Quality by Design Specifications for Solid Oral Dosage Forms: Multivariate Product and Process Monitoring for Managing Drug Quality Attributes

by the
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Preamble

The purpose of this paper is to stimulate discussion around the thought processes and activities that occur from creation through development and commercialization of a molecule that ultimately becomes a drug product that benefits patients. This includes exploring the scientific evidence and pharmacological underpinnings that link clinical concepts to drug product design, manufacturing controls and specifications for active pharmaceutical ingredients (API), excipients and impurities that may be present. We have taken a "concept car" approach to facilitate dialog on setting clinically relevant specifications with Quality by Design (QbD) principles for a drug product.

Executive Summary

In the future, multivariate analysis of pharmaceutical manufacturing processes equipped with Process Analytical Technology (PAT), or process monitoring and real time product testing, will lead to better assessment and understanding of the effect of process parameters on product quality attributes. This should enable the realization of correlations between dependent variables in multivariate analysis, or it may enable correlations between independent variables and their corresponding dependent variables as in univariate analysis. The potential exists for mathematical modeling of these multiple variables in ways that equate their input functions, such as qualitative and quantitative product components and manufacturing process parameters, to critical quality attributes (CQAs) linked to clinical activity relationships. Assuming this becomes possible, then safety and efficacy of a pharmaceutical product could be linked, in part, to product components and manufacturing process parameters.

Advantages gained by such an approach might include:

(i) specifications based on correlations of multiple variables rather than outputs of single variables;
(ii) specification criteria based on curve fitting factors rather than single output limits;
(iii) the elimination of some end product testing for product release,
(iv) arrival at a very thorough manufacturing process understanding, and
(v) the refinement of model based specifications by new knowledge gained during the lifecycle of a product.

Although futuristic in vision, this paper describes some fundamental principles of a Quality by Design approach that could lead to the development of product quality specifications based on concepts other than retrospective end product testing and past experience.

Outlined are the concepts of Quality by Design; a paradigm shift away from end product testing to real time monitoring; namely, the verification of clinical relevance of some quality attributes; a few perceived obstacles to QbD specifications in general; application of these QbD principles to two hypothetical solid oral product development scenarios (one simple, one complex); a comparison of conventional specification versus QbD specification under this approach; and a projected QbD development timeline. Although this is unlikely to be the only QbD specification approach developed by the pharmaceutical industry, it is one way in which clinical activity might be related to and controlled by real time manufacturing process monitoring measurements and product analysis. Elements of product design, specification design, and process design that can enable this are discussed in this paper. They are interrelated in the overall delivery of pharmacotherapy, and throughout the lifecycle of a drug product.

Introduction

Quality by Design is a systematic, risk based, scientific approach to the development and quality management of pharmaceutical products as described in ICH Q8 (1) and advocated by the FDA's cGMP 21st Century Initiative for submissions under the new CDER Pharmaceutical Quality Assessment Scheme (PQAS) program. The QbD optional approach is intended to build quality into drug substances, product components and dosage forms through comprehensive understanding and monitoring of the evolving relationship between the patient relevant Critical Quality Attributes (CQA) of a drug product and its manufacturing Critical Process Parameters (CPP), throughout the product life cycle, including both development and commercialization (2).

Applying QbD principles is currently voluntary. Receiving clearance to conduct clinical studies or gaining market approval is not contingent upon the use of QbD. QbD is not a regulatory expectation for all situations, but rather a unique set of principles that can be applied to science based pharmaceutical product and process development. Assuming the appropriate development work has been conducted, QbD principles can be invoked at any time during the lifecycle of a product.

Development and commercialization under QbD principles differ from conventional drug product development and regulatory approval by using quality management systems to ensure product quality dynamically in real time for selected CQAs through on line process monitoring and real time product testing, or Process Analytical Technology (PAT), versus traditional static quality control via end product testing alone. With traditional end product quality control, the processes are often narrowly defined, and locked in place at the time of approval through process validation using a limited number of product lots. Such traditionally validated processes can still be sensitive to changes in input materials and unit operation variables, thus requiring continued updating via regulatory supplements, as continuing commercial manufacture reveals a need to broaden or to shift the acceptable range of parameters. Such late stage modifications have triggered the need to change from traditional end product testing based specifications. By contrast, the goal with QbD is to develop robust, well understood formulations and processes that allow for adjustments of operating parameters or material attributes, within a Design Space, without the need to readjust specification acceptance criteria or to seek

regulatory approval for such chemistry, manufacturing, and control (CMC) related post-approval changes (3).

QbD starts with the intended patient needs and establishment of a target product profile. A product is then developed to meet those needs using flexible manufacturing approaches focused on gaining a detailed understanding of how Critical Process Parameters relate to Critical Quality Attributes. With the QbD approach, one links a well defined acceptable range of CPPs to CQAs, that reflect influences of input variables and process robustness, thus assuring conformance to product quality attributes that assure clinically relevant product performance. As such, future manufacturing changes within a Design Space can be allowed by regulatory agencies without the need for submission of Post-Approval Supplements. Ideally, according to Janet Woodcock, this new vision should create "…a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drug products without extensive regulatory oversight" (4).

As often articulated by Moheb Nasr, Quality by Design systems encompass the following features (5-8):

- The product is designed to meet patient needs and performance requirements.
- The process is designed to consistently meet product Critical Quality Attributes.
- The impact of starting raw materials and process parameters on product quality is understood.
- The process is evaluated and updated to allow for consistent quality over time.
- Critical sources of product and process variability are identified and controlled.

Traditional pharmaceutical development involves a trial and error, empirical approach with focus on selective, or limited, process optimization; whereas, QbD can utilize systematic design of univariate or multivariate experiments with emphasis on a control strategy to achieve robustness from a very thorough understanding of starting raw materials and process operations in relationship to prior knowledge. With the traditional approach, a manufacturing process can become fixed with the use of some in process testing to control CQAs via CPPs within narrow validation parameters, while QbD enables adjustment within a potentially much larger Design Space. The traditional quality control paradigm, with its reliance on batch release testing, based on approved specification acceptance criteria, can be contrasted against a QbD risk based quality control strategy that strives for Real Time Release Testing based on holistic product performance characteristics (5). QbD demands a new vision of how specifications are established and raw material characteristics and process parameters are developed and used in order to realize consistent product quality.

Scope

The charge of the PQRI Working Group for Specification Development and Life Cycle Management was to propose new ways of establishing, approving, and managing drug substance and drug product specification concepts to QbD principles. In order to keep this task manageable, the Working Group decided to focus this Concept Paper on QbD specifications associated with solid oral dosage forms containing small molecule, non-

biotechnology derived actives. This paper considers the relevance of active pharmaceutical ingredient (API) physical properties to product performance and the ability of these properties to change in the solid state. Properties of excipients, formulation design and the effect of process conditions and their variability are included among parameters considered for inclusion in Design Space.

The paper does not address issues of API synthesis or purification, but starts with API attributes as inputs. In addition, it does not deal with methods of ascertaining which process parameters are most critical, but accepts that such systematic methods can be derived from risk based models. The paper does not discuss statistics behind real time process monitoring or the estimation of variability in parametric relationships, Multivariate Statistical Process Control (MSPC), Principal Component Analysis (PCA), or Partial Least Squares (PLS), but assumes sufficient industry and regulatory agency expertise exists to apply multivariate data analysis techniques. The paper also assumes, for simplicity, that single dose pharmacokinetic thresholds can be proportionally modeled to multidosing steady state outcomes.

Specification Paradigm Shift

ICH Q6A guideline (9), defines a specification as "…a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the test described. It establishes a set of criteria to which a drug substance or drug product should conform in order to be considered acceptable for its intended use." Within this definition, each single specification attribute needs to have, at a minimum, (i) an analytical test method and procedure, (ii) an acceptable limit for test measurement results (upper, lower, or range), and (iii) a justification of how the specification's acceptance criteria assures product quality and consistency (9).

In order to establish a QbD specification, one needs to consider the additional unique technical elements of the QbD process. These elements include the following (10):

1. CQAs linked to clinical relevance by virtue of their impact on efficacy, safety, or reproducible therapeutic effect.
2. Clinically relevant CQAs linked to CPPs, either directly or indirectly.
3. One or more CPPs, which control the clinically relevant CQA enabled by real time monitoring or by PAT.
4. Acceptance Criteria (AC) defined by dimensional relationships between CPPs and CQAs in a manner that enables the operational criteria to be contained within a Design Space.

Considering these elements, QbD release and stability specifications can be defined as follows:

QbD Product Release Specifications are clinically relevant CQAs linked to API properties, nonactive drug product component attributes, and/or controlled Design Space CPPs in the manufacture of a product with real time process monitoring or PAT to enable Real Time Release Testing.

QbD Product Stability Specifications are clinically relevant CQAs governed by parametric relationships between CQAs and CPPs within a Design Space that express acceptable change in product characteristics with time.

A narrower operational space may be established within a Design Space, but movement of process parameters within the Design Space would not require a prior regulatory approval. This affords flexibility in the manufacture of a product throughout its lifecycle.

Clinically Relevant Quality Attributes

The most challenging aspect of establishing QbD specifications is the determination and demonstration of whether a product attribute is clinically relevant (10). At the onset of drug development, product attributes are conceived, but until development progresses to clinical studies, one can only project or speculate whether an attribute will impact clinical performance. It is normal practice to identify Key Quality Attributes (KQA) among an array of API and drug product quality attributes that might later prove to be primary determinants impacting intended safety, efficacy, or performance characteristics of a final product. If a quality attribute is determined to impact any of these clinically relevant facets, then it should be considered a Critical Quality Attribute under QbD. If a quality attribute does not impact clinical performance or safety, it might still be considered a KQA (e.g., color, shape, coating variability, etc.), for which an internal testing limit might be established, but it should *not* be considered a CQA upon which a QbD specification is established.

Clinically relevant quality attributes may be divided into three major categories: (i) Safety and Toxicology (along with communication of assessed toxicity risks), (ii) Efficacy, and (iii) Dosage Form Product Performance. The following situations are examples under each category for solid oral dosage forms. These examples are relevant, but not all inclusive.

Efficacy

Therapeutic Threshold - If a systemic concentration or target tissue accumulation requires a particular threshold concentration in order to achieve a therapeutic effect, then the quantity of active in a dosage form as well as its biopharmaceutical properties determines if a therapeutic threshold is reached. The quantity of active in a solid oral dosage form throughout its shelf-life becomes a CQA that can impact the therapeutic outcome. The allowable range of API should take into consideration the variability in the therapeutic threshold determined during clinical studies that account for any applicable at-risk patient population. Equally, multidosing regimens may be necessary to reach a sustained (steady state) concentration above a therapeutic threshold, so any factors impacting the time to reach steady state or the effective maintenance of the threshold may be a CQA, if it can be controlled by the product design or its delivery system.

Duration of Action – In general, the integration of the plasma concentration time curve to yield area under the curve (AUC) above a therapeutic threshold determines the duration

of action. If excipients in a dosage form extend the duration of action of an active, then the characteristics and quantities of these formulation components, in relation to release of active *in vivo*, become CQAs.

Safety and Toxicology

Therapeutic Window – The difference between a therapeutic threshold and a toxicological threshold constitutes the therapeutic window. If this window is narrow, then taking into account the inherent biopharmaceutical characteristics of the active, the dosage form excipients (as in a modified release drug product) may delay the dissolution or absorption in such a manner as to broaden the plasma concentration curve. Thus, the therapeutic threshold would be exceeded, but beneath the toxicological threshold during the drug exposure. Under these circumstances, specific excipients, their physical properties, and interactions with the active and other excipients may become CQAs as they impact the shape of the plasma concentration-time curve and the AUC within the therapeutic window.

