CERTARA

Demonstrating Virtual Bioequivalence (VBE) using the Simcyp Simulator™

Dr. Sebastian Polak, Senior Scientific Advisor and Head of Mechanistic Dermal Modelling of Certara's Simcyp division

CERTARA

Demonstrating Virtual Bioequivalence (VBE) using the Simcyp Simulator

What is Bioequivalence (BE)?

The US FDA has defined BE as, "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study".

In clinical BE studies, an applicant compares the systemic exposure profile of a test drug product to that of a reference drug product. As clinical BE studies can be costly and time-consuming, there is a regulatory process to achieve a biowaiver that enables approval based on evidence of equivalence other than an in vivo BE test.

Virtual BE uses in silico modeling to demonstrate BE and achieve regulatory approval.

Demonstrating bioequivalence (BE) remains the key regulatory hurdle for generic drug approval. As a result, some branded drugs remain on the market well past the originator's patent expiration, without cost-effective generic alternatives that could benefit patients. Model-informed drug development (MIDD), specifically physiologically-based pharmacokinetics (PBPK) leveraging *in vitro* data, is a proven, cost-effective option to consider in lieu of running an *in vivo* comparative clinical BE endpoint study.

The Landscape for Complex Generics

While there has been significant increase in generic drug approvals, two areas are lagging: 'first generics' and 'complex generics'. FDA defines 'first generics' as the first approval for a manufacturer to market a generic drug product in the US. Figure 1 shows the rapid increase in generic approvals via the Abbreviated New Drug Application (ANDA) process, but also highlights that first generics account for less than 10% of the total. This is the case even though there are important market incentives—the first generic drug to make it to market after drug patent expiration enjoys a significant market share advantage, up to 90% over later arrivals.

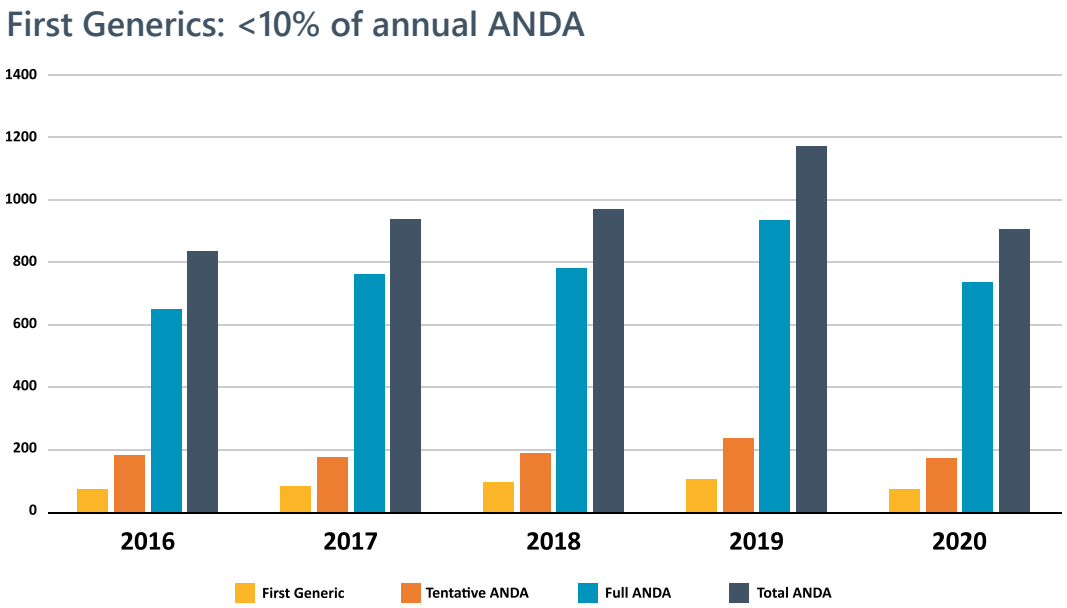


Figure 1: Past 5 years in ANDA approvals (data courtesy of US FDA)

'Complex generics' are defined as:

(i)-products with complex active ingredients, formulations, routes of delivery, or dosage forms

(ii)-complex drug–device combination products

(iii)-other products for which complexity or uncertainty concerning the approval pathway or possible alternative approach would benefit from early scientific engagement.

