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MINI REVIEW

Mechanistic modeling of ophthalmic, nasal, injectable, and implant generic drug products: A workshop summary report

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Abstract

For approval, a proposed generic drug product must demonstrate it is bioequivalent (BE) to the reference listed drug product. For locally acting drug products, conventional BE approaches may not be feasible because measurements in local tissues at the sites of action are often impractical, unethical, or cost-prohibitive. Mechanistic modeling approaches, such as physiologically-based pharmacokinetic (PBPK) modeling, may integrate information from drug product properties and human physiology to predict drug concentrations in these local tissues. This may allow clinical relevance determination of critical drug product attributes for BE assessment during the development of generic drug products. In this regard, the Office of Generic Drugs of the US Food and Drug Administration has recently established scientific research programs to accelerate the development and assessment of generic products by utilizing model-integrated alternative BE approaches. This report summarizes the presentations and panel discussion from a public workshop that provided research updates and information on the current state of the use of PBPK modeling approaches to support generic product development for ophthalmic, injectable, nasal, and implant drug products.

INTRODUCTION

The Office of Generic Drugs (OGD) at the US Food and Drug Administration (FDA) has implemented its Generic Drug User Fee Amendments (GDUFA)-funded research program to support regulatory decision making through external grants and contracts. One of the main research areas includes development of novel mechanistic modeling and simulation methodology and approaches, such as physiologically-based pharmacokinetic (PBPK) modeling and computational fluid dynamics (CFDs) modeling.[1] Many of these in silico research projects have focused on locally

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acting drug products during GDUFA I and II periods, for example, in the areas of ophthalmic, injectable, nasal, female reproductive, buccal, and sublingual drug products (Table 1). Through these research efforts, the FDA has driven advancements in modeling methods and platform performance for complex generic drug products. The ultimate goal is to provide acceptable alternative model-integrated approaches to establish bioequivalence (BE) in lieu of lengthy and insensitive comparative clinical end point BE studies in patients to support product development and regulatory decision making of complex generic products.

An update of GDUFA-funded research and information on the current state of using mechanistic modeling approaches to support generic product development and alternative BE approaches for ophthalmic, injectable, nasal, and female reproductive drug products was discussed at a recent FDA public workshop titled "Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches,"[2] cohosted online with the Center for Complex Generics (CRCG), on September 30 to October 1, 2021. This report summarizes the podium presentations and panel discussion with experts from the FDA and the generic drug industry in the workshop's Symposium I: "Mechanistic Modeling of Locally-Acting Generic Drug Products" session 3: "Mechanistic Modeling of Other Locally-Acting Generic Drug Products". Day 1, session 3 of the Workshop was focused on PBPK modeling of ophthalmic, injectable, nasal, and implant drug products. The presentations and the panel discussion focused on the utilization of mechanistic modeling approaches to advance drug development and regulatory assessment in these areas. In particular, some case studies were provided to demonstrate the successful applications of modeling approaches, existing challenges, and future directions of applying mechanistic modeling approaches to develop these locally acting drug products.

PRESENTATIONS

GDUFA research update on mechanistic modeling approaches for generic ophthalmic, nasal, implant, and injectable drug products

Ming-Liang Tan, PhD

The first presentation of session 3, given by Dr. Ming-Liang Tan (FDA), started with a research update on PBPK modeling for ophthalmic drug products, followed by PBPK modeling approaches for nasal drug products, model-integrated evidence for complex injectables, modeling approaches for buccal/sublingual products, and finally PBPK models for complex products delivered in the female reproductive tract.