Metabolism and Clearance of Active Metabolites – Some prodrugs (e.g., anticancer drugs) are intentionally designed to make a very toxic substance (to tumor cells) less toxic in the systemic circulation until they are enzymatically converted to the more toxic substance at the site of action (in cancerous tumors). Upon metabolism of these prodrugs, the released active drug substance will be more toxic than the prodrug. If this is the case, then the toxicokinetics, tissue exposure, and/or accumulation of this active metabolite will be affected by the rate of its production relative to the prodrug plasma concentration-time profile. In this case, the design and concentration of the prodrug becomes the CQA.

Therapeutically Inactive Related Compounds – These molecular entities that are structurally related to the active compound, may be present at low levels either as API process impurities or degradation products. These related compounds can be more or less toxic than the active compound. They can become CQAs depending on their levels and toxicological qualifications.

Dosage Form Product Performance

High Solubility and High Permeability (BCS I) – Actives which are highly soluble and easily absorbed, when contained in dosage forms that enable rapid dissolution, may have limited impact on a plasma concentration time curve. Under these circumstances, small changes in dissolution profile are unlikely to affect clinical performance, therefore disintegration of the dosage form can become a CQA.

Low Solubility and High Permeability (BCS II) – Actives which are slow to dissolve, but are readily absorbed into the plasma compartment, are dissolution rate limited. Any property of the API, dosage form or an excipient, and its interaction with the active *in vivo* that affects the rate of dissolution can become a CQA.

High Solubility and Low Permeability (BCS III) – Actives which are highly soluble and dissolve readily, but are slow to absorb into the plasma compartment are absorption rate

limited. Any excipient and its interaction with the active *in vivo* that may enhance either the rate of absorption of the active or the absolute amount of the active absorbed can become a CQA.

Low Solubility and Low Permeability (BCS IV) – Actives which are slow to dissolve, have low solubility, and are slow to be absorbed into the plasma compartment are both dissolution and absorption rate limited. Any property of the API, dosage form or an excipient that enhances solubilization, the rate of dissolution, the rate of absorption, or the absolute amount of active absorbed can become a CQA.

Quality by Design Principles

In order to implement the QbD specifications, it is necessary to understand the scientific principles that must come into play in order to support the use of this option. These QbD principles and some of their benefits can be summarized as follows:

- Use Clinically Relevant CQAs
- Link CPPs to CQAs
- Link product performance to clinically relevant CQAs and CPPs
- Make measurements of CPPs that affect CQAs and product performance with process monitoring, real time testing, or with PAT
- Enable Real Time Release Testing without end product testing, specifically when PAT is used and real time measurement of product attributes is made in lieu of end product testing as may be proposed and approved in an application
- Enable continuous improvement of quality systems by identifying and controlling causes of variability
- Establish risk based criteria and decisions on fit-for-use acceptability by allowing the best statistical estimates of measured CPPs linked to CQAs
- Do it right the first time with comprehensive process and manufacturing understanding rather than being limited by a locked down process description
- Use a single regulatory review cycle through establishment of Design Space with updates as needed, instead of using post approval supplements for communication of changes made outside of narrowly validated conditions.
- Refine a CPP range that lies within a Design Space using process knowledge gained over the lifecycle of the product to manufacture a predictably performing product.

Obstacles to Implementing Quality by Design Specifications

Under the traditional end product testing based product release regime, there are many obstacles to implementing QbD specifications that relate CPPs to clinically relevant CQAs in real time. If these obstacles can be identified and removed, the shift to a QbD specification paradigm may become a reality under selected circumstances. The following is a discussion of a few obstacles to the implementation of QbD specifications.

1. Single Component Specifications vs. Multivariate Specifications – Current practice dictates that conformance to a specification must be derived from the measurement of

each single component CQA by end product testing. In many cases product performance CQAs can be assessed based on correlations of several measured attributes (after appropriate validation and prior regulatory approval) rather than a particular single attribute measured at one point in time.

The potential solution to this obstacle would be for agencies to encourage specifications, where applicable, to be set on a combination of attributes by multivariate analysis (11-13), where specifications are built on correlations of attributes or parameters, rather than on an absolute measurement of a single attribute at the time of release or stability testing. As an example, it might be easy to say that dissolution is a function of API polymorphic form, API particle size, a disintegrant concentration, filler and binder, where each of these act as independent variables to affect dissolution. Understanding the combined effect of these variables can be more important than understanding their independent impacts. Dissolution, or any other quality attribute for that matter, can be a very complex function of input variables (i.e., polymorphic forms, mean particle size, particle size distributions, surface areas, porosities, densities, excipient intrinsic and extrinsic properties, component interactions, impurities, etc.) many of which are very dependent and dynamically interrelated to one another, when experienced in a broad Design Space.

Multivariate analyses in process monitoring become important tools in building a knowledge rich understanding of the dependency between input variables and process parameters. Correlations between variables and parameters can become as important or more important than empirical measurements of a single quality attribute. Early in the pharmaceutical evolution of multivariate analyses, Lindberg and Lundstedt (13), used 35 batches to investigate the relationship between particle size of prednimustine drug substance (i.e., existing as crystallites, aggregates, and agglomerates) and the dissolution rate, using 66 variables including 3 dissolution rate variables, 18 particle size variables, and 12 gas adsorption parameters for surface area, as well as impurity and process variables. No univariate relationship was found between dissolution rate and particle size alone, as might be expected from the inverse relationship of surface area and particle size (i.e. Noyes-Whitney equation). Instead, complex multivariate relationships were found between many variables including particle size measurements, impurity content, thermodynamic properties, process parameters, and gas absorption characteristics (13). More recent studies on other active ingredients and solid dosage forms reveal many types of multivariate correlations. Strachan, et al. (14) list a wide collection of multivariate applications using Raman spectroscopy on solid matrices for the study of active ingredients, polymorphs, amorphous materials, and solvate systems. Wu, et al. (15), using multivariate analyses, explored tablet hardness of a formulation of theophylline containing lactose, magnesium stearate, starch or Avicel. Pollanen, et al. (16) demonstrated the use of IR spectroscopy in the multivariate analysis of sulfathiazole crystal forms in the solid state. Heinz, et al. (17) demonstrated the use of Raman and near-IR spectroscopy along with multivariate analyses to study a ternary mixture of indomethacin crystal forms in the presence of an amorphous form.

From multivariate analysis one learns about complex relationships between variables, and from further study, builds mathematical models that enable predictive algorithms to be created around available product measurements and practical process monitoring.

2. Fixed Number of Lots at Registration with End Product Testing - An expectation that specifications should be established with a fixed number of product lots at registration using end product testing of single component attributes (some not clinically relevant) impedes quality improvement by locking down the process to a collection of narrow specification acceptance criteria at time of release.

The potential solution to this obstacle could be to encourage the following:

(i) Confine specifications to clinically relevant CQAs that are linked to CPPs via product characteristics that can be measured in real time as the CQA reaches its steady state within a desired range.
(ii) Use multivariate correlations in the Design Space as a basis for quality and process improvement, so that specifications become a set of process parameters and material attributes upon which a control strategy is defined, rather than a set of single measurement tests on the end product.
(iii) Allow acceptance criteria, defined by a set of parameters, to be refined using process knowledge gained during the development and then the commercial life of a product, thus using many lots to analyze quality relationships prior to establishing or updating quality attributes.
(iv) Enable multiple discriminatory rate processes, whereby a product stabilizes during manufacture, to reflect the product quality within the boundaries of a process, rather than allowing the quality to be defined by an end product measurement.

For a dosage form, the properties of API and its concomitant excipient interactions can be amongst the greatest contributors to formulation performance. For example, awareness of solid state polymorphic changes that impact product quality of solid dosage forms can be of relevance. Of equal importance are the kinetic phenomena encompassing solid state transitions. Three areas of particular interest include: (i) the kinetics of conversion between drug substance individual crystal forms and/or an amorphous form; (ii) the kinetics of particle size changes and particle redistribution; and (iii) the kinetics of transforming hydrates (API and excipients). For example, it is well known that API polymorph transitions can occur during drug product manufacturing when stress conditions trigger conversions. Once a polymorphic transformation process has been initiated in the solid state or semisolid state, conversion may slowly continue after the manufacturing process is completed. The end product measurement at this nonsteady state condition is not as pertinent as the rate of the process change that will lead to the desired steady state. In these circumstances, after completion of product manufacturing, it would be desirable to continue product monitoring nondestructively to assess the rate of change of these attributes over a discriminatory kinetic region that will enable prediction of the steady state. A review by Zeitler, et al. (18), describes how terahertz (i.e., near-microwave to far-infrared) pulsed spectroscopy can be applied to pharmaceutical API and product without a need for sample preparation (other than enclosure in a dry environment), to monitor on a very rapid time scale (seconds to minutes), the dynamic conversion of crystal forms or hydrates within a tablet matrix.

With the ability to understand and accommodate these interconversions, one could build QbD release specifications based on a measured rate during and after manufacture that predicts the steady state performance characteristics expected to be reached before the product is released. Equally, one could apply Terahertz spectroscopy nondestructively on product stability samples during development, thus enabling QbD stability specification rationale based on knowledge rich, mechanistic understandings to eliminate the need for product stability testing on these quality attributes.

3. Dissolution Testing – An expectation of having a dissolution test as a product release test for all immediate release solid oral dosage forms can be unnecessary; (a) for BCS I or III classification; (b) for sink (quick and high dilution effect) conditions in a dissolution test that is not discriminating, or (c) for test conditions and a dissolution profile that are unrelated to the dosage form's *in vivo* performance. Although dissolution testing may be useful during development, one needs to question whether such testing is necessary for the final commercial formulation. If the release of active is dissolution rate limited and if dissolution attributes are prone to change with time, then a dissolution test can be warranted for release and stability testing.

A potential solution to this obstacle would be to look more closely at the BCS classification of the compound and consider the implications of dissolution versus disintegration where dissolution is rapid, i.e., BCS Classes I and III. One can then relate the physical properties that are clinically relevant directly to the most appropriate manufacturing CPPs. If related physical properties, (e.g., particle size, surface area, density, hydrodynamic particle swept volume, etc.) can correlate with *in vitro* product performance, then these attributes (alone or collectively) can be used as predictors of *in vivo* product performance. In particular, when clinical studies have demonstrated a performance correlation based on an excipient level or a dosage form physical property, then that characteristic or collection of characteristics should form the basis of a QbD control strategy in place of traditional end product dissolution testing. The more important overriding issue for clinical relevance may not be whether a dissolution profile is ideal, but whether or not the delivery characteristics of the dosage form can reproducibly release the active *in vivo* for the intended use.

4. Fixed-in-Time Process Robustness – There is an expectation that a full understanding of the manufacturing process is available at the time of registration. The degree of process understanding at this time is often based on limited manufacturing experience which define narrowly probed CPPs.

A potential solution to this obstacle might be to enable a risk based modification of the Design Space CPPs derived from process experience and manufacturing science at the time of filing with a Post-Approval Management Plan (PMP). This evolving robustness becomes an integral part of continuous improvement aspects of the Pharmaceutical Quality Assessment System. By treating the parametrically monitored and controlled manufacturing process holistically, continuous improvement in robustness should involve adjustments and refinements in one or more material attributes or CPPs for the Design Space.

5. Potency Assays – The requirement to report a drug product assay result as determined by HPLC analysis at product release is redundant when a Real Time Release Testing [ICH Q8(R2)] method has been used to monitor potency during manufacture. A solution is to allow assurance of label claim based on manufacturing process controls and product quality measurement by on line or at line methods to confirm the potency and content uniformity of the product.

An understanding of the kinetics and mechanism of degradation should allow a risk based assessment of the necessity or frequency of stability analysis of the product by HPLC or other suitable methods.

