect heating, static solids bed shelf dryer subclasses have been identified.

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8. Indirect Conduction, Lyophilization

No lyophilizer subclasses have been identified.

9. Gas Stripping

Although gas stripping dryers may differ from one another in geometry, shape of agitator, and how fluidizing gas is moved through the bed, no gas stripping dryer subclasses have been identified.

10. Indirect Radiant Heating, Moving Solids Bed (Microwave Dryer)

Although microwave dryers may differ from one another in vessel geometry and the way microwaves are directed into the solids, no indirect radiant heating, moving solids bed dryer subclasses have been identified.

Note: If a single piece of equipment is capable of performing multiple discrete unit operations (mixing, granulating, drying), the unit was evaluated solely for its ability to dry. The drying equipment was sorted into similar classes of equipment, based upon the method of heat transfer and the dynamics of the solids bed.

VI. UNIT DOSING

A. Definitions

1. Unit Operation

Unit Dosing: The division of a powder blend into uniform single portions for delivery to patients.

2. Operating Principles

a. Tabletting. The division of a powder blend in which compression force is applied to form a single unit dose.

b. Encapsulating. The division of material into a hard gelatin capsule. Encapsulators should all have the following operating principles in common: rectification (orientation of the hard gelatin capsules), separation of capsule caps from bodies, dosing of fill material/formulation, rejoining of caps and bodies, and ejection of filled capsules.

c. Powder Filling. Division of a powder blend into a container closure system.

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Table 6 Unit Dosing

Class	Subclass	Examples
Tablet Press	Gravity	Colton (Vector)
		Manesty (Thomas Engineering)
		Stokes
	Power Assisted	Colton (Vector)
		Courtoy (AC Compacting)
		Fette
		Hata (Elizabeth Carbide)
		Kikusui
		Kilian
		Manesty (Thomas Engineering)
	Centrifugal	Comprima (IMA)
	Compression Coating	Manesty (Thomas Engineering)
		Kikusui
		Kilian
Encapsulator	Auger	Capsugel Type B
		Elanco No. 8
	Vacuum	Perry
	Vibratory	Osaka (Sharpley-Stokes)
	Dosing Disk	H&K/ Bosch
		Index
	Dosator	Macofar (Romaco)
		MG2
		Zanasi/Pharmatic/IMA
Powder Filler	Vacuum	Bosch
		Perry
		Zanasi
	Auger	All-Fill
		Calumatic

B. Equipment Classifications

1. Tablet Press

Tablet press subclasses primarily are distinguished from one another by the method that the powder blend is delivered to the die cavity. Tablet presses can deliver powders without mechanical assistance (gravity), with mechanical assistance (power assisted), by rotational forces (centrifugal), and in two different locations where a tablet core is formed and subsequently an outer layer of coating material is applied (compression coating).

- Gravity
- Power Assisted

- Centrifugal
- Compression Coating

2. Encapsulator

Encapsulator subclasses primarily are distinguished from one another by the method that is used for introducing material into the capsule.

Encapsulators can deliver materials with a rotating auger, vacuum, vibration of perforated plate, tamping into a bored disk (dosing disk), or cylindrical tubes fitted with pistons (dosator).

- Auger
- Vacuum
- Vibratory
- Dosing Disk
- Dosator

3. Powder Filler

Subclasses of powder fillers primarily are distinguished by the method used to deliver the predetermined amount for container fill.

- Vacuum
- Auger

VII. SOFT GELATIN CAPSULES

A. Definitions

1. Unit Operations

a. Gel Mass Preparation. The manufacture of a homogeneous, degassed liquid mass (solution) of gelatin, plasticizer, water, and other additives, either in solution or suspension, such as colorants, pigments, flavors, preservatives, etc., that comprise a unique functional gel shell formation. The operation may be performed in discreet steps or by continuous processing. Minor components can be added after the liquid gel mass is made.

b. Fill Mixing. The mixing of either liquids or solids with other liquids to form a solution; blending of limited solubility solid(s) with a liquid carrier and suspending agents used to stabilize the blend to form a suspension; or the uniform combination of dry inert and drug active substances to form a dry powder fill suitable for encapsulation. The reader should refer to the other sections of this document for dry fill manufacture.

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Table 7 Unit—Soft Gelatin Capsules

Class	Subclass	Examples
Mixers and Mixing Vessels	Low Energy	GEI-Collette (GEI International)
		GEI-Kreiger (GEI International)
		Hobart
		Koruma (Romaco)
		Lightnin
		Moorhouse-Cowles
		Quadro
	High Energy	Cowles
		GEI-Collette (GEI International)
		Koruma (Romaco)
	Planetary	Aaron
		Aeschbach
		AMF
		GEI-Collette (GEI International)
		Hobart
		Jaygo
		Littleford Day
		Ross
		Vrieco
	Jacketed with and without Vacuum	Becomix
		Fryma
		GEI-Kreiger (GEI International)
		Hicks
		Lee Industries
		Paul Mueller Co.
		Ross
		Koruma (Romaco)
	Conventional	Lee Industries
Deaggregators	Rotor Stator	Barinco
		Greerco
		Koruma (Romaco)
	Roller	Stokes-Merrill
	Cutting Mills	Alpine(Hosokawa)
		Fitzpatrick
		Urschel
	Stone Mills	Fryma
		Koruma (Romaco)

(Continued)

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Table 7 Continued.

Class	Subclass	Examples
	Tumbling Mills	Paul O. Abbe
		Fryma
		Premier Corp.
		U.S. Stoneware
Deaerators	Vacuum Vessel	Fryma
		GEI-Kreiger (GEI International)
		Koruma (Romaco)
		Lee Industries
		Paul Mueller Co.
		Processall
	Off Line/In Line	The Cornell Machine Co.
		Fryma
		Koruma (Romaco)
Holding Vessels	Jacketed Vessel with and without Mixing System	GEI-Kreiger (GEI International)
		Koruma (Romaco)
		Lee Industries
Encapsulators	Positive Displacement Pump	Chang Sung
		Gaberino International Consultants
		Higuchi, Inc. USA
		Hypak Industries
		In House Construction
		J.B. Engineering
		Technopar Equipment & Svcs., Ltd
	Gravity or Force Feed	Accogel® (Stern Machine)
Inspection/Sorting	Belt	Lakso
		Merrill
	Vibratory	Stokes
	Roller	Maschimpex
	Rotary Table	Lakso
		Merrill
	ElectroMechanical	Mocon

c. Core Enrobing. The gelatin coating of gravity or force fed pre-formed tablets or caplets.

d. Encapsulation. The continuous casting of gel ribbons, with liquid fill material being injected between the gel ribbons using a positive displacement

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pump or, for dry materials being gravity or force fed with capsule formation using a rotary die.

e. Washing. The continuous removal of a lubricant material from the outside of the formed capsule. The washing operation is unique to each manufacturer's operation and generally uses in-house fabricated equipment. This equipment will not be discussed in this guidance document.

f. Drying. The removal of the majority of water from the capsule's gel shell by tumbling and subsequent tray drying using conditioned air, which enhances the size, shape, and shell physical properties of the final product. The drying operation is unique to each manufacturer's operation and generally uses in-house fabricated equipment. This equipment will not be discussed in this guidance document.

g. Inspection/Sorting. The process wherein undesirable capsules are removed, including misshapen, leaking, and unfilled capsules as well as agglomerates of capsules.

h. Printing. The marking of a capsule surface for the purpose of product identification, using a suitable printing media or method.

2. Operating Principles

a. Mixing. The combination of solid and liquid components, including suspending aid(s) at either ambient or elevated temperatures to form a solution, suspension, or dry powder blend for the manufacture of gel mass or fill material. Mixing also includes the incorporation of minor components into the liquid gel mass.

b. Deaggregation. The removal of aggregates using a suitable homogenizer/mill to provide a pumpable fill material. The procedure has minimal effect on the particle size distribution of the initial solid component(s), and is viewed as a processing aid.[2]

c. Deaeration. The removal of entrapped air from either the gel mass or fill material, solution or suspension. This process can take place in either the mixing vessel, through the application of vacuum, or a separate off-line step.

d. Holding. The storage of liquid gel mass or fill material in a vessel, with a mixer or without, prior to encapsulation, which also may be equipped with a jacket for either heating or cooling.

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[2] Carstensen, J. T., "Theory of Pharmaceutical Systems, Volume 11 Heterogeneous Systems," *Academic Press*, New York, NY, 1973, p 51.

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e. Encapsulation. The formation of capsules using a rotary die machine.[3]

f. Inspection/Sorting. The physical removal of misshapen, leaking, or agglomerated capsules, using either a manual or automatic operation.

g. Printing. The user of this document is asked to refer to the coating/printing section, in which the use of various pieces of equipment are defined and categorized.

B. Equipment Classifications

1. Mixers and Mixing Vessels

Mixer and mixing vessel subclasses primarily are distinguished by the mixing energy, mixer type, and whether a jacketed vessel with vacuum capabilities is used in conjunction with a specific mixer.

- Low Energy Mixer
- High Energy Mixer
- Planetary
- Jacketed Vessel With and Without Vacuum
- Conventional

2. Deaggregators

Deaggregator subclasses primarily are distinguished by the type of mechanical action imparted to the material.

- Rotor/Stator
- Roller
- Cutting Mills
- Stone Mills
- Tumbling Mills

3. Deaerators

Deaerator subclasses primarily are distinguished by the air removal path, either through the bulk or through a thin film, and whether it is a batch or in-line process.

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[3] Lachman, L., H. A. Lieberman, and J. L. Kanig (Eds.), *The Theory and Practice of Industrial Pharmacy*, Chapter 3, p. 359 (Stanley, J. P.), Philadelphia: Lea & Febiger, 1971.
Tyle, P. (Ed.), *Specialized Drug Delivery Systems, Manufacturing and Production Technology,* Chapter 10, p. 409 (Wilkinson, P.K.and F.S. Hom), New York: M. Dekker, 1990.
Porter, S., *Remington's Pharmaceutical Sciences*, Edition 18, Chapter 89, pp. 1662–1665, Easton, Penn.: Mack Publishing Co.

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- Vacuum Vessel
- Off Line/In Line

4. Holding Vessels

Although holding vessels may differ from one another, based upon whether they are jacketed, with and without integrated mixing capabilities, no holding vessel subclasses have beeen identified.

5. Encapsulators

Encapsulator subclasses primarily are distinguished by the method used to inject the fill material.

- Positive Displacement Pump
- Gravity or Force Fed

6. Inspection/Sorting

Inspection/sorting equipment subclasses primarily are distinguished by the method used to present the capsule for viewing and mechanical method of separation.

- Belt
- Vibratory
- Roller
- Rotary Table
- Electromechanical

VIII. COATING/PRINTING/DRILLING

A. Definitions

1. Unit Operation

a. Coating. The uniform deposition of a layer of material on or around a solid dosage form, or component thereof, to:

- protect the drug from its surrounding environment (air, moisture, and light), with a view to improving stability.
- mask unpleasant taste, odor, or color of the drug.
- increase the ease of ingesting the product for the patient.
- impart a characteristic appearance to the tablets, which facilitates product identification and aids patient compliance.
- provide physical protection to facilitate handling. This includes minimizing dust generation in subsequent unit operations.

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Table 8 Unit Operation—Coating Equipment

Class	Subclass	Examples
Pan Coating	Conventional Coating	Bruck
		System O'Hara
		Pellegrini
		Stokes-Merrill
	Perforated Coating System	BWI Hüttlin (Thomas Engineering)
		Driam
		Glatt
		GS Coating Systems
		Nicomac
		O'Hara
		Raymond
		Strunck
		Thomas Engineering
		Vector
Gas Suspension	Fluidized Bed	Aeromatic-Fielder (GEA Niro)
		BWI Hüttlin (Thomas Engineering)
		Fluid Air
		Glatt
		Vector
	Spray Congealing/Drying	Allgaier
		APV
		BWI Hüttlin (Thomas Engineering)
		GEA-Niro
		Glatt
Vacuum Film Coating	None Identified	Glatt
Dip Coating	None Identified	None Identified
Electrostatic Coating	None Identified	None Identified
Ink-Based Printing	Off Set	Ackley
		Hartnett
		Markem
		Takeda
	Ink Jet	Image
		Linx
Laser Etching (Printing)	None Identified	Lumonics

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- reduce the risk of interaction between incompatible components. This would be achieved by coating one or more of the offending ingredients.
- modify the release of drug from the dosage form. This includes delaying, extending, and sustaining drug substance release.

The coating material deposition typically is accomplished through one of four major techniques:

1. Sugar Coating - Deposition of coating material onto the substrate from aqueous solution/suspension of coatings, based predominately upon sucrose as a raw material.
2. Film Coating - The deposition of polymeric film onto the solid dosage form.
3. Microencapsulation - The deposition of a coating material onto a particle, pellet, granule, or bead core. The substrate in this application ranges in size from submicron to several millimeters. It is this size range that differentiates it from the standard coating described in 1 and 2 above.
4. Compression Coating (This topic is addressed in the Unit Dosing section.)

b. Printing. The marking of a capsule or tablet surface for the purpose of product identification. Printing may be accomplished by either the application of a contrasting colored polymer (ink) onto the surface of a capsule or tablet, or by the use of laser etching.

The method of application, provided the ink formulation is not altered, is of no consequence to the physical-chemical properties of the product.

c. Drilling. The drilling or ablating of a hole or holes through the polymeric film coating shell on the surfaces of a solid oral dosage form using a laser. The polymeric film shell is not soluble in vivo. The hole or holes allow for the modified release of the drug from the core of the dosage form.

2. Operating Principles

a. Pan Coating. The uniform deposition of coating material onto the surface of a solid dosage form, or component thereof, while being translated via a rotating vessel.

Table 9 Unit Operation—Drilling Equipment

Class	Subclass	Examples
Laser Drilling	None Identified	Convergent Energies Coherent The Automation Partner Lumonics

b. Gas Suspension. The application of a coating material onto a solid dosage form, or component thereof, while being entrained in a process gas stream. Alternatively, this may be accomplished simultaneously by spraying the coating material and substrate into a process gas stream.

c. Vacuum Film Coating. This technique uses a jacketed pan equipped with a baffle system. Tablets are placed into the sealed pan, an inert gas (i.e., nitrogen) is used to displace the air and then a vacuum is drawn.

d. Dip Coating. Coating is applied to the substrate by dipping it into the coating material. Drying is accomplished using pan coating equipment.

e. Electrostatic Coating. A strong electrostatic charge is applied to the surface of the substrate. The coating material containing oppositely charged ionic species is sprayed onto the substrate.

f. Compression Coating. Refer to the Unit Dosing section of this document.

g. Ink-Based Printing. The application of contrasting colored polymer (ink) onto the surface of a tablet or capsule.

h. Laser Etching. The application of identifying markings onto the surface of a tablet or capsule using laser-based technology.

i. Drilling. A drilling system typically is a custom built unit consisting of a material handling system to orient and hold the solid dosage form, a laser (or lasers), and optics (lenses, mirrors, deflectors, etc.) to ablate the hole or holes, and controls. The drilling unit may include debris extraction and inspection systems as well. The sorting, orienting, and holding equipment commonly is provided by dosage form printing equipment manufacturers, and is considered ancillary in this use.

B. Equipment Classification

1. Pan Coating

Pan coating subclasses primarily are distinguished by the pan configuration, the pan perforations, and/or the perforated device used to introduce process air for drying purposes. Perforated coating systems include both batch and continuous coating processes.

- Conventional Coating System
- Perforated Coating System

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2. Gas Suspension

Gas suspension subclasses primarily are distinguished by the method by which the coating is applied to the substrate.

- Fluidized Bed
- Spray Congealing/Drying

3. Vacuum Film Coating

Although there may be differences in the jacketed pan, baffle system, or vacuum source, no vacuum film coating subclasses have been identified.

4. Dip Coating

Because of the custom design associated with this class of coating, no dip coating subclasses or examples have been identified.

5. Electrostatic Coating

Because of the custom design associated with this class of coating, no electrostatic coating subclasses or examples have been identified.

6. Compression Coating

Refer to the Unit Dosing section of this document.

7. Ink-Based Printing

Ink-based printing subclasses primarily are distinguished by the method by which the marking is applied to a capsule or tablet surface.

- Offset
- Ink Jet

8. Laser Etching (Printing)

Although laser etching systems may differ from one another, no laser etching subclasses have been identified.

9. Drilling

The method of producing the laser pulse that ablates the hole(s) is of no consequence to the physical-chemical properties of the product. Therefore, no dosage form drilling equipment subclasses have been identified.

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Appendix D

Guidance for Industry[1]—Extended Release Oral Dosage Forms

Development, Evaluation, and Application of In Vitro/In Vivo Correlations

I. INTRODUCTION

This guidance provides recommendations to pharmaceutical sponsors who intend to develop documentation in support of an in vitro/in vivo correlation (IVIVC) for an oral extended release (ER) drug product for submission in a new drug application (NDA), abbreviated new drug application (ANDA), or antibiotic drug application (AADA). The guidance presents a comprehensive perspective on (1) methods of developing an IVIVC and evaluating its predictability; (2) using an IVIVC to set dissolution specifications; and (3) applying an IVIVC as a surrogate for in vivo bioequivalence when it is necessary to document bioequivalence during the initial approval process or because of certain pre- or postapproval changes (e.g., formulation, equipment, process, and manufacturing site changes).

II. BACKGROUND

The concept of IVIVC, particularly for ER drug products, has been extensively discussed by pharmaceutical scientists. The ability to predict, accurately and pre-

[1] This guidance has been prepared by the Extended Release Dissolution Working Group of the Biopharmaceutics Coordinating Committee (BCC) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA). This guidance represents the Agency's current thinking on in vitro/in vivo correlations for extended release oral dosage forms. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the applicable statute, regulations, or both.

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cisely, expected bioavailability characteristics for an ER product from dissolution profile characteristics is a long sought after goal. Several workshops and publications have provided information in support of this goal.

These are discussed briefly as follows:

- A report from a 1987 ASCPT/DIA/APS/FDA-sponsored workshop entitled *Report of the Workshop on CR Dosage Forms: Issues and Controversies* (1987) indicated that the state of science and technology at that time did not permit consistently meaningful IVIVC for ER dosage forms and encouraged IVIVC as a future objective. Dissolution testing was considered useful only for process control, stability, minor formulation changes, and manufacturing site changes.
- A USP PF Stimuli Article in July 1988 established the classification of IVIVC into Levels A, B and C, which are currently in use.
- A report from a 1990 ASCPT/DIA/APS/FDA-sponsored workshop entitled *In vitro/In vivo Testing and Correlation for Oral Controlled/Modified Release Dosage Forms* (1990) concluded that, while the science and technology may not always permit meaningful IVIVC, the development of an IVIVC was an important objective on a product-by-product basis. Procedures for development, evaluation, and application of an IVIVC were described. Validation of dissolution specifications by a bioequivalence study involving two batches of product with dissolution profiles at the upper and lower dissolution specifications was suggested.
- USP Chapter 1088 similarly describes techniques appropriate for Level A, B, and C correlations and methods for establishing dissolution specifications.
- Further information related to IVIVCs was developed in a USP/AAPS/FDA-sponsored workshop, which resulted in a report entitled *Workshop II Report: Scale-up of Oral Extended Release Dosage Forms* (1993). This report identified the objectives of an IVIVC to be the use of dissolution as a surrogate for bioequivalency testing, as well as an aid in setting dissolution specifications. The report concluded that dissolution may be used as a sensitive, reliable, and reproducible surrogate for bioequivalence testing. The report gave support to the concepts of USP Chapter 1088 and further found that an IVIVC may be useful for changes other than minor changes in formulation, equipment, process, manufacturing site, and batch size.

These reports document increasing confidence in IVIVC to estimate the in vivo bioavailability characteristics for an ER drug product. In this regard, increased IVIVC activity in NDA submissions has been apparent. Still, the complete process of developing an IVIVC with high quality and predictability and identifying specific applications for such correlations has not been well defined.

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As part of the process of developing this guidance, the Agency conducted several surveys of NDA submissions for ER drug products to find out the number of times that IVIVCs were developed. The first survey included NDA submissions from 1982–1992 and found 9 IVIVCs in 60 submissions. A more recent survey included NDA submissions from October 1994 to October 1995 and found 9 IVIVCs in 12 submissions.

This guidance is based on these prior deliberations and publications as well as on current understanding at the FDA and elsewhere on approaches to developing reliable and useful IVIVCs. This guidance describes the levels of correlations that can be established with varying degrees of usefulness, important considerations for in vivo and in vitro experimentation, evaluation of the correlation by focusing on the critical feature of predictability, and practical applications that can be achieved using the IVIVC. With the availability of this guidance, sponsors are encouraged to develop IVIVCs for ER products in the expectation that the information will be useful in establishing dissolution specifications and will permit certain formulation and manufacturing changes without an in vivo bioequivalence study.

III. CATEGORIES OF IN VITRO/IN VIVO CORRELATIONS

A. Level A

A Level A correlation[2] is usually estimated by a two-stage procedure: deconvolution $_2$ followed by comparison of the fraction of drug absorbed to the fraction of drug dissolved. A correlation of this type is generally linear and represents a point-to-point relationship between in vitro dissolution and the in vivo input rate (e.g., the in vivo dissolution of the drug from the dosage form). In a linear correlation, the in vitro dissolution and in vivo input curves may be directly superimposable or may be made to be superimposable by the use of a scaling factor. Nonlinear correlations, while uncommon, may also be appropriate. Alternative approaches to developing a Level A IVIVC are possible. One alternative is based on a convolution procedure that models the relationship between in vitro dissolution and plasma concentration in a single step. Plasma concentrations predicted from the model and those observed are compared directly. For these methods, a reference treatment is desirable, but the lack of one does not preclude the ability to develop an IVIVC.

Whatever the method used to establish a Level A IVIVC, the model should predict the entire in vivo time course from the in vitro data. In this context, the

[2] Level A correlations are the most common type of correlation developed in NDAs submitted to the FDA. Level B correlations are rarely seen in NDAs; multiple Level C correlations are seen infrequently.

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model refers to the relationship between *in vitro* dissolution of an ER dosage form and an *in vivo* response such as plasma drug concentration or amount of drug absorbed.

B. Level B

A Level B IVIVC uses the principles of statistical moment analysis. The mean in vitro dissolution time is compared either to the mean residence time or to the mean in vivo dissolution time. A Level B correlation, like a Level A, uses all of the in vitro and in vivo data, but is not considered to be a point-to-point correlation. A Level B correlation does not uniquely reflect the actual in vivo plasma level curve, because a number of different in vivo curves will produce similar mean residence time values.

C. Level C

A Level C IVIVC establishes a single point relationship between a dissolution parameter, for example, $t_{50\%}$, percent dissolved in 4 hours and a pharmacokinetic parameter (e.g., AUC, C_{max}, T_{max}). A Level C correlation does not reflect the complete shape of the plasma concentration time curve, which is the critical factor that defines the performance of ER products.

D. Multiple Level C

A multiple Level C correlation relates one or several pharmacokinetic parameters of interest to the amount of drug dissolved at several time points of the dissolution profile.

IV. GENERAL CONSIDERATIONS:

The following general statements apply in the development of an IVIVC in an NDA or ANDA/AADA:

- Human data should be supplied for regulatory consideration of an IVIVC.
- Bioavailability studies for IVIVC development should be performed with enough subjects to characterize adequately the performance of the drug product under study. In prior acceptable data sets, the number of subjects has ranged from 6 to 36. Although crossover studies are preferred, parallel studies or cross-study analyses may be acceptable. The latter may involve normalization with a common reference treatment. The reference product in developing an IVIVC may be an intravenous solution, an aqueous oral solution, or an immediate release product.

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- IVIVCs are usually developed in the fasted state. When a drug is not tolerated in the fasted state, studies may be conducted in the fed state.
- Any in vitro dissolution method may be used to obtain the dissolution characteristics of the ER dosage form. The same system should be used for all formulations tested.
- The preferred dissolution apparatus is USP apparatus I (basket) or II (paddle), used at compendially recognized rotation speeds (e.g., 100 rpm for the basket and 50–75 rpm for the paddle). In other cases, the dissolution properties of some ER formulations may be determined with USP apparatus III (reciprocating cylinder) or IV (flow through cell).
  Appropriate review staff in CDER should be consulted before using any other type of apparatus.
- An aqueous medium, either water or a buffered solution preferably not exceeding pH 6.8, is recommended as the initial medium for development of an IVIVC. Sufficient data should be submitted to justify pH greater than 6.8. For poorly soluble drugs, addition of surfactant (e.g., 1% sodium lauryl sulfate) may be appropriate. In general, nonaqueous and hydroalcoholic systems are discouraged unless all attempts with aqueous media are unsuccessful. Appropriate review staff in CDER should be consulted before using any other media.
- The dissolution profiles of at least 12 individual dosage units from each lot should be determined. A suitable distribution of sampling points should be selected to define adequately the profiles. The coefficient of variation (CV) for mean dissolution profiles of a single batch should be less than 10%.
- A Level A IVIVC is considered to be the most informative and is recommended, if possible.
- Multiple Level C correlations can be as useful as Level A correlations. However, if a multiple Level C correlation is possible, then a Level A correlation is also likely and is preferred.
- Level C correlations can be useful in the early stages of formulation development when pilot formulations are being selected.
- Level B correlations are least useful for regulatory purposes.
- Rank order correlations are qualitative and are not considered useful for regulatory purposes.