In terms of ophthalmic generic products, less than 30% of the reference listed drug (RLD) products have approved generic versions on the US market for the three major ophthalmic complex dosage forms: suspensions, ointments, and emulsions.[3] For ophthalmic suspensions, a dexamethasone rabbit Ocular Compartmental Absorption and Transit (OCAT) model was developed through an FDA internal study conducted with pharmacokinetic (PK) sampling in multiple ocular tissues and plasma.[4,5] The model was then verified using literature PK data, with a focus on mean particle size and particle size distribution (PSD), nonlinear dose-exposure relationship, formulation viscosity, and tear dynamics impact on ocular absorption.[4,6] For ophthalmic ointments, dexamethasone and fluorometholone ointment rabbit OCAT models were developed to understand the impact of ointment formulation changes on ocular exposure through an external research project (Simulations Plus HHSF223201810255P).[7] For ophthalmic emulsions, a cyclosporine emulsion model was developed to study the impact of emulsion critical quality attributes (CQAs) on product performance.[8] In the meantime, tear film models were developed by including accurate eye anatomy and eye blink dynamics to simulate drug delivery and transport through an external research project (CFD Research Corporation HHSF223201810151C). Further model validation is under way through an external contract (Absorption Systems IDIQ 75F40119D10024) to measure tear film and tear film menisci thickness in rabbits using FDA manufactured formulations with differences in globule size and viscosity. In addition to development of the PBPK model, rabbit PBPK/pharmacodynamic (PD) models have been developed and preclinical-to-human model extrapolation has also been investigated through a couple of ongoing grants (Simulations Plus 1U01FD006927 and CFD Research Corporation 1U01FD006929).

In the nasal drug product area, several modeling research projects (Table 1) covered in vivo, in vitro, and in silico studies and the modeling studies focused on the influence of device and formulation differences on regional deposition and prediction of mucociliary clearance. The combined CFD and PBPK approach has been used to predict olfactory region absorption for nose-to-brain delivery as well as local tissue and systemic PK profiles.

For buccal/sublingual drug products, one research project (St. Louis College of Pharmacy 75F40120C00150) focused on assessing the effect of formulation excipients on active pharmaceutical ingredient (API) permeability in presence of artificial saliva by utilizing two separate cellular models for buccal and sublingual drug products. In the complex injectable area, one external research project (Institute of Quantitative Systems Pharmacology 75F40119C10139) aimed to develop an in silico systems-based multiscale model by capturing various biological

TABLE 1 Grants and contracts including mechanistic modeling and simulation approaches (including PBPK and CFD) for ophthalmic, nasal, injectable, buccal/sublingual, and female reproductive drug products awarded during GDUFA I and II regulatory research and science programs.

Area	Title	Duration	Institute	Award no.
Ophthalmic	Development and validation of a PBPK/PD modeling strategy for ophthalmic drug products to support translation from preclinical species to humans	2020–2023	Simulations Plus	1U01FD006927
	Computational Biology (Cobi) tools as a framework for PBPK/PD model extrapolation from rabbit to human for ophthalmic drug products	2020–2023	CFD Research Corporation	1U01FD006929
	An integrated multiscale-multiphysics modeling framework for evaluation of generic ophthalmic drug products	2018–2022	CFD Research Corporation	HHSF223201810151C
	Simulation plus ophthalmic ointment implementation	2018–2019	Simulations Plus	HHSF223201810255P
	PBPK modeling and simulation for ocular dosage forms	2014–2018	Simulations Plus	1U01FD005211
	An integrated multiscale-multiphysics modeling and simulation of ocular drug delivery with whole-body PK response	2014–2018	CFD Research Corporation	1U01FD005219
Nasal	Development of hybrid CFD-PBPK models for absorption of intranasal corticosteroids	2014–2018	Applied Research Associates, Inc.	1U01FD005201
	Nasal mucociliary clearance affecting local drug-absorption in subject-specific geometries	2018–2021	North Carolina State University	1U01FD006537
	Evaluating relationships between in vitro nasal spray characterization test metrics for bioequivalence and nasal deposition in silico and in vitro	2018–2021	Virginia Commonwealth University	HHSF223201810144C
	Modifications and improvements to hybrid CFD-PBPK models for prediction of nasal corticosteroid deposition, absorption, and bioavailability	2019–2022	Applied Research Associates, Inc.	75F40119C10079
	Evaluation of current approaches used to establish bioequivalence of nasal sprays for local action in children	2020–2023	Virginia Commonwealth University	75F40120C00172
LAI and complex injectables	MIDD approach to identify critical quality attributes and specifications for generic nanotechnology products	2019–2023	Institute of Quantitative Systems Pharmacology	75F40119C10139
	Enhancement and validation of IVIVC method for long-acting injectable drug products to accelerate their generic development	2021–2024	University of Connecticut	75F40121C00133
Female reproductive	Physiologically based model of the female reproductive tract: vaginal and intrauterine delivery components	2018–2024	State University of New York at Buffalo	HHSF223201810188C
Buccal/sublingual products	Robust in vitro/in silico model to accelerate generic drug product development for the oral cavity route of administration	2020–2023	University of Health Sciences and Pharmacy in St. Louis	75F40120C00150