Table 1: Summary of Obstacles to Implementing QbD Specifications

Current Obstacle	**Potential Opportunities for Change**	**QbD alternative**
Single component specification testing	Minimize or eliminate certain tests at the time of product release.	Multivariate correlations of input and process parameters
Locking down of specifications to limited batch history	Allow CQAs to link to product performance and CPPs	Univariate real time process monitoring or PAT vs. time curves
Dissolution testing	Eliminate need for dissolution testing when appropriate	Link to process parameter correlations at release and do only disintegration on stability
Establishing Robustness too early	Allow material attribute measurements and manufacturing controls to develop with experience	Enable Design Space to expand with more clinical experience and manufacturing science correlations
HPLC Potency Assay	Eliminate need for testing at release or on stability	Correlate to CPP and measured product attributes (as approved) at release and use mechanistic understanding of degradation kinetics for stability assessment

The challenge is to develop QbD product specifications based on mathematical models and link these to clinically relevant patient exposure or therapeutic effectiveness.

QbD Specifications based on Hypothetical Scenarios

In order to better understand how QbD specifications might be established, it is worthwhile to construct some hypothetical scenarios in order to envision how CQAs might be related to CPPs and QbD specifications. The challenge is to relate clinically relevant patient exposure to CQAs expressed in terms of mathematical relationships incorporating CPPs as measured parameters. In essence, one needs to express patient exposure as a combined function of product quality attributes with input functions derived from CPPs. To demonstrate how this might be achieved, two circumstances have been selected to illustrate, in principle, how such relationships might be derived. One example is straight forward; while the second example is intentionally complex. The

second example illustrates the potential strength of QbD to enable development of specifications based on multivariate correlations. These two scenarios focus on compounds whose therapeutic activity can be related to plasma concentration. Excluded from these examples are compounds whose therapeutic effect would necessitate a localized target tissue accumulation that could not be related to pharmacokinetic parameters.

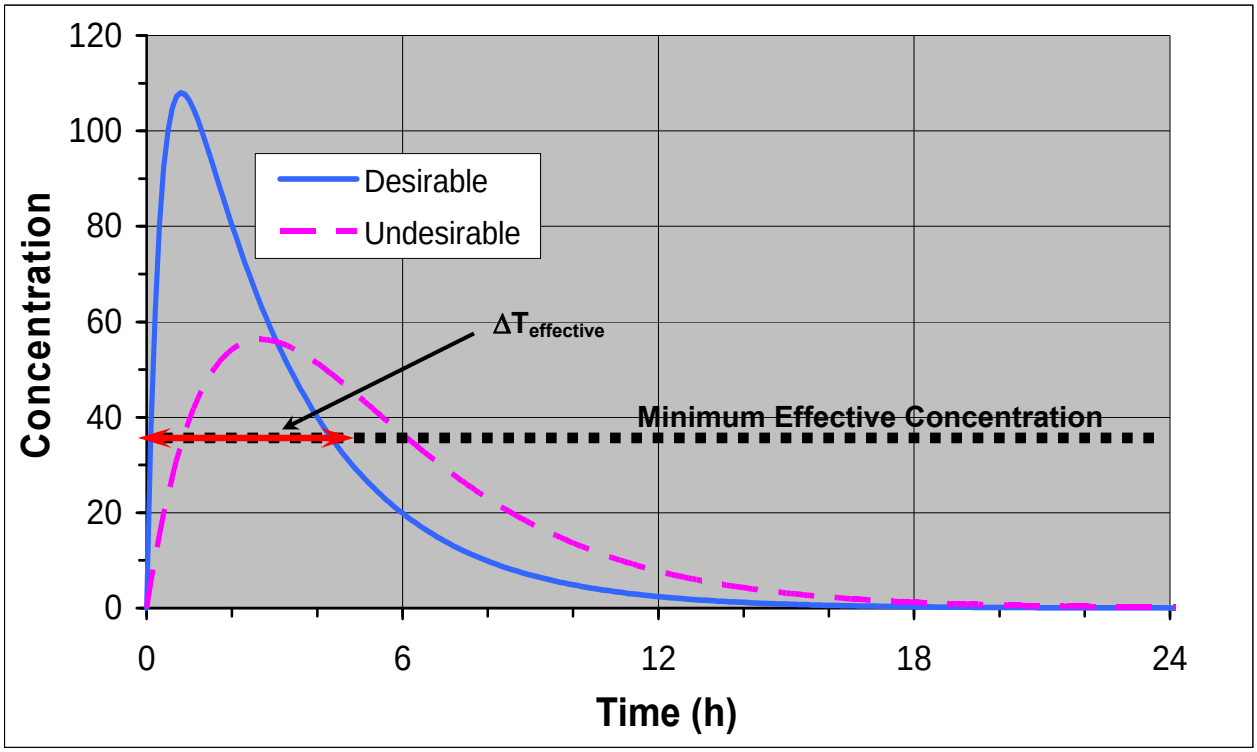
The first illustration involves a compound with a broad therapeutic window, while the second scenario deals with a compound with a narrow therapeutic window. These imaginary scenarios draw from two very important compound classifications: BCS II (low solubility, high permeability) and BCS IV (low solubility, low permeability). API in these BCS classifications receive a considerable amount of pharmaceutical development attention, so it is appropriate that hypothetical scenarios for these two types of compounds are selected for illustration.

Hypothetical Tablet Scenario (BCS Class II API) – Broad Therapeutic Window

To illustrate how QbD specifications might be established, the first scenario involves a BCS Class II API (high permeability, low solubility) formulated as a dry granulated (roller compacted), film coated immediate release compressed tablet. Clinical studies show that the compound has a very broad therapeutic window. It is indicated for treatment of insomnia, so a rapid onset of action followed by a constant dissolution rate is needed to induce, and then maintain sleep. If dissolution or disintegration is slowed, resulting in a longer gastrointestinal transit time, there is a risk that the drug will remain in the plasma at levels above the minimum effective concentration for a period beyond the desired time for sleep maintenance (maximum of 6 hours). Although uncontrolled by product specifications, it should not be forgotten that gastric emptying times also play a role in oral bioavailability.

Desirable and undesirable pharmacokinetic profiles for the sleep aid tablets are shown in Figure 1. To assure the desired systemic patient exposure (PE), the time that maximum plasma concentration is achieved (T_{max}) must be controlled to less than 30 minutes and the duration of time for plasma concentrations higher than the effective level ($\Delta T_{effective}$) must be controlled to less than six hours.

Figure 1: Desirable and undesirable pharmacokinetic profiles (19)



The API is isolated as a single, stable crystalline form through control of process parameters during final recrystallization. It is chemically stable in the tablet formulation, with no detectable formation of degradation products under ICH stability conditions for three years.

Due to the low solubility of the API, its dissolution is significantly affected by its particle size distribution. Correlation of patient systemic exposure with NIR mapping of API distribution in blends and tablets shows that T_{max} is slowed and $\Delta T_{effective}$ is prolonged for high fractions of either large or fine particles. Following tablet disintegration, large particles have a low surface area to contact ratio to gastric fluid. The very fine particles aggregate *in vivo* to create larger particle agglomerates (via hydrophobic interactions), which further decreases the effective overall disintegrated product surface area. This *in vivo* agglomeration reduces the effective surface area, which reduces the rate of dissolution and, ultimately, reduces the amount of dissolved drug available for absorption. There is a dose limiting point of diminishing returns on decrease in particles size; therefore, success of this product depends on an intermediate median particle size and a narrow distribution with low amounts of either very large or very small particles.

Control of API particle size distribution (API_{psd}), a critical control parameter for drug product manufacture, can be achieved through control of three critical process parameters within proven acceptable ranges (PARs) during final crystallization of drug substance: agitation rate (AR_{cry}), rate of solvent addition (SA_{cry}) and reaction temperature (T_{cry}).

$PE_{API} = f(API_{psd}) = f(AR_{cry}), f(SA_{cry}), f(T_{cry})$

Drug product formulation and manufacturing process parameters critical to rapid and consistent tablet disintegration (TAB_{disin}) and, therefore, critical to control of patient systemic exposure, were identified through development studies.

The tablets were formulated to rapidly disintegrate and present the API particles to the gastric fluid for dissolution by inclusion of intra- and extragranular disintegrant, and addition of only extragranular lubricant in the minimum quantity required to prevent sticking during tablet compression. Uniform blending of the disintegrant and lubricant is critical to control of patient systemic exposure. Manufacturing quality systems provide assurance that disintegrant and lubricant are included in the formulation in the correct quantities during the correct process steps; blend uniformity (BU) can be monitored and controlled using PAT techniques.

In this hypothetical example, development studies identified two manufacturing process parameters that are critical to control of patient systemic exposure because of their effect on the availability of API particles for dissolution in gastric fluid following drug product administration. The critical process parameters are within the granulation and milling steps of tablet manufacture: roller compactor roll force (RF_{gran}) and mill screen aperture size (MA_{gran}).

PE_{DP} (activity) = $f(TAB_{disin}) = f(BU_{disintegrant,\ lubricant}), f(RF_{gran}), f(MA_{gran})$

No additional process parameters for tablet compression or coating were shown to have an effect on patient exposure.

Control of Patient Exposure

Overall, patient exposure can be controlled to acceptable levels through control of critical API crystallization parameters, drug product formulation and critical drug product process parameters, represented by:

PE (activity) = $f(PE_{API}), f(PE_{DP}), = f(AR_{cry}), f(SA_{cry}), f(T_{cry}), f(BU_{disintegrant,\ lubricant}), f(RF_{gran}), f(MA_{gran})$

QbD specifications for the tablets are summarized in Table 2. The relationship of Critical Quality Attributes to product performance characteristics, key input variables, key process parameters, and Critical Process Parameters is summarized in Table 3. Table 4 provides a comparison between traditional and QbD specifications.

Table 2: QbD Product Performance Specifications (Compressed, Film coated tablet, BCS Class II)

QbD CQA Product Performance	**QbD Control Strategy**
Dissolution rate of API particles in the gut	All critical process parameters during API crystallization are within Design Space
Availability of API particles in the gut	All critical process parameters during tablet manufacture are within Design Space. PAT or real time measure to assure lubricant and disintegrant blend uniformity is within acceptance limits.
Dosing Reproducibility	PAT or real time measure to assure API blend uniformity is within acceptance limits. PAT or real time measure for sampling, analyzing and monitoring tablet potency throughout compression; potency of individual tablets is within acceptance limits.

614 **Table 3**: Hypothetical Film Coated Compressed Tablet (BCS Class II API) QbD parameters and Product QbD Specifications
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Critical Quality Attribute	**Product performance Characteristics**	**Key Input Variable or Process Parameter**	**Critical Process Parameter or Relationship**	**QbD Release and Shelf-life Specification**
Dissolution rate of API particles in the gut	T_{max} $\Delta T_{effective}$	API – rate of starting material addition API – drying temperature API – crystallization solvent water content	$PE_{API} = f(API_{psd}) = f(AR_{cry})$, $f(SA_{cry})$, $f(T_{cry})$	All CPPs for API crystallization are within Design Space PARs.
Availability of API particles in the gut	Disintegration rate in gastric fluid T_{max}	Blending – blender load Blending – blender speed Granulation – roll gap Granulation – mill speed Lubrication – time Lubrication – blender speed Tablet compression – force	$PE_{DP} = f(TAB_{disin}) = f(BU_{disintegrant, lubricant})$, $f(RF_{gran})$, $f(MA_{gran})$ Signal vs. blend time profiles for disintegrant and lubricant (PAT or real time measure)	All CPPs for tablet manufacture are within Design Space PARs. Signal vs. blend time profiles for disintegrant and lubricant conform with acceptance criteria (PAT or real time measure)
Repeat Dose Reproducibility	Uniform dispersion of active in drug product blend. Tablet to tablet uniformity.	Blending – blender load Blending – blender speed Tablet compression – press speed Tablet compression – hopper fill	Signal vs. Blend time profile for API (PAT or real time measure) Monitoring of tablet potency throughout compression (PAT or real time measure)	Signal vs. blend time profiles conformity with acceptance criteria. (PAT or real time measure) Tablets accepted/rejected based on individual potency measured by in line PAT method or real time measure.