V. DEVELOPMENT AND EVALUATION OF A LEVEL A IN VITRO/IN VIVO CORRELATION

A. Developing the Correlation

The most commonly seen process for developing a Level A IVIVC is to (1) develop formulations with different release rates, such as slow, medium, fast, or a

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single release rate if dissolution is condition independent; (2) obtain in vitro dissolution profiles and in vivo plasma concentration profiles for these formulations; (3) estimate the in vivo absorption or dissolution time course using an appropriate deconvolution technique for each formulation and subject (e.g., Wagner-Nelson, numerical deconvolution). These three steps establish the IVIVC model. Alternative approaches to developing Level A IVIVCs are possible. Further general information follows:

- The IVIVC relationship should be demonstrated consistently with two or more formulations with different release rates to result in corresponding differences in absorption profiles. Although an IVIVC can be defined with a minimum of two formulations with different release rates, three or more formulations with different release rates are recommended. Exceptions to this approach (i.e., use of only one formulation) may be considered for formulations for which in vitro dissolution is independent of the dissolution test conditions (e.g., medium, agitation, pH).
- Ideally, formulations should be compared in a single study with a crossover design.
- If one or more of the formulations (highest or lowest release rate formulations) does not show the same relationship between in vitro dissolution and in vivo performance compared with the other formulations, the correlation may still be used within the range of release rates encompassed by the remaining formulations.
- The in vitro dissolution methodology should adequately discriminate among formulations. Dissolution testing can be carried out during the formulation screening stage using several methods. Once a discriminating system is developed, dissolution conditions should be the same for all formulations tested in the biostudy for development of the correlation and should be fixed before further steps towards correlation evaluation are undertaken.
- During the early stages of correlation development, dissolution conditions may be altered to attempt to develop a 1-to-1 correlation between the in vitro dissolution profile and the in vivo dissolution profile.
- Time scaling may be used as long as the time scaling factor is the same for all formulations. Different time scales for each formulation indicate absence of an IVIVC.

B. Evaluating the Predictability of a Level A Correlation

An IVIVC should be evaluated to demonstrate that predictability of in vivo performance of a drug product from its in vitro dissolution characteristics is maintained over a range of in vitro dissolution release rates and manufacturing changes. Since the objective of developing an IVIVC is to establish a predictive

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mathematical model describing the relationship between an in vitro property and a relevant in vivo response, the proposed evaluation approaches focus on the estimation of predictive performance or, conversely, prediction error. Depending on the intended application of an IVIVC and the therapeutic index of the drug, evaluation of prediction error internally and/or externally may be appropriate. Evaluation of internal predictability is based on the initial data used to define the IVIVC model. Evaluation of external predictability is based on additional test data sets. Application of one or more of these procedures to the IVIVC modeling process constitutes evaluation of predictability.

An important concept is that the less data available for initial IVIVC development and evaluation of predictability, the more additional data may be needed to define completely the IVIVC's predictability. Some combination of three or more formulations with different release rates is considered optimal.

Another significant factor is the range of release rates studied. The release rates, as measured by percent dissolved, for each formulation studied, should differ adequately (e.g., by 10%). This should result in in vivo profiles that show a comparable difference, for example, a 10% difference in the pharmacokinetic parameters of interest (C_{max} or AUC) between each formulation.

Methodology for the evaluation of IVIVC predictability is an active area of investigation and a variety of methods are possible and potentially acceptable. A correlation should predict in vivo performance accurately and consistently. Once this relationship has been achieved, in vitro dissolution can be used confidently as a surrogate for in vivo bioequivalence of ER drug products in the situations described below.

1. Experimental Data Considerations

a. Dosage Form Properties: Dependence of In Vitro Release on Experimental Conditions.

CONDITION INDEPENDENT DISSOLUTION. If in vitro dissolution is shown to be independent of dissolution conditions (e.g., pH and agitation) and if the in vitro dissolution profile is shown to be equal to the in vivo absorption or in vivo dissolution profile, then the results for a single formulation (one release rate) may be sufficient. Evaluation of data for this formulation and evaluation of additional test data sets, as appropriate, for the purpose of estimation of internal and/or external predictability are recommended.

CONDITION DEPENDENT DISSOLUTION. In all other instances where an IVIVC model is presented, results from a single formulation (one release rate) should be considered insufficient. To estimate internal and/or external predictability, evaluation of data from two or more formulations with different release rates is recommended.

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b. Internal and External Predictability. Two distinct aspects of predictability can be considered. However, both aspects are not recommended in all instances.

ESTIMATION OF PREDICTION ERROR INTERNALLY. The first aspect relates to evaluating how well the model describes the data used to define the IVIVC and is appropriate in all instances.

If formulations with three or more release rates are used to develop the IVIVC model, no further evaluation beyond this initial estimation of prediction error may be necessary for non-narrow therapeutic index drugs (Category 2 a and b applications, see page 12). However, depending on the results of this internal prediction error calculation, determination of prediction error externally may be appropriate.

If only two formulations with different release rates are used, the application of the IVIVC is further limited to Category 2a applications (see page 12). In this circumstance, determination of prediction error externally is recommended for complete evaluation and subsequent full application of the IVIVC.

ESTIMATION OF PREDICTION ERROR EXTERNALLY. The second aspect relates to how well the model predicts data when one or more additional test data sets are used that differ from those used to define the correlation. This is appropriate in some situations, particularly when only two formulations with different release rates are used to develop the IVIVC model, when calculation of prediction error internally is inconclusive, or when a narrow therapeutic index drug is studied.

The additional test data sets used for external prediction error calculation may have several differing characteristics compared to the data sets used in IVIVC development. Although formulations with different release rates provide the optimal test of an IVIVC's predictability, a formulation need not be prepared solely for this purpose. In the absence of such a formulation, data from other types of formulations may be considered. In each case, bioavailability data should be available for the data set under consideration.

The following represent, in decreasing order of preference, formulations that may be used to estimate prediction error externally:

- A formulation with a different release rate than those used in IVIVC development. The release rate of the test formulation may be either within or outside the range used to define the IVIVC relationship.
- A formulation with the same or similar release rate, but involving some change in manufacture of this batch (e.g., composition, process, equipment, manufacturing site).
- A formulation with the same or similar release rate obtained from another batch/lot with no changes in manufacturing.

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c. Pharmacologic Properties of the Drug (Therapeutic Index).

NARROW THERAPEUTIC INDEX DRUGS. If an IVIVC model is to be used in estimating the in vivo performance of formulations of narrow therapeutic index drugs, the model's predictability should be tested further with a data set that differs from those data sets used to define the correlation. In other words, the external predictability of the correlation should be evaluated.

NON-NARROW THERAPEUTIC INDEX DRUGS. If an IVIVC model is to be used in estimating the in vivo performance of formulations of non-narrow therapeutic index drugs, testing the model's predictability with a data set that differs from those data sets used to define the correlation may be desirable, but is not considered as important as for a narrow therapeutic index drug.

Note—If the classification of a drug as a narrow therapeutic index drug is uncertain, appropriate review staff in CDER should be consulted.

2. Methods for Evaluation of Predictability

The objective of IVIVC evaluation is to estimate the magnitude of the error in predicting the in vivo bioavailability results from in vitro dissolution data. This objective should guide the choice and interpretation of evaluation methods. Any appropriate approach related to this objective may be used for evaluation of predictability.

a. Internal Predictability. All IVIVCs should be studied regarding internal predictability. One recommended approach involves the use of the IVIVC model to predict each formulation's plasma concentration profile (or C_{max} and/or AUC for a multiple Level C IVIVC) from each respective formulation's dissolution data. This is performed for each formulation used to develop the IVIVC model. The predicted bioavailability is then compared to the observed bioavailability for each formulation and a determination of prediction error is made.

CRITERIA.

- Average absolute percent prediction error (% PE) of 10% or less for C_{max} and AUC establishes the predictability of the IVIVC. In addition, the % PE for each formulation should not exceed 15%.
- If these criteria are not met, that is, if the internal predictability of the IVIVC is inconclusive, evaluation of external predictability of the IVIVC should be performed as a final determination of the ability of the IVIVC to be used as a surrogate for bioequivalence.

b. External Predictability. Most important when using an IVIVC as a surrogate for bioequivalence is confidence that the IVIVC can predict in vivo per-

formance of subsequent lots of the drug product. Therefore, it may be important to establish the external predictability of the IVIVC. This involves using the IVIVC to predict the in vivo performance for a formulation with known bioavailability that was not used in developing the IVIVC model.

CRITERIA.

- % PE of 10% or less for C and AUC establishes the external $_{max}$ predictability of an IVIVC.
- % PE between 10–20% indicates inconclusive predictability and the need for further study using additional data sets. Results of estimation of PE from all such data sets should be evaluated for consistency of predictability.
- % PE greater than 20% generally indicates inadequate predictability, unless otherwise justified.

With the exception of narrow therapeutic index drugs, the external predictability step in the IVIVC evaluation process may be omitted if the evaluation of internal predictability indicates acceptable % PE. However, when the evaluation of internal predictability is inconclusive, evaluation of external predictability is recommended.

VI. DEVELOPMENT AND EVALUATION OF A LEVEL C IN VITRO/IN VIVO CORRELATION

A single point Level C correlation allows a dissolution specification to be set at the specified time point. While the information may be useful in formulation development, waiver of an in vivo bioequivalence study (biowaiver) is generally not possible if only a single point correlation is available. A multiple point Level C correlation may be used to justify a biowaiver, provided that the correlation has been established over the entire dissolution profile with one or more pharmacokinetic parameters of interest. This could be achieved by correlating the amount dissolved at various time points with C_{max}, AUC, or any other suitable parameter. A relationship should be demonstrated at each time point with the same parameter such that the effect on the in vivo performance of any change in dissolution can be assessed. If such a multiple Level C correlation is achievable, then the development of a Level A correlation is likely. A multiple Level C correlation should be based on at least three dissolution time points covering the early, middle, and late stages of the dissolution profile. The recommendations for assessing the predictability of Level C correlations will depend on the type of application for which the correlation is to be used. These methods and criteria are the same as those for a Level A correlation (see Section V B2).

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VII. APPLICATIONS OF AN IVIVC

In vitro dissolution testing is important for (1) providing process control and quality assurance; (2) determining stable release characteristics of the product over time; and (3) facilitating certain regulatory determinations (e.g., absence of effect of minor formulation changes or of change in manufacturing site on performance). In certain cases, especially for ER formulations, the dissolution test can serve not only as a quality control for the manufacturing process but also as an indicator of how the formulation will perform in vivo. Thus, a main objective of developing and evaluating an IVIVC is to establish the dissolution test as a surrogate for human bioequivalence studies, which may reduce the number of bioequivalence studies performed during the initial approval process as well as with certain scale-up and postapproval changes. However, for the applications outlined below, the adequacy of the in vitro dissolution method to act as a surrogate for in vivo testing should be shown through an IVIVC for which predictability has been established.

A. Biowaivers for Changes in the Manufacturing of a Drug Product

1. Category 1: Biowaivers Without an IVIVC

For formulations consisting of beads in capsules, with the only difference between strengths being the number of beads, approval of lower strengths without an IVIVC is possible, provided bioavailability data are available for the highest strength.

Where the guidance for industry *SUPAC-MR: Modified Release Solid Oral Dosage Forms; Scale-Up and Postapproval changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* recommends a biostudy, biowaivers for the same changes made on lower strengths are possible without an IVIVC if (1) all strengths are compositionally proportional or qualitatively the same, (2) in vitro dissolution profiles of all strengths are similar, (3) all strengths have the same release mechanism, (4) bioequivalence has been demonstrated on the highest strength (comparing changed and unchanged drug product), and (5) dose proportionality has been demonstrated for this ER drug product. In the last circumstance (5), documentation of dose proportionality may not be necessary if bioequivalence has been demonstrated on the highest and lowest strengths of the drug product, comparing changed and unchanged drug product for both strengths, as recommended in SUPAC-MR.

For the above situations, waivers can be granted without an IVIVC if dissolution data are submitted in the application/compendial medium and in three other media (e.g., water, 0.1N HCl, and USP buffer at pH 6.8, comparing the drug product after the change to the drug product before the change).

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Biowaivers, as defined in SUPAC-MR, that do not necessitate either bioequivalence testing or an IVIVC will likely be granted in preapproval situations for both narrow and non-narrow therapeutic index ER drug products if dissolution data, as described in SUPAC-MR, are submitted.

a. Comparison of Dissolution Profiles. Dissolution profiles can be compared using model independent or model dependent methods. A model independent approach using a similarity factor, and comparison criteria are described in SUPAC-MR.

2. Category 2: Biowaivers Using an IVIVC: Non-Narrow Therapeutic Index Drugs

a. Two Formulations/Release Rates. A biowaiver will likely be granted for an ER drug product using an IVIVC developed with two formulations/release rates for (1) Level 3 manufacturing site changes as defined in SUPAC-MR; (2) Level 3 nonrelease controlling excipient changes as defined in SUPAC-MR, with the exception of complete removal or replacement of excipients (see below).

b. Three Formulations/Release Rates. A biowaiver will likely be granted for an ER drug product using an IVIVC developed with three formulations/release rates (or developed with two formulations/release rates with establishment of external predictability) for (1) Level 3 process changes as defined in SUPAC-MR; (2) complete removal of or replacement of nonrelease controlling excipients as defined in SUPAC-MR; and (3) Level 3 changes in the release controlling excipients as defined in SUPAC-MR.

c. Biowaivers for Lower Strengths. If an IVIVC is developed with the highest strength, waivers for changes made on the highest strength and any lower strengths may be granted if these strengths are compositionally proportional or qualitatively the same, the in vitro dissolution profiles of all the strengths are similar, and all strengths have the same release mechanism.

d. Approval of New Strengths. This biowaiver is applicable to strengths lower than the highest strength, within the dosing range that has been established to be safe and effective, if the new strengths are compositionally proportional or qualitatively the same; have the same release mechanism; have similar in vitro dissolution profiles; and are manufactured using the same type of equipment and the same process at the same site as other strengths that have bioavailability data available.

For generic products to qualify for this biowaiver, one of the following situations should exist:

- Bioequivalence has been established for all strengths of the reference listed product.

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- Dose proportionality has been established for the reference listed product, and all reference product strengths are compositionally proportional or qualitatively the same, have the same release mechanism, and the in vitro dissolution profiles of all strengths are similar.
- Bioequivalence is established between the generic product and the reference listed product at the highest and lowest strengths and, for the reference listed product, all strengths are compositionally proportional or qualitatively the same, have the same release mechanism, and the in vitro dissolution profiles are similar.

OBTAINING CATEGORY 2D BIOWAIVERS: The difference in predicted means of C_{max} and AUC should be no more than 10%, based on dissolution profiles of the highest strength and the lower strength product.

e. Changes in Release Controlling Excipients. Changes in release controlling excipients in the formulation should be within the range of release controlling excipients of the established correlation.

f. Obtaining Category 2a, 2b, and 2c Biowaivers. The difference in predicted means of C_{max} and AUC should be no more than 20% from that of the reference product and, where appropriate, the new formulation should meet the application/compendial dissolution specifications.

3. Category 3: Biowaivers Using an IVIVC: Narrow Therapeutic Index Drugs

If external predictability of an IVIVC is established, the following waivers will likely be granted if at least two formulations/release rates have been studied for the development of the IVIVC.

a. Situations in Which Biowaivers May be Granted. A biowaiver will likely be granted for an ER drug product using an IVIVC for (1) Level 3 process changes as defined in SUPAC-MR; (2) complete removal of or replacement of non-release controlling excipients as defined in SUPAC-MR; and (3) Level 3 changes in the release controlling excipients as defined in SUPAC-MR.

b. Biowaivers for Lower Strengths. If an IVIVC is developed with the highest strength, waivers for changes made on the highest strength and any lower strengths may be granted, if these strengths are compositionally proportional or qualitatively the same, the in vitro dissolution profiles of all the strengths are similar, and all strengths have the same release mechanism.

c. Approval of New Strengths. This biowaiver is applicable to strengths lower than the highest strength, within the dosing range that has been established to be safe and effective, provided that the new strengths are compositionally proportional or qualitatively the same, have the same release mechanism, have simi-

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lar in vitro dissolution profiles, and are manufactured using the same type of equipment, and the same process at the same site as other strengths that have bioavailability data available.

For generic products to qualify for this biowaiver, one of the following situations should exist:

- Bioequivalence has been established for all strengths of the reference listed product.
- Dose proportionality has been established for the reference listed product, all reference product strengths are compositionally proportional or qualitatively the same and have the same release mechanism, and the in vitro dissolution profiles of all strengths are similar.
- Bioequivalence is established between the generic product and the reference listed product at the highest and lowest strengths and, for the reference listed product, all strengths are compositionally proportional or qualitatively the same and have the same release mechanism, and the in vitro dissolution profiles are similar.

OBTAINING CATEGORY 3C BIOWAIVERS. The difference in predicted means of C_{max} and AUC should be no more than 10%, based on dissolution profiles of the highest strength and the lower strength product.

d. Changes in Release Controlling Excipients. Changes in release controlling excipients in the formulation should be within the range of release controlling excipients of the established correlation.

e. Obtaining Category 3a and 3b Biowaivers. The difference in predicted means of C_{max} and AUC should be no more than 20% from that of the reference product and, where appropriate, the new formulation meets the application/compendial dissolution specifications.

4. Category 4: Biowaivers When In Vitro Dissolution Is Independent of Dissolution Test Conditions

Situations in which biowaivers are likely to be granted for both narrow and non-narrow therapeutic index drugs:

a. Category 2 and Category 3 Biowaivers are Likely to be Granted with an IVIVC Established with One Formulation/Release Rate. Biowaivers may be granted if dissolution data are submitted in application/compendial medium and in three other media (e.g., water, 0.1 N HCl, USP buffer at pH 6.8) and the following conditions apply:

- In vitro dissolution should be shown to be independent of dissolution test conditions after change is made in drug product manufacturing.
- Comparison of dissolution profiles

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Dissolution profiles can be compared using model independent or model dependent methods. A model independent approach using a similarity factor and comparison criteria is described in SUPAC-MR.

b. Obtaining Category 4 Biowaivers. The difference in predicted means of C_{max} and AUC should be no more than 20% from that of the reference product and, where appropriate, the new formulation should meet the application/compendial dissolution specifications.

5. Category 5: Situations for Which an IVIVC Is Not Recommended

a. Approval of a New Formulation of an Approved ER Drug Product When the New Formulation has a Different Release Mechanism.

b. Approval of a Dosage Strength Higher or Lower Than the Doses That Have Been Shown to be Safe and Effective in Clinical Trials.

c. Approval of Another Sponsor's ER Product Even with the Same Release Controlling Mechanism.

d. Approval of a Formulation Change Involving a Nonrelease Controlling Excipient in the Drug Product That May Significantly Affect Drug Absorption.

B. Setting Dissolution Specifications

In vitro dissolution specifications should generally be based on the performance of the clinical/bioavailability lots. These specifications may sometimes be widened so that scale-up lots, as well as stability lots, meet the specifications associated with the clinical/bioavailability lots. This approach is based on the use of the in vitro dissolution test as a quality control test without any in vivo significance, even though in certain cases (e.g., ER formulations), the rate limiting step in the absorption of the drug is the dissolution of the drug from the formulation. An IVIVC adds in vivo relevance to in vitro dissolution specifications, beyond batch-to-batch quality control. In this approach, the in vitro dissolution test becomes a meaningful predictor of in vivo performance of the formulation, and dissolution specifications may be used to minimize the possibility of releasing lots that would be different in in vivo performance.

1. Setting Dissolution Specifications Without an IVIVC

- The recommended range at any dissolution time point specification is $\pm$ 10% deviation from the mean dissolution profile obtained from the clinical/bioavailability lots.
- In certain cases, reasonable deviations from the $\pm$ 10 % range can be accepted provided that the range at any time point does not exceed 25%.

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Specifications greater than 25% may be acceptable based on evidence that lots (side batches) with mean dissolution profiles that are allowed by the upper and lower limit of the specifications are bioequivalent.

- Specifications should be established on clinical/bioavailability lots. Widening specifications based on scale-up, stability, or other lots for which bioavailability data are unavailable is not recommended.
- A minimum of three time points is recommended to set the specifications. These time points should cover the early, middle, and late stages of the dissolution profile. The last time point should be the time point where at least 80% of drug has dissolved. If the maximum amount dissolved is less than 80%, the last time point should be the time when the plateau of the dissolution profile has been reached.
- Specifications should be established based on average dissolution data for each lot under study, equivalent to USP Stage 2 testing. Specifications allow that all lots to pass at Stage 1 of testing may result in lots with less than optimal in vivo performance passing these specifications at USP Stage 2 or Stage 3.
- USP acceptance criteria for dissolution testing are recommended unless alternate acceptance criteria are specified in the ANDA/NDA.

2. Setting Dissolution Specifications Where an IVIVC Has Been Established

Optimally, specifications should be established such that all lots that have dissolution profiles within the upper and lower limits of the specifications are bioequivalent. Less optimally but still possible, lots exhibiting dissolution profiles at the upper and lower dissolution limits should be bioequivalent to the clinical/bioavailability lots or to an appropriate reference standard.

a. Level A Correlation Established.

- Specifications should be established based on average data.
- A minimum of three time points is recommended to establish the specifications. These time points should cover the early, middle and late stages of the dissolution profile. The last time point should be the time point where at least 80% of drug has dissolved. If the maximum amount dissolved is less than 80%, then the last time point should be the time where the plateau of the dissolution profile has been reached.
- Calculate the plasma concentration time profile using convolution techniques or other appropriate modeling techniques and determine whether the lots with the fastest and slowest release rates that are allowed by the dissolution specifications result in a maximal difference of 20% in the predicted C_{max} and AUC.

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- An established IVIVC may allow setting wider dissolution specifications. This would be dependent on the predictions of the IVIVC (i.e., 20% differences in the predicted C_{max} and AUC).
- USP acceptance criteria for dissolution testing are recommended unless alternate acceptance criteria are specified in the ANDA/NDA.

b. Multiple Level C Correlation Established.

- If a multiple point Level C correlation has been established, establish the specifications at each time point such that there is a maximal difference of 20% in the predicted C_{max} and AUC.
- Additionally, the last time point should be the time point where at least 80% of drug has dissolved.

c. Level C Correlation Based on Single Time Point Established. This one time point may be used to establish the specification such that there is not more than a 20% difference in the predicted AUC and C_{max}. At other time points, the maximum recommended range at any dissolution time point specification should be $\pm$ 10% of label claim deviation from the mean dissolution profile obtained from the clinical/bioavailability lots. Reasonable deviations from $\pm$ 10% may be acceptable if the range at any time point does not exceed 25%.

3. Setting Specifications Based on Release Rate

If the release characteristics of the formulation can be described by a zero-order process for some period of time (e.g., 5%/hr from 4 to 12 hours), and the dissolution profile appears to fit a linear function for that period of time, a release rate specification may be established to describe the dissolution characteristics of that formulation. A release rate specification may be an addition to the specifications established on the cumulative amount dissolved at the selected time points. Alternatively, a release the rate specification may be the only specification except for the specification for time when at least 80% of drug has dissolved.

DEFINITION OF TERMS

Batch: A specific quantity of a drug or other material produced according to a single manufacturing order during the same cycle of manufacture and intended to have uniform character and quality, within specified limits *(21 CFR 210.3(b)(2)*).
Batch Formula (Composition): A complete list of the ingredients and their amounts to be used for the manufacture of a representative batch of the drug product. All ingredients should be included in the batch formula whether or not they remain in the finished product *(Guideline for Submitting Documentation for the Manufacture of and Controls for Drug Products, FDA, February 1987*).

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Bioavailability: The rate and extent to which the active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the site of drug action *(21 CFR 320.1(a))*.

Biobatch: A lot of drug product formulated for purposes of pharmacokinetic evaluation in a bioavailability/bioequivalency study. This lot should be 10% or greater than the proposed commercial production batch or at least 100,000 units, whichever is greater.

Bioequivalent Drug Products: Pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the therapeutic moiety under similar experimental conditions, either single dose or multiple dose. Some pharmaceutical equivalents or pharmaceutical alternatives may be equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on chronic use, or are considered medically insignificant for the particular drug product studied *(21 CFR 320.1(e))*.