Abbreviations: CFD, computational fluid dynamics; GDUFA, Generic Drug User Fee Amendments; IVIVC, in vitro in vivo correlation; LAI, long-acting injectable; MIDD, model-informed drug development; PBPK, physiologically-based pharmacokinetic; PD, pharmacodynamic; PK, pharmacokinetic.

and physicochemical events that affect the transport and residence of nanoparticles and their API cargo among different extracellular and intracellular compartments to identify formulation CQAs that may potentially influence target tissue bioavailability of API. In the long acting injectable (LAI) area, one contract was awarded (University of Connecticut 75F40121C00133) that aims to increase our understanding on the in vivo behavior of LAI suspension drug products by identifying formulation CQAs, establishing a mechanistic (i.e., PBPK model based) in vitro in vivo correlation (IVIVC) model and narrowing down our knowledge gap in this area. Another research effort (University at Buffalo HHSF223201810188C) was awarded to develop an open-source, user-friendly, generalized PBPK modeling and simulation platform for complex products administered to the female reproductive tract.

Current scientific considerations in modeling for in vitro BE of topically administered ophthalmics

Sajeev Chandran, PhD

The second talk, delivered by Dr. Sajeev Chandran (Lupin), summarized various formulation variables influencing barriers to drug diffusion in the precorneal (tear-film) and corneal space for ophthalmic suspension and emulsion formulations that need to be considered to successfully model ophthalmic drug delivery. He also deliberated upon various scientific considerations (drug PSD and viscosity in case of ophthalmic suspensions, and globule size distribution and surface area in case of ophthalmic emulsions) used to establish in vitro BE for topically applied ophthalmic drug products. Drug PSD and dispersion viscosity are two CQAs that govern the performance of topical ophthalmic suspensions, such as suspension physical stability, ocular retention, and drug release characteristics, and thereby the availability of the applied drug in the aqueous humor or anterior chamber of the eye. The target drug PSD in an ophthalmic suspension is achieved either by using sterile micronized API of target PSD followed with homogenization of the suspension composition, or by aseptic milling of the coarser drug and other excipients, like surfactants and viscosity imparting polymers, to obtain target drug PSD in the final suspension. The aseptic milling process variables, such as the mill type, micronization technique, bead size and quantity used (% occupancy), and the number of milling cycles influence the drug PSD and viscosity of ophthalmic suspension formulation and thereby the drug release kinetics and ocular drug availability.

For the case of ophthalmic emulsions designed for poorly water-soluble drugs, the formulation components of the emulsion, like the solubilized drug, surfactant, or emulsifier, can distribute in various phases depending on their physicochemical properties and the manufacturing process used. For example, surfactants at the oil–water interface can act as an emulsifier to stabilize oil droplets as well as exist as micelles in the aqueous phase. Drug dissolved in the oil droplet phase can partially partition into the surfactant micelle or the aqueous phase or remain at the oil–water interface. For modeling in vitro/in vivo drug release kinetics from such systems, a biphasic drug release phenomenon needs to be considered with initial rapid drug release caused by drug diffusion from the aqueous phase, including micelles followed by a slower release controlled by drug diffusion from the oil globules.[9]

For topically applied ophthalmic suspension/emulsion type drug products, the in vitro release measurement method should be able to obtain drug release data in a timeframe akin to the very short ocular residence time of the applied dose. To simulate and aid in modeling of in vitro BE behavior of the applied dosage form in relation to the precorneal fluid dynamics, the developed in vitro drug release method therefore should measure both the static responses (factors impacting contact time in the precorneal region) and the kinetic responses (factors impacting drug availability to ocular tissue).