Per the US FDA, these products were not foreseen in 1984, the time of the Hatch-Waxman Amendments, which established the generic drug approval pathway. In general, complex generics products are harder to develop using traditional BE methods and therefore, fewer exist, resulting in less market competition for these products. To address this, the US FDA established the Competitive Generic Therapy Exclusivity pathway in 2017, which allows the agency to designate a drug as a 'competitive generic therapy' providing the first company to obtain FDA approval to be rewarded with 180 days of exclusivity. Yet even with these incentives, the high cost of running clinical BE trials has diminished companies' appetite to develop generic versions of these drugs.

FDA's Commitment to Supporting Generic Drug Approvals

In 2012, the Generic Drug User Fee Act (GDUFA) was signed into law as part of the Food and Drug Administration Safety and Innovation Act. Its purpose was to speed access to safe and effective generic drugs to the public and reduce costs to industry. GDUFA II followed in 2017, which includes a set of annual scientific priorities for funding, determined via public workshops focused on addressing top challenges and opportunities for complex generics.

In the past several years, MIDD (also called biosimulation) has been identified by the FDA as a promising technology to advance generic drug approval. At its 2019 workshop, the agency stated that the use of quantitative methods and computational modeling has become a part of modern drug development and assessment. For generic drugs, that is a combined use of MIDD and model integrated evidence (MIE).

Physiologically Based Pharmacokinetics (PBPK) has emerged as a lead technology to support drug development as shown in Figure 2. For generics, we have seen PBPK examples of all areas outlined in the graphic with a special focus on demonstrating VBE.