Convolution: Prediction of plasma drug concentrations using a mathematical model based on the convolution integral. For example, the following convolution integral equation may be used to predict the plasma concentration *(c(t))* resulting from the absorption rate time course *(r_{abs})*:

$$c(t) = \int_0^t c_\delta\,(t - u)\, r_{abs}\,(u)\, du$$

The function c_δ represents the concentration time course that would result from the instantaneous absorption of a unit amount of drug and can be estimated from either i.v. bolus data, oral solution, suspension or rapidly releasing (in vivo) immediate release dosage forms.

Correlation: As used in this guidance, a relationship between in vitro dissolution rate and in vivo input (absorption) rate.

Deconvolution: Estimation of the time course of drug input (usually in vivo absorption or dissolution) using a mathematical model based on the convolution integral. For example, the absorption rate time course *(r_{abs})* that resulted in the plasma concentrations *(c(t))* may be estimated by solving the following convolution integral equation for r_{abs}:

$$c(t) = \int_0^t c_\delta\,(t - u)\, r_{abs}\,(u)\, du$$

The function c_δ represents the concentration time course that would result from the instantaneous absorption of a unit amount of drug and is typically estimated from either i.v. bolus data, oral solution, suspension or rapidly releasing (in vivo) immediate release dosage forms.

Development: Establishing an in vitro/in vivo correlation.

Drug Product: A finished dosage form, e.g., tablet, capsule, or solution, that

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contains a drug substance, generally, but not necessarily, in association with one or more other ingredients *(21 CFR 314.3(b)*).

Extended Release Dosage Form: A dosage form that allows a reduction in dosing frequency as compared to that presented by a conventional dosage form, e.g., a solution or an immediate release dosage form.

Evaluation: In the context of in vitro/in vivo correlation, a broad term encompassing experimental and statistical techniques used during development and evaluation of a correlation which aid in determining the predictability of the correlation.

Formulation: A listing of the ingredients and composition of the dosage form.

In Vitro/In Vivo Correlation: A predictive mathematical model describing the relationship between an in vitro property of an extended release dosage form (usually the rate or extent of drug dissolution or release) and a relevant in vivo response, e.g., plasma drug concentration or amount of drug absorbed.

In Vivo Dissolution: The process of dissolution of drug in the gastro-intestinal tract.

In Vitro Release: Drug dissolution (release) from a dosage form as measured in an in vitro dissolution apparatus.

In Vivo Release: In vivo dissolution of drug from a dosage form as determined by deconvolution of data obtained from pharmacokinetic studies in humans (patients or healthy volunteers).

Level A Correlation: A predictive mathematical model for the relationship between the entire in vitro dissolution/release time course and the entire in vivo response time course, e.g., the time course of plasma drug concentration or amount of drug absorbed.

Level B Correlation: A predictive mathematical model for the relationship between summary parameters that characterize the in vitro and in vivo time courses, e.g., models that relate the mean in vitro dissolution time to the mean in vivo dissolution time, the mean in vitro dissolution time to the mean residence time in vivo, or the in vitro dissolution rate constant to the absorption rate constant.

Level C Correlation: A predictive mathematical model of the relationship between the amount dissolved in vitro at a particular time (or the time required for in vitro dissolution of a fixed percent of the dose, e.g., T_{50} %) and a summary parameter that characterizes the in vivo time course (e.g., C_{max} or AUC).

Lot: A batch, or a specific identified portion of a batch, having uniform character and quality within specified limits or, in the case of a drug product produced by continuous process, a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits *(21 CFR 210.3(b)(10)*).

Mean Absorption Time: The mean time required for drug to reach systemic circulation from the time of drug administration. This term commonly refers to the

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mean time involved in the in vivo release and absorption processes as they occur in the input compartment and is estimated as $MAT = MRT_{oral} - MRT_{i.v.}$.

Mean In Vitro Dissolution Time: The mean time for the drug to dissolve under in vitro dissolution conditions. This is calculated using the following equation:

$$MDT_{vitro} = \frac{\int_0^\infty (M_\infty - M(t))dt}{M_\infty}$$

Mean In Vivo Dissolution Time: For a solid dosage form: $MDT_{solid} = MRT_{solid} - MRT_{solution}$. This reflects the mean time for drug to dissolve in vivo.

Mean Residence Time: The mean time that the drug resides in the body. MRT may also be the mean transit time. MRT = AUMC/AUC.

Narrow Therapeutic Index Drugs: Drugs having, for example, less than a two-fold difference in the minimum toxic concentrations and the minimum effective concentrations *(21 CFR 320.33 (c)).*

Nonrelease Controlling Excipient (Noncritical Compositional Variable): An inactive ingredient in the final dosage form that does not significantly affect the release of the active drug substance from the dosage form.

Predictability: Verification of the model's ability to describe in vivo bioavailability results from a test set of in vitro data (external predictability) as well as from the data that was used to develop the correlation (internal predictability).

Percent Prediction Error: % PE = [(Observed value − Predicted value) / Observed value] × 100

Release Controlling Excipient (Critical Compositional Variable): An inactive ingredient in the final dosage form that functions primarily to extend the release of the active drug substance from the dosage form.

Release Mechanism: The process by which the drug substance is released from the dosage form.

Release Rate: Amount of drug released per unit of time as defined by in vitro or in vivo testing.

Statistical Moments: Parameters that describe the characteristics of the time courses of plasma concentration (area, mean residence time, and variance of mean residence time) and of urinary excretion rate.

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Appendix E

Guidance for Industry[1]— Nonsterile Semisolid Dosage Forms

Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation SUPAC-SS

I. INTRODUCTION

This guidance provides recommendations to pharmaceutical sponsors of new drug applications (NDAs), abbreviated new drug applications (ANDAs), and abbreviated antibiotic drug applications (AADAs) who intend to change (1) the components or composition, (2) the manufacturing (process and equipment), (3) the scale-up/scale-down of manufacture, and/or (4) the site of manufacture of a semisolid formulation during the postapproval period. This guidance addresses nonsterile semisolid preparations (e.g., creams, gels, lotions, and ointments) intended for topical routes of administration. The guidance defines (1) the levels of change; (2) recommended chemistry, manufacturing, and controls (CMC) tests to support each level of change; (3) recommended in vitro release tests

[1] This guidance has been prepared by the Scale-Up and Post Approval Change Semisolids (SUPAC-SS) Working Group operating under the direction of the Chemistry Manufacturing Controls Coordinating Committee (CMC CC) and the Biopharmaceutics Coordinating Committee (BCC) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on semisolid dosage forms scale-up and postapproval changes. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirement of the applicable statute, regulations, or both.

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and/or in vivo bioequivalence tests to support each level of change; and (4) documentation to support the change.

The guidance specifies the application information that should be provided to the Center for Drug Evaluation and Research (CDER) to ensure continuing product quality and performance chacteristics of the semisolid topical formulation for specified changes. The guidance does not comment on or otherwise affect compliance/inspection documentation defined by the Office of Compliance in CDER or the Office of Regulatory Affairs at FDA.

The guidance provides recommendations on application documentation for the following multiple changes, provided appropriate test and filing documents are submitted (1) multiple level 1 changes with level 1 test and filing documentation; (2) multiple level 1 changes; one level 2 change with level 2 test and filing documentation; (3) multiple level 2 changes with level 2 test documentation and a prior approval supplement (PAS) and (4) level 3 manufacturing site change and any other level 1 change with level 3 manufacturing site change test and filing documentation. The documentation to support the changes varies depending on the type and the complexity of the semisolid dosage form. For those changes filed in a Changes Being Effected (CBE) Supplement (21 CFR 314.70(c)), the FDA may review the supplemental information and decide that the changes are not approvable. Sponsors should contact the appropriate CDER review division and staff for information about tests and application documentation for changes not addressed in this guidance, or for successive level 2 or 3 changes submitted over a short period.

The regulations provide that applicants may make changes to an approved application in accordance with a guidance, notice, or regulation published in the *Federal Register* that provides for a less burdensome notification of the change (e.g., by notification at the time a supplement is submitted or in the next annual report) (21 CFR 314.70(a)). This guidance permits less burdensome notice of certain postapproval changes within the meaning of § 314.70(a).

II. GENERAL BACKGROUND

In general, semisolid dosage forms are complex formulations having complex structural elements. Often they are composed of two phases (oil and water), one of which is a continuous (external) phase, and the other of which is a dispersed (internal) phase. The active ingredient is often dissolved in one phase, although occasionally the drug is not fully soluble in the system and is dispersed in one or both phases, thus creating a three-phase system. The physical properties of the dosage form depend upon various factors, including the size of the dispersed particles, the interfacial tension between the phases, the partition coefficient of the active ingredient between the phases, and the product rheology. These factors combine to determine the release characteristics of the drug, as well as other characteristics, such as viscosity.

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A. Critical Manufacturing Parameters

For a true solution, the order in which solutes are added to the solvent is usually unimportant. The same cannot be said for dispersed formulations, however, because dispersed matter can distribute differently depending on to which phase a particulate substance is added. In a typical manufacturing process, the critical points are generally the initial separation of a one-phase system into two phases and the point at which the active ingredient is added. Because the solubility of each added ingredient is important for determining whether a mixture is visually a single homogeneous phase, such data, possibly supported by optical microscopy, should usually be available for review. This is particularly important for solutes added to the formulation at a concentration near or exceeding that of their solubility at any temperature to which the product may be exposed. Variations in the manufacturing procedure that occur after either of these events are likely to be critical to the characteristics of the finished product. This is especially true of any process intended to increase the degree of dispersion through reducing droplet or particle size (e.g., homogenization). Aging of the finished bulk formulation prior to packaging is critical and should be specifically addressed in process validation studies.

B. General Stability Considerations

The effect that SUPAC changes may have on the stability of the drug product should be evaluated. For general guidance on conducting stability studies, see the FDA *Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics*. For SUPAC submissions, the following points should also be considered:

1. In most cases, except those involving scale-up, stability data from pilot scale batches will be acceptable to support the proposed change.
2. Where stability data show a trend towards potency loss or degradant increase under accelerated conditions, it is recommended that historical accelerated stability data from a representative prechange batch be submitted for comparison. It is also recommended that under these circumstances, all available long-term data on test batches from ongoing studies be provided in the supplement. Submission of historical accelerated and available long-term data would facilitate review and approval of the supplement.
3. A commitment should be included to conduct long-term stability studies through the expiration dating period, according to the approved protocol, on either the first or first three (see section III-VI for details) production batches, and to report the results in subsequent annual reports.

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C. The Role of In Vitro Release Testing

The key parameter for any drug product is its efficacy as demonstrated in controlled clinical trials. The time and expense associated with such trials make them unsuitable as routine quality control methods. Therefore, in vitro surrogate tests are often used to assure that product quality and performance are maintained over time and in the presence of change. A variety of physical and chemical tests commonly performed on semisolid products and their components (e.g., solubility, particle size and crystalline form of the active component, viscosity, and homogeneity of the product) have historically provided reasonable evidence of consistent performance. More recently, in vitro release testing has shown promise as a means to comprehensively assure consistent delivery of the active component(s) from semisolid products.

An in vitro release rate can reflect the combined effect of several physical and chemical parameters, including solubility and particle size of the active ingredient and rheological properties of the dosage form. In most cases, in vitro release rate is a useful test to assess product sameness between prechange and postchange products. However, there may be instances where it is not suitable for this purpose. In such cases, other physical and chemical tests to be used as measures of sameness should be proposed and discussed with the Agency. With any test, the metrics and statistical approaches to documentation of "sameness" in quality attributes should be considered.

The evidence available at this time for the in vitro-in vivo correlation of release tests for semisolid dosage forms is not as convincing as that for in vitro dissolution as a surrogate for in vivo bioavailability of solid oral dosage forms. Therefore, the Center's current position concerning in vitro release testing is as follows:

1. In vitro release testing is a useful test to assess product "sameness" under certain scale-up and postapproval changes for semisolid products.
2. The development and validation of an in vitro release test are not required for approval of an NDA, ANDA or AADA nor is the in vitro release test required as a routine batch-to-batch quality control test.
3. In vitro release testing, alone, is not a surrogate test for in vivo bioavailability or bioequivalence.
4. The in vitro release rate should not be used for comparing different formulations across manufacturers.

III. COMPONENTS AND COMPOSITION

This section of the guidance focuses on changes in excipients in the drug product. Qualitative changes in excipients should include only those excipients which are

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present in approved drug products for the specific route of administration. Quantitative changes in excipients should not exceed the amount previously approved in products with the same specific route of administration.[2] The chronology of changes in components and composition should be provided. Changes in components or composition that have the effect of adding a new excipient or deleting an existing excipient are defined as level 3 changes (see section III.C below), except as described below. These changes generally result in the need to change the labeling. Compositional changes in preservatives are considered separately and are not included as part of the total additive effect under sections III.A, B and C.

A. Level 1 Change

1. Definition of Level

Level 1 changes are those that are unlikely to have any detectable impact on formulation quality and performance.
Examples:

- Deletion or partial deletion of an ingredient intended to affect the color, fragrance, or flavor of the drug product.
- Any change in an excipient up to 5% of approved amount of that excipient. The total additive effect of all excipient changes should not be more than 5%. Changes in the composition should be based on the approved target composition and not on previous level 1 changes in the composition. A change in diluent (q.s. excipient) due to component and composition changes in excipient may be made and is excluded from the 5% change limit.
- Change in a supplier of a structure forming excipient that is primarily a single chemical entity (purity$95%) or change in a supplier or technical grade of any other excipient.

2. Test Documentation

a. Chemistry Documentation. Application/compendial product release requirements and stability testing. Stability testing: First production batch on long-term stability reported in annual report.

b. In Vitro Release Documentation. None.

c. In Vivo Bioequivalence Documentation. None.

[2] FDA, CDER, *Inactive Ingredient Guide,* 1996, Division of Drug Information Resources.

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3. Filing Documentation

Annual report (all information including long-term stability data).

B. Level 2 Change

1. Definition of Level

Level 2 changes are those that could have a significant impact on formulation quality and performance.
Examples:

- Changes of >5% and <=10% of approved amount of an individual excipient. The total additive effect of all excipient changes should not be more than 10%. Changes in the composition should be based on the approved target composition and not on previous level 1 or level 2 changes in the composition. Changes in diluent (q.s. excipient) due to component and composition changes in excipients are acceptable and are excluded from the 10% change limit.
- Change in supplier of a structure forming excipient not covered under level 1.
- Change in the technical grade of structure forming excipient.
- Change in particle size distribution of the drug substance, if the drug is in suspension.

2. Test Documentation

a. Chemistry Documentation. Application/compendial product release requirements and executed batch records.

Stability testing: One batch with three months accelerated stability data reported in changes being effected supplement and long-term stability data of first production batch reported in annual report.

b. In Vitro Release Documentation. The in vitro release rate of a lot of the new/modified formulation should be compared with that of a recent lot of comparable age of the pre-change formulation of the product. The median in vitro release rates (as estimated by the estimated slope from each cell, see section VII) of the two formulations should be demonstrated to be within acceptable limits using the testing procedure described in section VII (IN VITRO RELEASE TEST) below.

c. In Vivo Bioequivalence Documentation. None.

3. Filing Documentation

Changes being effected supplement (all information including accelerated stability data); annual report (long-term stability data).

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C. Level 3 Change

1. Definition of Level

Level 3 changes are those that are likely to have a significant impact on formulation quality and performance.
Examples:

- Any qualitative and quantitative changes in an excipient beyond the ranges noted in level 2 change.
- Change in crystalline form of the drug substance, if the drug is in suspension.

2. Test Documentation

a. Chemistry Documentation. Application/compendial product release requirements and executed batch records.Significant body of information available: One batch with three months accelerated stability data reported in prior approval supplement and long-term stability data of first three production batches reported in annual report.

Significant body of information not available: Three batches with three months accelerated stability data reported in prior approval supplement and long-term stability data of first three production batches reported in annual report.

b. In Vitro Release Documentation. The in vitro release rate of the new/modified formulation should be established as a point of reference. Under this level 3 change, in vitro release documentation is not required, but sponsors are encouraged to develop this information for use in subsequent changes under this guidance.

c. In Vivo Bioequivalence Documentation. Full bioequivalence study on the highest strength, with in vitro release/other approach on the lower strength(s).

3. Filing Documentation

Prior approval supplement (all information including accelerated stability data); annual report (long-term stability data).

D. Preservative

For semisolid products, any change in the preservative may affect the quality of the product. If any quantitative or qualitative changes are made in the formulation, additional testing should be performed. No in vitro release documentation or in vivo bioequivalence documentation is needed for preservative changes.

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1. Level 1 Change

a. Definition of Level. Quantitatively 10% or less change in the approved amount of preservative.

b. Test Documentation.

- Application/compendial product release requirements.
- Preservative Effectiveness Test carried out at lowest specified preservative level.

c. Filing Documentation. Annual report

2. Level 2 Change

a. Definition of Level. Quantitatively greater than 10% and up to 20% change in the approved amount of preservative.

b. Test Documentation.

- Application/compendial product release requirements.
- Preservative Effectiveness Test at lowest specified preservative level.

c. Filing Documentation. Changes being effected supplement.

3. Level 3 Change

a. Definition of Level. Quantitatively greater than 20% change in the approved amount of preservative (including deletion) or use of a different preservative.

b. Test Documentation.

- Application/compendial product release requirements.
- Preservative Effectiveness Test at lowest specified preservative level.
- Analytical method for identification and assay for new preservative.
- Validation studies to show that the new preservative does not interfere with application/compendial test.
- Executed batch records.
- Stability testing: One batch with three months accelerated stability data reported in prior approval supplement and long-term stability data of first production batch reported in annual report.

c. Filing Documentation. Prior approval supplement (all information including accelerated stability data); annual report (long-term stability data).

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IV. MANUFACTURING

Manufacturing changes may affect both equipment used in the manufacturing process and the process itself.

A. Equipment

1. Level 1 Change

a. Definition of Level. Change from nonautomated or nonmechanical equipment to automated or mechanical equipment to transfer ingredients. Change to alternative equipment of the same design and operating principles.

b. Test Documentation.

I. CHEMISTRY DOCUMENTATION. Application/compendial product release requirements. Notification of change and submission of updated executed batch records. Stability testing: First production batch on long-term stability reported in annual report.

II. IN VITRO RELEASE DOCUMENTATION. None.

III. IN VIVO BIOEQUIVALENCE DOCUMENTATION. None.

c. Filing Documentation. Annual report (all information including long-term stability data).

2. Level 2 Change

a. Definition of Level. Change in equipment to a different design or different operating principles. Change in type of mixing equipment, such as high shear to low shear and vice versa.

b. Test Documentation.

I. CHEMISTRY DOCUMENTATION. Application/compendial product release requirements. Notification of change and submission of updated executed batch records. Significant body of information available: One batch with three months accelerated stability data reported in changes being effected supplement and long-term stability data of first production batch reported in annual report.

Significant body of information not available: Three batches with three months accelerated stability data reported in changes being effected supplement and long-term stability data of first three production batches reported in annual report.

II. IN VITRO RELEASE DOCUMENTATION. The in vitro release rate of a lot of the dosage form prepared in new equipment should be compared with the re-

lease rate of a recent lot of comparable age of the product prepared using original equipment. The median in vitro release rates (as estimated by the estimated slope from each cell, see section VII) of the two formulations should be demonstrated to be within acceptable limits, using the testing procedure described in section VII (IN VITRO RELEASE TEST) below.

III. IN VIVO BIOEQUIVALENCE DOCUMENTATION. None.

c. Filing Documentation. Changes being effected supplement (all information including accelerated stability data); annual report (long-term stability data).

3. Level 3 Change

No level 3 changes are anticipated in this category.

B. Process

1. Level 1 Change

a. Definition of Level. Process changes, including changes such as rate of mixing, mixing times, operating speeds, and holding times within approved application ranges. Also, order of addition of components (excluding actives) to either oil or water phase.

b. Test Documentation.

I. CHEMISTRY DOCUMENTATION. None beyond application/compendial product release requirements.

II. IN VITRO RELEASE DOCUMENTATION. None.

III. IN VIVO BIOEQUIVALENCE DOCUMENTATION. None.

c. Filing Documentation. Annual report.

2. Level 2 Change

a. Definition of Level. Process changes, including changes such as rate of mixing, mixing times, rate of cooling, operating speeds, and holding times outside approved application ranges for all dosage forms. Also, any changes in the process of combining the phases.

b. Test Documentation.

I. CHEMISTRY DOCUMENTATION. Application/compendial product release requirements. Notification of change and submission of updated executed batch records. Significant body of information available: One batch with three

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months accelerated stability data reported in changes being effected supplement and long-term stability data of first production batch reported in annual report.

Significant body of information not available: Three batches with three months accelerated stability data reported in changes being effected supplement and long-term stability data of first three production batches reported in annual report.

II. IN VITRO RELEASE DOCUMENTATION. The in vitro release rate of a lot of the dosage form prepared by the new/modified process should be compared with the in vitro release rate of a recent lot of comparable age of the dosage form prepared by the prechange process. The median in vitro release rates (as estimated by the estimated slope from each cell, see VII) of the lots prepared by the two processes should be demonstrated to be within acceptable limits, using the testing procedure described in section VII (IN VITRO RELEASE TEST) below.

III. IN VIVO BIOEQUIVALENCE DOCUMENTATION. None.

c. Filing Documentation. Changes being effected supplement (all information including accelerated stability data); annual report (long-term stability data).

3. Level 3 Change

No level 3 changes are anticipated in this category.

V. BATCH SIZE (SCALE-UP/SCALE-DOWN)

This guidance recommends that the minimum batch size for the NDA pivotal clinical trial batch or the ANDA/AADA biobatch be at least 100 kg or 10% of a production batch, whichever is larger. Deviations from this recommendation should be discussed with the appropriate agency review division. All scale changes should be properly validated and may be inspected by appropriate agency personnel.

A. Level 1 Change

1. Definition of Level

Change in batch size, up to and including a factor of ten times the size of the pivotal clinical trial/biobatch, where: (1) the equipment used to produce the test batch(es) are of the same design and operating principles; (2) the batch(es) is manufactured in full compliance with cGMPs; and (3) the same standard operating procedures (SOPs) and controls, as well as the same formulation and manufacturing procedures, are used on the test batch(es) and on the full-scale production batch(es).

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2. Test Documentation

a. Chemistry Documentation. Application/compendial product release requirements. Notification of change and submission of updated executed batch records in annual report. Stability testing: First production batch on long-term stability reported in annual report.

b. In Vitro Release Documentation. None.

c. In Vivo Bioequivalence Documentation. None.

3. Filing Documentation

Annual report (all information including long-term stability data).

B. Level 2 Change

1. Definition of Level

Changes in batch size from beyond a factor of ten times the size of the pivotal clinical trial/biobatch, where: (1) the equipment used to produce the test batch(es) are of the same design and operating principles; (2) the batch(es) is manufactured in full compliance with cGMPs; and (3) the same standard operating procedures (SOPs) and controls, as well as the same formulation and manufacturing procedures, are used on the test batch(es) and on the full-scale production batch(es).

2. Test Documentation

a. Chemistry Documentation. Application/compendial product release requirements. Notification of change and submission of updated executed batch records. Stability testing: One batch with three months accelerated stability data reported in changes being effected supplement and long-term stability data of first production batch reported in annual report.

b. In Vitro Release Documentation. The in vitro release rate of a lot of the scaled-up batch should be compared with the in vitro release rate of a recent lot, of comparable age, of the prechange scale. The median in vitro release rates (as estimated by the estimated slope from each cell, see section VII) of the lots of the two scales should be demonstrated to be within acceptable limits, using the testing procedure described in section VII (IN VITRO RELEASE TEST) below.

c. In Vivo Bioequivalence Documentation. None.

3. Filing Documentation

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C. Level 3 Change

No level 3 changes are anticipated in this category.

VI. MANUFACTURING SITE

Manufacturing site changes consist of changes in location in the site of manufacture, packaging/filling operations, and/or testing for both company owned and contract manufacturing facilities and do not include any other level 2 or 3 changes, e.g., changes in scale, manufacturing (including process and/or equipment), and components or composition. New manufacturing locations should have had a satisfactory cGMP inspection within the past two years.

A stand-alone analytical testing laboratory site change may be submitted as a changes being effected supplement if the new facility has a current and satisfactory cGMP compliance profile with FDA for the type of testing operation in question. The supplement should contain a commitment to use the same test methods employed in the approved application, written certification from the testing laboratory stating that they are in conformance with cGMPs, and a full description of the testing to be performed by the testing lab. If the facility has not received a satisfactory cGMP inspection for the type of testing involved, a prior approval supplement is recommended. No stability data are needed for a change in a stand alone analytical facility.