PBPK modeling for different locally administered drug products

Rebeka Jereb, PhD

The third presentation, given by Dr. Rebeka Jereb (Sandoz), provided mechanistic PBPK modeling cases for intramuscular injection and ophthalmic ointment formulations. Drug products for intramuscular injection can be in the form of a solution, a suspension, in situ forming depot, or oil-based formulations. In a mechanistic model, a depot site within the muscle used for intramuscular injection is usually represented as a single compartment with specified drug-dependent parameters and physiological parameters. The model should account for drug absorption into the systemic circulation or the lymph, drug binding, and metabolism in the muscle. As a case study for intramuscular injection modeling, Dr. Jereb presented a GastroPlus model (version 9.6, Simulations Plus) which was developed for intramuscular injection with an oily solution of API to predict the in vivo behavior of different formulations. Multiple parameters affect the behavior of oily drug solutions in vivo, such as the concentration of the API in the oil, the thickness of the diffusion layer

and the diffusion coefficient in both the oily and aqueous phases, the partition coefficient between the oil and tissue fluid, and the surface of the depot area. An in vitro release test was developed, which incorporated most of these parameters and would therefore be able to capture the difference between the test and reference formulations. An in vitro release test profile was incorporated into the model as an in vivo release profile. Thus, the model was able to predict the expected in vivo plasma concentration profiles for different formulations based on the in vitro release test results.

As a second case, Dr. Jereb presented a mechanistic model which was developed using GastroPlus for a topically applied ophthalmic ointment to evaluate the impact of API particle size on a drug's in vivo behavior. During model development, numerous challenges were encountered – many parameters of the model were unknown and had to be fitted or optimized, the model was developed on rabbit in vivo data and used to make predictions for humans, and there were significant differences between the reported in vivo concentrations in different studies used for model development and validation. Despite all the challenges, the model was used to estimate the impact of API particle size on aqueous humor maximum concentration and area under the concentration-time curve.

PANEL DISCUSSION AND KEY MESSAGES

The session was concluded by a panel discussion that was moderated by Dr. Maxime Le Merdy (Simulations Plus) and Dr. Andrew Babiskin (FDA). The panel included the three presenters mentioned above in this paper, as well as Drs. Khondoker Alam (FDA), Robert Bies (SUNY at Buffalo), Darby Kozak (FDA), and Ross Walenga (FDA).

Preclinical study for ophthalmic drug product development

The panelists first discussed the need to perform preclinical studies for generic ophthalmic drug product development. Dr. Tan began the conversation by stating that the impetus for conducting preclinical modeling work is due to the challenge of directly developing and validating human ophthalmic models, because measurements in humans are often impractical, unethical, and cost-prohibitive, whereas on the other hand, there are relatively rich animal ophthalmic data available, and it is also feasible to obtain tissue PK data in preclinical species. The validated animal ophthalmic models may be extrapolated to human models by considering the likely changes in anatomy and physiology among species in PBPK models. Dr. Kozak pointed out that the effect of the formulation changes can be tested in the preclinical space so that we can learn what formulation CQAs may have the biggest clinical effect. Based on his industrial experience, Dr. Chandran stated that animal models are useful as they can provide rank order of formulations that are manufactured with minor differences in CQAs, such as viscosity and particle size distributions, even if the models may not be directly extrapolatable to human. Dr. Babiskin added that to conduct a BE study in preclinical species for ophthalmic products, the focus would be on whether these products would be BE in human, as there may exist challenges in interspecies model extrapolation.

