
DEVELOPING AND DEMONSTRATING BIOEQUIVALENCE OF SEMI-SOLID DOSAGE FORMS:

Both an Art and a Science

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Manish Munjal, Ph.D.
Associate Director, Product Development & CTM Manufacturing

Pi-hsia Su, MS
Manager, Analytical Services

Kang Wang, Ph.D.
Vice President, Analytical Services




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Introduction

The US Food and Drug Administration (FDA) issued new draft guidance in December 2016 indicating that generic manufacturers can demonstrate bioequivalence for a specific semi-solid dosage form using predictive in vitro testing as a surrogate for in vivo testing.

HOW CAN BIOEQUIVALENCE BE ACHIEVED FOR GENERICS IN SEMI-SOLID DOSAGE FORMS?

We cannot know if this suggests a growing openness on the agency's part to grant biowaivers on the basis of in vitro test results for semi-solid dosage forms in general. However, at the very least it is one more example of the value of in vitro testing in the drug development cycle.

Gaining market approval via an in vitro pathway, of course, is dramatically less expensive and more expedient than conducting clinical trials; it could save generic manufacturers tens of millions of dollars and slash years off of the development timeline. Nonetheless, the process of developing a topical drug and demonstrating that the test product is qualitatively and quantitatively the same as the Reference Listed Drug (RLD) is a very complex undertaking. It requires deep expertise in what is a very niche discipline led by a very few specialists. In fact, the process is so heavily dependent upon the knowledge of the formulators and analytical scientists that it is recognized as an art as much as a science.

The following paper explains in general terms how bioequivalence can be achieved for generics in semi-solid dosage forms, including the role of in vitro release testing (IVRT) and in vitro permeation testing (IVPT).

The Nature of Topical, Semi-solid Drugs

Of all pharmaceuticals, only a small percentage is created in semi-solid doses—topicals that are designed to interact with skin. They can take the form of creams, lotions, ointments, gels, pastes, foams, and patches and can be applied to dermal, buccal, nasal, ophthalmic, otic, rectal, or vaginal tissue.

These mixtures typically contain numerous active and inactive ingredients, to include oleaginous bases, preservatives, anti-oxidants, humectants, emollients, solvents, polymers, gelling agents, emulsifiers, and buffers, making them quite complex multi-phasic formulations.

New Regulatory Guidance: A Trend in the Making?

Since 1984, generic manufacturers have been able to seek marketing approval in the US via an abbreviated new drug application (ANDA), which generally does not require data from preclinical and clinical research to establish safety and effectiveness.¹ Rather, generic manufacturers must demonstrate that their product is the bioequivalent of the originator product. Draft guidance from the FDA published in 1998 states, "For a topical solution drug product, in vivo bioequivalence may be waived if the inactive ingredients in the product are qualitatively (Q1) identical and quantitatively (Q2) essentially the same compared to the listed drug."²

Three Characterizations of Generics in Comparison to Reference List Drugs

- **Q1 Sameness:** The test product contains the same components as the Reference Listed Drug (RLD)
- **Q2 Sameness:** The test product contains the same components in the same concentration ($\pm 5\%$) as the RLD
- **Q3 Sameness:** The test product has Q1 and Q2 similarities, and its microstructure is similar to that of the RLD, having the same arrangement of matter and state of aggregation. This is not an absolute necessity for FDA approval, but is important in matching the properties of the RLD.

¹"Drug Price Competition and Patent Term Restoration Act of 1984," Public Law 98-417, September 24, 1984.

²"Guidance for Industry: Topical Dermatological Drug Product NDAs and ANDAs—In Vivo Bioavailability, Bioequivalence, In Vitro Release, and Associated Studies," FDA, June 1998.