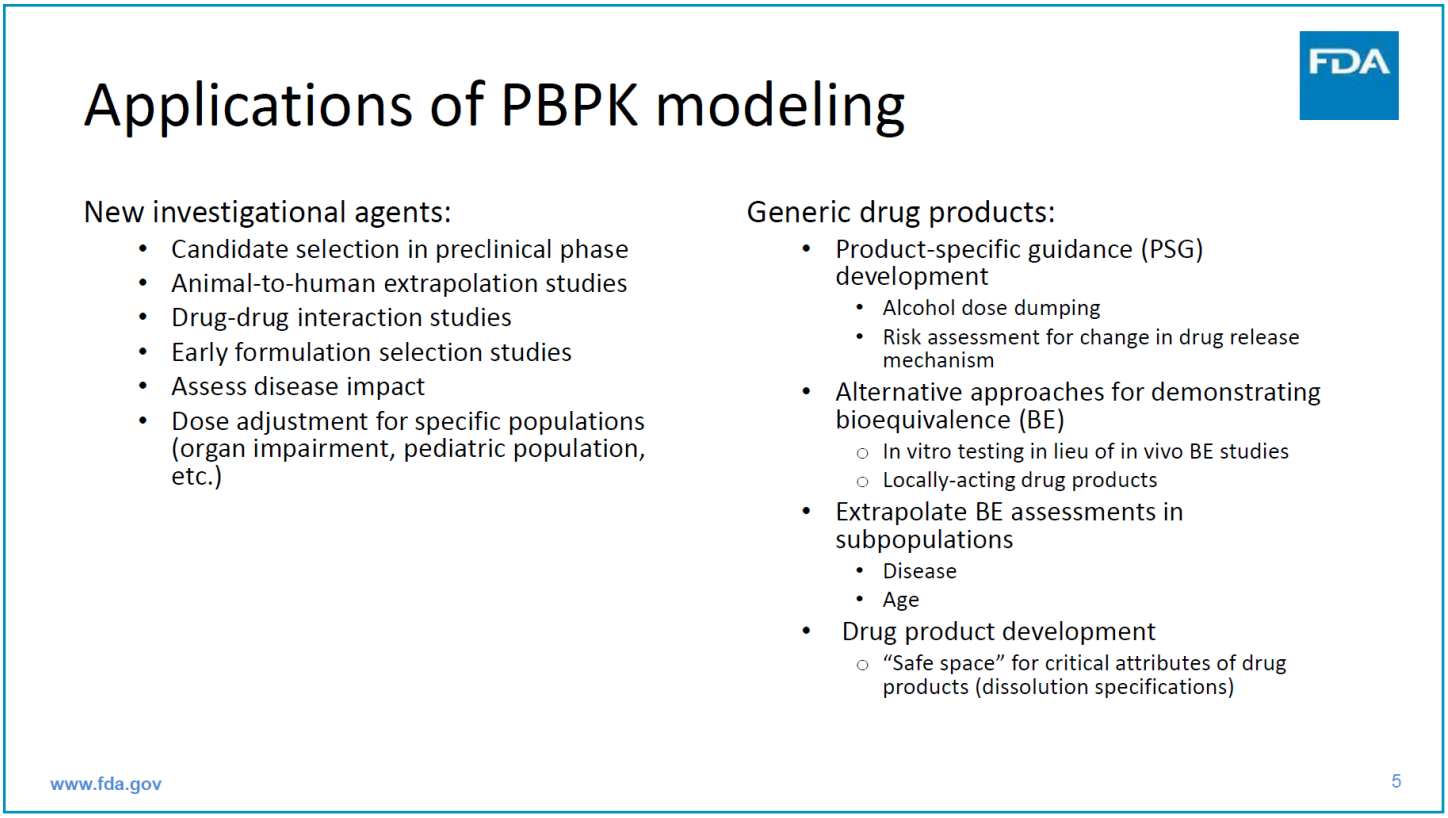


Figure 2: Presented at its 2019 generic drug workshop, the FDA perspective on the vast benefits of PBPK in novel and generic drug development.

Establishing Bioequivalence for Dermal Products

As per Figure 3, there are multiple types of dermal product formulations broadly classified as solutions, emulsions, and suspensions. All have different physical and structural properties (sometimes referred to as Q3 or arrangement of matter) and characteristics. These topical formulations can be complex with multiple critical formulation attributes varying through both the chemical properties of their formulation and mechanism of delivery such as drug solubility and vehicle viscosity, permeation, partitioning, and binding. It is also important to understand not just the formulation but how that behaves when it is applied on the skin where vehicle evaporation, supersaturation precipitation, and re-dissolution of precipitated particle may occur (all of which are collectively referred to as metamorphosis). The complexity of these processes increase with the increasing complexity of formulations from a relatively simple solution to various types of emulsions or suspensions. Finally, transdermal patches are a separate group of complex transdermal formulations and require proper methodology and mathematical machinery to describe their behavior after application.

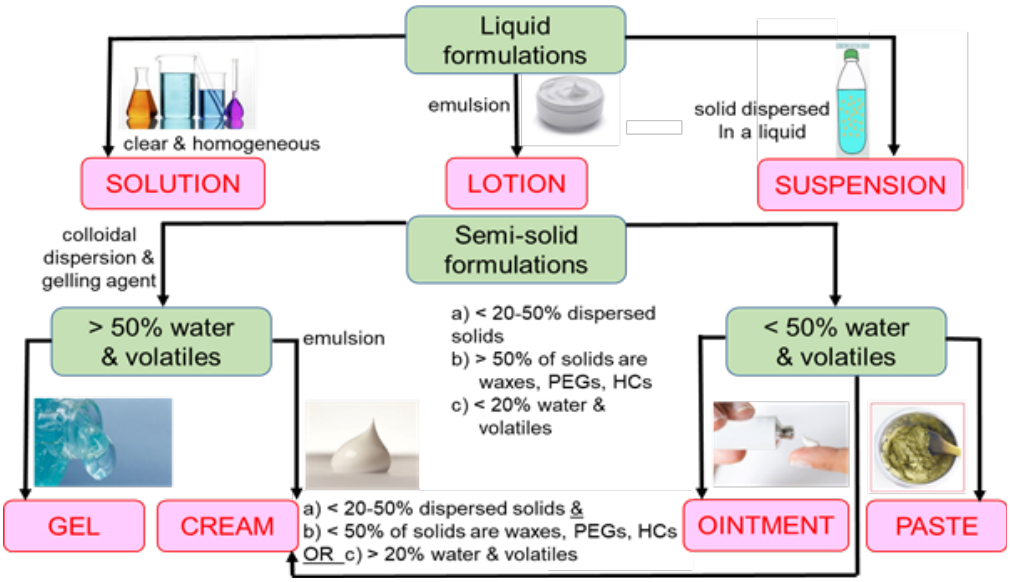
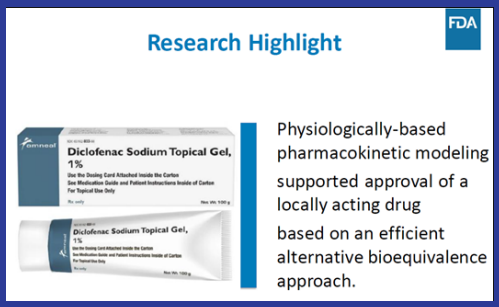