Interstudy variability and data for model validation

Next, the panel discussed the issue of interstudy variability and how much data should be utilized for the model validation – should all available data be used, or would it be adequate to use a selected portion of the data? Dr. Kozak started to address this question by stating that the more data you have, the more confidence you may have in your models in general. However, other factors such as how a specific study was conducted and what type of instruments were used need to be considered as well, as potential outliers or bias may exist. Dr. Jereb commented to collect as much data as possible and then make a scientific decision on which one to include and which one to discard in model development and validation. The selection of the data should not be based on how they fit your models but based on the knowledge you have on the dataset to have a scientific judgment in selecting data. Dr. Walenga added that you may miss something if you just ignore some data which fall outside of your model predictions unless you have some basis to reject it. “Unwanted” data in model validation may also serve as an opportunity to lead you to understand what your model might be missing. For example, your model might be based on one species of rabbit data, but there may exist some interspecies differences if another set of data from different species that may be a potential opportunity to refine your models.

Role of ocular PBPK models for establishing BE

Regarding its utilization in demonstrating BE, Dr. Tan described that an ocular PBPK model may play an important role in the development and assessment of generic ophthalmic drug products. One of the GDUFA-funded

research areas is focused on studying the impact of differences in formulation quality attributes on in vivo eye tissue exposure between the RLD product and proposed generic products using the validated models. Subsequently, virtual BE studies may be performed and evaluated by considering the physiological variabilities in human populations. This mechanistic modeling approach has the potential to be used as a BE approach for generic ophthalmic products as it may provide all the evidence necessary to demonstrate BE. Dr. Chandran commented on the utilization of RLD information for PBPK model validation for generic ophthalmic products that are Q1 (qualitatively) and Q2 (quantitatively) the same to the RLD product in terms of inactive excipients. The differences in physicochemical properties between RLD and generic products, caused by manufacturing variables like the sequence of the additions of ingredients, autoclaving or filtration process, or particle size reduction techniques, may be captured in the models for BE establishment. Dr. Le Merdy added that the target tissue expression level in preclinical species and human tissues may differ, which could represent a challenge for extrapolating human PDs based on preclinical responses.

Role of PBPK models for establishing BE for female reproductive tract products

Dr. Bies stated that PBPK modeling approaches may be critical for demonstrating BE for uterine and vaginal products. For example, for uterine and vaginal products, it is particularly challenging to measure drug concentrations in local tissues for these long-term release agents to evaluate BE between a proposed generic drug product and the RLD. Modeling approaches may be used to get insights on key measures to identify efficiencies in study designs necessary to establish BE for products such as vaginal films or rings for HIV prevention or uterine administered products, such as the levonorgestrel implants. In terms of the challenges and knowledge gaps in this area, getting appropriate measurements of the tissue concentrations is rather difficult, as is the case for most locally acting complex drug products. In addition, the utilization of animal models is also limited, as typically the models are for non-human primates, so it is difficult to implement these models for humans. One current gap is the lack of a method to refine the experimental techniques to avoid measurement outliers in these experiments that are likely an artifact of the experimental or sampling technique as opposed to the actual representative sample.

Regarding drug release testing during generic product development for female reproductive tract drug products, there exist some unique challenges in understanding the in vivo drug release through in vitro dissolution measurements. One of the key aspects in particular for implants is to consider an in vitro release system where the dissolution/receptor media are biorelevant. One of the challenges is that the media tends to be very small in volume. Another challenge would be to consider the bacterial growth in dissolution media which may affect drug release when mimicking the in vivo environment. On the other hand, a physiologically based model could be used to account for some of these physiologic conditions. For example, in the uterine space, fluid production and resorption occur continuously and that may need to be accounted for in order to obtain complete in vivo mapping with a greater level of confidence. Dr. Kozak discussed that another major challenge with in vitro release testing for female reproductive tract drug products are the lengthy time release characteristics, particularly from implants. For example, some long-acting intrauterine devices may be active in vivo for up to 5 years and conducting an in vitro release study under a similar timeframe would be an exceptional challenge. One possible solution would be to understand the mechanism of drug release and then determine what would be appropriate ways for accelerating conditions to mimic the in vivo release by using the mechanistic modeling approaches. The key is the mechanistic understanding of the drug release mechanism for these long-acting drug products that have a rate controlling membrane (or something similar). Dr. Alam suggested that utilization of a modeling approach may play a role in determining whether the in vitro release is biorelevant or biopredictive for this category of products. Deconvolution of an existing PK profile may provide useful information for the in vitro release experimental settings. Dr. Babiskin added that the focus is more about developing the models around the formulation itself and understanding how the data can be integrated into your in vivo model. This approach appears to be slightly different from traditional IVIVC, where direct in vitro inputs allow prediction of in vivo release rate and absorption.