A. Level 1 Change

1. Definition of Level

Level 1 changes consist of site changes within a single facility where the same equipment, standard operating procedures (SOPs), environmental conditions (e.g., temperature and humidity) and controls, and personnel common to both manufacturing sites are used, and where no changes are made to the manufacturing batch records, except for administrative information and the location of the facility. Common is defined as employees already working on the campus who have suitable experience with the manufacturing process.

2. Test Documentation

a. Chemistry Documentation. None beyond application/compendial product release requirements.

b. In Vitro Release Documentation. None.

c. In Vivo Bioequivalence Documentation. None.

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3. Filing Documentation

Annual report.

B. Level 2 Change

1. Definition of Level

Level 2 changes consist of site changes within a contiguous campus, or between facilities in adjacent city blocks, where similar equipment, standard operating procedures, (SOPs), environmental conditions (e.g., temperature and humidity) and controls, and personnel common to both manufacturing sites are used, and where no changes are made to the manufacturing batch records, except for administrative information and the location of the facility.

2. Test Documentation

a. Chemistry Documentation. Location of new site and updated executed batch records. None beyond application/compendial product release requirements. Stability testing: First production batch on long-term stability reported in annual report.

b. In Vitro Release Documentation. None.

c. In Vivo Bioequivalence Documentation. None.

3. Filing Documentation

Changes being effected supplement; annual report (long-term stability data).

C. Level 3 Change

1. Definition of Level

Level 3 changes consist of a site change in manufacturing site to a different campus. A different campus is defined as one that is not on the same original contiguous site or where the facilities are not in adjacent city blocks. To qualify as a Level 3 change, similar equipment, SOPs, environmental conditions, and controls should be used in the manufacturing process at the new site. Changes should not be made to the manufacturing batch records except when consistent with other level 1 changes. Administrative information, location, and language translation may be revised as needed. Any change to a new contract manufacturer also constitutes a level 3 change.

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2. Test Documentation

a. Chemistry Documentation. Location of new site and updated executed batch records. Application/compendial product release requirements.

Significant body of information available: One batch with three months accelerated stability data reported in changes being effected supplement and long-term stability data of first three production batches reported in annual report.

Significant body of information not available: Three batches with three months accelerated stability data reported in changes being effected supplement and long-term stability data of first three production batches reported in annual report.

b. In Vitro Release Documentation. The in vitro release rate of a lot of the dosage form from the new manufacturing site should be compared with the in vitro release rate of a recent lot of comparable age of the dosage form manufactured at the prior site. The median in vitro release rates (as estimated by the estimated slope from each cell, see section VII) of the lots from the two sites should be demonstrated to be within acceptable limits, using the testing procedure described in section VII (IN VITRO RELEASE TEST) below.

c. In Vivo Bioequivalence Documentation. None.

3. Filing Documentation

Changes being effected supplement (all information including accelerated stability data); annual report (long-term stability data).

VII. IN VITRO RELEASE TEST

In vitro release is one of several standard methods which can be used to characterize performance characteristics of a finished topical dosage form, i.e., semisolids such as creams, gels, and ointments. Important changes in the characteristics of a drug product formula or the thermodynamic properties of the drug(s) it contains should show up as a difference in drug release. Release is theoretically proportional to the square root of time (/t) when the formulation in question is in control of the release process because the release is from a receding boundary. In vitro release method for topical dosage forms is based on an open chamber diffusion cell system such as a Franz cell system, fitted usually with a synthetic membrane. The test product is placed on the upper side of the membrane in the open donor chamber of the diffusion cell and a sampling fluid is placed on the other side of the membrane in a receptor cell. Diffusion of drug from the topical product to and across the membrane is monitored by assay of sequentially collected samples

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of the receptor fluid. The in vitro release methodology should be appropriately validated. Sample collection can be automated.

Aliquots removed from the receptor phase can be analyzed for drug content by high pressure liquid chromatography (HPLC) or other analytical methodology. A plot of the amount of drug released per unit area (mcg/cm) against the square root of time yields a straight line, the slope of 2 which represents the release rate. This release rate measure is formulation-specific and can be used to monitor product quality. The release rate of the biobatch or currently manufactured batch should be compared with the release rate of the product prepared after a change as defined in this guidance.

One possible in vitro release study design is summarized below. Sponsors are encouraged to review the reference articles listed here.

Diffusion Cell System: A diffusion cell system with a standard open cap ground glass surface with 15 mm diameter orifice and total diameter of 25 mm.

Synthetic Membrane: Appropriate inert and commercially available synthetic membranes such as polysulfone, cellulose acetate/nitrate mixed ester, or Polytetrafluoroethylene 70 Fm membrane of appropriate size to fit the diffusion cell diameter (e.g., 25 mm in above case).

Receptor Medium: Appropriate receptor medium such as aqueous buffer for water soluble drugs or a hydro-alcoholic medium for sparingly water soluble drugs or another medium with proper justification.

Number of Samples: Multiple replicates (six samples are recommended) to determine the release rate (profile) of the topical dermatological product.

Sample Applications: About 300 mg of the semisolid preparation is placed uniformly on the membrane and kept occluded to prevent solvent evaporation and compositional changes. This corresponds to an infinite dose condition.

Sampling Time: Multiple sampling times (at least 5 times) over an appropriate time period to generate an adequate release profile and to determine the drug release rate (a 6-hour study period with not less than five samples, i.e., at 30 minutes, 1, 2, 4 and 6 hours) are suggested. The sampling times may have to be varied depending on the formulation. An aliquot of the receptor phase is removed at each sampling interval and replaced with fresh aliquot, so that the lower surface of the membrane remains in contact with the receptor phase over the experimental time period.

Sample Analysis: Appropriate validated specific and sensitive analytical procedure should be used to analyze the samples and to determine the drug concentration and the amount of drug released.

In Vitro Release Rate: A plot of the amount of drug released per unit membrane area (mcg/cm) versus square 2 root of time should yield a straight line. The slope of the line (regression) represents the release rate of the product. An X intercept typically corresponding to a small fraction of an hour is a normal characteristic of such plots.

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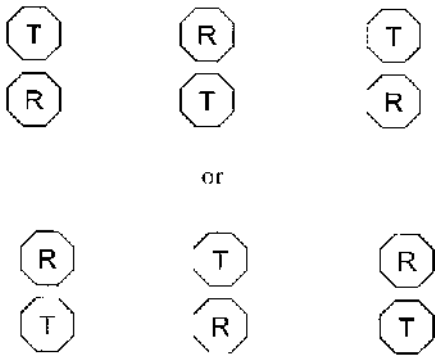
Design of the Rate (Profile) Comparison Study: The typical in vitro release testing apparatus has six cells. For each run of the apparatus, the two products being compared should be assigned to the six cells as follows:



where T represents the *Postchange Lot* (Test product) and R represents the *Prechange Lot* (Reference product). This approach of including both products in each run of the in vitro apparatus will help ensure an unbiased comparison in the event of a systematic difference between runs.

- The choice of the assignment of products to cells (i.e., whether the prechange lot or the postchange lot is assigned to the "upper left corner cell" of the apparatus) may either be made systematically (i.e., alternate the pattern for each successive run) or randomly (i.e., flip a coin or use some other random mechanism).
- For the case of a nonstandard apparatus, with other than six cells, the principle of including both the prechange lot and the postchange lot in the same run should still be used. If the apparatus has only a single cell, the runs on the prechange and postchange lots should be intermixed, rather than obtaining all observations on one product followed by all observations on the other product.

Details of the In Vitro Release Comparison Test

The in vitro release comparison should be carried out as a two-stage test. At the first stage, two runs of the (six cells) in vitro apparatus should be carried out, yielding six slopes (estimated in vitro release rates) for the prechange lot (R) and six slopes for the postchange lot (T). A 90% confidence interval (to be described below) for the ratio of the median in vitro release rate (in the population) for the postchange lot over the median in vitro release rate (in the population) for the

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prechange lot should be computed, expressed in percentage terms. If, at the first stage, this 90% confidence interval falls within the limits of 75% to 133.33%, no further in vitro testing is necessary. If the test is not passed at the first stage, 4 additional runs of the (six cells) in vitro apparatus should be carried out, yielding 12 additional slopes for each product, or 18 in all (including the first-stage results). The 90% confidence interval (to be described below) should be computed using all 18 slopes for each product, including the first-stage results. At the second stage, this 90% confidence interval should fall within the limits of 75% to 133.33%.

Computation of Confidence Interval—an Example

Because outliers are expected to occur on occasion with this testing (for example, due to an air bubble between the product sample and the membrane), a nonparametric method is proposed, whose performance tends to be resistant to the presence of outliers.
The computations are illustrated in the following example:
Suppose that the slope data obtained at the first stage are as follows:

Postchange	Prechange
Lot (T)	Lot (R)
1.3390	1.1331
1.3496	1.1842
1.4946	1.0824
1.4668	1.3049
1.1911	1.0410
1.2210	1.2419

The first step in the computation of the confidence interval is to form the 36 ($= 6 \times 6$) individual T/R ratios. This is illustrated in the following table, where the prechange lot slopes (R) are listed across the top of the table, the postchange lot slopes (T) are listed down the left margin of the table, and the individual T/R ratios are the entries in the body of the table:

	1.1331	1.1842	1.0824	1.3049	1.0410	1.2419
1.3390	1.1817	1.1307	1.2371	1.0261	1.2863	1.0782
1.3496	1.1911	1.1397	1.2469	1.0343	1.2964	1.0867
1.4946	1.3190	1.2621	1.3808	1.1454	1.4357	1.2035
1.4668	1.2945	1.2386	1.3551	1.1241	1.4090	1.1811
1.1911	1.0512	1.0058	1.1004	0.9128	1.1442	0.9591
1.2210	1.0776	1.0311	1.1280	0.9357	1.1729	0.9832

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The second step in the computation of the confidence interval is to order these individual T/R ratios from lowest to highest:

0.9128 0.9357 0.9591 0.9832 1.0058 1.0261 1.0311 1.0343. . .1.2863 1.2945 1.2964 1.3190 1.3551 1.3808 1.4090 1.4357.

In the third step, the ***8th*** and ***29th*** ordered individual ratios are the lower and upper limits, respectively, of the 90% confidence interval for the ratio of the median in vitro release rate (slope) for T over the median in vitro release rate for R. In the example, this confidence interval is 1.0343 to 1.2863, or in percentage terms, 103.43% to 128.63%.

Because this confidence interval falls within the limits of 75% to 133.33%, the product passes at the first stage.

If the product had not passed at the first stage, an additional 4 runs would have been carried out, yielding 12 additional slopes per lot, for a total of 18 slopes per lot altogether (including the first-stage slopes).

All 324 ($= 18 \times 18$) individual T/R ratios would be obtained, and these would be ranked from lowest to highest. It should be evident that even the computations at the first stage would be tedious to do by hand, and doing the computations at the second stage by hand is infeasible. A computer should be used.

At the second stage, the ***110th*** and the ***215th*** ordered individual ratios are the lower and upper limits, respectively, of the 90% confidence interval for the ratio of the median in vitro release rate (slope) for T over the median in vitro release rate for R. If this confidence interval falls within the limits of 75% to 133.33%, the product passes the test at the second stage.

Further Remarks on the In Vitro Release Comparison Test

The statistical test described above is based on a standard confidence interval procedure related to the Wilcoxon Rank Sum/Mann-Whitney rank test, applied to the log slopes. References to this confidence interval procedure include:

Conover, W.J., *Practical Nonparametric Statistics* (Second Edition), John Wiley & Sons, page 223ff, 1980.

Hollander, M. and D.A.Wolfe, *Nonparametric Statistical Methods*, John Wiley & Sons, page 78ff, 1973.

However, as was seen in the example, it is not necessary to actually compute logs in order to carry out the test.

- The example illustrates the case of full data, i.e., where there are 6 slopes per lot at the first stage and, if the second stage is necessary, 18 slopes per lot at the second stage. If slopes are missing, the computations will need to be modified. For example, if a single slope were missing from one of the lots (it does not matter if it is the prechange lot or the postchange lot) at the first stage, there would only be 30 ($= 5 \times 6$) indi-

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vidual T/R ratios, and the limits of the 90% confidence interval would no longer be the eighth and twenty-ninth ordered individual T/R ratio, but rather would be the sixth and twenty-fifth ordered individual T/R ratio. If data are missing at either stage of the test, the correct computation should be determined either by reference to a statistical text or consultant, or by consultation with CDER staff.

- The statistical procedure as described above does not take the block structure of the test (i.e., the fact that data are obtained in runs of six slopes at a time, rather than all at once) into account. This is justified by the following:

  1. In vitro release data available to the Center at this time show no evidence of an important run-to-run effect.
  2. The proposed experimental design, in which both products are included in each run, will help to ensure unbiasedness if a run-to-run effect should occur.

VIII. IN VIVO BIOEQUIVALENCE STUDIES

The design of in vivo bioequivalence studies for semisolid dosage forms varies depending on the pharmacological activity of the drug and dosage form. A brief general discussion of such tests follows.

Objective

To document the bioequivalence of the drug product for which the manufacture has been changed, as defined in this guidance, compared to the drug product manufactured prior to the change or compared to the reference listed drug (RLD).

Design

The study design is dependent on the nature of the active drug. The bioequivalence study can be a comparative skin blanching study as in glucocorticoids (FDA, *Topical Dermatological Corticosteroids: In Vivo Bioequivalence*, June 2, 1995.) or a comparative clinical trial or any other appropriate validated bioequivalence study (e.g., dermatopharmacokinetic study) for the topical dermatological drug product.

Analytical Method

The assay methodology selected should ensure specificity, accuracy, interday and intraday precision, linearity of standard curves, and adequate sensitivity, recovery, and stability of the samples under the storage and handling conditions associated with the analytical method.

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GLOSSARY OF TERMS[3]

Approved Target Composition: The components and amount of each ingredient for a drug product used in an approved pivotal clinical study or bioequivalence study.

Batch: A specific quantity of a drug or other material produced according to a single manufacturing order during the same cycle of manufacture and intended to have uniform character and quality, within specified limits. (21 CFR 210.3(b)(2)).

Contiguous Campus: Contiguous or unbroken site or a set of buildings in adjacent city blocks.

Creams/Lotions: Semisolid emulsions that contain fully dissolved or suspended drug substances for external application. Lotions are generally of lower viscosity.

Diluent: A vehicle in a pharmaceutical formulation commonly used for making up volume and/or weight (e.g., water, paraffin base).

Drug Product: A drug product is a finished dosage form (e.g., cream, gel, or ointment) in its marketed package. It also can be a finished dosage form (e.g., tablet, capsule, or solution) that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients (21 CFR 314.3(b)).

Drug Release: The disassociation of a drug from its formulation thereby allowing the drug to be distributed into the skin or be absorbed into the body where it may exert its pharmacological effect.

Drug Substance: An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of a disease, or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient (21 CFR 314.3(b)).

Emulsion: Emulsions are two phase systems in which an immiscible liquid (dispersed phase) is dispersed throughout another liquid (continuous phase or external phase) as small droplets. Where oil is the dispersed phase and an aqueous solution is the continuous phase, the system is designated as an oil-in-water emulsion. Conversely, where water or an aqueous solution is the dispersed phase and oil or oleaginous material is the continuous phase, the system is designated as a water-in-oil emulsion. Emulsions are stabilized by emulsifying agents that prevent coalescence, the merging of small droplets into larger droplets and, ultimately, into a single separated phase. Emulsifying agents (surfactants) do this by concentration in the interface between the droplet and external phase and by providing a physical barrier around the particle to coalesce. Surfactants also reduce the interfacial tension between the phases, thus increasing the ease of emulsification upon mixing. Emulsifying agents substantially prevent or delay the time needed for emulsion droplets to coalesce. Emulsification is the act of forming an

[3] See Workshop Report: Scale-up of liquid and semisolids disperse systems. G.A. Van Buskirk, V.P. Shah, D. Adair, et al. Pharm. Res. 11:1216–1220, 1994.

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emulsion. Emulsification can involve the incorporation of a liquid within another liquid to form an emulsion or a gas in a liquid to form a foam.

Formulation: A listing of the ingredients and quantitative composition of the dosage form.

Gel: A semisolid system in which a liquid phase is constrained within a three dimensional, cross-linked matrix. The drug substance may be either dissolved or suspended within the liquid phase.

Homogenization: A method of atomization and thereby emulsification of one liquid in another in which the liquids are pressed between a finely ground valve and seat under high pressure (e.g., up to 5,000 psi).

Internal phase: The internal phase or the dispersed phase of an emulsion comprises the droplets that are found in the emulsion.

In Vitro Release Rate: Rate of release of the active drug from its formulation, generally expressed as amount/unit area/time$^{0.5}$.

Ointment: An unctuous semisolid for topical application. Typical ointments are based on petrolatum. An ointment does not contain sufficient water to separate into a second phase at room temperature. Water soluble ointments may be formulated with polyethylene glycol.

Pilot Scale Batch: The manufacture of drug product by a procedure fully representative of and simulating that intended to be used for full manufacturing scale.

Preservative: An agent that prevents or inhibits microbial growth in a formulation to which it has been added.

Process: A series of operations, actions and controls used to manufacture a drug product.

Scale-down: The process of decreasing the batch size.

Scale-up: The process of increasing the batch size.

Shear: A strain resulting from applied forces that cause or tend to cause contiguous parts of a body to slide relative to one another in direction parallel to their plane of contact. In emulsification and suspensions, the strain produced upon passing a system through a homogenizer or other milling device.

Low shear: Processing in which the strain produced through mixing and/or emulsifying shear is modest.

High shear: Forceful processes which, at point of mixing or emulsification place a great strain on the product. Homogenization, by its very nature, is a high shear process which leads to a small and relatively uniform emulsion droplet size. Depending on their operation, mills and mixers are categorized as either high shear or low shear devices.

Significant Body of Information: A significant body of information on the stability of the product is likely to exist after five years of commercial experience for new molecular entities, or three years of commercial experience for new dosage forms.

Strength: Strength is the concentration of the drug substance (for example, weight/weight, weight/volume, or unit dose/volume basis), and/or the potency,

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that is, the therapeutic activity of the drug product as indicated by appropriate laboratory tests or by adequately developed and controlled clinical data (expressed, for example, in terms of units by reference to a standard) (21 CFR 210.3(b)(16)). For semisolid dosage forms the strength is usually stated as a weight/weight (w/w) or weight/volume (w/v) percentage.

Structure Forming Excipient: An excipient which participates in the formation of the structural matrix which gives an ointment, cream or gel etc., its semisolid character. Examples are gel forming polymers, petrolatum, certain colloidal inorganic solids (e.g., bentonite), waxy solids (e.g., cetyl alcohol, stearic acid), and emulsifiers used in creams.

Suspending Agent: An excipient added to a suspension to control the rate of sedimentation of the active ingredients.

Technical Grade: Technical grades of excipients differ in their specifications and intended use. Technical grades may differ in: (1) specifications and/or functionality, (2) impurities, and (3) impurity profiles.

Validation: A procedure to establish documented evidence that provides a high degree of assurance that a specific process or test will consistently produce a product or test outcome meeting its predetermined specifications and quality attributes. A validated manufacturing process or test is one that has been proven to do what it purports or is represented to do. The proof of process validation is obtained through collection and evaluation of data, preferably beginning with the process development phase and continuing through the production phase. Process validation necessarily includes process qualification (the qualification of materials, equipment, systems, building, personnel), but it also includes the control of the entire processes for repeated batches or runs.

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Table 1 Components and Composition

Level	Change	Test documentation	Filing documentation
1	• Deletion or partial deletion of color, fragrance, or flavor • Up to 5% change in approved amount of an excipient with the total additive effect of all excipient changes <=5% • Supplier of structure forming excipient that is primarily a single chemical entity (purity >=95%) or change in supplier or technical grade of any other excipient	• Application/compendial product release requirements • Stability: First production batch on long-term stability	• Annual report (all information including long-term stability data)
2	• Change of >5% and <=10% of approved amount of an excipient with the total additive effect of all excipient changes <=10% • Change in supplier of a structure forming excipient (not covered under level 1) • Change in technical grade of a structure forming excipient • Change in particle size distribution of the drug substance, if the drug is in suspension	• Application/compendial product release requirements • Executed batch records • Stability: One batch with three months accelerated stability data and first production batch on long-term stability • In vitro release test	• Changes being effected supplement (all information including accelerated stability data) • Annual report (long-term stability data)

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Table 1 Continued.

Level	Change	Test documentation	Filing documentation
3	• Any qualitative and quantitative changes in an excipient beyond the ranges noted in level 2 change • Change in crystalline form of the drug substance, if the drug is in suspension	• Application/compendial product release requirements • Executed batch records • Stability: Significant body of information available: One batch with three months accelerated stability data and first three production batches on long-term stability. Significant body of information not available: Three batches with three months accelerated stability data and first three production batches on long-term stability. • In vitro release test (encouraged only) • In vivo bioequivalence test	• Prior approval supplement (all information including accelerated stability data) • Annual report (long-term stability data)

Note: See text for additional information.

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Table 2 Components and Composition—Preservative

Level	Change	Test documentation	Filing documentation
1	• Quantitatively 10% or less change in the approved amount of preservative	• Application/compendial product release requirements • Preservative effectiveness test at lowest specified preservative level	• Annual report
2	• Quantitatively greater than 10% and up to 20% change in the approved amount of preservative	• Application/compendial product release requirements • Preservative effectiveness test at lowest specified preservative level	• Changes being effected supplement
3	• Quantitatively greater than 20% change in the approved amount of preservative (including deletion) or use of a different preservative	• Application/compendial product release requirements • Executed batch records • Preservative effectiveness test at lowest specified preservative level • For new preservative: analytical method for identification and assay; validation studies showing new preservative does not interfere with application/compendial tests • Stability: One batch with three months accelerated stability data and first production batch on long-term stability	• Prior approval supplement (all information including accelerated stability data) • Annual report (long-term stability data)

Note: See text for additional information.

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Table 3 Manufacturing Equipment

Level	Change	Test documentation	Filing documentation
1	• Nonautomated or nonmechanical equipment to automated or mechanical equipment to transfer ingredients • Alternative equipment of same design and operating principles	• Application/compendial product release requirements • Stability: First production batch on long-term stability	• Annual report (all information including long-term stability)
2	• Equipment of a different design or different operating principles • Type of mixing equipment: e.g., high shear to low shear or vice versa.	• Application/compendial product release requirements • Executed batch records • Stability: Significant body of information available: One batch with three months accelerated stability data and first production batch on long-term stability. Significant body of information not available: Three batches with three months accelerated stability data and first three production batches on long-term stability. • In vitro release test	• Changes being effected supplement (all information including accelerated stability data) • Annual report (long-term stability data)

Note: See text for additional information.

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Table 4 Manufacturing Process

Level	Change	Test documentation	Filing documentation
1	• Process changes within approved applications ranges requirements • Order of addition of components (excluding actives)	• Application/compendial product release requirements	• Annual report
2	• Process changes outside approved application ranges • Process of combining phases	• Application/compendial product release requirements • Executed batch records • Stability: Significant body of information available: One batch with three months accelerated stability data and first production batch on long-term stability. Significant body of information not available: Three batches with three months accelerated stability data and first three production batches on long-term stability. • In vitro release test	• Changes being effected supplement (all information including accelerated stability data) • Annual report (long-term stability data)

Note: See text for additional information.

Table 5 Batch Size

Level	Change	Test documentation	Filing documentation
1	• Change in batch size up to and including ten times the size of the pivotal clinical trial/biobatch	• Application/compendial product release requirements • Executed batch records • Stability: First production batch on long-term stability	• Annual report (all information including long-term stability)
2	• Change in batch size beyond a factor of ten times the size of the pivotal clinical trial/biobatch	• Application/compendial product release requirements • Executed batch records • Stability: One batch with three months accelerated stability data and first production batch on long-term stability • In vitro release test	• Changes being effected supplement (all information including accelerated stability data) • Annual report (long-term stability data)

Note: See text for additional information.

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Table 6 Manufacturing Site Change

Level	Change	Test documentation	Filing documentation
1	• Within a single facility	• Application/compendial product release requirements	• Annual report
2	• Within the same contiguous campus or between facilities in adjacent city blocks	• Application/compendial product release requirements • Executed batch records • Location of new site • Stability: First production batch on long-term stability	• Changes being effected supplement • Annual report (long-term stability data)
3	• Different campus • Contract manufacturer	• Application/compendial product release requirements • Executed batch records • Location of new site • Stability: Significant body of information available: One batch with three months accelerated stability data and first three production batches on long-term stability. Significant body of information not available: Three batches with three months accelerated stability data and first three production batches on long-term stability. • In vitro release test	• Changes being effected supplement (all information including accelerated stability data) • Annual report (long-term stability data)

Note: See text for additional information.