Figure 3: Types of dermal products include solutions, lotions, and suspensions

Demonstrating BE remains the key regulatory hurdle for generic drug approval. In many cases, depending on the product specific guidelines, options such as combination of information on Q1/Q2 sameness and Q3 similarity, *in vitro* release (IVRT) and *in vitro* permeation testing (IVPT) results can be used to demonstrate BE. For some formulations, however, including many topicals, these approaches may fall short. PBPK has been proven to be a successful alternative to running an *in vivo* comparative clinical BE endpoint study as shown in the case study below.

FDA's First and Only Dermal ANDA to Achieve VBE Leveraged the Simcyp Simulator

For the first (and only) time, the FDA approved an ANDA for a dermal drug using VBE with PBPK in lieu of a clinical in vivo pharmacodynamic endpoint study. That approval leveraged the Simcyp™ Simulator MechDermA model as an alternative for typical clinical BE study.



FDA's published paper on this topic states, "This report illustrates the United States Food and Drug Administration approval of a generic diclofenac sodium topical gel that was based on a totality of evidence, including qualitative and quantitative sameness and physical and structural similarity to the reference product, an *in vivo* BE study with PK endpoints, and, more importantly for the purposes of this report, a virtual BE assessment leveraging dermal PBPK modeling and simulation instead of a comparative clinical endpoint study in patients."

The Simcyp MPML MechDermA™ Model

Initially developed under a grant from FDA and the National Institutes of Health, Simcyp expanded its PBPK Simulator to incorporate an advanced dermal model. As shown in Figure 4, MPML MechDermA™ multi-phase, multi-dimensional, mechanistic dermal absorption model is based on detailed description of skin physiology (stratum corneum (SC), viable epidermis, dermis, subcutis, deep tissue, and skin appendages). The model also allows accounting for drug formulation specific components covering all major types of formulations and for simulating disease specific modifications to the skin.

The mechanistic MPML-MechDermA model of the skin absorption accounts for the active pharmaceutical ingredient (API), formulation, physiology, and environmental parameters enabling the simulation of complex diffusion processes through the SC and deeper regions of the skin for drugs with different physicochemical properties as well for different formulations, namely gels, emulsions, patches, suspensions, and pastes. The model can also simulate drug partitioning to sebum and absorption through the follicular pathway with blood flow to the dermis modeled as a function of cardiac output, body weight, and body surface area.