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618 **Table 4**: Contrast of Traditional Specification against Potential QbD Specification for a Hypothetical Film Coated Tablet (BCS Class II API).
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Traditional Specification		**QbD Specification**	
Test	**Consequences of using end product testing vs. QbD**	**Real time process monitoring or PAT Relationship**	**Benefits of using QbD vs. end product testing**
Description – visual	None – must pass test	Description – visual	None – must pass test
Identification – IR	None – must pass test	Identification - IR	None – must pass test
Microbial Quality – compendia	None – must pass test	Microbial Quality – compendia	None – must pass test
Potency Assay – HPLC	Small sample size is not representative of batch. Testing on stability testing does not add value for a stable compound.	PAT or real time monitoring of individual tablet potency during manufacture. Tablets out of limits are rejected from batch.	In line nondestructive testing of a large number of tablets in each batch provides greater assurance that all tablets are within limits. No routine annual stability testing required because of thorough prior knowledge and mechanistic understanding of degradation products.
Related Compounds – HPLC	Control of related compounds through control of CPPs during API manufacture. Testing on stability does not add value for a stable compound.	Related Compounds controlled by CPPs for API manufacture within Design Space.	Beyond an ongoing commitment, stability testing can be reduced, if product shelf life is sufficiently supported by development studies.
Content Uniformity – USP/PhEur Harmonized Compendia	Small sample size is not representative of batch.	Monitoring of blend uniformity and potency of all tablets.	Monitoring of blend uniformity or testing a large number of tablets for distribution of active can be more representative of the entire batch than end product testing with small sampling.
Dissolution – compendia	Dissolution testing may fail, thus rejecting the batch, when test may not represent product performance in vivo.	Monitoring of blend uniformity for extragranular lubricant. Monitoring of blend uniformity for intra- and extragranular disintegrant. All CPPs for API and tablet manufacture within Design Space PARs.	Monitoring of blend uniformity for excipients critical to granule and tablet disintegration provides greater assurance of drug availability for dissolution/absorption.
API Particle Size (not typically included as end product specification)*	Lot may fail if not within absolute particle size limits.	API particle size controlled by crystallization CPPs within Design Space PARs.	API particle size is controlled by control of CPPs during manufacture.

620 * Note: This example of API Particle Size assumes prior knowledge and quality assurance from product process and API development history.

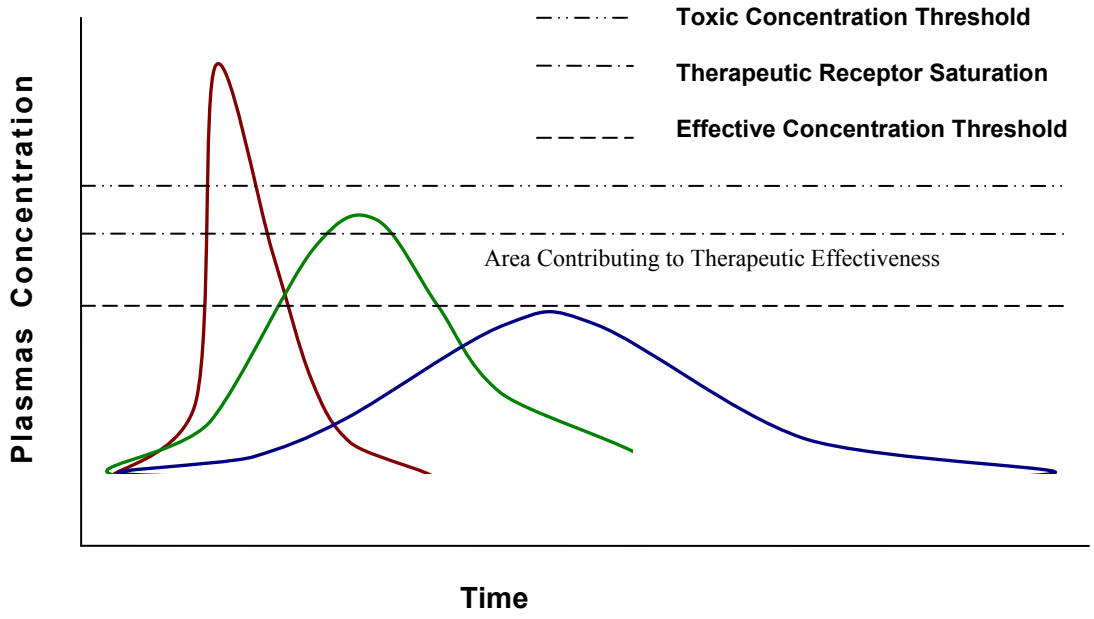
Hypothetical Tablet Scenario (BCS Class IV API) - Narrow Therapeutic Window

To illustrate how QbD specifications might be established for a more complicated multivariate circumstance, the second hypothetical scenario involves a slow release uncoated compressed tablet containing a BCS Class IV API (low solubility, low permeability). Clearly, this illustration could be simplified by reducing the number of variables or factors. The complexity of the example is retained to demonstrate how the interplay between variables could be utilized, in principle, to offset each other in producing a desirable activity (or patient exposure) by balancing of terms within a Design Space.

The compound is dissolution rate limited and absorption rate limited, because the API dissolves slowly in gastric fluid and absorbs slowly by passive diffusion. Clinical studies, for this imaginary compound, indicate a narrow therapeutic window, with therapeutic activity governed by the AUC above the therapeutic threshold. The most desirable therapeutic effect is realized with an AUC that incorporates a given duration of exposure. The compound has a low bioavailability, thus without a solubility/absorption enhancer the inherent *in vivo* release and absorption is such that an adequate AUC above the therapeutic threshold might not be achieved, and consequently the desired therapeutic effect might not be achieved. The solubility/absorption enhancer effectively increases the solubility and absorption of the drug so that plasma concentrations above the therapeutically effective level are achieved. With too much solubility/absorption enhancer, the drug might be absorbed too rapidly, resulting in a shorter duration of exposure above the therapeutic threshold; therefore, producing less therapeutic effectiveness and leading to higher C_{max}, which could put a patient at risk.

Figure 2 illustrates pharmacokinetic plasma concentration time curves with availability that is too rapid (exceeds toxic threshold – red curve), within therapeutic window (optimum duration of patient exposure - green curve) and too slow (below therapeutic threshold – blue curve).

Figure 2: Pharmacokinetic profiles with differing systemic effectiveness (19)



This hypothetical compressed tablet was designed with mechanical properties to generate a disintegration mechanism that will present the low solubility drug substance particles to the gastric fluid in a manner commensurate with a coordinated amount of absorption enhancer. The problem is further complicated by the fact that the API exists in two crystal forms as well as an amorphous form, and it is difficult to isolate the compound in any one form due to interconversion in the solid state. Crystal Form I (CF1) produces a distribution of small sized, low porosity particles; while Crystal Form II (CF2) produces larger sized highly porous particles. On purification, the API exists primarily as Crystal Form I, but it changes slowly to Crystal Form II with time in the solid state during storage. The dissolution profiles of the crystal forms differ, but, to some degree, each offsets the other because of complementary internal vs. external surface areas generated. Being unstable, a given amount of both Crystal Form I and II can convert to the amorphous form during product manufacture. Neither of the two crystal forms are physically stable enough to enable a product to be made with only one form. The amorphous form, alone, is not an option due to its difficult handling properties.

Process monitoring of a product with two API crystal forms and an amorphous form has traditionally been considered unachievable. However, Taday, et al. (20), Strachan, et al. (21) and Zeitler, el al. (22), using terahertz pulsed spectroscopy, have demonstrated, in principle with model compounds, that two crystal forms along with an amorphous form can be monitored in API and product real time, nondestructively, and rapidly with little or no sample preparation. As a monitoring tool, terahertz spectroscopy is discriminatory for crystal lattice phonon modes, which can be complimentary to x-ray powder diffraction (XRPD) or solid state NMR spectroscopy (18). With process monitoring of multiple

crystal forms and an amorphous form in API and product potentially feasible, future monitoring of such challenging compounds can be envisioned.

In this Quality by Design scenario, the intent is to link the desired patient systemic exposure, a CQA, to manufacturing input variables and process parameters. In principle, and for the purposes of this hypothetical example, we can assume for each crystal form we would have a crystal form release coefficient, which could be a function of particle size distribution (psd), particle porosity (pp), effective contact surface area (csa), and time. Equally, one could include a term to represent the gastric availability of amorphous material (AM) and its relationship to formation during manufacture.

CF1 = f(psd1), f(pp1), f(csa1), f(t)

CF2 = f(psd2), f(pp2), f(csa2), f(t)

AM = f(solubility), f(crst1/crst2), f(blend agitation), f(temp/ humidity during blend), f(t),

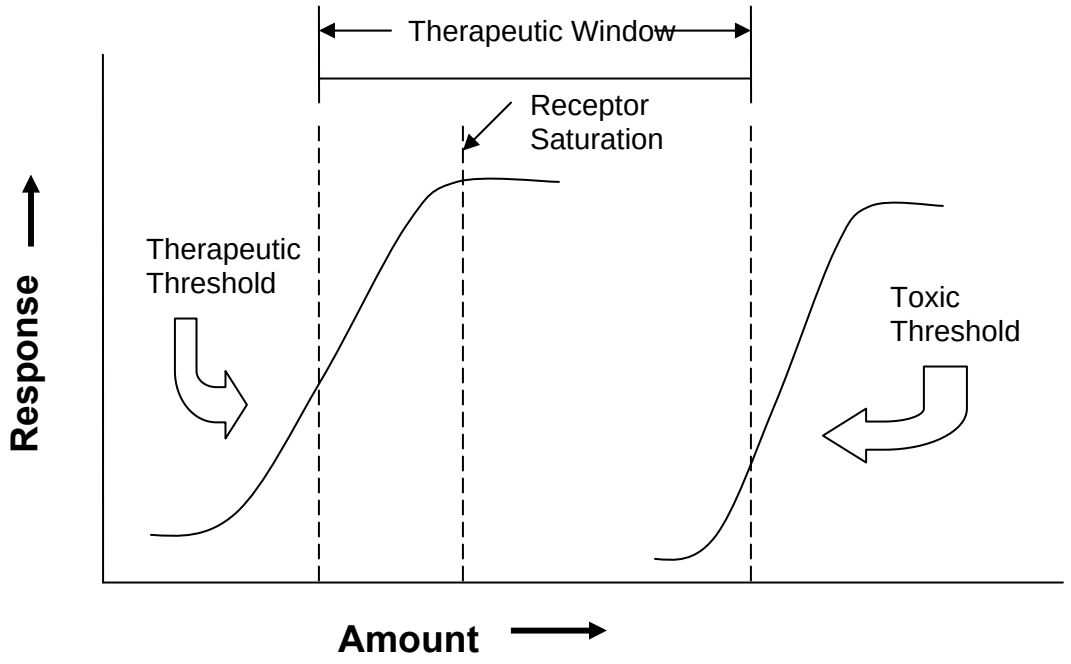
where crst1 and crst2 represent crystal form 1 and crystal form 2.

Further, we assume for the purpose of discussion that the disintegration rate of the compressed tablet in the gut could be best represented by a bonding strength (Bs), which is a function of compression force, press speed, lubrication time, disintegrant concentration, etc., and that the disintegration rate is inversely related to the bonding strength.