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For most dosage forms, bioequivalence can be achieved using pharmacokinetic (PK) and pharmacodynamics (PD) studies that measure the rate of absorption, or bioavailability, of the innovator drug. To be approved by the FDA, the “generic version must deliver the same amount of active ingredients into a patient’s bloodstream in the same amount of time as the innovator drug.”³

Topical dermatologic semi-solids, however, pose special challenges in evaluating bioequivalence because they are not intended to be absorbed systemically. Most deliver very small (if any) amounts of drug in patients’ blood or plasma, requiring ultra-sensitive PK and PD tests.^{4,5} Thus, most topical generic formulations have had to undergo time-consuming and costly comparative clinical trials in order to demonstrate bioequivalence, which in some cases could be insensitive as well.

In 2000, the FDA waived the requirement for in vivo bioequivalence studies for immediate-release solid oral dosage forms. Then, in 2012, the agency issued draft guidance that provides for both an in vivo and an in vitro option for demonstrating bioequivalence for topical ointment formulations of the anti-viral Acyclovir. And, the same provisions were made for topical creams containing Acyclovir in new draft guidance released in late 2016.⁶ The document states that in applying for approval, manufacturers of such generic products can demonstrate bioequivalence to the RLD using either an in vivo or in vitro option. Using the in vitro option requires that:

- The test product is qualitatively and quantitatively the same as the reference listed drug (referred to as Q1 and Q2, respectively);
- The two products are physically and structurally similar (based on a comparative physicochemical characterization of at least three lots of each);
- They have equivalent rates of active ingredient release based upon an IVRT; and
- They are bioequivalent based upon an IVPT.

While the guidance is not transferable to other active ingredients, it may be that regulators will, in time, consider a similar pathway for other topicals and grant biowaivers on the basis of in vitro test results. At any rate, there appears to be a trend forming, and a precedent has been set. The increasing number and complexity of ANDAs, together with the need to inspect the increasing number of international generic manufacturing facilities, pose additional pressures on the need to streamline generic evaluation.

Challenges in Development of Semi-solid Formulations: Complexities and Unknowns

As the FDA acknowledges, “Semi-solid dosage forms are complex formulations having complex structural elements.”⁷

Often, they are composed of two phases (oil and water) one of which is a continuous (external) phase, and the other of which is a dispersed (internal) phase. The active ingredient is often dissolved in one phase, although occasionally the drug is not fully soluble in the system and is dispersed in one or both phases, thus creating a three-phase system. The physical properties of the dosage form depend upon various factors, including the size of the dispersed particles, the interfacial tension between the phases, the partition coefficient of the active ingredient between the phases, and the rheology. These factors combine to determine the release characteristics of the drug, as well as other characteristics, such as viscosity.⁸

Due to thermodynamic imbalance, the phases tend to separate over time on a microscopic level. Eventually this translates to macroscopic-phase separation (into aqueous and oil layers) (milk being a very common example in our daily life) and syneresis. The inclusion of a multitude of excipients of different nature, including emulsifiers, polymers, solvents, oleaginous vehicles, etc. in different ratios has a direct influence on the physical (in) stability. The multi-component matrix interaction and dynamism on the molecular level, and the semi-solid nature imparts viscous (liquid-like) and elastic (solid-like) behavior to the system, making it highly complex.

CLINICAL TRIALS CAN BE TIME-CONSUMING AND COSTLY IN ORDER TO DEMONSTRATE BIOEQUIVALENCE

³<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/default.htm>

⁴Rohr, U.D., Altenburger, R. & Kissel, T., “Pharmacokinetics of the Transdermal Reservoir Membrane System Delivering β -Estradiol: In Vitro/In Vivo-Correlation,” *Pharmaceutical Research*, Vol. 15, No. 6, 1998.

⁵Shah, Vinod P, et al. “Bioequivalence of Topical Dermatological Dosage Forms – Methods of Evaluation of Bioequivalence,” *Pharmaceutical Research*, Vol. 15, No. 2, 1998.

⁶“Draft Guidance on Acyclovir,” FDA, Revised Dec. 2016.