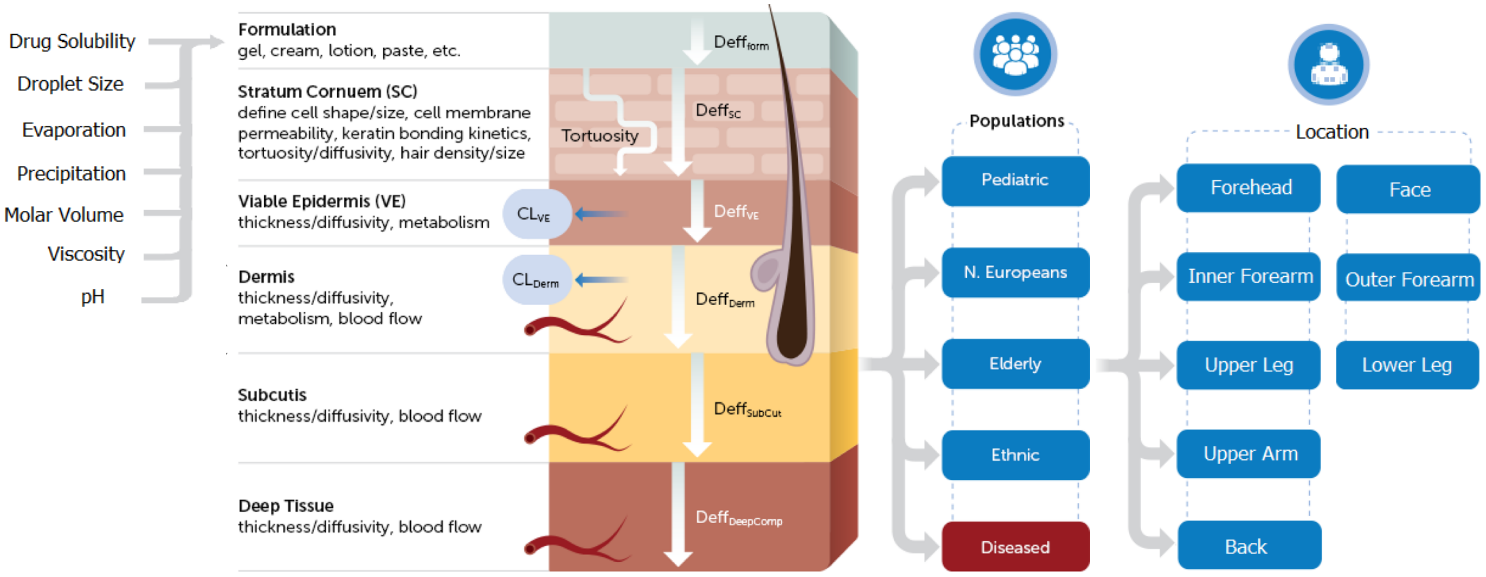


Figure 4: Consisting of multiple compartments or layers, the model enables analysis of inter-individual and intra-individual variability, covering a range of patient populations and multiple locations for skin absorption.

Introducing Simcyp's Virtual IVPT Capability

In its most recent version of the Simulator, Simcyp introduced functionally with the same structure as MPML MechDermA to simulate IVPT in vitro experiments. IVPT is used for evaluating drug delivery to the various skin layers. Our in silico IVPT allows us to simulate and thus optimize an IVPT experiment or replace IVPT study with the use of a properly verified model. We can then optimize chosen parameters of the in vivo MPML MechDermA Simulator to assess BE while predicting local and systemic concentrations for different populations (Figure 5). This helps us increase confidence in in vivo modeling to assess VBE or formulation optimization.