Bs = f(comp force), f(press speed), f(lub time), f(disint conc) etc.

The therapeutic window is the difference between the therapeutic threshold and the toxic threshold (Figures 2 and 3), but the AUC in this region is *not the therapeutic effectiveness*, for beyond the therapeutic saturation point (Figures 2 and 3) additional drug does not contribute to effectiveness. As such, the most clinically relevant Critical Quality Attribute is the area of the plasma concentration time curve above the therapeutic threshold, but below the saturation level (see shaded region in Figure 2). This area is the effective therapeutic duration of Patient Exposure (**PE**). It is desirable to link this most clinically relevant CQA of **PE** to the dosage form via the solubility-absorption enhancer content, which will determine the bioavailability; and the bonding strength, which will determine the rate of tablet disintegration and drug substance particle availability.

Figure 3: Therapeutic Window (19)



The therapeutic effectiveness, **PE**, may be linked to the API inputs and critical process parameters through the following hypothetical relationship to the active, which is the effective amount of active, where **P** is API purity, **S** is the amount of solubility enhancer, **Bs** is the Bonding strength of the compressed tablet, and **b** the inherent bioavailability in the absence of solubility-absorption enhancer.

Patient Exposure (PE) is proportional to Activity,

$$\textbf{PE (Activity)}_{\textbf{release}} = (CF1)(P)(b)(S^{Y1}/(Bs+1)^{Y2} + (CF2)(P)(b)(S^{Y3}/(Bs+1)^{Y4} + (AM)(P)(b)(S^{Y5}/(Bs+1)^{Y6}$$

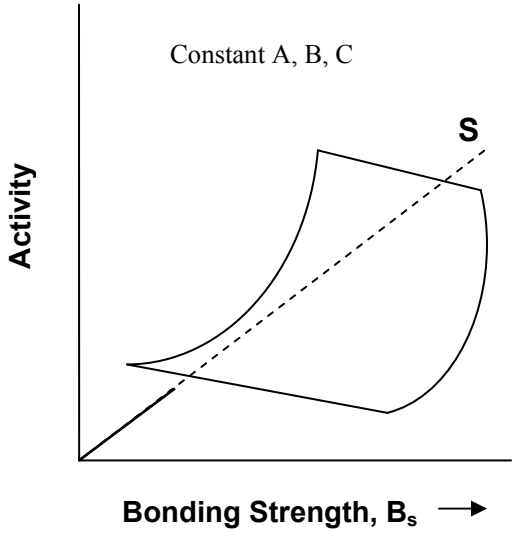
where CF1 and CF2 are crystal form release coefficients, as defined above; and where Y1, Y2, - ···- Y6 represent curve fitting variables for model unknown exponents. This equation is created only for the purpose of illustration.

For simplicity and illustration, if we assume that the activity is nonlinear in S, say cubic; while Bs is first order in (Bs+1), the relationship reduces to:

$$\textbf{PE (Activity)}_{\textbf{release}} = \textbf{A}\,(S^3/(Bs+1)) + \textbf{B}\,(S^2/(Bs+1)) + \textbf{C}\,(S/(Bs+1)),$$

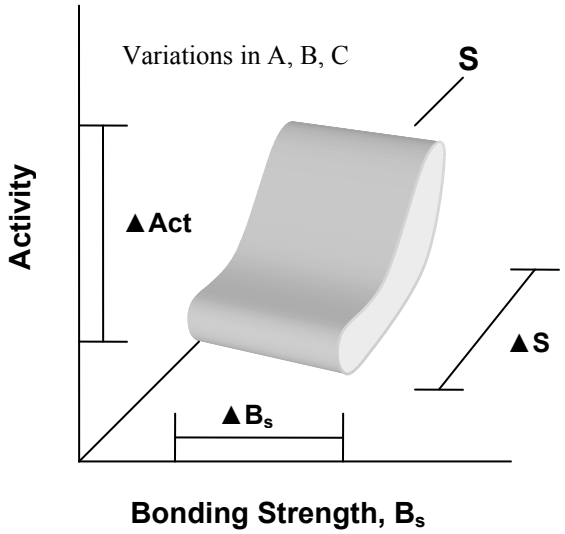
where A, B, and C are coefficients.
Plotting the effective amount of Activity on a Y axis against the Bonding Strength (Bs) on the X axis and Enhancer amount (S) on the Z axis, one would create a nonlinear response surface during development for any set of A, B and C values (Figure 4).

Figure 4: Activity (PE) vs. Bonding Strength vs. Enhancer Concentration at constant coefficients (19)



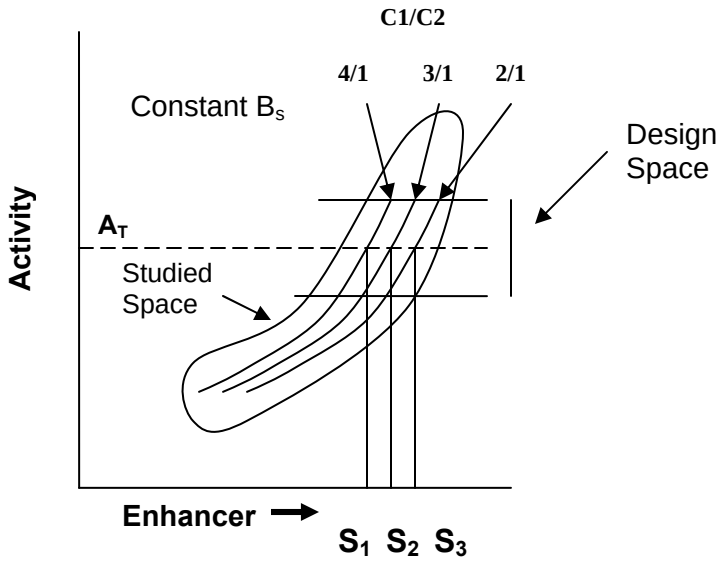
The combination of the response surface and experience with variations in A, B and C should generate a Design Space volume (Figure 5).

Figure 5: Activity (PE) vs. Bonding Strength vs. Enhancer Concentration with variation in coefficients (19)



During any one manufacture run, B_s and S are assumed to be constant, so PE would be represented by one point in the space as a function of A, B, and C. For any given Bs, a slice of the Design Space at time of manufacture reveals a set of curves for different crystal form ratios (C1/C2); whereupon, the selection of optimum S_i for this batch would be target activity (Figure 6).

Figure 6: Activity at constant bonding strength B_s enables adjustment of enhancer amount S_i to achieve targeted activity A_T (12)



Since A and B are a function of API storage time and since C is a function of manufacturing time, activity will vary for any combination of manufacturing circumstances. Further, B_s might be a function of shelf-life as the tablet ages, so activity might change nonlinearly with time during the shelf-life, but it may still remain well within the Design Space. As such, the activity can become a function of multiple time domains: API storage time, manufacturing time, and product shelf-life time.

$$\textbf{Activity}_{\textbf{time}} = f(\mathbf{A})_{t\text{-api}} \left(S^3/(f(Bs)_{t\text{-shelf}}+1)\right) + f(\mathbf{B})_{t\text{-api}} \left(S^2/(f(Bs)_{t\text{-shelf}}+1)\right) + f(\mathbf{C})_{t\text{-man}} \left(S/(f(Bs)_t+1)\right)$$

In addition to changes of parameters within A, B and C, the impact of time also defines the limits of the Design Space.

Reviewing Table 5 below, one can see how the CQAs for this hypothetical scenario could relate to the product performance characteristics, key input variables, key process parameters, and critical process parameters.

778 **Table 5**: Hypothetical Compressed Tablet QbD parameters and Product QbD Specification (BCS Class IV API)
779

Critical Quality Attribute	**Product Performance Characteristics**	**Key Input Variable or Key Process Parameter**	**Critical Process Parameter or Parametric Relationship**	**QbD Release Specification**
Patient Systemic Exposure	ΔT ± CV AUC > Threshold ± CV % Bioavail. (BA) ± CV **Patient Exposure (PE)** **PE** ~ f(AUC), f(ΔT) above therapeutic threshold **PE** is proportional to **Activity**	API – active content API – crystal form I API – crystal form II API – amorphous form API – particle size API – porosity sol-absorption enhancer (S) pH solubility	**Activity** $\mathbf{Activity_{release}} = \mathbf{A}\,(S^{Y1}/(Bs+1)^{Y2} + \mathbf{B}\,(S^{Y3}/(Bs+1)^{Y4} + \mathbf{C}\,(S^{Y5}/(Bs+1)$ $\mathbf{Activity_{time}} = f(\mathbf{A})_{t\text{-}api}\,(S^{Y1}/(f(Bs)_{t\text{-}shelf}+1)^{Y2} + f(\mathbf{B})_{t\text{-}api}\,(S^{Y3}/(f(Bs)_{t\text{-}shelf}+1)^{Y4} + f(\mathbf{C})_{t\text{-}man}\,(S^{Y5}/(f(Bs)_{t}+1)^{Y6}$	<u>Release</u> **Activity** $_{release}$ in Design Space limits at time of release <u>Shelf-life</u> **Activity** $_{time}$ in Design Space limits during shelf-life
Availability of active ingredient particles in gut	Disintegration rate in gastric fluid Rate of DP swelling	Hardness Density Porosity Wetting Granular size Lubrication Compaction	Compression force (cf) Press speed (ps) Lubrication time (lt) Bonding strength (B_s) Disintegration rate = $1/(B_s+1)$ $B_s \sim f(cf), f(ps), f(lt), f(dc)$	
Dose Reproducibility	Uniform dispersion of active in DP blend	Blend time Agitation rate Rotation rate Room temp and humidity	Blending Time Rotation and Agitation Rate Variable vs. Blend Time Profile (PAT or real time measure)	Curve conforms to within nonlinear regression limits
Dosage Form Active Stability	Moisture of final DP Rate of moisture uptake	API moisture Excipient moisture Drying effectiveness Room temp and humidity	Drying time Air flow rate Air temperature Moisture vs. Drying Time Profile (PAT or real time measure)	Curve conforms to within nonlinear regression limits
Blister Packaging Integrity	Degree of moisture exclusion	Moisture barrier transport properties and package sealing	Foil pouch material release testing by vendor	Vendor data

		operation		

Given these relationships between the CQAs, Input Variables, CPPs, and Parametric Relationship, the QbD specification might be as shown in Tables 6 and 7.

Table 6: QbD Release Specification (Tablet, BCS Class IV API)

QbD CQA Specification on Release	QbD Specification Acceptance Criteria
Activity	Activity is within Design Space
Dosing Reproducibility	Blend Curve within regression limits
Moisture	Drying Curve within regression limits
Blister Pack Integrity	Vendor data acceptable

Table 7: Compressed Tablet QbD Shelf-life Specification (Tablet, BCS Class IV API)

QbD CQA Specification during Shelf-life	QbD Specification Acceptance Criteria
Activity	Activity is always in Design Space
Moisture by KF (Bs)	Activity in Design Space per impact on Bs
Degradation products by HPLC	Activity within benefit/risk safety qualification of degradation product profile
Disintegration test (Bs)	Activity in Design Space per impact on Bs

Contrasting the traditional product specification to the potential QbD product specification (Table 8), the greater flexibility for this hypothetical complicated BCS Class IV QbD approach is evident. With API differences, crystal form changes, impact of moisture, and degradation, it may be difficult to develop a product that can continually meet independent, narrow test limits with traditional end product specification, because each tested CQA may not necessarily alone have a direct impact on product performance in accordance with its test limit. With the QbD specification approach, however, one can take advantage of the real contribution of each attribute to the clinically relevant delivery of activity. In this case, one has an opportunity to adjust the amount of solubility/absorption enhancer during manufacture and/or adjust other CPPs to compensate for API input variables.