⁷“Guidance for Industry: Nonsterile Semisolid Dosage Forms, Scale-Up and Postapproval Changes,” FDA, May 1997.

⁸“Guidance for Industry: Nonsterile Semisolid Dosage Forms, Scale-Up and Postapproval Changes,” FDA, May 1997.



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This complexity has a direct bearing on the difficulties that formulators encounter in developing and reverse engineering a semi-solid formulation in an effort to match the RLD. What's more, because topicals make up only a small percentage of pharmaceuticals, the industry has not amassed a wide body of knowledge on the best methodologies to use in their development and analysis. It is a highly specialized area. In fact, the first attempt at even classifying topical drug products scientifically and unambiguously was only undertaken in 2005.⁹ At this writing, the FDA is sponsoring research into the behavior of topicals both at the University of Mississippi and the University of Queensland in Australia.¹⁰

The challenges to developing a generic topical semi-solid product include:

- **Unknown concentrations of inactive ingredients in the RLD.** The strength of the RLD's active pharmaceutical ingredient (API) is given on the product label or package insert. Although the inactive ingredients are also listed by name, their concentration and grade are not specified.

This can have a profound effect on the long-term physical and chemical stability of the product.

- **Too many inactive ingredients.** Commonly, topicals are comprised of many excipients and preservatives. Creams often have 8-10 such inactive ingredients, and it is not unheard of for products to have as many as 20. The sheer number of these excipients, combined with the fact that many are available in different grades, complicates the process of determining the original's formula.

- **Instability.** A trivial compositional adjustment can cause problems, especially with phase stability. The multi-component dynamic matrix interaction can be affected by the oil/water ratio, emulsifier/solvent ratio, polarity/charge indices, and grade of the excipients.

- **The order in which substances are added matters.** In true solutions, the order in which solutes are added usually does not matter.¹¹ This is not the case with semi-solids; the sequence with which components are added affects the critical quality attributes of the finished product.

- **Many factors in the manufacturing process impact the product microstructure and quality.** The attributes of semi-solid drugs are affected by the various steps in the development process, including heating temperature, heating rate, cooling temperature, cooling rate, mixing speed, vacuum pressure,

and homogenization speed and time. Incorrect processing can cause degradation and phase separation as early as during compounding.

- **Standard analytical instruments often are not sufficiently sensitive for reverse engineering.** Typical instruments using UV detectors are not sensitive enough to measure low concentrations of excipients in semi-solid forms, and cannot identify some individual ingredients in the finished product. Scientists must, therefore, use a variety of techniques and instruments, sometimes using pragmatic approaches, to quantify inactive ingredients. These include liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS), Ion Chromatography (IC), Inductively Coupled Plasma (ICP), Refractive Index Detector (RID), Charged Aerosol Detector (CAD), Gas Chromatography (GC), Gas Chromatography-Mass Spectrometry (GC-MS), and titration.

The Formulation Development Process: A Blend of Science and Art

Successfully developing a topical drug product is a very painstaking process that involves many steps. Scientists must:

- **Define the Target Product Profile and Critical Quality Attributes of the Generic Drug Product.** Since the goal for the generic product will be to achieve qualitative and quantitative (Q1 and Q2) sameness to the RLD, it is essential to analyze a sample of the originator systematically and comprehensively. Scientists begin with the intricate process of identifying and quantifying each excipient in the RLD, referring to its package insert as well as to all relevant patents and published literature.

- **Reverse Engineer/Quantify the Composition.** In order to determine the exact concentration of all inactive ingredients in the RLD, scientists must develop analytical methods specific for these—a time-consuming business that often can take a week or more, per ingredient. Determining the appropriate analytical methods for doing so is a matter of some deliberation and experimentation. Often, scientists must explore various methods, taking cues from those that have reportedly been used successfully with similar products.