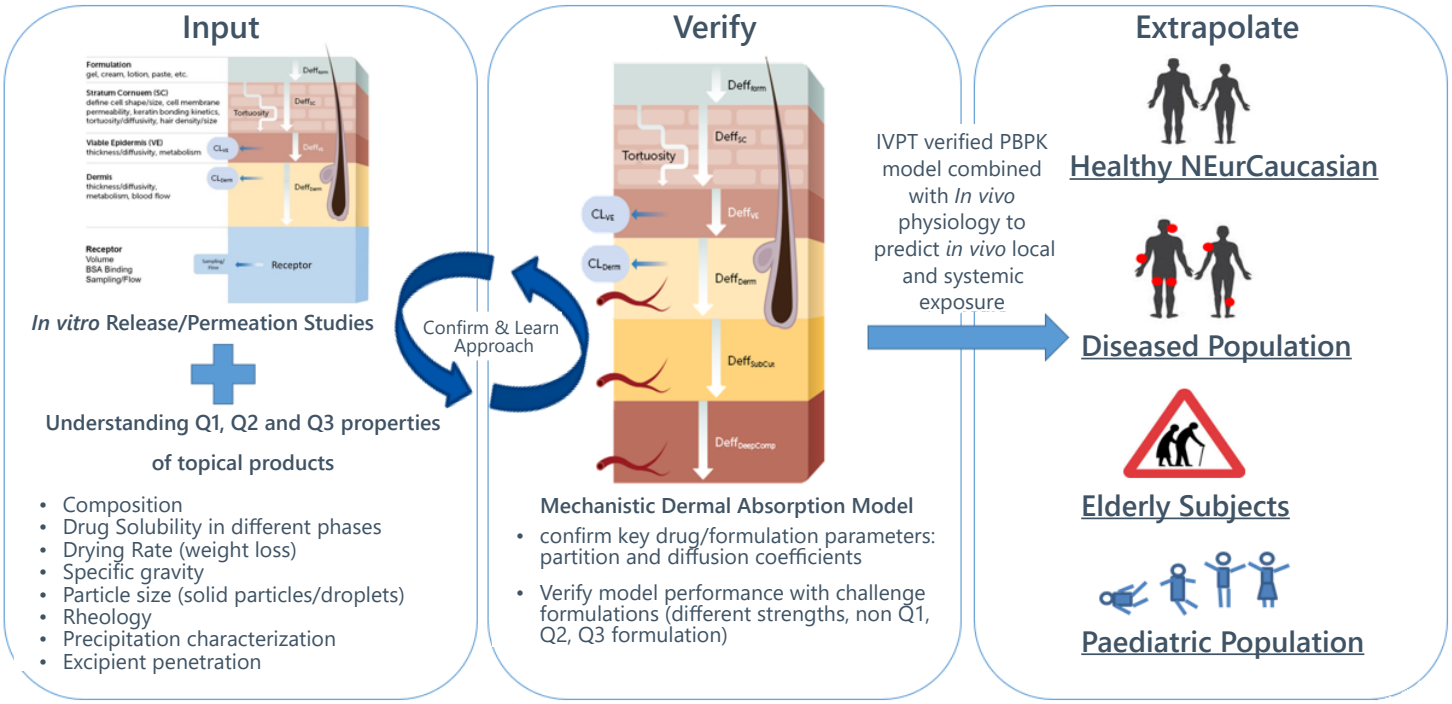


Figure 5: A best practice is to optimize the parameters for the in vivo model with the data from the *in vitro* (IVPT) experiment. Alternatively, you can replace *in vitro* with *in silico*: both require information on the drug and formulation.

PBPK for Long-Acting Injectable Formulations

Long-acting injectable (LAI) drug formulations are on the rise for novel, re-formulations of existing products and generic drugs. Specific applications include diseases with challenging patient adherence requirements such as anti-psychotic and other mental health medications, oncology, and endocrinology.

In its September 2020 workshop for establishing GDUFA II research priorities, the US FDA identified LAI as another opportunity for innovation using VBE (figure 6). At that meeting, the agency shared its increasing interest in employing modeling solutions for *in silico* experimentation with formulation design parameters increasing the speed of development and prototype testing and in silico bioequivalence (BE) testing.