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Appendix F

Guidance for Industry[1]— SUPAC-SS: Nonsterile Semisolid Dosage Forms

Manufacturing Equipment Addendum

Draft—Not for Implementation

I. INTRODUCTION

This guidance is intended to provide recommendations to pharmaceutical manufacturers using the Center for Drug Evaluation and Research's guidance for industry, *SUPAC-SS: Nonsterile Semisolid Dosage Forms, Scale-Up and Post Approval Changes: Chemistry Manufacturing and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation* (SUPAC-SS), which published in June 1997. This document should be used in conjunction with the SUPAC-SS guidance document in determining what documentation should be submitted to the Food and Drug Administration (FDA) on equipment changes made in accordance with the recommendations of the SUPAC-SS guidance document. The earlier SUPAC guidance document defines (1) levels of change; (2) recommended chemistry, manufacturing, and controls tests for each level of change; (3) recommended in vitro release tests and/or in vivo bioequivalence tests to support each level of change; and (4) documentation that should support the change for new drug applications (NDAs) and abbreviated new drug applications (ANDAs).

This document is only an aid and, in some cases, specific equipment may not

[1] This guidance has been prepared under the auspices of the Chemistry, Manufacturing, and Controls Coordinating Committee in the Center for Drug Evaluation and Research (CDER) and the Office of Regulatory Affairs (ORA) at the Food and Drug Administration, with the assistance of the International Society of Pharmaceutical Engineering (ISPE). This guidance represents the Agency's current thinking on equipment changes under SUPAC-SS. It does not create or confer any rights for or on any person and does not operate to bind the FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations or both.

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be listed. It does, however, include a representative list of equipment commonly used in the industry. This guidance does not address equipment that has been modified by a pharmaceutical manufacturer to fit its specific needs. If questions arise in using this guidance, please contact the appropriate reviewing office at CDER.

Although this guidance does not discuss validation, any equipment changes should be validated in accordance with current good manufacturing practices (CGMPs). The resulting data will be subject to examination by field investigators during routine GMP inspections. The information here is presented in broad categories of unit operation (particle size reduction and/or separation, mixing, emulsification, deaeration, transfer, and packaging). Definitions and classifications are provided. For each operation, a table categorizes equipment by class (operating principle) and subclass (design characteristic). Examples are given within the subclasses.

Under SUPAC-SS, equipment within the same class and subclass are considered to have the same design and operating principle. For example, a change from a planetary mixer from manufacturer A to another planetary mixer from manufacturer B would not represent a change in design or operating principle and would be considered the same.

A change from equipment in one class to equipment in a different class would usually be considered a change in design and operating principle. For example, a change from a planetary mixer to a dispersator mixer demonstrates a change in operating principle from low-shear convection mixing to high-shear convection mixing. These types of equipment would be considered different under SUPAC-SS.

Applicants should carefully consider and evaluate on a case-by-case basis changes in equipment that are in the same class, but different subclasses.[2] In many situations, these changes in equipment would be considered similar. For example, in Section III, Mixing, under the convection mixers, low shear, a change from an impeller mixer (subclass) to a planetary mixer (subclass) represents a change within a class and between subclasses. Provided the manufacturing process with the new equipment is validated, this change would likely not need a changes being effected (CBE) supplement. At the time of such a change the applicant should have available the scientific data and rationale used to make this determination. It is up to the applicant to determine the filing category.

This guidance will be updated as needed to reflect the introduction and discontinuation of specific types of manufacturing equipment. Manufacturers are en-

[2] In the guidance for industry, SUPAC-SS Nonsterile Semisolid Dosage Forms, Scale-Up and Post Approval Changes: Chemistry Manufacturing and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation (SUPAC-SS), a changes being effected (CBE) supplement is recommended for a change in equipment to a "different design **or** operating principle." On further review, CDER has determined this should state "different design **and** operating principle." The SUPAC-SS guidance will be revised to make this change after the comment period closes on this Addendum and it is finalized.

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couraged to help keep the document current by communicating changes to the Agency and by making suggestions on what equipment should be put in the same class or subclass. The information submitted will be reviewed by FDA and incorporated in an updated guidance document, as appropriate.

On November 21, 1997, the President signed the Food and Drug Administration Modernization Act (FDAMA).[3] Section 116 of FDAMA amended the Food, Drug, and Cosmetic Act by adding section 506A (21 U.S.C. 356a), which provides requirements for making and reporting manufacturing changes to an approved human and animal drug application and for distributing a drug product made with such change. The FDA is currently preparing a proposed rule to amend its regulations (21 CFR 314.70 and 21 CFR 514.8) for supplements and other changes to approved applications to implement the manufacturing changes provision of FDAMA. This draft guidance will be revised as and when appropriate to take into consideration the revised regulations in 21 CFR 314.70 and 21 CFR 514.8 when they are finalized.

II. PARTICLE SIZE REDUCTION/SEPARATION

A. Definitions

1. Unit Operations

a. Particle Size Reduction. The mechanical process of breaking particles into smaller pieces via one or more size reduction mechanisms. The mechanical process used is generally referred to as milling.

i. Particle - Either a discrete crystal or a grouping of crystals, generally known as an agglomerate
ii. Particle Size Reduction Mechanisms

- Impact - Particle size reduction by applying an instantaneous force perpendicular to the particle and/or agglomerate surface. The force can result from particle-to-particle or particle-to-mill surface collision.
- Attrition - Particle size reduction by applying force parallel to the particle surface
- Compression - Particle size reduction by applying a force slowly (as compared to impact) to the particle surface toward the center of the particle
- Cutting - Particle size reduction by applying a shearing force to a material

b. Particle Separation. Particle size classification according to particle size alone

[3] Pub. L. 105–115

Table 1 Unit Operation—Particle Size Reduction

Class	Subclass	Examples
Fluid Energy Mills	Fixed Target	None Identified
	Fluidized Bed	None Identified
	Loop/Oval	Fluid Energy Aljet
	Moving Target	None Identified
	Opposed Jet	Garlock
	Opposed Jet with Dynamic Classifier	Alpine (Hosokawa) Fluid Energy Aljet
	Tangential Jet	Alpine (Hosokawa) Fluid Energy Aljet Sturtevant
Impact Mills	Cage	Stedman
	Hammer Air Swept	Alpine (Hosokawa) Bepex (Hosowaka) Sturtevant
	Hammer Conventional	Alpine (Hosokawa) Fitzpatrick Fluid Air Mikro (Hosokawa) Rietz (Hosokawa) Stokes-Merrill
	Pin/Disc	Alpine (Hosokawa) Kemutec Sturtevant
Cutting Mills	None Identified	Alpine (Hosokawa) Fitzpatrick Urschel
Compression Mills	None Identified	MCA International Ross Stokes-Merrill
Screening Mills	Oscillating Bar	Bepex (Hosokawa) Frewitt Jackson-Crockatt Stokes-Merrill Vector
	Rotating Impeller	Bepex (Hosokawa) Fitzpatrick Fluid Air Kemutec Quadro Stokes-Merrill Zanchetta (Romaco)
	Rotating Screen	Glatt
Tumbling Mills	Ball Media	US Stoneware
	Rod Media	None Identified
	Vibrating	Sweco

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2. Operating Principles

a. Fluid Energy Milling: Particle size reduction by high-speed particle-to-particle impact and/or attrition (also known as micronizing)
b. Impact Milling: Particle size reduction by high-speed mechanical impact or impact with other particles (also known as milling, pulverizing, or comminuting)
c. Cutting: Particle size reduction by mechanical shearing
d. Compression Milling: Particle size reduction by compression stress and shear between two surfaces
e. Screening: Particle size reduction by mechanically-induced attrition through a screen (commonly referred to as milling or deagglomeration)
f. Tumble Milling: Particle size reduction by attrition, using grinding media
g. Separating: Particle segregation based on size alone, without any significant particle size reduction (commonly referred to as screening or bolting)

B. Equipment Classifications

1. Fluid Energy Mills

Fluid energy mill subclasses have no moving parts and primarily differ in the configuration and/or shape of their chambers, nozzles, and classifiers.

- Fixed target
- Fluidized bed
- Loop and/or oval
- Moving target
- Opposed jet
- Opposed jet with dynamic classifier
- Tangential jet

2. Impact Mills

Impact mill subclasses primarily differ in the configuration of the grinding heads, chamber grinding liners (if any), and classifiers.

- Cage
- Hammer air swept
- Hammer conventional
- Pin or disc

3. Cutting Mills

Although cutting mills can differ in whether the knives are movable or fixed, and in classifier configuration, no cutting mill subclasses have been identified.

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4. Compression Mills

Although compression mills, also known as roller mills, can differ in whether one or both surfaces move, no compression mill subclasses have been identified.

5. Screening Mills

Screening mill subclasses primarily differ in the rotating element.

- Oscillating bar
- Rotating impeller
- Rotating screen

6. Tumbling Mills

Tumbling mill subclasses primarily differ in the grinding media used and whether the mill is vibrated.

- Ball media
- Rod media
- Vibrating

7. Separators

Separator subclasses primarily differ in the mechanical means used to induce particle movement.

- Centrifugal
- Vibratory or shaker

Note: If a single piece of equipment is capable of performing multiple discrete unit operations, it has been evaluated solely for its ability to impact particle size or separation.

Table 2 Unit Operation—Separation

Class	Subclass	Examples
Separators	Centrifugal	AZO
		Kason
		Kemutec
		Sweco
	Vibratory/Shaker	Allgaier
		McLanahan
		Rotex
		Russell Finex
		Sweco
		Vortisiv

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III. MIXING

A. Definitions

1. Unit Operation

Mixing: The reorientation of particles relative to one another to achieve uniformity or randomness. This process can include wetting of solids by a liquid phase, dispersion of discrete particles, or deagglomeration into a continuous phase. Heating and cooling via indirect conduction may be used in this operation to facilitate phase mixing or stabilization.

2. Operating Principles

a. Convection Mixing, Low Shear. Mixing process with a repeated pattern of cycling material from top to bottom, in which dispersion occurs under low power per unit mass through rotating low shear forces

b. Convection Mixing, High Shear. Mixing process with a repeated pattern of cycling material from top to bottom, in which dispersion occurs under high power per unit mass through rotating high shear forces

c. Roller Mixing (Milling). Mixing process by high mechanical shearing action where compression stress is achieved by passing material between a series of rotating rolls. This is commonly referred to as compression or roller milling.

d. Static Mixing. Mixing process in which material passes through a tube with stationary baffles. The mixer is generally used in conjunction with an in-line pump.

B. Equipment Classification

1. Convection Mixers, Low Shear

This group normally operates under low shear conditions and is broken down by impeller design and movement. Design can also include a jacketed vessel to facilitate heat transfer.

- Anchor or sweepgate
- Impeller
- Planetary

2. Convection Mixers, High Shear

This group normally operates only under high shear conditions. Subclasses are differentiated by how the high shear is introduced into the material, such as by a dispersator with serrated blades or homogenizer with rotor stator.

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Table 3 Unit Operation—Mixing

Class	Subclass	Examples
Convection Mixers, Low Shear	Anchor/Sweepgate	Brogli
		Fryma
		GEI Krieger (GEI North America)
		Groen
		Koruma (Romaco)
		Lee Industries
		Ross
		Waukesha Cherry Burrell
	Impeller	Bematek
		Chemineer
		Gate
		IKA
		Lightnin
		Moorhouse-Cowles
		Quadro
		Ross
	Planetary	Aaron
		Aeschbach
		AMF
		GEI-Collette (GEI North America/Vector)
		Hobart
		Jaygo
		Littleford Day
		Ross
		Vrieco
Convection Mixers, High Shear	Dispersator	Chemineer
		Cowles
		Gate
		IKA
		Koruma (Romaco)
		Lightnin
		Ross
	Roto Stator	Arde-Barinco
		Bematek
		Fryma
		Gaulin
		Greerco
		Koruma (Romaco)
		Manton Gaulin

Table 3 Continued.

Class	Subclass	Examples
		Moorhouse-Cowles
		Premier
		Ross
		Silverson
		Tri-Homo
		Ultra Turex
		Urschel
Roller Mixers (Mills)	None Identified	MCA International
		Ross
		Stokes Merrill
Static Mixers	None Identified	Ross

- Dispersator
- Rotor stator

3. Roller Mixers (Mills)

No roller mixer subclasses have been identified.

4. Static Mixers

No static mixer subclasses have been identified.

Note: If a single piece of equipment is capable of performing multiple discrete unit operations, it has been evaluated solely for its ability to mix materials.

IV. EMULSIFICATION

A. Definitions

1. Unit Operation

Emulsification: The application of physical energy to a liquid system consisting of at least two immiscible phases, causing one phase to be dispersed into the other.

2. Operating Principles

a. Low Shear Emulsification. Use of low shear energy using mechanical mixing with an impeller to achieve a dispersion of the mixture. The effectiveness of this operation is especially dependent on proper formulation.

Table 4 Unit Operation—Emulsification

Class	Subclass	Examples
Low Shear Emulsifiers	None Identified	Bematek
		Lightnin
		Moorhouse-Cowles
		Ross
High Shear Emulsifiers	Dispersator	Chemineer
		Cowles
		Gate
		IKA
		Koruma (Romaco)
		Lightnin
		Ross
	Rotor Stator	Arde-Barinco
		Bematek
		Fryma
		Gaulin
		Greerco
		Koruma (Romaco)
		Manton Gaulin
		Moorhouse-Cowles
		Premier
		Ross
		Silverson
		Tri-Homo
		Ultra Turex
		Urschel
	Valve or Pressure Homogenizer	Manton Gaulin
		Microfluidics

b. High Shear Emulsification. Use of high shear energy to achieve a dispersion of the immiscible phases. High shear can be achieved by the following means:

i. Stirring the mixture with a high speed chopper or saw-tooth dispersator
ii. Passing the mixture through the gap between a high-speed rotor and a stationary stator
iii. Passing the mixture through a small orifice at high pressure (valve-type homogenizer) or through a small orifice at high pressure followed by impact against a hard surface or opposing stream (valve-impactor type homogenizer), causing sudden changes of pressure

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B. Equipment Classification

1. Low Shear Emulsifiers

Although low shear emulsification equipment (mechanical stirrers or impellers) can differ in the type of fluid flow imparted to the mixture (axial-flow propeller or radial-flow turbines), no subclasses have been defined.

2. High Shear Emulsifiers

Subclasses of high shear emulsification equipment differ in the method used to generate high shear.

- Dispersator
- Rotor stator
- Valve or pressure homogenizer

Note: If a single piece of equipment is capable of performing multiple discrete unit operations, the unit has been evaluated solely for its ability to emulsify materials.

V. DEAERATION

A. Definitions

1. Unit Operation

Deaeration: The elimination of trapped gases to provide more accurate volumetric measurements and remove potentially reactive gases

Table 5 Unit of Operation—Deaeration

Class	Subclass	Examples
Deaerators	Off Line/In Line	Cornell Machine Co. Fryma Jaygo Koruma (Romaco)
	Vacuum Vessel	Fryma GEI-Kreiger (GEI North America) Groen Koruma (Romaco) Lee Industries Paul Mueller Co.

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2. Operating Principles

The use of vacuum or negative pressure, alone or in combination with mechanical intervention or assistance

B. Equipment Classification

1. Deaerators

Deaerator subclasses differ primarily in their air removal paths, either through the bulk material or through a thin film, and in whether they use a batch or in-line process.

- Off-Line or in-line
- Vacuum vessel

Note: If a single piece of equipment is capable of performing multiple discrete unit operations, it has been evaluated solely for its ability to deaerate materials.

VI. TRANSFER

A. Definition

1. Unit Operation

Transfer: The controlled movement or transfer of materials from one location to another

2. Operating Principles

a. Passive. The movement of materials across a non-mechanically-induced pressure gradient, usually through conduit or pipe

b. Active. The movement of materials across a mechanically-induced pressure gradient, usually through conduit or pipe

B. Equipment Classification

1. Low Shear

Active or passive material transfer, with a low degree of induced shear

- Diaphragm
- Gravity
- Peristaltic

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Table 6 Unit Operation—Transfer

Class	Subclass	Examples
Low Shear	Diaphragm	APV
		Pulsafeeder
		TL Systems
		Tri-Clover
		Wilden
	Gravity	None Identified
	Peristaltic	Barnant Co
		Cole Palmer
		Pulsafeeder
		Vanton
		Watson-Marlow
	Piston	APV
		Graco
		National
		Nordson
		Waukesha
		Wilden
	Pneumatic	None Identified
	Rotating Lobe	Flowteck
		Fristam
		Sine
		Tri-Clover
		Viking
		Waukesha
	Screw or Helical Screw	Moyno
High Shear	Centrifugal or Turbine	APV
		BMS
		Fristam
		Pulsafeeder
		Tri-Clover
		Vanton
		Waukesha
	Piston	APV
		Graco
		National Instrument
		Nordson
		Waukesha
		Wilden
	Rotating Gear	APV
		BSM
		Ertel Engineering
		Pulsafeeder
		Viking
		Waukesha

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- Piston
- Pneumatic
- Rotating lobe
- Screw or helical screw

2. High Shear

Active or mechanical material transfer with a high degree of induced shear

- Centrifugal or turbine
- Piston
- Rotating gear

Note: This section is intended to deal with the transfer of shear sensitive materials, including product or partially manufactured product. A single piece of equipment can be placed in either a low or high shear class, depending on its operating parameters. If a single piece of equipment is capable of performing multiple discrete unit operations, the unit has been evaluated solely for its ability to transfer materials.

VII. PACKAGING

A. Definitions

1. Unit Operation

a. Holding. The process of storing product after completion of manufacturing process and prior to filling final primary packs

b. Transfer. The process of relocating bulk finished product from holding to filling equipment using pipe, hose, pumps and/or other associated components

c. Filling. The delivery of target weight or volume of bulk finished product to primary pack containers

d. Sealing. A device or process for closing and/or sealing primary pack containers following the filling process

2. Operating Principles

a. Holding. The storage of liquid, semi-solids, or product materials in a vessel that may or may not have temperature control and/or agitation

b. Transfer. The controlled movement or transfer of materials from one location to another

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Table 7 Unit Operation—Holding

Class	Subclass	Examples
Holders	Auger	Bonafacci
		Bosch
		Cozzoli Machine
		Erweka
		Fryma-Maschinenbau
		Inova
		Loeb Equipment
		Sarong
		Young Industries
	Gravity	Bonafacci
		Bosch
		Cozzoli Machine
		Erweka
		Fryma-Maschinenbau
		Inova
		Loeb Equipment
		Sarong
		Young Industries
	Pneumatic (nitrogen, air, etc.)	Bonafacci
		Bosch
		Cozzoli Machine
		Erweka
		Fryma-Maschinenbau
		Inova
		Loeb Equipment
		Sarong
		Young Industries

c. Filling. Filling operating principles involve several associated subprinciples. The primary package can be precleaned to remove particulates or other materials by the use of ionized air, vacuum, or inversion. A holding vessel equipped with an auger, gravity, or pressure material feeding system should be used. The vessel may or may not be able to control temperature and/or agitation. Actual filling of the dosage form into primary containers can involve a metering system based on an auger, gear, orifice, peristaltic, or piston pump. A head-space blanketing system can also be used.

d. Sealing. Primary packages can be sealed using a variety of methods, including conducted heat and electromagnetic (induction or microwave) or mechanical manipulation (crimping or torquing).

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Table 8 Unit Operation—Filling

Class	Subclass	Examples
Fillers	Auger	Bonafacci
		Bosch
		Erweka
		Fryma-Maschinenbau
		IWKA
		Kalish
		Norden
		Sarong
	Gear pump	APV
		BMS
		Bonafacci
		Bosch
		Ertel Engineering
		Erweka
		Fryma-Maschinenbau
		IWKA
		Kalish
		Norden
		Pulsafeeder
		Sarong
		Viking
		Waukesha
	Orifice	Bonafacci
		Bosch
		Erweka
		Fryma-Maschinenbau
		IWKA
		Kalish
		Norden
		Sarong
	Peristaltic pump	Barnant Co.
		Bonafacci
		Bosch
		Cole-Parmer
		Erweka
		Fryma-Maschinenbau
		IWKA
		Kalish
		Norden
		Pulsafeeder
		Sarong
		Vanton
		Watson-Marlow

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Table 8 Continued.

Class	Subclass	Examples
	Piston	APV
		Bonafacci
		Bosch
		Erweka
		Fryma-Maschinenbau
		Graco
		IWKA
		Kalish
		National
		Norden
		Sarong
		Waukesha
		Wilden

Table 9 Unit Operation—Sealing

Class	Subclass	Examples
Sealers	Heat	Harro Höfliger Packaging
		Hutchins and Hutchins
		Loeb Equipment
		Prodo-Pak
		Romaco
		VWR Scientific Products
	Induction	Pillar
	Microwave	None Identified
	Mechanical/Crimping	Austin Reed
		Bishop International
		Chase-Logeman
		Cozzoli Machine
		Integrated Packaging System
		Loeb Equipment
		Romaco
		VWR Scientific Products
	Torque	Bausch and Stroebel Machine
		Cozzoli Machine
		Electronic Liquid Filler
		Madison Equipment
		Sure Torque

B. Equipment Classification

1. Holders

Although holding vessels can differ in their geometry and ability to control temperature or agitation, their primary differences are based on how materials are fed.

- Auger
- Gravity
- Pneumatic (nitrogen, air, etc.)

2. Fillers

The primary differences in filling equipment are based on how materials are metered.

- Auger
- Gear pump
- Orifice
- Peristaltic pump
- Piston

3. Sealers

The differences in primary container sealing are based on how energy is transferred or applied.

- Heat
- Induction
- Microwave
- Mechanical or crimping
- Torque

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Appendix G

Guidance for Industry[1]—Changes to an Approved NDA or ANDA

I. INTRODUCTION

On November 21, 1997, the President signed the Food and Drug Administration Modernization Act (the Modernization Act).[2] Section 116 of the Modernization Act amended the Food, Drug, and Cosmetic Act (the Act) by adding section 506A (21 U.S.C. 356a), which provides requirements for making and reporting manufacturing changes to an approved application and for distributing a drug product made with such changes.

The purpose of this guidance is to provide recommendations to holders of new drug applications (NDAs) and abbreviated new drug applications (ANDAs) who intend to make postapproval changes in accordance with Section 506A. The guidance covers recommended reporting categories for postapproval changes for drugs, other than specified biotechnology and specified synthetic biological products. Recommendations are provided for postapproval changes in (1) components and composition, (2) manufacturing sites, (3) manufacturing process, (4) specifications, (5) package, (6) labeling, (7) miscellaneous changes, and (8) multiple related changes.

Recommendations on reporting categories for changes relating to specified biotechnology and specified synthetic biological products regulated by CDER are found in the guidance for industry entitled *Changes to an Approved Appli-*

[1] This guidance has been prepared under the direction of the Chemistry, Manufacturing and Controls Coordinating Committee in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on how it will apply the requirements of section 506A of the Act for NDA and ANDA products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both.

[2] Pub. L. 105–115.

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cation for Specified Biotechnology and Specified Synthetic Biological Products (July 1997).[3]

This guidance does not provide recommendations on the specific information that should be developed by an applicant to assess the effect of the change on the identity, strength (e.g., assay, content uniformity), quality (e.g., physical, chemical, and biological properties), purity (e.g., impurities and degradation products), or potency (e.g., biological activity, bioavailability, bioequivalence) of a product as they may relate to the safety or effectiveness of the product. An applicant should consider all relevant CDER guidance documents for recommendations on the information that should be submitted to support a given change.[4]

CDER has published guidances, including the SUPAC (scale-up and postapproval changes) guidances, that provide recommendations on reporting categories. To the extent that the recommendations on ***reporting categories*** in this guidance are found to be inconsistent with guidances published before this guidance was finalized, the recommended reporting categories in such previously published guidances are superseded by this guidance. This guidance does not provide extensive recommendations on reporting categories for components and composition changes (see section V). Therefore, recommended reporting categories for components and composition changes provided in previously published guidances, such as the SUPAC guidances, still apply. Section 506A of the Act provides for two types of changes being effected supplements (see section II) while previously there was only one type. It is important for applicants to use this guidance to determine which type of changes being effected supplement is recommended. CDER intends to update the previously published guidances to make them consistent with this guidance.

If guidance for either recommended filing categories and/or information that should be submitted to support a particular change is not available, the appropriate CDER chemistry or microbiology review staff can be consulted for advice.

II. REPORTING CATEGORIES

Section 506A of the Act provides for four reporting categories that are distinguished in the following paragraphs.

A ***major change*** is a change that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product (506A(c)(2)). A ma-

[3] FDA is currently revising the 1997 guidance and intends to issue it in draft for public comment.

[4] A list of CDER guidances is available on the Internet at http://www.fda.gov/cder/guidance/index.htm.