801 **Table 8**: Contrast of traditional specification against potential QbD Specification for hypothetical tablet product (BCS Class IV API)

Traditional Specification		**QbD Specification**	
Test	**Consequences of using end product testing vs. QbD**	**Real time process monitoring or PAT Relationship**	**Benefits of using QbD vs. end product testing**
Description – visual	None – must pass test	Description-visual	None – must pass test
Identification – IR	None – must pass test	Identification – IR	None – must pass test
Microbial Quality-compendia	None - must pass test	Microbial Quality-compendia	None - must pass test
Potency Assay – HPLC	Could fail 90-110% purity spec at release or on stability, but could still be within activity limits by QbD	Activity with acceptability range by equation with API and real time inputs (PAT or real time measure)	Determined with combination of correlated inputs, so impact of each change is not absolute
Content Uniformity- USP/PhEur Harmonized Compendia	A finite sampling at release may fail a lot when in fact it may be acceptable.	curve conforms to nonlinear regression limits (PAT or real time measure)	Curve conformity could be more representative of entire batch.
Dissolution – Compendia	Dissolution testing may fail, thus rejecting batch, when test may not represent product performance	Calculation of Bs via CPPs and correlate to disintegration rate	Bs acceptable as it contributes to product performance, release of Activity per other correlation parameters.
Moisture – KF or LOD	Lot may fail absolute moisture limit but moisture impact on release activity may be acceptable	Curve conforms to nonlinear regression limits during drying as correlated to Bs (PAT or Real time measure)and API degradation rate	Moisture may impact product Activity as Bs decreases or degradation products increase during shelf-life.
Particle Size	Lot may fail if not in absolute particle size limits	API particle size measurements factored into product batch manufacture	API particle size is compensated by adjustment of CPPs during manufacture.
Hardness/Friability	Lot may fail due to absolute limits	Calculation of Bs via CPPs and correlate to hardness/friability	Bs may or may not provide acceptable Activity depending on impact relative to other parameters.

802

Toxicology of Actives and Degradation Products - A QbD Approach

Although a detailed description of toxicology is beyond the scope of this paper, under QbD one should explore all available risk based options that enable the acquisition of scientific understanding on specific *in vivo* mechanisms as early in development as possible with safety assurance from preclinical toxicology. One excellent option for conducting screening for QbD clinical relevance is the Exploratory IND Guidance (23).

If a drug candidate will allow microdosing at 1/100 of the expected pharmacological dose, single dose human studies can be conducted under an Exploratory IND to gain pharmacokinetic information. For single dose human microdosing, a single dose toxicology study in one animal species with 14 day post dosing observations may be sufficient for toxicological qualification, using the same API batch in both the toxicological study and clinical study. With a single dose pharmacokinetic Exploratory IND study, one could quickly assess biodistributions on more than one element to assess clinical relevance. This might include different amounts of an absorption enhancer or a range of selected crystal form mixture ratios or different excipient combinations or different processing parameters, etc. Equally, one could use an Exploratory IND to assess the pharmacological effects on repeat dosing for seven days in humans with toxicological qualifications based on two week repeat dosing in a sensitive animal species with the use of toxicokinetics for the selection of a safe starting dose and maximum dose (e.g., use rat to determine NOAEL, then dog repeat dosing to evaluate CNS, respiratory and cardiovascular effects). If a discriminatory therapeutic surrogate marker is available, one could build a comparative map of pharmacological activity across process parameter ranges for a product by conducting an Exploratory IND study with a collection of potential formulation selections, each with a set of process parameter values.

With some knowledge of clinical relevance, gained from Exploratory IND studies, one could proceed further to establish human safety margins by using higher doses with selected formulation parameters within a targeted Design Space. It is expected that progressive clinical studies would be supported by preclinical safety evaluation elaborated in ICH guidelines (24). These preclinical studies could include safety pharmacology, toxicokinetics, single dose and repeat dose toxicology, local tolerance, genotoxicity, carcinogenicity, and reproductive toxicity. The phase appropriate preclinical animal toxicology studies are undertaken in stages through the development to support the planned clinical studies (Table 9) with minimum durations commensurate with the length of the clinical trials (Table 10).

Table 9: Phase Appropriate Toxicology Studies to Support Clinical Studies

Prior to Phase 1	Phase 1/2	Phase 2/3
Acute Mouse Acute Rat 2, 4, or 13 week Rodent 2, 4, or 13 week Rodent Safety Pharmacology Genotoxicity (Ames-point mutation and chromosomal aberration)	6 month Rodent 9-12 month non-Rodent 2 and 3 weeks carcinogenicity dose range finding Reproductive Toxicology	Carcinogenicity (mouse or alternative model) Carcinogenicity (Rodent)

Table 10: Duration of Repeated Dose Toxicity Studies to Support Phase 1 and 2 Clinical Studies in Europe and Phase 1, 2, and 3 Clinical Studies in US and Japan (see ICH Guideline M3(R1) for more details at reference 24)

Duration of Clinical Trials	Minimum Duration of Repeated Dose Toxicity Studies	
	Rodents	Non-Rodents
Single Dose	2 weeks	2 weeks
Up to 2 weeks	2 weeks	2 weeks
Up to 1 month	1 month	1 month
Up to 3 months	3 months	3 month
Up to 6 months	6 months	6 month
Greater than 6 months	6 months	chronic

Beyond the Exploratory IND, with the preclinical toxicological regime shown above, a company could use a single batch of API to conduct typically 2 weeks of toxicology studies in 2 species, in addition to genotoxicity assessment (25), and use the same API batch for Phase 1 trials. Alternatively, an API batch with a higher level of impurities could be used in toxicology studies for impurities qualification with additional API batches of lower impurities levels manufactured for Phase 1 studies. In addition, known impurities could be spiked into an API batch for use in preclinical toxicology studies. New impurities observed in subsequent batches, can be qualified with additional toxicology studies, or qualified by literature safety information, if structure activity relationships are well known and documented. With some exceptions, metabolites normally do not require separate qualification, for metabolites are included in the profiling of the active, as they inherently contribute to the overall toxicokinetics. If an active metabolite is more toxic than the administered prodrug from which it is derived, the *in vivo* concentration of the active metabolite becomes a CQA requiring control by molecular complexation, or by controlled release of the prodrug, or by inhibition of metabolic enzymes or cofactors releasing the active metabolite.

Degradation products can vary greatly from compound to compound, typically broader limits are allowed during early development compared to late stage clinical studies and registration. It is common practice to qualify organic impurities in preclinical studies

with animal dosing in significant excess per body weight compared to amounts administered to humans in order to provide safety margins.

Based on a comprehensive scientific understanding of the active relative to the benefit/risk to a select patient population, a company should make adjustments in the Design Space to eliminate toxic effects altogether by optimization of pharmacokinetics, as illustrated in Figure 2.

Discussion

To understand QbD specifications, one can look back to the QbD framework established by Janet Woodcock, M.D. in 2004 (26), when she defined Quality by stating that *"…good pharmaceutical quality represents an acceptable low risk of failing to achieve the desired clinical attributes;"* and when she defined Quality by Design by stating that QbD *"…means that product and process performance characteristics are scientifically designed to meet specific objectives, not merely empirically derived from performance of test batches."*

Inherent in this QbD definition is a systematic, scientifically designed product with critical performance characteristics that enable a high probability of achieving clinical effectiveness without the need for end product batch release testing. This means that product performance is unambiguously associated with an ability to safely deliver an intended therapeutic activity by means of patient relevant Critical Quality Attributes that are linked to manufacturing Critical Process Parameters. Quantitative parametric relationships that link CQAs to CPPs are monitored and controlled by PAT. These mathematical relationships dynamically yield activity, as an output, in proportion to an effective Patient Exposure, which is a plasma concentration per unit time above a therapeutic threshold but below a toxic threshold for a duration needed to generate a desired therapeutic effect.

During the design, development, and commercial phases of a product life cycle, the challenge of developing a QbD specification is to systematically design into product performance the key input variables and key process parameters (Tables 3 and 5) that allow the real time adjustment of Critical Process Parameters to yield the activity within a Design Space over the shelf-life of a product. To achieve this QbD specification development goal of finding the desirable Design Space within the overall Studied Space, it becomes imperative to focus attention on the clinical impact of each variable, as it influences the functional combination of variables. Much of this study of how process parameters relate to quality attributes begins with modeling of molecular attributes, modeling of formulation design, modeling of process operations, and modeling of manufacturing systems (27).

Development of a systematic parametric approach to assessing the influence of each product manufacturing variable on biopharmaceutics of each product under development could be an expensive venture. An alternative approach could be to establish model systems which can be assessed using appropriate pharmacokinetic and toxicokinetic studies in animals. Once acceptable systems are obtained, these models need to be cross-

correlated and verified against normal human subjects and diseased patients in clinical studies.

If every QbD functional model were independent and unique, the cost of engaging in this optional approach might be prohibitive. Fortunately, most active ingredients found in solid oral dosage forms fall easily into one of the four BCS classifications. Furthermore, many compounds of high therapeutic value with formulation challenges, coincidentally, can be found in either BCS Class II or IV. This being the case, development of model systems, based on product and process understanding, that apply to a breadth of compounds within BCS classifications II and IV could prove a worthy investment towards utilization of prior knowledge. Compounds within a given BCS class generally exhibit similar biopharmaceutic profile. This means that the knowledge gained from one compound within a BCS class for a given in-house formulation can be applied to other compounds of the same class, using the same formulation principles. In this manner, companies can build on their QbD investment and leverage scientific understanding.

With this approach, one needs to focus attention on three areas: (i) identifying elements that impact clinical relevance and safety; (ii) facilitating development timeline considerations; and (iii) preparing for interactions with regulatory authorities.

Clinical Relevance and Safety

The lifecycle of a product roughly consists of a Design Phase, a Development Phase, and a Commercialization Phase. In each of these phases, one must make every effort to identify critical attributes which link clinical efficacy and safety to product performance through parameters and coefficients that can be expressed and controlled by parametric relationships. As shown in Table 3 (BCS Class II) and in Table 5 (BCS Class IV) with the two hypothetical scenarios presented, there are many traditional input variables and process parameters that need to be considered in building a QbD formulation model. Beyond the obvious inputs, many other aspects also need to be addressed, particularly toxicology.

During the *Design Phase* (Preclinical, Preformulation and Formulation Design), much attention should be given to the selection of the best excipients to gain the most desirable uniformity of dispersion of active in the drug product blend for PAT or real time monitoring to result in uniformity amongst the dosage form units as well as within a single dosage unit. In addition to other factors that affect *in vivo* performance, slow dissolution (BCS Class II and IV) dictates that each physical part of a solid oral dosage unit will release active in the same amount and at the same rate. Clearly, excipient interactions that may lead to non-homogeneity issues, dose dumping, *in vivo* precipitation, or other physical phenomena impacting absorption must be carefully considered; so a good product design can lead to a robust formulation and robust manufacturing process. The history of collected GRAS excipient characteristics, as well as newly measured novel excipient characteristics, need to be thoroughly evaluated for potential incompatibility with or degradation of the API that may lead to safety issues. A combination of actives with differing therapeutic targets will require special attention to assure that common excipients will deliver each active appropriately, or that multiple excipients with layered, sandwiched, or capsule dosage forms will deliver each active as expected. Ultimately,

the dosage form design must focus on the most important patient group for which the therapeutic indication is intended (i.e., adult, geriatric, pediatric, cancerous, immune compromised, etc.) with due consideration given to additional clinical indications that may be established in the future. Physiological differences among the targeted patient populations should be identified compared to normal subjects in order to gain an appreciation for how these differences may drive the dosage form design and the active drug delivery.