- **Compare the Microstructure.** While Q3 is not a regulatory requirement for a generic version of a topical drug product, it is desirable from a technical and marketing standpoint; ideally, the product's observable characteristics, the user's experience,

⁹Buhse, Lucinda and Kolinski, Richard, et al. "Topical Drug Classification," International Journal of Pharmaceutics 295 (2005) 101-102.

¹⁰Pharmaceutical Technology Editors, "Topical Formulation: Moving from Art to Science," Pharmaceutical Technology, Volume 2016 Supplement, Issue 3, page s26-s29.

¹¹"Guidance for Industry: Non-Sterile Semisolid Dosage Forms, Scale-Up and Postapproval Changes," FDA, May 1977.



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and the critical quality attributes of the product should be similar to the RLD. In order to ensure structural similarity, in other words that the same amounts of the same components are arranged in the microstructure in the same way, scientists must measure the size and distribution of particles/droplets, their spatial arrangement, and surface chemistry which can have a direct impact on the physical (in) stability. The analytics include polymorphic form, particle size and shape, globule size, shape and density, content uniformity, viscosity/rheology, and pH.

- **Develop a Prototype.** Based on the formula derived from the steps above, formulators then prepare small batches of the generic in an attempt to emulate the physical characteristics and quality attributes of the RLD. Following a Quality by Design (QbD) approach, as expected by the FDA, they must develop a “systematic understanding of critical material attributes (CMAs) of drug substance and excipients, and critical process parameters (CPPs) used during manufacturing that affect critical quality attributes of the drug product.”¹² To complicate matters, ingredients can react differently in different formulations.¹³ On average, developing the proper formulation takes anywhere from three to six months—a time frame that is directly proportional to the number of ingredients involved and inversely proportional to the experience of the formulators. This, further, does not include the time needed to assess the long-term physical behavior of the product in terms of phase separation. Techniques can be made available connecting specific parameters with long-term physical stability, however, these techniques again are product specific and cannot be generalized, unless corroborated with extensive studies and data assessment.

- **Develop a Process.** In developing the compounding process, understanding of the ingredient’s physical-chemical properties and nature goes a long way. However, pragmatic trials must necessarily still be involved because, much like in the culinary arts, the result is impacted by the order that ingredients are added, the size of the API particles, the temperature of the mixture, how long the mixture is stirred, and at what speed it is stirred. Indeed, the manufacturing process of topicals can affect the formulation microstructure and how the compound is delivered into the skin. The process will, of course, need to be scalable to large batches as the product progresses from various clinical phases towards registration and commercialization.

- **Test the Product’s Performance.** Once a prototype has been developed, it must be tested for bioequivalence. Two measures that are fundamental to evaluating product performance for semi-solid dosage forms are the rate at which the API is released and the rate at which it permeates the skin and is absorbed.

Many research studies have found a strong correlation between in vitro and in vivo results. In properly modeled and well-controlled studies, in vitro has accurately predicted human in vivo percutaneous absorption of active pharmaceutical ingredient on the basis of the potential dose. More such studies with validation can in future open gateways for such in vivo prediction using in vitro techniques.

As it is, the FDA’s confidence in in vitro release testing (IVRT) has extended to comparisons of product release rates pre- and post-change, as detailed in SUPAC-SS guidance from 1997. It is, therefore, good for sponsors to understand what is possible with both the IVRT, used to measure API release rates, and the in vitro permeation testing (IVPT), used to measure the permeation of the API based on dermal absorption.

A product’s release of API across the skin barrier can be affected by many product variables either related to the API (such as partition coefficient and solubility), or the formulation (such as choice and ratio of excipients). The IVRT is used to measure the release rate of the API across a synthetic membrane in a vertical diffusion cell (e.g., the Franz Cell or Hanson Cell), as discussed fully in Frontage’s 2014 paper, “IVRT Insights from CMC Experts of Frontage Labs”.¹⁶ IVRT methodologies are complex, and they must be validated and require specific expertise and operational components to generate reliable, reproducible results.