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jor change requires the submission of a supplement and approval by FDA prior to distribution of the product made using the change (506A(c)(1)). This type of supplement is called, and should be clearly labeled, a ***Prior Approval Supplement***. An applicant may ask FDA to expedite its review of a prior approval supplement for public health reasons (e.g., drug shortage) or if a delay in making the change described in it would impose an extraordinary hardship on the applicant. This type of supplement is called, and should be clearly labeled, a *Prior Approval Supplement—Expedited Review Requested*.[5] Requests for expedited review based on extraordinary hardship should be reserved for manufacturing changes made necessary by catastrophic events (e.g., fire) or by events that could not be reasonably foreseen and for which the applicant could not plan.

A ***moderate change*** is a change that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product. There are two types of moderate change. One type of moderate change requires the submission of a supplement to FDA at least 30 days before the distribution of the product made using the change (506A(d)(3)(B)(i)). This type of supplement is called, and should be clearly labeled, a ***Supplement—Changes Being Effected in 30 Days.*** The product made using a moderate change cannot be distributed if FDA informs the applicant within 30 days of receipt of the supplement that a prior approval supplement is required (506A(d)(3)(B)(i)). For each change, the supplement must contain information determined by FDA to be appropriate and must include the information developed by the applicant in assessing the effects of the change (506A(b)). If FDA informs the applicant within 30 days of receipt of the supplement that information is missing, distribution must be delayed until the supplement has been amended with the missing information.

FDA may identify certain moderate changes for which distribution can occur when FDA receives the supplement (506A(d)(3)(B)(ii)). This type of supplement is called, and should be clearly labeled, a ***Supplement—Changes Being Effected.*** If, after review, FDA disapproves a changes being effected in 30 days supplement or changes being effected supplement, FDA may order the manufacturer to cease distribution of the drugs that have been made using the disapproved change (506A(d)(3)(B)(iii)).

A ***minor change*** is a change that has minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product. The applicant must describe minor changes in its next ***Annual Report*** (506A(d)(1)(A) and (d)(2)).

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[5] Internal Agency policies and procedures relating to processing requests for expedited review of supplements to approved ANDAs and NDAs are documented in CDER's Manual of Policies and Procedures (MAPP) at 5240.1 and 5310.3, respectively. MAPPs can be located on the Internet at http://www.fda.gov/cder/mapp.htm.

An applicant can submit one or more protocols (i.e., comparability protocols) describing tests, validation studies, and acceptable limits to be achieved to demonstrate the absence of an adverse effect from specified types of changes. A comparability protocol can be used to reduce the reporting category for specified changes. A proposed comparability protocol should be submitted as a prior approval supplement, if not approved as part of the original application. FDA intends to issue separate guidance on comparability protocols.

III. GENERAL REQUIREMENTS

Other than for editorial changes in previously submitted information (e.g., correction of spelling or typographical errors, reformatting of batch records), an applicant must notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application (506A(a)).

An applicant making a change to an approved application under section 506A of the Act must also conform to other applicable laws and regulations, including current good manufacturing practice (CGMP) requirements of the Act (21 U.S.C. 351(a)(2)(B)) and applicable regulations in Title 21 of the *Code of Federal Regulations* (e.g., 21 CFR parts 210, 211, 314). For example, manufacturers must comply with relevant CGMP validation and recordkeeping requirements and ensure that relevant records are readily available for examination by authorized FDA personnel during an inspection. A changes being effected supplement for labeling changes must include 12 copies of the final printed labeling (21 CFR 314.50(e)(2)(ii)).

Except for a supplemental application providing for a change in labeling, an applicant should include a statement in a supplemental application or amendment certifying that the required field copy (21 CFR 314.50) of the supplement or amendment has been provided.[6]

IV. ASSESSING THE EFFECT OF MANUFACTURING CHANGES

A. Assessment of the Effects of the Change

A drug made with a manufacturing change, whether a major manufacturing change or otherwise, may be distributed only after the holder validates (i.e., as-

[6] Mailing information for field copies is provided in 21 CFR 314.440(a)(4). FDA recommends that the *applicant's home FDA district office* referred to in the regulations be the district office where the applicant's headquarters is located.

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sesses) the effects of the change on the identity, strength, quality, purity, and potency of the product as these factors may relate to the safety or effectiveness of the product (506A(b)).[7] For each change, the supplement or annual report must contain information determined by FDA to be appropriate and must include the information developed by the applicant in assessing the effects of the change (506A(b), (c)(1), (d)(2)(A), and (d)(3)(A)). Recommendations on the type of information that should be included in a supplemental application or annual report is available in guidance documents. If no guidance is available on the type of information that should be submitted to support a change, the applicant is encouraged to contact the appropriate chemistry or microbiology review staff.

1. Conformance to Specifications

An assessment of the effect of a change on the identity, strength, quality, purity, or potency of the drug product should include a determination that the drug substance intermediates, drug substance, in-process materials, and/or drug product affected by the change conform to the approved specifications.[8] A *specification* is a quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, and other components, including container closure systems and their components and in-process materials. For the purpose of defining specifications, *acceptance criteria* are numerical limits, ranges, or other criteria for the tests described. Conformance to a specification means that the material, when tested according to the analytical procedures listed in the specification, will meet the listed acceptance criteria.

2. Additional Testing

In addition to confirmation that the material affected by manufacturing changes continues to meet its specification, the applicant should perform additional testing, when appropriate, to assess whether the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product have been or will be affected. The assessment should include, as appropriate,

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[7] *Validate the effects of the change* means to assess the effect of a manufacturing change on the identity, strength, quality, purity, or potency of a drug as these factors relate to the safety or effectiveness of the drug. The term *assess* or *assessment,* as used in this guidance, is not the same as CGMP validation. Unless otherwise specified by FDA, CGMP validation (e.g., process, equipment) data need not be filed in the application but should be retained at the facility and be available for review by FDA at the Agency's discretion. For example, in addition to the information assessing the effects of the change specified in 506A(b) of the Act, validation information on sterilization processes should be submitted in an NDA or ANDA.

[8] If a specification needs to be revised as a result of the change, this would be considered a multiple change (See sections VIII and XII).

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evaluation of any changes in the chemical, physical, microbiological, biological, bioavailability, and/or stability profiles. This additional assessment could involve testing of the postchange drug product itself or, if appropriate, the component directly affected by the change. The type of additional testing that an applicant should perform would depend on the type of manufacturing change, the type of drug substance and/or drug product, and the effect of the change on the quality of the product. For example:

- Evaluation of changes in the impurity or degradant profile could first involve profiling using appropriate chromatographic techniques and then, depending on the observed changes in the impurity profile, toxicology tests to qualify a new impurity or degradant or to qualify an impurity that is above a previously qualified level.[9]
- Evaluation of the hardness or friability of a tablet after certain changes.
- Assessment of the effect of a change on bioequivalence when required under 21 CFR part 320 could include, for example, multipoint and/or multimedia dissolution profiling and/or an in vivo bioequivalence study.
- Evaluation of extractables from new packaging components or moisture permeability of a new container closure system.

An applicant should refer to all relevant CDER guidance documents for recommendations on the information that should be submitted to support a given change. If guidance for information that should be submitted to support a particular change is not available, applicants can consult the appropriate CDER chemistry or microbiology review staff for advice.

B. Equivalence

When testing is performed, the applicant should usually assess the extent to which the manufacturing change has affected the identity, strength, quality, purity, or potency of the drug product. Typically this is accomplished by comparing test results from pre- and postchange material and determining if the test results are equivalent. Simply stated: Is the product made after the change equivalent to the product made before the change? An exception to this general approach is that when bioequivalence should be redocumented for certain ANDA postapproval changes, the comparator should be the reference listed drug. Equivalence comparisons frequently require a criterion for comparison with calculation of confidence intervals relative to a predetermined equivalence interval. For this, as well as for other reasons, *equivalent* does not necessarily mean *identical*. Equivalence may also re-

[9] Recommendations on identifying, qualifying, and reporting impurities can be found in relevant guidances (e.g., ICH Q3B *Impurities in New Drug Products* (November 1996)).

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late to maintenance of a quality characteristic (e.g., stability) rather than a single performance of a test.

C. Adverse Effect

Sometimes manufacturing changes have an adverse effect on the identity, strength, quality, purity, or potency of the drug product. In many cases, the applicant chooses not to implement these manufacturing changes, but sometimes the applicant wishes to do so. If an assessment concludes that a change has adversely affected the identity, strength, quality, purity, or potency of the drug product, **the change should be filed in a prior approval supplement, regardless of the recommended reporting category for the change.** For example, a type of process change with a recommended filing category of a supplement—changes being effected in 30 days, could cause a new degradant to be formed that requires qualification and/or identification.[10] However, the applicant's degradation qualification procedures may indicate that there are no safety concerns relating to the new degradant. The applicant should submit this change in a prior approval supplement with appropriate information to support the continued safety and effectiveness of the product. During the review of the prior approval supplement, the FDA will assess the impact of any adverse effect on the product as it may relate to the safety or effectiveness of the product.

Applicants are encouraged to consult with the appropriate CDER chemistry or microbiology review staff if there are any questions on whether a change in a characteristic would be viewed by CDER as adversely affecting the identity, strength, quality, purity, or potency of the product.

V. COMPONENTS AND COMPOSITION

Changes in the qualitative or quantitative formulation, including inactive ingredients, as provided in the approved application, are considered major changes and should be filed in a prior approval supplement, unless exempted by regulation or guidance (506A(c)(2)(A)). The deletion or reduction of an ingredient intended to affect only the color of a product may be reported in an annual report. Guidance on changes in components and composition that may be filed in a changes being effected supplement or annual report is not included in this document because of the complexity of these recommendations, but may be covered in one or more guidance documents describing postapproval changes (e.g., SUPAC documents).

[10] Recommendations on identifying, qualifying, and reporting impurities can be found in relevant guidances.

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VI. MANUFACTURING SITES [11]

A. General Considerations

CDER should be notified about a change to a different manufacturing site used by an applicant to (1) manufacture or process drug products,[12] in-process materials, drug substances, or drug substance intermediates, (2) package drug products, (3) label drug products, and (4) test components, drug product containers, closures, packaging materials, in-process materials, or drug products. Sites include those owned by the applicant or contract sites used by an applicant. Testing sites include those performing physical, chemical, biological, and microbiological testing to monitor, accept, or reject materials, as well as those performing stability testing. Sites used to label drug products are considered those that perform labeling of the drug product's primary or secondary packaging components. Sites performing operations that place identifying information on the dosage form itself (e.g., ink imprint on a filled capsule) are considered to be facilities that manufacture or process the drug product. The supplement or annual report should identify whether the proposed manufacturing site is an alternative or replacement to those provided for in the approved application.

A move to a different manufacturing site, when it is a type of site routinely subject to FDA inspection, should be filed as a prior approval supplement if the site does not have a ***satisfactory CGMP inspection***[13] for the ***type of operation***[14] being moved (see sections VI.B.1 and 2).

For labeling, secondary packaging, and testing site changes, the potential for adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product is considered to be independent of the type of drug product dosage form or specific type of operation being performed. Therefore, the recommended reporting category for any one of these manufacturing site changes will be the same for all types of drug products and operations. For manufacturing sites used to (1) manufacture or process drug products, in-process materials, drug substances, or drug substance intermediates or (2) perform primary packaging operations, the potential for adverse impact and, consequently, the recommended reporting category depends on various factors such as the type of product and operation being performed. For this reason, recommended reporting categories may differ depending on the type of drug product and operations.

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[11] See Attachment A for a discussion of the definition of *same manufacturing site* and *different manufacturing site*.

[12] Manufacturing or processing drug product would also include the preparation (e.g., sterilization, depyrogenation, irradiation, washing) by the applicant or applicant's contractor of container closure systems or packaging components.

[13] See Glossary for a definition of *satisfactory CGMP inspection*.

[14] See Attachment B for a discussion of the term *type of operation*.

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Except for those situations described in sections VI.B.4, VI.C.1.b, and VI.D.5, moving production operations between buildings at the same manufacturing site or within a building, or construction activities occurring at a manufacturing site, do not have to be reported to CDER. A move to a different manufacturing site that involves other changes (e.g., process, equipment) should be evaluated as a multiple related change (see section XII) to determine the appropriate reporting category.

B. Major Changes (Prior Approval Supplement)

The following are examples of changes that are considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. A move to a different manufacturing site, except one used to manufacture or process a drug substance intermediate, when the new manufacturing site has never been inspected by FDA for the type of operation that is being moved or the move results in a restart at the new manufacturing site of a type of operation that has been discontinued for more than two years.
2. A move to a different manufacturing site, except those used to manufacture or process a drug substance intermediate, when the new manufacturing site does not have a satisfactory CGMP inspection for the type of operation being moved.
3. A move to a different manufacturing site for (1) the manufacture, processing, or primary packaging of drug products when the primary packaging components control the dose delivered to the patient or the formulation modifies the rate or extent of availability of the drug, or (2) the manufacture or processing of in-process materials with modified-release characteristics. Examples of these types of drug products include modified-release solid oral dosage forms,[15] transdermal systems, liposomal products, depot products, oral and nasal metered-dose inhalers (MDIs), dry powder inhalers (DPIs), and nasal spray pumps.
4. Transfer of manufacturing of an aseptically processed sterile drug substance or aseptically processed sterile drug product to (1) a newly constructed or refurbished aseptic processing facility or area or (2) an existing aseptic processing facility or area that does not manufacture similar (including container types and sizes) approved products. For

[15] Certain operations relating to the manufacture, processing, or primary packaging of modified-release solid oral dosage form products need not be reported in a prior approval supplement (see sections VI.C.1.c and VI.D.6).

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example, transferring the manufacture of a lyophilized product to an existing aseptic process area where no approved lyophilized products are manufactured or the approved lyophilized products being manufactured have dissimilar container types and/or sizes to the product being transferred. See section VI.C.1.b for recommendations for other manufacturing site changes relating to aseptically processed sterile drug substance or aseptically processed sterile drug product.

5. Transfer of the manufacture of a finished product sterilized by terminal processes to a newly constructed facility at a different manufacturing site. Once this change has been approved, subsequent site changes to the facility for similar product types and processes may be filed as a supplement—changes being effected in 30 days (see section VI.C.1.a).

C. Moderate Changes (Supplement—Changes Being Effected)

The following are examples of changes that are considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

The following manufacturing site changes (excluding changes relating to drug substance intermediate manufacturing sites) should be filed in a prior approval supplement if the new site does not have a satisfactory CGMP inspection for the type of operation being moved (see sections VI.B.1 and 2).

1. Supplement—Changes Being Effected in 30 Days

a. A move to a different manufacturing site for the manufacture or processing of any drug product, in-process material, or drug substance that is not otherwise provided for in this guidance.
b. For aseptically processed sterile drug substance or aseptically processed sterile drug product, a move to an aseptic processing facility or area at the same or different manufacturing site, except as provided for in section VI.B.4.
c. A move to a different manufacturing site for the primary packaging of (1) any drug product that is not otherwise listed as a major change and (2) modified-release solid oral dosage form products.
d. A move to a different manufacturing site for testing if (1) the test procedures approved in the application or procedures that have been implemented via an annual report are used, (2) all postapproval commitments made by the applicant relating to the test procedures have been fulfilled (e.g., providing methods validation samples), and (3) the new testing facility has the capability to perform the intended testing.

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2. Supplement—Changes Being Effected

   a. A move to a different manufacturing site for the manufacture or processing of the final intermediate.

D. Minor Changes (Annual Report)

The following are examples of changes that are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

The following manufacturing site changes (excluding changes relating to drug substance intermediate manufacturing sites) should be filed in a prior approval supplement if the new site does not have a satisfactory CGMP inspection for the type of operation being moved (see sections VI.B.1 and 2).

1. A move to a different manufacturing site for secondary packaging.
2. A move to a different manufacturing site for labeling.
3. A move to a different manufacturing site for the manufacture or processing of drug substance intermediates, other than the final intermediate.
4. A change in the contract sterilization site for packaging components when the process is not materially different from that provided for in the approved application and the facility has a satisfactory CGMP inspection for the type of operation being performed.
5. A transfer of the manufacture of a finished product sterilized by terminal processes to a newly constructed building or existing building at the same manufacturing site.
6. A move to a different manufacturing site for the ink imprinting of solid oral dosage form products.

VII. MANUFACTURING PROCESS

A. General Considerations

The potential for adverse effects on the identity, strength, quality, purity, or potency of a drug product as they may relate to the safety or effectiveness of the product depends on the type of manufacturing process and the changes being instituted for the drug substance or drug product.

In some cases there may be a substantial potential for adverse effect, regardless of direct testing of the drug substance or drug product for conformance with the approved specification. When there is a substantial potential for adverse effects, a change should be filed in a prior approval supplement.

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B. Major Changes (Prior Approval Supplement)

The following are examples of changes that are considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. Changes that may affect the controlled (or modified) release, metering or other characteristics (e.g., particle size) of the dose delivered to the patient, including the addition or deletion of a code imprint by embossing, debossing, or engraving on a modified-release solid oral dosage form.
2. Changes that may affect product sterility assurance including, where appropriate, process changes for sterile drug substances and sterile packaging components. These include:

   - Changes in the sterilization method (e.g., gas, dry heat, irradiation). These include changes from sterile filtered or aseptic processing to terminal sterilization, or vice versa.
   - Addition, deletion, or substitution of sterilization steps or procedures for handling sterile materials in an aseptic processing operation.
   - Replacing sterilizers that operate by one set of principles with sterilizers that operate by another principle (e.g., substituting a gravity displacement steam process with a process using superheated water spray).
   - Addition to an aseptic processing line of new equipment made of different materials (e.g., stainless steel versus glass, changes between plastics) that will come in contact with sterilized bulk solution or sterile drug components, or deletion of equipment from an aseptic processing line.
   - Replacing a Class 100 aseptic fill area with a barrier system or isolator for aseptic filling. Once this change has been approved, subsequent process changes for similar product types in the same barrier system or isolator may be filed as a Supplement—changes being effected in 30 days.
   - Replacement or addition of lyophilization equipment of a different size that uses different operating parameters or lengthens the overall process time.
   - Changes from bioburden-based terminal sterilization to the use of an overkill process, and vice versa.
   - Changes to aseptic processing methods, including scale, that extend the total processing, including bulk storage time, by more than 50 percent beyond the validated limits in the approved application.

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- Changes in sterilizer load configurations that are outside the range of previously validated loads.
- Changes in materials or pore size rating of filters used in aseptic processing.

3. The following changes for a natural product:[16]
   - Changes in the virus or adventitious agent removal or inactivation methods. This is applicable to any material where such procedures are necessary, including drug substance, drug product, reagents, and excipients.
   - For drug substance and drug product, changes in the source material (e.g., microorganism, plant) or cell line.
   - For drug substance and drug product, establishment of a new master cell bank or seed.
4. Any fundamental change in the manufacturing process or technology from that currently used by the applicant. For example:
   a. Drug product
      - Dry to wet granulation or vice versa.
      - Change from one type of drying process to another (e.g., oven tray, fluid bed, microwave).

   b. Drug substance
      - Filtration to centrifugation or vice versa.
      - Change in the route of synthesis of a drug substance.
5. The following changes for drug substance
   - Any process change made after the final intermediate processing step in drug substance manufacture.
   - Changes in the synthesis or manufacture of the drug substance that may affect its impurity profile and/or the physical, chemical, or biological properties.
6. Addition of an ink code imprint or change to or in the ink used for an existing imprint code for a solid oral dosage form drug product when the ink as changed is not currently used on ***CDER-approved products***.[17]
7. Establishing a new procedure for reprocessing a batch of drug substance or drug product that fails to meet the approved specification.

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[16] For the purposes of this guidance, *natural product* refers to materials (e.g., drug substance, excipients) that are derived from plants, animals, or microorganisms. The specific recommendations for natural products are not applicable to inorganic compounds (e.g., salts, minerals).

[17] See Attachment C for a discussion of *CDER-approved*.

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C. Moderate Changes (Supplement—Changes Being Effected)

The following are examples of changes that are considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. Supplement—Changes Being Effected in 30 Days

a. For drug products, any change in the process, process parameters and/or equipment, except as otherwise provided for in this guidance.
b. For drug substances, any change in process and/or process parameters, except as otherwise provided for in this guidance.
c. For natural protein drug substances and drug products:

- Any change in the process, process parameters, and/or equipment, except as otherwise provided for in this guidance.
- An increase or decrease in production scale during finishing steps that involves new or different equipment.
- Replacement of equipment with that of similar, but not identical, design and operating principle that does not affect the process methodology or process operating parameters.

d. For sterile products, drug substances, and components, as appropriate:

- Changes in dry heat depyrogenation processes for glass container systems for products that are produced by terminal sterilization processes or aseptic processing.
- Changes to filtration parameters for aseptic processing (including flow rate, pressure, time, or volume, but not filter materials or pore size rating) that require additional validation studies for the new parameters.
- Filtration process changes that provide for a change from single to dual product sterilizing filters in series, or for repeated filtration of a bulk.
- Changes from one qualified sterilization chamber to another for in-process or terminal sterilization that results in changes to validated operating parameters (time, temperature, F, and 0 others).
- Changes in scale of manufacturing for terminally sterilized products that increase the bulk solution storage time by more than 50 percent beyond the validated limits in the approved application when bioburden limits are unchanged.

e. For drug substances, redefinition of an intermediate, excluding the final intermediate, as a starting material.

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2. Supplement—Changes Being Effected

   a. A change in methods or controls that provides increased assurance that the drug substance or drug product will have the characteristics of identity, strength, purity, or potency that it purports or is represented to possess.
   b. For sterile drug products, elimination of in-process filtration performed as part of the manufacture of a terminally sterilized product.

D. Minor Changes (Annual Report)

The following are examples of changes that are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. For drug products and protein drug substances, changes to equipment of the same design and operating principle and/or changes in scale, except as otherwise provided for in this guidance (e.g., section VII.C.1.c).
2. A minor change in an existing code imprint for a dosage form. For example, changing from a numeric to alphanumeric code.
3. Addition of an ink code imprint or a change in the ink used in an existing code imprint for a solid oral dosage form drug product when the ink is currently used on CDER-approved products.
4. Addition or deletion of a code imprint by embossing, debossing, or engraving on a solid dosage form drug product other than a modified-release dosage form.
5. A change in the order of addition of ingredients for solution dosage forms or solutions used in unit operations (e.g., granulation solutions).
6. Changes in scale of manufacturing for terminally sterilized products that increase the bulk solution storage time by no more than 50 percent beyond the validated limits in the approved application when bioburden limits are unchanged.

VIII. SPECIFICATIONS

A. General Considerations

All changes in specifications from those in the approved application must be submitted in a prior approval supplement unless otherwise exempted by regulation or guidance (506A(c)(2)(A)). *Specifications* (i.e., tests, analytical procedures, and acceptance criteria) are the quality standards provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw ma-

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terials, reagents, and other components, including container and closure systems and in-process materials. For the purpose of defining specifications, *acceptance criteria* are numerical limits, ranges, or other criteria for the tests described. An example of a test, analytical procedure, and acceptance criteria is: assay, a specific fully described high pressure liquid chromatography (HPLC) procedure, and 98.0–102.0 percent. The recommendations in this section also apply to specifications associated with sterility assurance that are included in NDA and ANDA submissions.[18]

A *regulatory* analytical procedure is the analytical procedure used to evaluate a defined characteristic of the drug substance or drug product. The analytical procedures in the *U.S. Pharmacopeia/National Formulary* (USP/NF) are those legally recognized under section 501(b) of the Act as the regulatory analytical procedures for compendial items.

The applicant may include in its application *alternative* analytical procedures to the approved regulatory procedure for testing the drug substance and drug product. However, for purposes of determining compliance with the Act, the regulatory analytical procedure is used.

In sections B-D below, the use of the term *analytical procedure* without a qualifier such as *regulatory* or *alternative* refers to analytical procedures used to test materials other than the drug substance or drug product.

B. Major Changes (Prior Approval Supplement)

The following are examples of changes in specifications that are considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. Relaxing an acceptance criterion, except as otherwise provided for in this guidance (e.g., section VIII.C.1.b).
2. Deleting any part of a specification, except as otherwise provided for in this guidance (e.g., section VIII.D.2).
3. Establishing a new regulatory analytical procedure.
4. A change in a regulatory analytical procedure that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the regulatory analytical procedure described in the approved application.
5. A change in an analytical procedure used for testing components, packaging components, the final intermediate, in-process materials after the final intermediate, or starting materials introduced after the final inter-

[18] See FDA guidance for industry on the *Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products* (November 1994).

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mediate that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application, except as otherwise noted. For example, a change from an HPLC procedure that distinguishes impurities to (1) one that does not, (2) another type of analytical procedure (e.g., titrimetric) that does not, or (3) one that distinguishes impurities but the limit of detection and/or limit of quantitation is higher.

6. Relating to testing of raw materials for viruses or adventitious agents:[19](1) relaxing an acceptance criteria, (2) deleting a test, or (3) a change in the analytical procedure that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application.