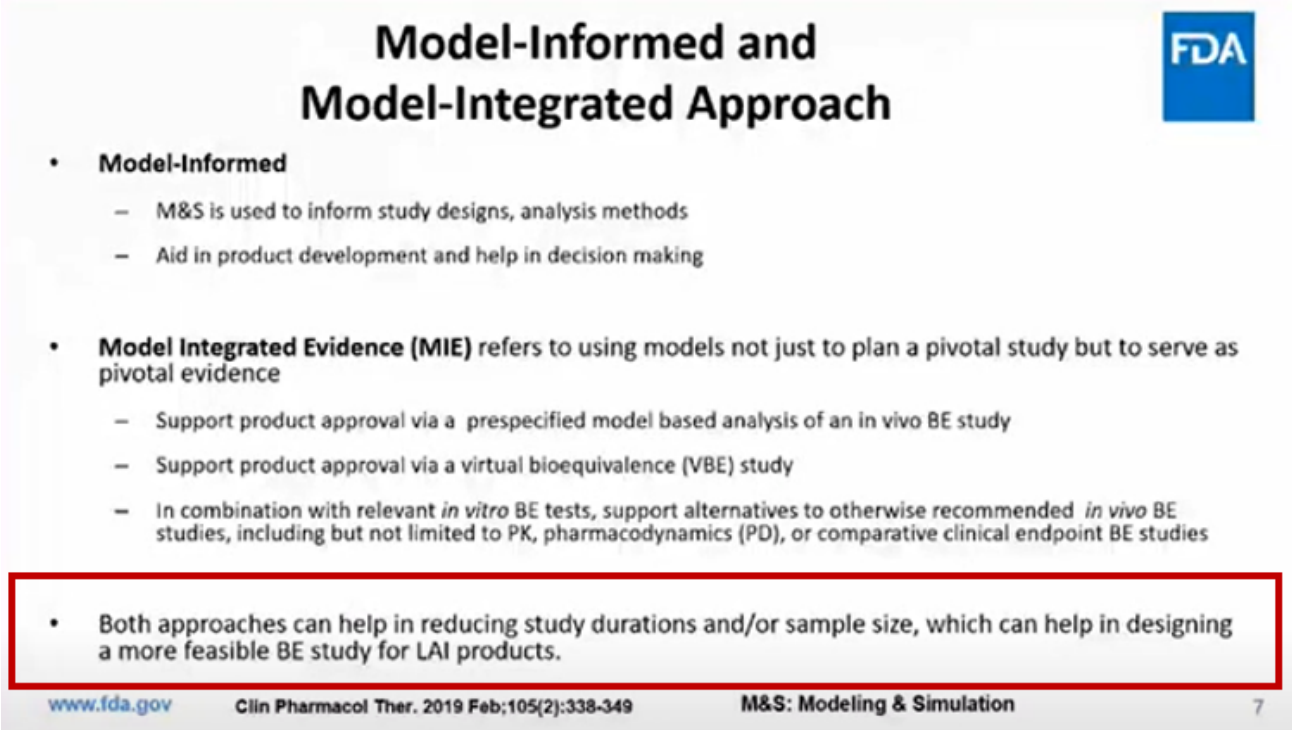


Figure 6: Both MIDD and MIE approaches are encouraged for LAI formulated drugs

PBPK models are a natural fit for complex generics including LAI because of its flexibility across many different areas and types of drugs. Much like in dermal VBE, we repeat the same methodology which enables us to describe the drug and its behavior in polymer-based formulations that contain the API. These can be either solid implant, in-situ gel forming or microsphere depot implants. The PBPK model for these polymer-based drugs accounts for all major phenomena such as dissolution, diffusion, and erosion to account for the dynamics of the formulation and the API when it is injected into different tissues of the body such as subcutaneous, intramuscular, or ocular sub-regions. The compartmental model can be re-parameterized to account for many diverse physiologies.

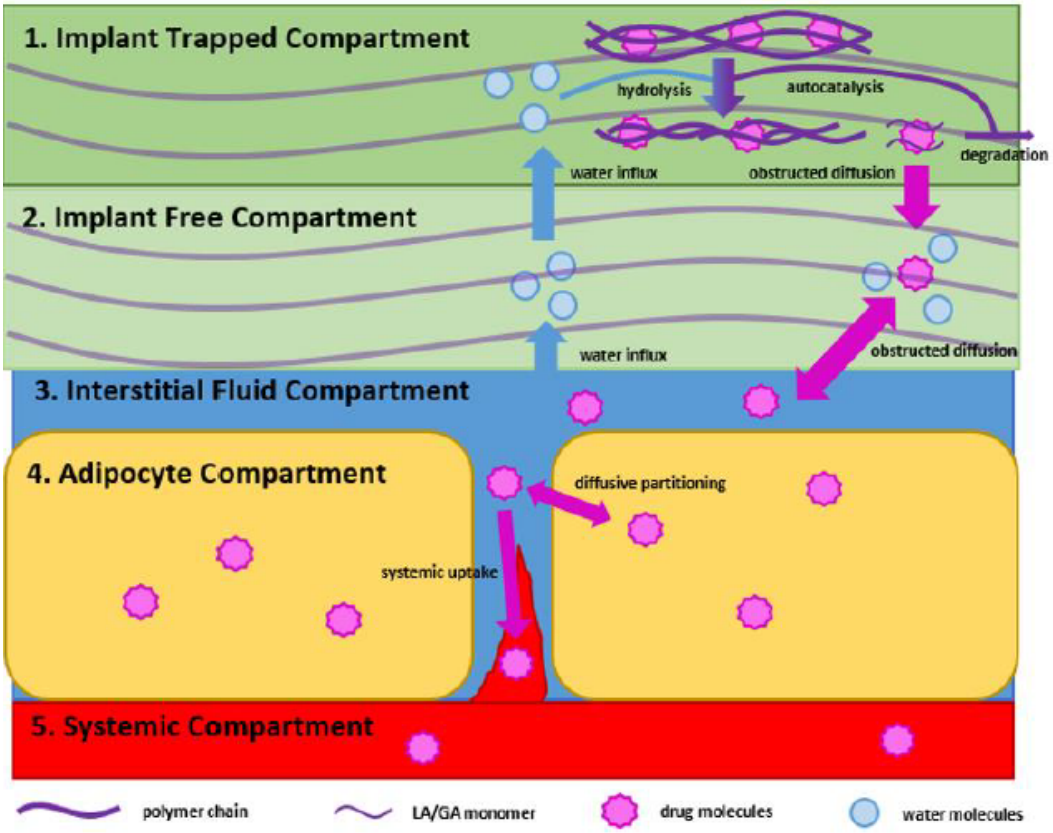


Figure 7: Mechanistic PLGA-based Polymer Erosion Model

The same PBPK model can be used to design new LAI formulations to achieve desirable systemic or local concentration profiles. We first use the model to design experiments, then to narrow down promising formulation candidates, determine the type of trials needed (animal, clinical, or *in silico*), and then to fine-tune based on study details. This learn and confirm cycle is similar to the IVPT and PBPK model iteration described in the dermal case.