During the ***Development Phase*** (Phase 1, 2 and Early Phase 3), clinical studies begin to reveal Critical Quality Attributes and, in parallel with multivariate process monitoring, links these attributes to Critical Process Parameters that become better defined as new mechanistic understanding builds on the ever important prior knowledge, which is integral to QbD. The deliberate variation of CPPs within the manufacturing Design Space to affect pharmacokinetics, first in animals and later in humans, will build this knowledge rich scientific understanding and will slowly generate an operational region within the clinically relevant studied space. The impact on this operational space, viewed as the delivery of an acceptable amount of real time measurable activity that will generate a desired patient exposure, now becomes the overriding objective during this phase; as all the critical aspects of formulation development (e.g., excipient interactions, polymorph changes, moisture uptake, degradation, etc.) and process development (e.g., particle sizing, blending, tableting, etc.) are assessed against their impact on clinically relevant product performance to arrive at a Design Space. During this development phase because of the linked attributes, the opportunity to tighten or broaden the criteria boundaries of this Design Space, which defines the QbD Specification, is now based on clinical and pharmaco-toxicological relevance as well as manufacturing performance experience.

Upon entering the Precommercialization Phase (Late Phase 3 Clinical), using a commercial formulation upon which a QbD model and real time monitoring (PAT or real time process monitoring) has been developed and clinically verified, one directs attention to finalizing: (i) formulation Critical Quality Attributes, (ii) degradation product characterization and toxicological qualification; (iii) API commercial synthesis; (iv) levels of expected contaminants (i.e., residual solvents, heavy metals, etc.); (vi) API process impurities toxicological qualifications; (vii) any changes in organoleptic properties (i.e., taste, color, odor, or feel); (viii) any stability or leachable considerations from the product contact surface primary packaging (e.g., blisters, pouch, foils, bottles, etc.); and (ix) Design Space boundaries that might lead to subpotent or super potent dosage forms. Once the impact on clinical relevance of all critical safety and efficacy aspects have been assessed, certain parts or arms of the Late Phase 3 clinical studies can be designed to utilize the desired commercial QbD formulation along with real time monitoring and release of Late Phase 3 clinical supplies with the proposed registration QbD specification. Conversely, one may employ QbD principles during development, but may elect not to link QbD aspects to clinical studies or registration.

Development Timeline Considerations

In order to succeed with the QbD systematic risk based, scientific approach to product development, very careful consideration must be given to timelines and the generation of

data to support the entire QbD development process, so scientific knowledge and mechanistic understanding is available at critical milestones. The following is a summary of important considerations necessary for success with the QbD approach:

Preclinical

- Assess BCS classification (or other categorization) of active and consider use of prior knowledge and *in silico* modeling to predict *in vivo* performance to build QbD models
- Assess physical properties of API that may impact clinical performance and build a thorough understanding of these attributes relative to potential PAT or real time process monitoring. In addition, develop a toxicology formulation strategy to maximize subjects' exposure to the compound during preclinical studies.
- Assess toxicology of isomers, enantiomers, diastereomers, process impurities and degradation products.

Phase 1 Clinical Studies

- Design Phase 1 studies to gain understanding of relationship between API and product quality attributes and clinical PK performance and safety by conducting studies in a controlled manner with planned variations.
- Use *in vitro* surrogate testing to identify extremes of formulation and process variables, and link these extremes to *in vivo* performance.
- Compare accumulated plasma profiles of other BCS Class compounds (with similar structure) using similar formulations to leverage prior knowledge.

Phase 2 Clinical Studies

- Attempt to build pharmacokinetic models and process parametric relationships from first principles by linking CQAs to CPPs with cooperative input from clinical development and process engineering staff collaborations.
- Attempt to confirm CQAs through existing *in vivo* studies.
- Refine formulation and process effects of CPPs on CQAs for commercial formulation and manufacturing process
- Affirm relationship between patient exposure and CPPs
- Develop PAT and QbD plan for implementation by End-of-Phase 2 (EOP2) CMC meeting.
- As appropriate, apply risk based science and management approaches described under ICH Q9 (24).

Phase 3 Clinical Studies

- Whenever possible, use the intended commercial formulation and commercial manufacturing process with real time monitoring for Phase 3 clinical studies.
- Start using new QbD Release Specifications for process monitoring and Real Time Release Testing of Phase 3 clinical supplies.

- Start using new QbD Stability Specifications for conducting registration stability studies.
- Build real time process monitoring database during Phase 3 and refine proposed Pharmaceutical Quality Assessment System (see glossary) strategy.
- Finalize mechanistic understanding of QbD science rationale and prepare for Pre-NDA meeting by early preparation of Pharmaceutical Development and Control of Drug Product CTD sections.

Regulatory Interactions

Interactions with regulatory authorities on QbD Specifications should begin with the End-of-Phase 2 meeting. A CMC only discipline meeting should be scheduled at the EOP2 for the sponsor to introduce the QbD based product specification strategy and direction of all supporting QbD activities. This QbD specification strategy might include: (i) identification of CQAs; (ii) description of parametric model; (iii) identification of input variables; (iv) explanation of CPP linkages and correlations between input variables and outputs; (v) description of real time process monitoring methodology; (vi) QbD data collected during clinical development phase; (vii) the QbD scientific rationale for clinical relevance of CQAs; and (viii) a proposed Pharmaceutical Quality Assessment System strategy. In describing and justifying the quality assessment system, the sponsor should provide all historical data regarding previous use of the parametric model and associated process monitoring experience. This could include previous failure mode effects analysis (FMEA) and failure mode effects and criticality analysis (FMECA) for product design (component quality control) and for process parameters. As an outcome of the EOP2 CMC meeting, the regulatory agency and the sponsor, collectively, could arrive at the registration and stability (shelf-life) assessment and monitoring strategy for the Real Time Release Testing of product. This strategy could be utilized for release of Phase 3 clinical supplies. Additional information will also be collected over the product and process development period on drug products that will be used in Phase 3 clinical studies. This data would also be included in the QbD submission data package.

During the Phase 3 clinical studies, dialog with the regulatory agency regarding QbD is suggested. Upon completion of Phase 3 clinical studies, the sponsor could plan a Pre-NDA CMC only meeting. At this meeting, a post approval management plan for QbD specifications and CMC Design Space could be refined for registration by obtaining agency concurrence on the QbD mathematical model and the real time monitoring strategy based product release criteria in terms of Design Space. Inherent in this discussion will be a status review of the proposed quality assessment system, and how new information and knowledge will be utilized to verify and update the Design Space throughout the product lifecycle (4). For this meeting, the sponsor could provide draft registration dossier sections of Pharmaceutical Development (CTD 3.2.P.2) and Control of Drug Product (CTD 3.2.P.5) as background knowledge to communicate the QbD manufacturing control strategy. This sharing of QbD product knowledge and process understanding prior to registration dossier submission should enable a regulatory management plan, at time of product approval, to best accommodate implementation of QbD principles by assuring means to (4):

- Facilitate sharing of QbD information
    - to verify, refine, and update Design Space with experience
- Reduce regulatory hurdles while providing higher assurance of product quality
- Determine the type of manufacturing changes to be made without preapproval.

Lifecycle Management

The lifecycle management of a product begins during development, continues at registration, and proceeds throughout post-approval marketing. Lifecycle management of QbD specifications begins during the development of a Design Space model as CQAs are linked to CPPs and as acceptability criteria are identified for conformance of parameters to acceptable ranges of CQAs. As the model is validated and revalidated during clinical supply manufacture, API or product technology transfer, and commercial scale-up, QbD specification criteria may be refined within an agreed upon Design Space without submitting post-approval supplements as new knowledge is gained. This refinement can support the Real Time Release Testing of product per a QbD specification, based on thorough scientific knowledge and robust process control. PAT or real-time analysis of data, generated from processes run within Normal Operating Ranges, may shift off center of a model without risk to quality because of the sound scientific understanding and acceptability of the clinically relevant Design Space within which these movements are confined. Flexibility of adjustment in process parameters to maintain conformity or to allow for shifts in conformity or other inputs within the Design Space without compromising quality inherently provides a new dimension of flexibility in managing the overall quality of drug product throughout a product's lifecycle.

Conclusion

One of the most important concerns of the pharmaceutical industry is the fact that its primary customer, the patient, inherently cannot discern, by observation or by use, the quality of a product. Therefore, a pharmaceutical manufacturer has a responsibility to produce a quality product that ensures safety, efficacy, and performance. QbD challenges industry and regulators to partner in an effort to move beyond empirical, end product testing for ensuring quality to a new knowledge rich, systematic scientific approach that builds in and manages product quality though understanding, modeling, and monitoring. Central to this new paradigm is the creation of science based QbD specifications that link the manufacturing process to critical quality attributes that are in turn linked to clinical performance. Achieving these ends, maximizes prior knowledge with careful risk management to shape a robust, yet flexible, process that can evolve and improve quality throughout a product lifecycle. A dynamic QbD program defines the clinically relevant Design Space, capitalizes on process monitoring, employs appropriate mathematical models, utilizes multivariate analyses, establishes parametric based specifications, facilitates Real Time Release Testing, eliminates quality control waste, provides a mechanism for updating control strategies, and, above all, recognizes the multivariate nature of quality. Having elaborated the fundamentals of QbD specifications, the next step is to apply these concepts to real product development circumstances so as to yield mathematical models that link CPPs to CQAs to clinical activity, and then devise

appropriate process monitoring and control strategies using risk management principles. Ultimately, QbD specifications based on proven scientific rationale utilizing thorough understanding of flexible process conditions that affect quality attributes relative to clinical performance, serve to offer a better quality product to the patient. Pharmaceutical industry investment and regulatory agency cooperation, however limited or substantial, requires objectivity and discipline in the adoption and adaptation of the QbD paradigm to manufacture quality drug products.

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Glossary

The definitions in italics are taken from FDA, ICH Q8(R2), ICH Q9 and ICH Q10 guidance documents. Additional text are elaborations of ICH definitions by the authors of this concept paper.

Activity is a term used interchangeably to communicate the labeled strength of the drug product, or a product's therapeutic effectiveness, or an expected drug concentration in plasma, or patient exposure, or a clinical effect in patients when the drug product is used as labeled.

Control Strategy is *a planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substances and drug product materials and components, facility and equipment operation conditions, in process controls, finished product specifications, and the associated methods, and frequency of monitoring and control* [ICH Q10]. Furthermore, a control strategy encompasses a set of operating parameters, quality attributes, and monitoring systems used to ensure process capability and product quality. The control strategy is derived from product and process understanding while establishing Design Space. A control strategy that includes real time monitoring of products and processes, and correlations between input variables, CPPs and CQAs may become the product's pharmaceutical quality assessment system.

Critical Process Parameter (**CPP**) is *a process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality* [ICH Q8(R2)]. A CPP is a clinically relevant process parameter or modeled, relational combination of process parameters, that impacts clinical activity by virtue of its link to Critical Quality Attributes, or where a Normal Operating Range (NOR) is close to a Proven Acceptable Range (PAR) (or combination of NORs and PARs). Excursions into the region beyond the PAR represents a risk of failure to meet the acceptance criteria for a CQA or parametric combination of CQAs. The CPPs, PARs, NORs, and parametric relationships to CQAs become part of the QbD Postapproval Management Plan (PMP).

Critical Quality Attribute (**CQA**) is *a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired quality* [ICH Q8(R2)]. A CQA is a quantifiable property of an intermediate or final product that is considered critical for establishing the intended purity, efficacy, and safety of the product by virtue of its impact on clinical relevance. That is, the property (or combination of properties) must be within a predetermined range of Design Space to ensure final product quality based on clinical relevance. CPPs should be linked to one or more CQAs. The CQAs, with links to CPPs and to clinical relevance, become a part of the QbD PMP.