C. Moderate Changes (Supplement—Changes Being Effected)

The following are examples of changes in specifications that are considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. Supplement—Changes Being Effected in 30 Days

a. Any change in a regulatory analytical procedure other than editorial or those identified as major changes.
b. Relaxing an acceptance criterion or deleting a test for raw materials used in drug substance manufacturing, in-process materials prior to the final intermediate, starting materials introduced prior to the final drug substance intermediate, or drug substance intermediates (excluding final intermediate), except as provided for in section VIII.B.6.
c. A change in an analytical procedure used for testing raw materials used in drug substance manufacturing, in-process materials prior to the intermediate, starting materials introduced prior to the final drug substance intermediate, or drug substance intermediates (excluding final intermediate) that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application, except as provided for in section VIII.B.6.

[19] In this context, testing for adventitious agents is not considered to include tests that are found in an official compendium (e.g., USP <61>).

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d. Relaxing an in-process acceptance criterion associated with microbiological monitoring of the production environment, materials, and components that are included in NDA and ANDA submissions. For example, increasing the microbiological alert or action limits for critical processing environments in an aseptic fill facility or increasing the acceptance limit for bioburden in bulk solution intended for filtration and aseptic filling.

2. Supplement—Changes Being Effected

a. An addition to a specification that provides increased assurance that the drug substance or drug product will have the characteristics of identity, strength, purity, or potency that it purports or is represented to possess. For example, adding a new test and associated analytical procedure and acceptance criterion.
b. A change in an analytical procedure used for testing components, packaging components, the final intermediate, in-process materials after the final intermediate, or starting materials introduced after the final intermediate that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application.

D. Minor Changes (Annual Report)

The following are examples of changes in specifications that are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. Any change in a specification made to comply with an official compendium.
2. For drug substance and drug product, the addition, deletion or revision of an alternative analytical procedure that provides the same or greater level of assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application.
3. Tightening of acceptance criteria.
4. A change in an analytical procedure used for testing raw materials used in drug substance synthesis, starting materials introduced prior to the final drug substance intermediate, in-process materials prior to the final intermediate, or drug substance intermediates (excluding final intermediate) that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application.

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IX. PACKAGE

A. General Considerations

The potential for adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product when making a change to or in the container closure system is generally dependent on the route of administration of the drug product, performance of the container closure system, and the likelihood of interaction between the packaging component and the dosage form. In some cases there may be a substantial potential for adverse effect, regardless of direct product testing for conformance with the approved specification.

A change to or in a packaging component will often result in a new or revised specification for the packaging component. This situation does not have to be considered a multiple related change. Only the reporting category for the packaging change needs to be considered.

B. Major Changes (Prior Approval Supplement)

The following are examples of changes that are considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. For liquid (e.g., solution, suspension, elixir) and semisolid (e.g., creams, ointments) dosage forms, a change to or in polymeric materials (e.g., plastic, rubber) of primary packaging components, when the composition of the component as changed has never been used in a CDER-approved product of the same dosage form and same route of administration. For example, a polymeric material that has been used in a CDER-approved topical ointment would not be considered CDER-approved for use with an ophthalmic ointment.
2. For liquid (e.g., solution, suspension, elixir) and semisolid (e.g., creams, ointments) dosage forms in permeable or semipermeable container closure systems, a change to an ink and/or adhesive used on the permeable or semipermeable packaging component to one that has never been used in a CDER-approved product of the same dosage form, same route of administration, ***and*** same type of permeable or semipermeable packaging component (e.g., low density polyethylene, polyvinyl chloride).
3. A change in the primary packaging components for any product when the primary packaging components control the dose delivered to the patient (e.g., the valve or actuator of a metered-dose inhaler).

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4. For sterile products, any other change that may affect product sterility assurance such as:[20]
   - A change from a glass ampule to a glass vial with an elastomeric closure.
   - A change to a flexible container system (bag) from another container system.
   - A change to a prefilled syringe dosage form from another container system.
   - A change from a single unit dose container to a multiple dose container system.
   - Changes that add or delete silicone treatments to container closure systems (such as elastomeric closures or syringe barrels).
   - Changes in the size and/or shape of a container for a sterile drug product.
5. Deletion of a secondary packaging component intended to provide additional protection to the drug product (e.g., carton to protect from light, overwrap to limit transmission of moisture or gases).
6. A change to a new container closure system if the new container closure system does not provide the same or better protective properties than the approved container closure system.

C. Moderate Changes (Supplement—Changes Being Effected)

The following are examples of changes that are considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. Supplement—Changes Being Effected in 30 Days

a. A change to or in a container closure system, except as otherwise provided for in this guidance.
b. Changes in the size or shape of a container for a sterile drug substance.

2. Supplement—Changes Being Effected

a. A change in the size and/or shape of a container for a nonsterile drug product, except for solid dosage forms (see section IX.D.2 regarding solid dosage forms).
b. A change in or addition or deletion of a desiccant.

[20] Some of these identified changes, depending on the circumstances, may have to be filed as new NDAs or ANDAs instead of as supplements. Applicants can consult the appropriate CDER chemistry division/office if there are questions.

D. Minor Changes (Annual Report)

The following are examples of changes that are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. A change in the container closure system for a nonsterile drug product, based on a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium.
2. A change in the size and/or shape of a container containing the same number of dose units, for a nonsterile solid dosage form.
3. The following changes in the container closure system of solid oral dosage form products as long as the new package provides the same or better protective properties (e.g., light, moisture) and any new primary packaging component materials have been used in and been in contact with CDER-approved solid oral dosage form products:[21]

   - Adding or changing a child-resistant closure, changing from a metal to plastic screw cap, or changing from a plastic to metal screw cap.
   - Changing from one plastic container to another of the same type of plastic (e.g., high density polyethylene (HDPE) container to another HDPE container).
   - Changes in packaging materials used to control odor (e.g., charcoal packets).
   - Changes in bottle filler (e.g., change in weight of cotton or amount used) without changes in the type of filler (e.g., cotton to rayon).
   - Increasing the wall thickness of the container.
   - A change in or addition of a cap liner.
   - A change in or addition of a seal (e.g., heat induction seal).
   - A change in an antioxidant, colorant, stabilizer, or mold releasing agent for production of the container and/or closure to one that is used at similar levels in the packaging of CDER-approved solid oral dosage form products.
   - A change to a new container closure system when the container closure system is already approved in the NDA or ANDA for other strengths of the product.

4. The following changes in the container closure system of nonsterile liquid products, as long as the new package provides the same or better

[21] For sections IX.D.3 to 6, changes in the container closure system that result in product contact with a component material that has never been used in any CDER-approved product of the same type should be filed as a supplement—changes being effected in 30 days (IX.C.1) or prior approval supplement (IX.B.1).

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protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved liquid products with the same route of administration (i.e., the material in contact with a liquid topical should already have been used with other CDER-approved liquid topical products):

- Adding or changing a child-resistant closure, changing from a metal to plastic screw cap, or changing from a plastic to metal screw cap.
- Increasing the wall thickness of the container.
- A change in or addition of a cap liner.
- A change in or addition of a seal (e.g., heat induction seal).

5. A change in the container closure system of unit dose packaging (e.g., blister packs) for nonsterile solid dosage form products, as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved products of the same type (e.g., solid oral dosage form, rectal suppository).
6. The following changes in the container closure system of nonsterile semisolid products, as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved semisolid products:

   - Changes in the closure or cap.
   - Increasing the wall thickness of the container.
   - A change in or addition of a cap liner.
   - A change in or addition of a seal.
   - A change in the crimp sealant.

7. A change in the flip seal cap color, as long as the cap color is consistent with any established color coding system for that class of drug products.

X. LABELING

A. General Considerations

A drug product labeling change includes changes in the package insert, package labeling, or container label. An applicant should promptly revise all promotional labeling and drug advertising to make it consistent with any labeling change implemented in accordance with the regulations. All labeling changes for ANDA products must be consistent with section 505(j) of the Act.

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B. Major Changes (Prior Approval Supplement)

Any proposed change in the labeling, except those that are designated as moderate or minor changes by regulation or guidance, should be submitted as a prior approval supplement. The following list contains some examples of changes that are currently considered by CDER to fall into this reporting category.

1. Changes based on postmarketing study results, including, but not limited to, labeling changes associated with new indications and usage.
2. Change in, or addition of, pharmacoeconomic claims based on clinical studies.
3. Changes to the clinical pharmacology or the clinical study section reflecting new or modified data.
4. Changes based on data from preclinical studies.
5. Revision (expansion or contraction) of population based on data.
6. Claims of superiority to another product.
7. Change in the labeled storage conditions, unless exempted by regulation or guidance.

C. Moderate Changes (Supplement—Changes Being Effected)

A changes being effected supplement should be submitted for any labeling change that (1) adds or strengthens a contraindication, warning, precaution, or adverse reaction, (2) adds or strengthens a statement about drug abuse, dependence, psychological effect, or overdosage, (3) adds or strengthens an instruction about dosage and administration that is intended to increase the safe use of the product, (4) deletes false, misleading, or unsupported indications for use or claims for effectiveness, or (5) is specifically requested by FDA. The submission should include 12 copies of final printed labeling. The following list includes some examples of changes that are currently considered by CDER to fall into this reporting category.

1. Addition of an adverse event due to information reported to the applicant or Agency.
2. Addition of a precaution arising out of a postmarketing study.
3. Clarification of the administration statement to ensure proper administration of the product.
4. Labeling changes, normally classified as major changes, that FDA specifically requests be implemented using a changes being effected supplement.

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D. Minor Changes (Annual Report)

Labeling with editorial or similar minor changes or with a change in the information concerning the description of the drug product or information about how the drug is supplied that does not involve a change in the dosage strength or dosage form should be described in an annual report. The following list includes some examples that are currently considered by CDER to fall into this reporting category.

1. Changes in the layout of the package or container label that are consistent with FDA regulations (e.g., 21 CFR part 201), without a change in the content of the labeling.
2. Editorial changes, such as adding a distributor's name.
3. Foreign language versions of the labeling, if no change is made to the content of the approved labeling and a certified translation is included.
4. Labeling changes made to comply with an official compendium.

XI. MISCELLANEOUS CHANGES

A. Major Changes (Prior Approval Supplement)

The following are examples of changes that are considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. Changes requiring completion of studies in accordance with 21 CFR part 320 to demonstrate equivalence of the drug to the drug as manufactured without the change or to a reference listed drug (506A(c)(2)(B)).
2. Addition of a stability protocol or comparability protocol.
3. Changes to an approved stability protocol or comparability protocol unless otherwise provided for in this guidance (e.g., VIII.C, VIII.D, XI.C.2).
4. An extension of an expiration dating period based on (1) data obtained under a new or revised stability testing protocol that has not been approved in the application or (2) full shelf life data on pilot scale batches using an approved protocol.

B. Moderate Changes (Supplement—Changes Being Effected)

The following are examples of changes that are considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

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1. Supplement—Changes Being Effected in 30 Days

    a. Reduction of an expiration dating period to provide increased assurance of the identity, strength, quality, purity, or potency of the drug product. Extension of an expiration date that has previously been reduced under this provision should be filed in a supplement—changes being effected in 30 days even if it is based on data obtained under a protocol approved in the application.

2. Supplement—Changes Being Effected

No changes have been identified.

C. Minor Changes (Annual Report)

The following are examples of changes that are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. An extension of an expiration dating period based on full shelf life data on full production batches obtained under a protocol approved in the application.
2. Addition of time points to the stability protocol or deletion of time points beyond the approved expiration dating period.
3. A change from previously approved stability storage conditions to storage conditions recommended in International Conference on Harmonisation (ICH) guidances.
4. Non-USP reference standards:

    - Replacement of an in-house reference standard or reference panel (or panel member) according to procedures in an approved application.
    - Tightening of acceptance criteria for existing reference standards to provide greater assurance of product purity and potency.

XII. MULTIPLE RELATED CHANGES

Multiple related changes involve various combinations of individual changes. For example, a site change may also involve equipment and manufacturing process changes or a components and composition change may necessitate a change in a specification. For multiple related changes where the recommended reporting categories for the individual changes differ, CDER recommends that the filing be in accordance with the most restrictive of those recommended for the individual

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changes. When the multiple related changes all have the same recommended reporting category, CDER recommends that the filing be in accordance with the reporting category for the individual changes.

ATTACHMENT A: MANUFACTURING SITES

All owners or operators of all drug establishments (not exempt by regulation) that engage in the manufacture, preparation, propagation, compounding, or processing of a drug or drugs are required to register with the FDA (21 CFR 207.20). An *establishment* means a place of business under one management at one general physical location (21 CFR 207.3(a)(7)). A *general physical location* is reasonably construed to include separate buildings within the same city ***if*** the activities in them are closely related to the same business enterprise, under the supervision of the same local management, and all inspected at the same time (ORA Field Management Directive No. 132).

For the purposes of determining the reporting category for moves between buildings, the terms *different manufacturing site* and *same manufacturing site* mean:

A. Domestic Establishments

1. Same Manufacturing Site

- The new and old building are included under the same drug establishment registration number[22]

and

- The same FDA district office is responsible for inspecting the operations in both the new and old building.

2. Different Manufacturing Site

- The new and old building have different drug establishment registration numbers

or

- Different FDA district offices are responsible for inspecting operations in the new and old building.

[22] The registration number is the number assigned to the establishment by the district (ORA Field Management Directive No. 92). Currently, the registration number is the seven digit central file number (CFN).

For domestic establishments, the terms *same* and *different manufacturing site* supersede the terms *contiguous campus*, *same campus*, and *different campus* as used in the SUPAC guidances.

B. Foreign Establishments

Foreign establishments are not currently required to register with the FDA. On May 14, 1999 FDA published a proposed rule to require registration of foreign establishments (64 FR 26330). Until the time registration of foreign establishments is required, same and different manufacturing sites mean:

1. Same Manufacturing Site

    - A contiguous or unbroken site or a set of buildings in adjacent city blocks.

2. Different Manufacturing Site:

    - New and old building not on a contiguous site or not in adjacent city blocks.

ATTACHMENT B: TYPE OF OPERATION AND CGMP INSPECTIONS

Section VI states that a change to a different manufacturing site should be filed in a prior approval supplement when (1) the new manufacturing site has never been inspected by FDA for the type of operation being moved, (2) the move results in a restart at the new manufacturing site of a type of operation that has been discontinued for more than two years, or (3) the new manufacturing site does not have a satisfactory current good manufacturing practice (CGMP) inspection for the type of operation being moved.

A *profile class system* is used by FDA to assist in (1) managing the CGMP inspection process, (2) evaluating the findings and the compliance follow-up needed, and (3) communicating the results of inspections. A profile class can relate to the manufacture of a particular dosage form (e.g., large volume parenterals, oral liquids), type of drug substance (e.g., sterile bulk by chemical synthesis), or specific function performed at a site (e.g., control testing laboratory). There are profile class codes for major categories of drug substance processes, dosage forms, and manufacturing functions (see table below).

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However, the system is not comprehensive for all operations performed in the pharmaceutical industry (see not elsewhere classified (NEC) profile class code).

The term *type of operation* refers to the specialized or even unique conditions and practices which are employed to manufacture a class or category of drug substance or drug product or to perform a limited segment of the manufacturing process. These conditions and practices exist and are performed within the framework of CGMPs, along with general conditions and practices that contribute to the manufacture of all products at a given manufacturing site. Both the general and the specific conditions and practices are inspected to evaluate the CGMP acceptability of a manufacturing site. A wide variety of classes or categories of drug substances and products may be produced at a manufacturing site or the manufacturing site may only produce a single class of drug substance and/or drug product or perform a limited segment of a manufacturing process. Each type of operation is represented by a ***profile class code.***

Generally, a satisfactory CGMP rating for a profile class code is used to communicate a satisfactory CGMP clearance for all of the products and for all of the operations included within the category that code represents. Thus the profile class code for a particular dosage form or type of drug substance is used to communicate the CGMP status for all aspects of manufacturing, processing, packing, or holding that are performed at the specific manufacturing site relating to that particular dosage form or type of drug substance, including packaging and labeling operations, testing, and quality control. The profile class code for a particular dosage form or type of drug substance is also used to communicate the CGMP status for manufacturing sites that produce in-process material (e.g., controlled-release beads), package drug products, or label drug products, even if these are stand-alone (e.g., contractor) operations.

A few profile class codes that describe certain types of operations (see items in boldface in table) are provided to report the CGMP status for contractor firms whose only function in the manufacturing process is to perform this operation. If one of these operations (e.g., steam sterilization process) is performed at the manufacturing site involved in producing the drug product/drug substance, the CGMP status for that operation is reported as part of the profile class code for the particular dosage form or type of drug substance. For example, a manufacturing site producing a terminally sterilized small volume parenteral product would be reported with the profile class code for the dosage form (SVT), not by the profile code for the sterilization process (SSP).

Certain inspections may be required by program priorities even if a profile class code indicates an acceptable CGMP status. The current profile codes/classes for human drugs are:

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ADM	Aerosol dispensed medication	NEC	Not elsewhere classified (when using this class, tinctures)
CBI	Biotechnology crude drug	OIN	Ointment, nonsterile (includes cream, jelly, paste)
CEX	Plant/animal extraction crude drug	POW	Powders (includes oral and topical)
CFS	Sterile bulk by fermentation crude drug	RAD	Radiopharmaceutical
CFN	Nonsterile bulk by fermentation crude drug	**RSP**	**Radiation sterilization process**
CHG	Capsule, prompt release	SNI	Sterile noninjectable
CRU	Crude bulk drugs-nonsynthesized	SOP	Soap
CSG	Capsules, soft gelatin	**SSP**	**Steam sterilization process**
CSN	Nonsterile bulk by chemical synthesis	SUP	Suppositories
CSP	**Chemical sterilization process**	SVL	Small volume parenterals (lyophilized)
CSS	Sterile bulk by chemical synthesis	SVS	Sterile-filled small volume parenterals
CTL	**Control testing laboratories**	SVT	Terminally sterilized small volume parenteral
CTR	Capsules, modified-release	TCM	Tablets, prompt-release
GAS	Medical gas (includes liquid oxygen and other)	TCT	Tablets, delayed-release
GSP	**Gas sterilization process**	TDP	Transdermal patches
HSP	**Dry heat sterilization process**	**TSP**	**Fractional (tyndallization) sterilization process**
LIQ	Liquid (includes solutions, suspension, elixirs, and tinctures)	TTR	Tablets, extended-release
LVP	Large volume parenterals	**WSP**	**Water sterilization process**

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CGMP inspectional status, based on the profile class, is available through FDA's Freedom of Information (FOI) Office. (See Glossary under Satisfactory Current Good Manufacturing Practice (CGMP) Inspection for more information regarding FOI requests.)

Examples of postapproval manufacturing site changes and filing consequences:

- An applicant wants to move the manufacture of an immediate-release tablet (TCM) to a different manufacturing site that currently manufactures, and has satisfactory CGMP status for, capsules (CHG) and powders for oral solution (POW). This manufacturing site change should be filed in a prior approval supplement because the new manufacturing site doesn't have a satisfactory CGMP inspection for immediate-release tablets.
- An applicant wants to contract out their packaging operations for immediate-release tablets (TCM) and capsules (CHG), and modified-release capsules (CTR). The potential contract packager has a satisfactory CGMP status for immediate-release and modified-release capsules but has never packaged immediate-release tablets. The packaging site change for the immediate-release tablet products should be filed in a prior approval supplement. The packaging site change for the capsule products should be filed as recommended in section VI of this guidance for packaging sites with a satisfactory CGMP inspection.
- An applicant wishes to consolidate their product testing to a single analytical laboratory at a manufacturing site. This manufacturing site produces various solid oral dosage form products, has an operational analytical laboratory currently at the site, and satisfactory CGMP inspections for the manufacturing occurring at the facility. Some of the products that will be tested at the analytical laboratory when the consolidation occurs are not solid oral dosage form products. Unlike most other production operations, testing laboratories (and other operations in boldface in the table) are not inspected on a dosage form/type of drug substance specific basis. The satisfactory CGMP inspection of the analytical laboratory, which was performed as part of the CGMP inspection for manufacture of the solid oral dosage form products, is considered to apply to all dosage forms, including those not actually produced at the site.

ATTACHMENT C: CDER-APPROVED

In several places throughout the guidance, different reporting categories are proposed for changes to or the addition of certain components based on whether the

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component/material has been used in and has been in contact with CDER-approved products. Different reporting categories are recommended once CDER has reviewed certain components/materials in association with a product approval because similar subsequent changes then have a reduced potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product. For example, certain changes in the container closure systems of solid oral dosage form products may be included in the annual report, as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved solid oral dosage form products (see section IX.D.3). If the primary packaging component material has not been used in or has not been in contact with CDER-approved solid oral dosage form products, then submission of the change in an annual report is not recommended.

CDER-approved products are considered those subject to an approved NDA or ANDA. Some information on which components/materials are used in CDER-approved products is available from the Agency (e.g., FDA, CDER, *Inactive Ingredient Guide*, 1996, Division of Drug Information Resources). When information is not available, an applicant should use reliable sources of information to determine that the component or material has been used in and has been in contact with a CDER-approved product of the same dosage form and route of administration, as appropriate. The applicant should identify in the supplement or annual report the basis for the conclusion that the component or material is used in a CDER-approved product.

If an applicant cannot confirm that a component or material has been used in and has been in contact with a CDER-approved product of the same dosage form and route of administration, the applicant has the option of filing the change for a single NDA or ANDA using the higher recommended reporting category and, after approval, filing similar subsequent changes for other NDAs and ANDAs using the lower recommended reporting category.

GLOSSARY

Acceptance Criteria: Numerical limits, ranges, or other criteria for the tests described.

Active Ingredient/Drug Substance: Any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of a disease, or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient. The term includes those components that may undergo chemical change in the manufacture of the drug product and are present in the drug product

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in a modified form intended to furnish the specified activity or effect (21 CFR 210.3(b)(7) and 314.3).

Component: Any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product (21 CFR 210.3(b)(3)).

Container Closure System: The sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product.

Drug Product: A finished dosage form, for example, tablet, capsule, or solution, that contains an active ingredient, generally, but not necessarily, in association with inactive ingredients (21 CFR 210.3(b)(4)).

Final Intermediate: The last compound synthesized before the reaction that produces the drug substance. The final step forming the drug substance must involve covalent bond formation or breakage; ionic bond formation (i.e., making the salt of a compound) does not qualify. Consequently, when the drug substance is a salt, the precursors to the organic acid or base, rather than the acid or base itself, should be considered the final intermediate.

Inactive Ingredients: Any intended component of the drug product other than an active ingredient.

In-process Material: Any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of the drug product (21 CFR 210.3(b)(9)). For drug substance, in-process materials are considered those materials that are undergoing change (e.g., molecular, physical).

Intermediate: A material produced during steps of the synthesis of a drug substance that must undergo further molecular change before it becomes a drug substance.

Package: The container closure system and labeling, associated components (e.g., dosing cups, droppers, spoons), and external packaging (e.g., cartons, shrink wrap).

Packaging Component: Any single part of a container closure system.

Primary Packaging Component: A packaging component that is or may be in direct contact with the dosage form.

Reference Listed Drug: The listed drug identified by FDA as the drug product on which an applicant relies in seeking approval of its abbreviated application (21 CFR 314.3).

Satisfactory Current Good Manufacturing Practice (CGMP) Inspection: A satisfactory CGMP inspection is an FDA inspection during which (1) no objectionable conditions or practices were found during (No Action Indicated (NAI)) or (2) objectionable conditions were found, but, corrective action is left to the firm to take voluntarily and the objectionable conditions will not be the subject of further administrative or regulatory actions (Voluntary Action Indicated (VAI)).

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Information about the CGMP status of a firm may be obtained by requesting a copy of the Quality Assurance Profile (QAP) from the FDA's Freedom of Information (FOI) Office. The QAP reports information on the CGMP compliance status of firms that manufacture, package, assemble, repack, relabel, or test human drugs, devices, biologics, and veterinary drugs. All FOI requests must be in writing and should follow the instructions found in the reference entitled *A Handbook for Requesting Information and Records from FDA*. An electronic version of this reference is available on the Internet at http://www.fda.gov/opacom/backgrounders/foiahand.html.

Secondary Packaging Component: A packaging component that is not and will not be in direct contact with the dosage form.

Specifications: The quality standards (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, and other components including container closure systems, and in-process materials.

Validate the Effects of the Change: To assess the effect of a manufacturing change on the identity, strength, quality, purity, or potency of a drug as these factors relate to the safety or effectiveness of the drug.