PBPK for Attaining Biowaivers in BCS Class III Drugs

Since the publication of the BCS (Biopharmaceutics Classification System) and FDA's 2000 guidance on biowaivers for immediate-release solid oral dosed drugs, many global regulatory agencies have advanced their approval framework in this area. In 2020, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) coordinated those efforts and published its guidance. FDA released its own guidance in December 2017 which finalizes earlier guidance and extended biowaivers to include Class III products.

The BCS-based biowaiver approach is intended to reduce the need for in vivo bioequivalence studies i.e., it can provide a surrogate for *in vivo* bioequivalence.

BCS Class I	High solubility	High permeability
BCS Class II	Low solubility	High permeability
BCS Class III	High solubility	Low permeability
BCS Class IV	Low solubility	Low permeability

According to the guideline, two drugs containing the same drug substance(s) are considered bioequivalent if their bioavailabilities (rate and extent of drug absorption) after administration at the same dose lie within acceptable, predefined limits. These principles may be applied for BE purposes not explicitly specified in the guideline provided they can be supported by a thorough scientific rationale.

While the use of conventional in vitro-in vivo correlation (IVIVC) using mass balance deconvolution techniques has been well established and often accepted by regulators for BCS Class I drugs, the situation with Class III is more complex. This has been overcome as shared in a recent paper authored by FDA, the University of Florida, and Certara, "Scientific Considerations to Move towards Biowaiver for BCS Class III Drugs: How Modeling and Simulation Can Help?" The paper focuses on the use of PBPK models as a pathway toward determining BE—to disentangle different processes contributing to the input function, e.g., dissolution, gastrointestinal transit, and permeation. It establishes IVIVC using variants of the compartmental absorption and transit model supporting biowaiver for Q1/Q2 formulations containing BCS III drugs.

Summary

FDA's FY 2020 GDUFA Research Science Priorities, "Tools and methodologies for BE and therapeutics equivalence evaluation," highlights the role of PBPK and BE:

- Improvement of quantitative pharmacology and BE trial simulation for complex generic drug products
- integration of predictive dissolution, physiologically-based pharmacokinetic (PBPK) and pharmacokinetics (PK) / pharmacodynamics (PD) models for BE standards establishment
- recognition of the role of excipients to expand biowaivers of the BCS class 3 drug products
- development of methods and integrated technological solutions to leverage large datasets

PBPK has already demonstrated its benefits for novel drugs. It is now replicating these efforts for complex and complicated generic drugs.

CERTARA

References:

- Eleftheria Tsakalozou, Andrew Babiskin, Liang Zhao, Physiologically-based pharmacokinetic modeling to support bioequivalence and approval of generic products: a case for diclofenac sodium topical gel, 1%. CPT Pharmacometrics Syst Pharmacol, 2021 Feb 6. doi: 10.1002/psp4.1260
- Center for Drug Evaluation and Research (2003). "Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations"
- https://www.fda.gov/drugs/regulatory-education-industry-advancing-innovative-science-generic-drug-development-workshop
- https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/regulatory-education-industry-2019-complex-generic-drug-product-development-workshop-sep-25-26-2019#:~:text=Event%20Title-,Regulatory%20Education%20for%20Industry%3A%202019%20Complex%20Generic%20Drug%20Product%20Development,September%2025%20%2D%2026%2C%202019
- GDUFA 2021 priorities: https://www.fda.gov/media/144140/download
- https://www.ema.europa.eu/en/documents/scientific-guideline/ich-m9-biopharmaceutics-classification-system-based-biowaivers-step-5_en.pdf
- Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System Guidance for Industry. https://www.fda.gov/media/70963/download
- Christofoletti, R et al, "Scientific Considerations to Move Towards Biowaiver for BCS Class III Drugs: How Modeling and Simulation Can Help? Biopharmaceuticals and Drug Disposition, March 2021

About Certara

Certara accelerates medicines using biosimulation software and technology to transform traditional drug discovery and development. Its clients include 1,650 global biopharmaceutical companies, leading academic institutions, and key regulatory agencies across 61 countries.

For more information visit www.certara.com or email sales@certara.com.