Design Space is *the multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the Design Space is not considered a change. Movement out of the Design Space is considered to be a change and would normally initiate a regulatory postapproval change process. Design Space is proposed by the applicant and is subject to regulatory assessment and approval* [ICH Q8(R2)].

Edge of Failure is *the boundary to a variable or parameter, beyond which the relevant quality attributes or specification cannot be met* [ICH Q8(R1)]. The edge of failure is the farthest Design Space modeled boundary beyond which a QbD specification criterion cannot be met, even with the adjustment of orthogonally linked and offsetting process parameters.

Key Quality Attribute (**KQA**) is a quantifiable property of an intermediate or final product that is considered ***non-critical*** for establishing the intended clinical purity, efficacy, and safety of the product; however, it may be key in determining some physical or quality attribute that satisfies a process characteristic or business need that does not directly impact clinical product performance as a variable. In early development, prior to clinical studies, all attributes that impact perceived quality may be considered Key Quality Attributes. A Key Quality Attribute may become a Critical Quality Attribute, if clinical studies reveal an impact on clinical product performance. Key Quality Attributes need not be filed as regulatory commitments or be part of a PMP under the QbD approach.

Manufacturing Science is the body of prior knowledge available for a specific product and process, including knowledge of Critical Quality Attributes to Key Quality Attributes (API or product) and process parameters, process capability, manufacturing and process control technologies, and the quality system infrastructure.

Normal Operating Range (NOR) is a defined range, within the Proven Acceptable Range, specified in the manufacturing instructions as the range within which a process parameter is controlled, while producing unit operation material or final product meeting release criteria and Critical Quality Attributes.

Pharmaceutical Quality Assessment System is a control strategy that includes real time monitoring and control of a modeled, relational combination of CPPs and input variables linked to one or more CQAs.

Patient Exposure (PE) is the effective dose dependent duration of therapeutic systemic effect represented by the integrated area below the plasma concentration time curve between the therapeutic receptor saturation level and the effective therapeutic plasma concentration threshold. Patient Exposure and Activity are proportionally related via appropriate clinical factors and parameters.

Process Analytical Technology (PAT) *is a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality*.

Proven Acceptable Range (PAR) is *a characteristic range of a process parameter for which operation within this range, while keeping other parameters constant will result in producing a material meeting relevant quality criteria* [ICH Q8(R2)]. PAR is the upper and/or lower limits for process parameter values between which the parameter is known to produce a process output (e.g. intermediate, API or product) that meets the CQAs. The PAR may or may not represent the point of failure. The PAR for a given process parameter may be dependent upon the PAR values for one or more other process parameters (e.g. multivariate).

Quality *is the suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity* [ICH Q6A]. Quality is degree to which a product, a process, or a system meets a set of predetermined requirements, and this degree represents an acceptable low risk of failing to achieve the desired clinical benefit.

Quality System is a formalized system that documents the structure, responsibilities and procedures required to achieve effective quality management.

Quality by Design (QbD) is *a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management* [ICH Q8(R2)]. QbD means that product and process performance characteristics measured by PAT or real time process monitoring are scientifically designed to meet specific objectives, and these characteristics are not empirically derived from performance of test batches alone**.**

QbD Release Specification is a clinically relevant CQA that is expressed and controlled by associated CPPs within a Design Space with real time process monitoring or with PAT to enable Real Time Release Testing.

QbD Stability Specification is a clinically relevant CQA that is governed by a parametric relationship between CQAs and CPPs within a Design Space that expresses change in performance activity with time.

Real Time Release Testing is *the ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of assessed material attributes and process controls* [ICH Q8(R2)]. Real Time Release with QbD specifications based on parametric modeled Design Space involves the use of

PAT or real time process monitoring along with conformance to the model's output acceptance quality criteria. Real time monitoring differs from PAT by encompassing only designing and analyzing a manufacturing process, but not controlling the process as in PAT (see PAT definition above).

Repeatability is a measure which includes the mean and the variability in the result of a test or a procedure performed several times by same operator.

Reproducibility is a measure which includes the mean and the variability in the result due to different operators performing the same test (or procedure) on same or similar samples (or material).

Robustness is the ability of a product/process to demonstrate acceptable quality and performance while tolerating variability in inputs (e.g. raw materials and process parameters).

References

1. Guidance for Industry, ICH Q8 Pharmaceutical Development May 2006, www.fda.gov/cder/guidance/8084dft.htm.
2. Robert G. Baum, Pfizer Global Research and Development, "Progress on Quality by Design: A PhRMA Perspective" presented to the FDA Advisory Committee for Pharmaceutical Sciences, October 5, 2006.
3. Process Robustness – A PQRI White Paper, Pharmaceutical Engineering On-Line Exclusive, www.ispe.org/PE_Online_Exclusive, November/December 2006, Vol. 26, No. 6.
4. Moheb M. Nasr, CDER, FDA, "Quality by Design (QbD) – A Modern System Approach to Pharmaceutical Development and Manufacturing – FDA Perspective", presentation delivered in Beijing, China, August 31, 2007; (Comments by Janet Woodcock, M.D., of October 5, 2005 on "The Desired State: A Mutual Goal of Industry, Society and Regulators", was taken from slide 2.)
5. Moheb M. Nasr, CDER, FDA, "Pharmaceutical Quality Assessment for New Drugs in the 21st Century", presentation at Schering-Plough, October 2, 2006.
6. Moheb M. Nasr, CDER, FDA, "FDA's Pharmaceutical Quality Assessment Systems in the 21st Century – A Modern Risk-Based Approach", presented at the Pharmaceutical Technology Annual Conference, July 24, 2007.
7. Moheb M. Nasr, CDER, FDA, "Implementation of Quality by Design (QbD) – Progress and Challenges", presented to ISPE 2007 Washington Conference, June 6, 2007.
8. Moheb M. Nasr, CDER, FDA, "Quality by Design in the New Pharmaceutical Quality Assessment System (PQAS)", presented to the Quality-International 2005 Conference, London, November 21, 2005.
9. ICH Harmonized Tripartite Guideline Q6A, "Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances", October 6, 1999.
10. PQRI-FDA Workshop on Setting Drug Specifications for the 21st Century, Bethesda, MD, March 16-18, 2005.
11. Theodora Kourti, "Process Analytical Technology Beyond Real-Time Analyzers: The Role of Multivariate Analysis", Critical Reviews in Analytical Chemistry, **36**:257-278, 2006.
12. Theodora Kourti, "Process Analytical Technology and Multivariate Statistical Process Control", Journal of Process Analytical Technology, **3**(3):18-24, 2006.
13. N.O. Lindberg and T. Lundstedt, "Multivariate Data Analysis of Variables Influencing the Dissolution Rate of Prednimustine: Case of Disconformity with the Noyes-Whitney Equation", European Journal of Pharmaceutics and Biopharmaceutics, **41**:101-113, 1995.
14. Clare J. Strachan, Thomas Rades, Keith C. Gordon, and Jukka Rantanen, "Raman Spectroscopy for Quantitative Analysis of Pharmaceutical Solids", Journal of Pharmacy and Pharmacology **59**:179-192, 2007.
15. Huiquan Wu, Edwin J. Heilweil, Ajaz S. Hussain, Mansoor A. Khan, "Process Analytical Technology (PAT): Quantification Approaches in Terahertz Spectroscopy for Pharmaceutical Application", Journal of Pharmaceutical Sciences, **97**(2):970-984, 2008.

16. Kati Pollanen, Antti Hakkinen, Satu-Pia Reinikainen, Jukka Rantanen, Milja Karjalainen, Jarmatta Louhi-Kultanen, Lars Nystrom, "IR Spectroscopy together with Multivariate Data Analysis as a Process Analytical Tool for In-line Monitoring of Crystallization Process and Solid-State Analysis of Crystalline Product", Journal of Pharmaceutical and Biomedical Analysis, **38**:275-284, 2005.
17. Andrea Heinz, Marja Savolainen, Thomas Rade, Clare J. Strachan, "Quantifying Ternary Mixtures of Different Solid-State Forms of Indomethacin by Raman and Near-Infrared Spectroscopy", European Journal of Pharmaceutical Sciences **32**:182-192, 2007.
18. J. Axel Zeitler, Philip F. Taday, David A. Newnham, Michael Pepper, Keith C. Gordon, and Thomas Rades, "Terahertz Pulsed Spectroscopy and Imaging in the Pharmaceutical Setting – A Review", Journal of Pharmacy and Pharmacology, **59**:209-223, 2007.
19. Note: The figures are drawn for illustration only. The figures do not represent actual calculations or compounds.
20. Philip F. Taday, I. V. Bradley, D. D. Arnone, Michael Pepper, "Using Terahertz Pulse Spectroscopy to Study the Crystalline Structure of a Drug: A Case Study of the Polymorphs of Ranitidine Hydrochloride.", Journal of Pharmaceutical Sciences, **92**:831, 2003.
21. Clare J. Strachan, Thomas Rades, David A. Newnham, Keith C. Gordon, Michael Pepper, and Philip F. Taday, "Using Terahertz Pulsed Spectroscopy to Study Crystallinity of Pharmaceutical Materials." Chemical Physics Letters, **390**:20-24, 2004.
22. J. Axel Zeitler, David A. Newnham, Philip F. Taday, T. L. Threlfall, R.W. Lancaster, R. W. Berg, Clare J. Strachan, Michael Pepper, Keith C. Gordon, Thomas Rades, "Characterization of Temperature Induced Phase Transitions in the five Polymorphic Forms of Sulfathiazole by Terahertz Pulsed Spectroscopy and Differential Scanning Calorimetry", Journal of Pharmaceutical Sciences **95**:2486-2498, 2006.
23. FDA Guidance for Industry, Investigators, and Reviewers - Exploratory IND Studies, January 2006, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078933.pdf.
24. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use - ICH Harmonised Tripartite Guidelines: www.ich.org/cache/compo/276-254-1.html
25. Lutz Muller, Robert J. Mauthe, Christopher M. Riley, Marta M. Andino, David DeAnonis, Chris Beels, Joseph DeGeorge, Alfons G.M. DeKnaep, Dean Ellison, Jane Al Fagerland, Rebecca Frand, Betsy Fritschel, Sheila Gallowary, Ernie Harpur, Charles D.N. Humfrey, Alexander S. Jacks, Nirdosh Jagota, John Mackinnon, Ganapathy Mohan, Daniel K. Ness, Michael R. O'Donovan, Mark D. Smith, Gopi Vudathala, Larry Yotti, "A Rational for Determining, Testing, and Controlling Specific Impurities in Pharmaceuticals that Posses Potential for Genotoxicity", Regulatory Toxicology and Pharmacology, **44**:198-211 (2006).
26. Comments by Janet Woodcock, M.D. in 2004, taken from presentation by Steven Kozlowski, Director Office of Biotechnology Products OPS/CDER FDA, "Implementation of QbD for Biotechnology Products", June 20, 2007.

27. Paul Mckenzie, San Kiang, Jean Tom, Erik A. Rubin, Mauricio Futran, "Can Pharmaceutical Process Development become High Tech ?" AIChE Journal **52**(12): 3990-3994, 2006.

Links to Regulatory Guidances

ICH Quality Guidances:

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065005.htm

Q8(R2): Guidance for Industry, Q8(R2) Pharmaceutical Development
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073507.pdf

Q9: ICH Harmonized Tripartite Guideline, Quality Risk Management
http://www.fda.gov/cder/guidance/7153fnl.htm

Q10: ICH Harmonized Tripartite Guideline, Pharmaceutical Quality System
http://www.fda.gov/cder/guidance/7891dft.htm

FDA Guidances:

Guidances webpage:
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

FDA regulations: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm

FD&C Act: http://www.fda.gov/opacom/laws/fdcact/fdctoc.htm