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Appendix H

Guidance for Industry[1]— Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System

I. INTRODUCTION

This guidance provides recommendations for sponsors of investigational new drug applications (INDs), new drug applications (NDAs), abbreviated new drug applications (ANDAs), and supplements to these applications who wish to request a waiver of in vivo bioavailability (BA) and/or bioequivalence (BE) studies for immediate release (IR) solid oral dosage forms. These waivers are intended to apply to (1) subsequent in vivo BA or BE studies of formulations after the initial establishment of the in vivo BA of IR dosage forms during the IND period, and (2) in vivo BE studies of IR dosage forms in ANDAs. Regulations at 21 CFR part 320 address the requirements for bioavailability (BA) and BE data for approval of drug applications and supplemental applications. Provision for waivers of in vivo BA/BE studies (biowaivers) under certain conditions is provided at 21 CFR

[1] This guidance has been prepared by the Biopharmaceutics Classification System Working Group of the Biopharmaceutics Coordinating Committee in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA). This guidance represents the Agency's current thinking on the topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such an approach satisfies the requirements of the applicable statutes, regulations, or both.

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320.22. This guidance explains when biowaivers can be requested for IR solid oral dosage forms based on an approach termed the Biopharmaceutics Classification System (BCS).

II. THE BIOPHARMACEUTICS CLASSIFICATION SYSTEM

The BCS is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. When combined with the dissolution of the drug product, the BCS takes into account three major factors that govern the rate and extent of drug absorption from IR solid oral dosage forms: dissolution, solubility, and intestinal permeability.[2] According to the BCS, drug substances are classified as follows:

Class 1: High Solubility—High Permeability
Class 2: Low Solubility—High Permeability
Class 3: High Solubility—Low Permeability
Class 4: Low Solubility—Low Permeability

In addition, IR solid oral dosage forms are categorized as having rapid or slow dissolution. Within this framework, when certain criteria are met, the BCS can be used as a drug development tool to help sponsors justify requests for biowaivers.

Observed in vivo differences in the rate and extent of absorption of a drug from two pharmaceutically equivalent solid oral products may be due to differences in drug dissolution in vivo.2 However, when the in vivo dissolution of an IR solid oral dosage form is rapid in relation to gastric emptying and the drug has high permeability, the rate and extent of drug absorption is unlikely to be dependent on drug dissolution and/or gastrointestinal transit time. Under such circumstances, demonstration of in vivo BA or BE may not be necessary for drug products containing Class 1 drug substances, as long as the inactive ingredients used in the dosage form do not significantly affect absorption of the active ingredients. The BCS approach outlined in this guidance can be used to justify biowaivers for *highly soluble* and *highly permeable* drug substances (i.e., Class 1) in IR solid oral dosage forms that exhibit *rapid in vitro dissolution* using the recommended test methods (21 CFR 320.22(e)). The recommended methods for determining solubility, permeability, and in vitro dissolution are discussed below.

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[2] Amidon, G. L., H. Lennernäs, V. P. Shah, and J. R. Crison, AA Theoretical Basis For a Biopharmaceutics Drug Classification: The Correlation of In Vitro Drug Product Dissolution and In Vivo Bioavailability,@ *Pharmaceutical Research*, 12: 413–420 (1995).

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A. Solubility

The solubility class boundary is based on the highest dose strength of an IR product that is the subject of a biowaiver request. A drug substance is considered *highly soluble* when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1–7.5. The volume estimate of 250 ml is derived from typical BE study protocols that prescribe administration of a drug product to fasting human volunteers with a glass (about 8 ounces) of water.

B. Permeability

The permeability class boundary is based indirectly on the extent of absorption (fraction of dose absorbed, not systemic BA) of a drug substance in humans and directly on measurements of the rate of mass transfer across human intestinal membrane. Alternatively, nonhuman systems capable of predicting the extent of drug absorption in humans can be used (e.g., in vitro epithelial cell culture methods). In the absence of evidence suggesting instability in the gastrointestinal tract, a drug substance is considered to be *highly permeable* when the extent of absorption in humans is determined to be 90% or more of an administered dose based on a mass balance determination or in comparison to an intravenous reference dose.

C. Dissolution

In this guidance, an IR drug product is considered *rapidly dissolving* when no less than 85% of the labeled amount of the drug substance dissolves within 30 minutes, using *U.S. Pharmacopeia* (USP) Apparatus I at 100 rpm (or Apparatus II at 50 rpm) in a volume of 900 ml or less in each of the following media: (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) a pH 4.5 buffer; and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes.

III. METHODOLOGY FOR CLASSIFYING A DRUG SUBSTANCE AND FOR DETERMINING THE DISSOLUTION CHARACTERISTICS OF A DRUG PRODUCT

The following approaches are recommended for classifying a drug substance and determining the dissolution characteristics of an IR drug product according to the BCS:

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A. Determining Drug Substance Solubility Class

An objective of the BCS approach is to determine the equilibrium solubility of a drug substance under physiological pH conditions. The pH-solubility profile of the test drug substance should be determined at 37 ± 1 ° C in aqueous media with a pH in the range of 1–7.5. A sufficient number of pH conditions should be evaluated to accurately define the pH-solubility profile. The number of pH conditions for a solubility determination can be based on the ionization characteristics of the test drug substance. For example, when the pKa of a drug is in the range of 3–5, solubility should be determined at pH = pKa, pH = pKa +1, pH = pKa−1, and at pH = 1 and 7.5. A minimum of three replicate determinations of solubility in each pH condition is recommended. Depending on study variability, additional replication may be necessary to provide a reliable estimate of solubility. Standard buffer solutions described in the USP are considered appropriate for use in solubility studies. If these buffers are not suitable for physical or chemical reasons, other buffer solutions can be used. Solution pH should be verified after addition of the drug substance to a buffer. Methods other than the traditional shake-flask method, such as acid or base titration methods, can also be used with justification to support the ability of such methods to predict equilibrium solubility of the test drug substance. Concentration of the drug substance in selected buffers (or pH conditions) should be determined using a validated stability-indicating assay that can distinguish the drug substance from its degradation products.[3] If degradation of the drug substance is observed as a function of buffer composition and/or pH, it should be reported along with other stability data recommended in section III.B.3.

The solubility class should be determined by calculating the volume of an aqueous medium sufficient to dissolve the highest dose strength in the pH range of 1–7.5. A drug substance should be classified as highly soluble when the highest dose strength is soluble in < 250 ml of aqueous media over the pH range of 1–7.5.

B. Determining Drug Substance Permeability Class

The permeability class of a drug substance can be determined in human subjects using mass balance, absolute BA, or intestinal perfusion approaches. Recommended methods not involving human subjects include in vivo or in situ intestinal perfusion in a suitable animal model (e.g., rats), and/or in vitro permeability methods using excised intestinal tissues, or monolayers of suitable epithelial cells. In many cases, a single method may be sufficient (e.g., when the absolute BA is 90%

[3] See the FDA guidance for industry on *Submitting Documentation for the Stability of Human Drugs and Biologics* (February 1987), posted at http://www.fda.gov/guidance/index.htm.

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or more, or when 90% or more of the administered drug is recovered in urine). When a single method fails to conclusively demonstrate a permeability classification, two different methods may be advisable. Chemical structure and/or certain physicochemical attributes of a drug substance (e.g., partition coefficient in suitable systems) can provide useful information about its permeability characteristics. Sponsors may wish to consider use of such information to further support a classification.

1. Pharmacokinetic Studies in Humans

a. Mass Balance Studies. Pharmacokinetic mass balance studies using unlabeled, stable isotopes or a radiolabeled drug substance can be used to document the extent of absorption of a drug. Depending on the variability of the studies, a sufficient number of subjects should be enrolled to provide a reliable estimate of extent of absorption. Because this method can provide highly variable estimates of drug absorption for many drugs, other methods described below may be preferable.

b. Absolute Bioavailability Studies. Oral BA determination using intravenous administration as a reference can be used. Depending on the variability of the studies, a sufficient number of subjects should be enrolled in a study to provide a reliable estimate of the extent of absorption. When the absolute BA of a drug is shown to be 90% or more, additional data to document drug stability in the gastrointestinal fluid is not necessary.

2. Intestinal Permeability Methods

The following methods can be used to determine the permeability of a drug substance from the gastrointestinal tract: (1) in vivo intestinal perfusion studies in humans; (2) in vivo or in situ intestinal perfusion studies using suitable animal models; (3) in vitro permeation studies using excised human or animal intestinal tissues; or (4) in vitro permeation studies across a monolayer of cultured epithelial cells.

In vivo or in situ animal models and in vitro methods, such as those using cultured monolayers of animal or human epithelial cells, are considered appropriate for passively transported drugs. The observed low permeability of some drug substances in humans could be caused by efflux of drugs via membrane transporters such as P-glycoprotein (P-gp). When the efflux transporters are absent in these models, or their degree of expression is low compared to that in humans, there may be a greater likelihood of misclassification of permeability class for a drug subject to efflux compared to a drug transported passively. Expression of known transporters in selected study systems should be characterized. Functional expression of efflux systems (e.g., P-gp) can be demonstrated with techniques

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such as bidirectional transport studies, demonstrating a higher rate of transport in the basolateral-to-apical direction as compared to apical-to-basolateral direction using selected model drugs or chemicals at concentrations that do not saturate the efflux system (e.g., cyclosporin A, vinblastine, rhodamine 123). An acceptance criterion for intestinal efflux that should be present in a test system cannot be set at this time. Instead, this guidance recommends limiting the use of nonhuman permeability test methods for drug substances that are transported by passive mechanisms. Pharmacokinetic studies on dose linearity or proportionality may provide useful information for evaluating the relevance of observed in vitro efflux of a drug. For example, there may be fewer concerns associated with the use of in vitro methods for a drug that has a higher rate of transport in the basolateral-to-apical direction at low drug concentrations but exhibits linear pharmacokinetics in humans.

For application of the BCS, an apparent passive transport mechanism can be assumed when one of the following conditions is satisfied:

- A linear (pharmacokinetic) relationship between the dose (e.g., relevant clinical dose range) and measures of BA (area under the concentration-time curve) of a drug is demonstrated in humans
- Lack of dependence of the measured in vivo or in situ permeability is demonstrated in an animal model on initial drug concentration (e.g., 0.01, 0.1, and 1 times the highest dose strength dissolved in 250 ml) in the perfusion fluid
- Lack of dependence of the measured in vitro permeability on initial drug concentration (e.g., 0.01, 0.1, and 1 times the highest dose strength dissolved in 250 ml) is demonstrated in donor fluid and transport direction (e.g., no statistically significant difference in the rate of transport between the apical-to-basolateral and basolateral-to-apical direction for the drug concentrations selected) using a suitable in vitro cell culture method that has been shown to express known efflux transporters (e.g., P-gp)

To demonstrate suitability of a permeability method intended for application of the BCS, a rank-order relationship between test permeability values and the extent of drug absorption data in human subjects should be established using a sufficient number of model drugs. For in vivo intestinal perfusion studies in humans, six model drugs are recommended. For in vivo or in situ intestinal perfusion studies in animals and for in vitro cell culture methods, twenty model drugs are recommended. Depending on study variability, a sufficient number of subjects, animals, excised tissue samples, or cell monolayers should be used in a study to provide a reliable estimate of drug permeability. This relationship should allow precise differentiation between drug substances of low and high intestinal permeability attributes.

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For demonstration of suitability of a method, model drugs should represent a range of low (e.g., $< 50\%$), moderate (e.g., 50–89%), and high $\geq 90\%$) absorption. Sponsors may select compounds from the list of drugs and/or chemicals provided in Attachment A or they may choose to select other drugs for which there is information available on mechanism of absorption and reliable estimates of the extent of drug absorption in humans.

After demonstrating suitability of a method and maintaining the same study protocol, it is not necessary to retest all selected model drugs for subsequent studies intended to classify a drug substance. Instead, a low and a high permeability model drug should be used as internal standards (i.e., included in the perfusion fluid or donor fluid along with the test drug substance). These two internal standards are in addition to the fluid volume marker (or a zero permeability compound such as PEG 4000) that is included in certain types of perfusion techniques (e.g., closed loop techniques). The choice of internal standards should be based on compatibility with the test drug substance (i.e., they should not exhibit any significant physical, chemical, or permeation interactions). When it is not feasible to follow this protocol, the permeability of internal standards should be determined in the same subjects, animals, tissues, or monolayers, following evaluation of the test drug substance. The permeability values of the two internal standards should not differ significantly between different tests, including those conducted to demonstrate suitability of the method. At the end of an in situ or in vitro test, the amount of drug in the membrane should be determined.

For a given test method with set conditions, selection of a high permeability internal standard with permeability in close proximity to the low/high permeability class boundary may facilitate classification of a test drug substance. For instance, a test drug substance may be determined to be highly permeable when its permeability value is equal to or greater than that of the selected internal standard with high permeability.

3. Instability in the Gastrointestinal Tract

Determining the extent of absorption in humans based on mass balance studies using total radioactivity in urine does not take into consideration the extent of degradation of a drug in the gastrointestinal fluid prior to intestinal membrane permeation. In addition, some methods for determining permeability could be based on loss or clearance of a drug from fluids perfused into the human and/or animal gastrointestinal tract either in vivo or in situ. Documenting the fact that drug loss from the gastrointestinal tract arises from intestinal membrane permeation, rather than a degradation process, will help establish permeability. Stability in the gastrointestinal tract may be documented using gastric and intestinal fluids obtained from human subjects. Drug solutions in these fluids should be incubated at 37 ° C for a period that is representative of in vivo drug contact with these fluids; for example,

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1 hour in gastric fluid and 3 hours in intestinal fluid. Drug concentrations should then be determined using a validated stability-indicating assay method. Significant degradation (>5%) of a drug in this protocol could suggest potential instability. Obtaining gastrointestinal fluids from human subjects requires intubation and may be difficult in some cases. Use of gastrointestinal fluids from suitable animal models and/or simulated fluids such as Gastric and Intestinal Fluids USP can be substituted when properly justified.

C. Determining Drug Product Dissolution Characteristics and Dissolution Profile Similarity [4]

Dissolution testing should be carried out in USP Apparatus I at 100 rpm or Apparatus II at 50 rpm using 900 ml of the following dissolution media: (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) a pH 4.5 buffer; and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes. For capsules and tablets with gelatin coating, Simulated Gastric and Intestinal Fluids USP (with enzymes) can be used.

Dissolution testing apparatus used in this evaluation should conform to the requirements in USP (<711> Dissolution). Selection of the dissolution testing apparatus (USP Apparatus I or II) during drug development should be based on a comparison of in vitro dissolution and in vivo pharmacokinetic data available for the product. The USP Apparatus I *(basket method)* is generally preferred for capsules and products that tend to float, and USP Apparatus II *(paddle method)* is generally preferred for tablets. For some tablet dosage forms, in vitro (but not in vivo) dissolution may be slow due to the manner in which the disintegrated product settles at the bottom of a dissolution vessel. In such situations, USP Apparatus I may be preferred over Apparatus II. If the testing conditions need to be modified to better reflect rapid in vivo dissolution (e.g., use of a different rotating speed), such modifications can be justified by comparing in vitro dissolution with in vivo absorption data (e.g., a relative BA study using a simple aqueous solution as the reference product).

A minimum of 12 dosage units of a drug product should be evaluated to support a biowaiver request. Samples should be collected at a sufficient number of intervals to characterize the dissolution profile of the drug product (e.g., 10, 15, 20, and 30 minutes).

When comparing the test and reference products, dissolution profiles should be compared using a similarity factor (f_2). The similarity factor is a logarithmic reciprocal square root transformation of the sum of squared error and is

[4] See the FDA guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms* (August 1997).

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a measurement of the similarity in the percent (%) of dissolution between the two curves.

$$f_2 = 50 \cdot \log \{[1 + (1/n)\Sigma_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \cdot \times 100\}^2$$

Two dissolution profiles are considered similar when the f_2 value is ≥ 50. To allow the use of mean data, the coefficient of variation should not be more than 20% at the earlier time points (e.g., 10 minutes), and should not be more than 10% at other time points. Note that when both test and reference products dissolve 85% or more of the label amount of the drug in ≤ 15 minutes using all three dissolution media recommended above, the profile comparison with an f_2 test is unnecessary.

IV. ADDITIONAL CONSIDERATIONS FOR REQUESTING A BIOWAIVER

When requesting a BCS-based waiver for in vivo BA/BE studies for IR solid oral dosage forms, applicants should note that the following factors can affect their request or the documentation of their request:

A. Excipients

Excipients can sometimes affect the rate and extent of drug absorption. In general, using excipients that are currently in FDA-approved IR solid oral dosage forms will not affect the rate or extent of absorption of a highly soluble and highly permeable drug substance that is formulated in a rapidly dissolving IR product. To support a biowaiver request, the quantity of excipients in the IR drug product should be consistent with the intended function (e.g., lubricant). When new excipients or atypically large amounts of commonly used excipients are included in an IR solid dosage form, additional information documenting the absence of an impact on BA of the drug may be requested by the Agency. Such information can be provided with a relative BA study using a simple aqueous solution as the reference product. Large quantities of certain excipients, such as surfactants (e.g., polysorbate 80) and sweeteners (e.g., mannitol or sorbitol) may be problematic, and sponsors are encouraged to contact the review division when this is a factor.

B. Prodrugs

Permeability of prodrugs will depend on the mechanism and (anatomical) site of conversion to the drug substance. When the prodrug-to-drug conversion is shown to occur predominantly after intestinal membrane permeation, the permeability of the prodrug should be measured. When this conversion occurs prior to intestinal permeation, the permeability of the drug should be determined. Dissolution and

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pH-solubility data on both prodrug and drug can be relevant. Sponsors may wish to consult with appropriate review staff before applying the BCS approach to IR products containing prodrugs.

C. Exceptions

BCS-based biowaivers are not applicable for the following:

1. Narrow Therapeutic Range Drugs[5]

This guidance defines narrow therapeutic range drug products as those containing certain drug substances that are subject to therapeutic drug concentration or pharmacodynamic monitoring, and/or where product labeling indicates a narrow therapeutic range designation. Examples include digoxin, lithium, phenytoin, theophylline, and warfarin. Because not all drugs subject to therapeutic drug concentration or pharmacodynamic monitoring are narrow therapeutic range drugs, sponsors should contact the appropriate review division to determine whether a drug should be considered to have a narrow therapeutic range.

2. Products Designed to be Absorbed in the Oral Cavity

A request for a waiver of in vivo BA/BE studies based on the BCS is not appropriate for dosage forms intended for absorption in the oral cavity (e.g., sublingual or buccal tablets).

V. REGULATORY APPLICATIONS OF THE BCS

A. INDs/NDAs

Evidence demonstrating in vivo BA or information to permit FDA to waive this evidence must be included in NDAs (21 CFR 320.21(a)). A specific objective is to establish in vivo performance of the dosage form used in the clinical studies that provided primary evidence of efficacy and safety. The sponsor may wish to determine the relative BA of an IR solid oral dosage form by comparison with an oral solution, suspension, or intravenous injection (21 CFR 320.25 (d)(2) and 320.25 (d)(3)). The BA of the clinical trial dosage form should be optimized during the IND period.

Once the in vivo BA of a formulation is established during the IND period, waivers of subsequent in vivo BE studies, following major changes in compo-

[5] This guidance uses the term *narrow therapeutic range* instead of *narrow therapeutic index*, although the latter is more commonly used.

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nents, composition, and/or method of manufacture (e.g., similar to SUPAC-IR Level 3 changes[6]) may be possible using the BCS. BCS-based biowaivers are applicable to the to-be-marketed formulation when changes in components, composition, and/or method of manufacture occur to the clinical trial formulation, as long as the dosage forms have rapid and similar in vitro dissolution profiles (see sections II and III). This approach is useful only when the drug substance is highly soluble and highly permeable (BCS Class 1), and the formulations pre- and postchange are *pharmaceutical equivalents* (under the definition at 21 CFR 320.1 (c)). BCS-based biowaivers are intended only for BE studies. They do not apply to food effect BA studies or other pharmacokinetic studies.

B. ANDAs

BCS-based biowaivers can be requested for rapidly dissolving IR test products containing highly soluble and highly permeable drug substances, provided that the reference listed drug product is also rapidly dissolving and the test product exhibits similar dissolution profiles to the reference listed drug product (see sections II and III). This approach is useful when the test and reference dosage forms are pharmaceutical equivalents. The choice of dissolution apparatus (USP Apparatus I or II) should be the same as that established for the reference listed drug product.

C. Postapproval Changes

BCS-based biowaivers can be requested for significant postapproval changes (e.g., Level 3 changes in components and composition) to a rapidly dissolving IR product containing a highly soluble, highly permeable drug substance, provided that dissolution remains rapid for the postchange product and both pre- and postchange products exhibit similar dissolution profiles (see sections II and III). This approach is useful only when the drug products pre- and postchange are pharmaceutical equivalents.

VI. DATA TO SUPPORT A REQUEST FOR BIOWAIVERS

The drug substance for which a waiver is being requested should be highly soluble and highly permeable. Sponsors requesting biowaivers based on the BCS should submit the following information to the Agency for review by the Office

[6] See the FDA guidance for industry on *Immediate Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes* (November 1995).

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of Clinical Pharmacology and Biopharmaceutics (for NDAs) or Office of Generic Drugs, Division of Bioequivalence (for ANDAs):

A. Data Supporting High Solubility

Data supporting high solubility of the test drug substance should be developed (see section III.A). The following information should be included in the application:

- A description of test methods, including information on analytical method and composition of the buffer solutions
- Information on chemical structure, molecular weight, nature of the drug substance (acid, base, amphoteric, or neutral), and dissociation constants (pKa(s))
- Test results (mean, standard deviation, and coefficient of variation) summarized in a table under solution pH, drug solubility (e.g., mg/ml), and volume of media required to dissolve the highest dose strength
- A graphic representation of mean pH-solubility profile

B. Data Supporting High Permeability

Data supporting high permeability of the test drug substance should be developed (see section III.B). The following information should be included in the application:

- For human pharmacokinetic studies, information on study design and methods used along with the pharmacokinetic data
- For direct permeability methods, information supporting the suitability of a selected method that encompasses a description of the study method, criteria for selection of human subjects, animals, or epithelial cell line, drug concentrations in the donor fluid, description of the analytical method, method used to calculate extent of absorption or permeability, and where appropriate, information on efflux potential (e.g., bidirectional transport data)
- A list of selected model drugs along with data on extent of absorption in humans (mean, standard deviation, coefficient of variation) used to establish suitability of a method, permeability values for each model drug (mean, standard deviation, coefficient of variation), permeability class of each model drug, and a plot of the extent of absorption as a function of permeability (mean $\pm$ standard deviation or 95% confidence interval) with identification of the low/high permeability class boundary and selected internal standard. Information to support high permeability of a test drug substance should include permeability data on the test drug

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substance, the internal standards (mean, standard deviation, coefficient of variation), stability information, data supporting passive transport mechanism where appropriate, and methods used to establish high permeability of the test drug substance.

C. Data Supporting Rapid and Similar Dissolution

For submission of a biowaiver request, an IR product should be rapidly dissolving. Data supporting rapid dissolution attributes of the test and reference products should be developed (see section III.C). The following information should be included in the application:

- A brief description of the IR products used for dissolution testing, including information on batch or lot number, expiry date, dimensions, strength, and weight
- Dissolution data obtained with 12 individual units of the test and reference products using recommended test methods in section III.C. The percentage of labeled claim dissolved at each specified testing interval should be reported for each individual dosage unit. The mean percent dissolved, range (highest and lowest) of dissolution, and coefficient of variation (relative standard deviation) should be tabulated. A graphic representation of the mean dissolution profiles for the test and reference products in the three media should also be included.
- Data supporting similarity in dissolution profiles between the test and reference products in each of the three media, using the f2 metric

D. Additional Information

The manufacturing process used to make the test product should be described briefly to provide information on the method of manufacture (e.g., wet granulation vs. direct compression). A list of excipients used, the amount used, and their intended functions should be provided. Excipients used in the test product should have been used previously in FDA-approved IR solid oral dosage forms.

ATTACHMENT A

This attachment includes model drugs suggested for use in establishing suitability of a permeability method as described in section III. The permeability of these compounds was determined based on data available to the FDA. Potential *internal standards* (IS) and *efflux pump substrates* (ES) are also identified.

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Drug	Permeability class
Antipyrine	High (Potential IS candidate)
Caffeine	High
Carbamazepine	High
Fluvastatin	High
Ketoprofen	High
Metoprolol	High (Potential IS candidate)
Naproxen	High
Propranolol	High
Theophylline	High
Verapamil	High (Potential ES candidate)
Amoxicillin	Low
Atenolol	Low
Furosemide	Low
Hydrochlorthiazide	Low
Mannitol	Low (Potential IS candidate)
•-Methyldopa	Low
Polyethylene glycol (400)	Low
Polyethylene glycol (1000)	Low
Polyethylene glycol (4000)	Low (Zero permeability marker)
Ranitidine	Low

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