The IVPT is used to create a drug penetration profile similar to measures of API in blood plasma of clinical trial subjects. It measures how well the drug product permeates and passes through different layers of skin. IVPT can be used to evaluate specific qualities of a topical drug product, including: how it will influence drug diffusion in the vehicle, partitioning, skin structure and chemistry, and diffusion in skin. In the ideal situation, the test actually reveals what will happen when the

MANY RESEARCH STUDIES HAVE FOUND A **STRONG CORRELATION BETWEEN IN VITRO AND IN VIVO RESULTS**

¹⁴Chang, Rong-Kun, et al. “Generic Development of Topical Dermatologic Products, Part II: Quality by Design for Topical Semisolid Products,” AAPS Journal, April 1, 2013

¹⁵Toxicology Unit, Institute for Research on Environment and Sustainability and School of Clinical Laboratory Sciences, The Medical School, University of Newcastle upon Tyne, “In vitro studies—how good are they at replacing in vivo studies for measurement of skin absorption?”, Environmental Toxicology and Pharmacology 21 (2006) 199-203

¹⁶“IVRT Insights from CMC Experts of Frontage Labs”, Frontage Laboratories, Inc., June 2014



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drug product is used by patients. It is useful when designing a formulation, when comparing a generic to an innovator, or when exploring a different excipient.

The challenges to using IVPT stem from the complex qualities of topical dosage forms themselves (their rheology, particle size, penetration enhancers, solubility, and excipients), the unique characteristics of skin (the trans-appendageal pathway, skin donor variability, skin disease, and region of the body), and application variables including the applied dosage and dose duration.

- **Test the Product's Physical and Chemical Stability.** Since product degradation may occur rapidly in semi-solid forms, it is very important to gather real-time and accelerated physical stability data as well as chemical stability data to establish that the generic formulation remains as stable as the RLD. This can be challenging because topicals typically contain a matrix of different classes of excipients in a very dynamic system. There is much interaction on a molecular level, making semi-solids unstable. There are accelerated techniques for testing stability, and additional technical advancement remains to be seen.

The Keys to Success: Trust the Experts

Developing a topical pharmaceutical efficiently requires considerable background knowledge and on-the-job experience, a thorough analytical process, and sufficient time for pragmatic trials and exhaustive testing. The greater the formulators' baseline knowledge, the more expedient the process. Best practices for completing the process efficiently and in a manner that will produce a bioequivalent product acceptable to the FDA include:

- Examine the patent landscape and evaluate the various pathways to market. Determine which approach will best satisfy regulators, based on an understanding of what evidence they will require as proof of bioequivalence.
- Select a partner whose portfolio of expertise extends end-to-end, but whose business model allows for providing selected services as needed.
- Work with acknowledged experts who have a track record

of success. The knowledge that they bring to the process will drastically reduce the time needed to complete the process.

- Focus sufficient effort on the formulation process (that is scalable) and the selection of the lead formulation in order to reduce difficulties later on.
- Ensure that your development partner follows Quality by Design (QbD) principles.
- Recognize that the timeline for developing and reverse-engineering a product is quite variable, depending upon the complexity of the RLD. It is not unusual for the process to take six to nine months.
- Prepare for there to be unexpected findings and events along the way.

Conclusion

The methodology for developing a topical drug is complex, and made more so by the fact that each formula is unique and affected by scores of variables. The work requires substantial hands-on experience, and the efficiency with which a matching generic formulation can be developed is directly related to the knowledge that formulators and analytical scientists are able to bring to the challenge. While regulators (with very few exceptions), do not yet accept in vitro tests (such as the IVRT and IVPT) as proof of Q1/Q2 sameness, if that day were to come, it would dramatically reduce the resources that firms must commit to bring a generic semi-solid dosage form to market. Nonetheless, IVRT and IVPT are an important part of testing product performance today and, again, require specialized background and skill sets to be accurate and valid.

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