Role of nasal PBPK models for establishing BE

Dr. Walenga commented that modeling and simulation may play a role in understanding the performance of nasal drug products that target nose-to-brain delivery. This is an emerging area where research efforts have been made for drugs targeting the treatment of central nervous system diseases, such as Alzheimer's and Parkinson's diseases. For a product approved to target nose-to-brain delivery via the olfactory region, mechanistic modeling may be a useful approach to understand how the product works, because it may be difficult to only use systemic PK data to

infer BE if the clinical effect is dependent on the precision of olfactory region targeting.

Challenges and risks in developing and submitting PBPK models for locally acting products

Last, the panel discussed the challenges of developing the PBPK models and risks that the industry perceives when submitting these models for locally acting products to regulatory authorities. Dr. Jereb described that while challenges may depend on the specific product area, there seems to be some common limitations and risks. One such challenge is that inconsistent literature data may exist, where decisions must be made on which dataset should be used to develop and validate a model as well as what are the associated model prediction errors based on the data sets selected. Another challenge is for unknown model parameters, where sometimes parameter optimization needs to be performed but you need to decide how many and which model parameter(s) should be chosen for the optimization (from the model default or predicted value[s]). Dr. Chandran encouraged more generic companies to proactively pursue PBPK modeling approach and do more preclinical in vivo studies to correlate in vitro parameters during generic product development. Dr. Alam commented on the risk assessment of using a PBPK model in the virtual BE assessment in the regulatory space, such as whether the right model structure is used to describe the disposition of drug through the relevant physiology, whether the formulation CQAs are incorporated into the model and if assumptions in your model bring in or inflate the type I error. Finally, Dr. Tan suggested that given the complexities around utilizing mechanistic modeling as an integrated approach to establish BE for a proposed generic product, communication between the FDA and industry is highly encouraged through currently available mechanisms, such as pre-abbreviated new drug application (pre-ANDA) meetings and controlled correspondences.

CONCLUSION

The session provided an update on the current research efforts and status of using mechanistic models to support decision making for several areas of locally acting drug products. In the topical ophthalmic area, multiple ocular PBPK models have been developed in preclinical species where the focus was on the effect of formulation quality attributes on in vivo exposure and bioavailability.[4,6–8] For the nasal products, several hybrid CFD-PBPK models have been developed where drug regional deposition was predicted by CFD models and local tissue and systemic distributions were predicted by PBPK models.[10–16] In the complex injectable area, an in silico systems-based multiscale model integrated approach has been used to understand nanoparticle dispositions in the human body and the model is aimed to predict bioavailability in the target site (e.g., tumor tissue).[17,18] In the LAI area, PBPK modeling has been utilized to establish mechanistic IVIVC model by incorporating formulation CQAs into the PBPK model. PBPK models have also been developed to describe drug delivery to the female reproductive tract and an open-source, generalized PBPK modeling and simulation platform for complex products has been developed.[19–22] A variety of challenges were identified, such as lack of good strategy to choose and optimize unknown model parameters, lack of biorelevant/predictive in vitro experiment settings and data for model development, lack of in vivo tissue data for model validation, significant interstudy variabilities, and inconsistent literature data such as sparse data for ophthalmic products. One strategy would be to further develop novel in vitro experiments to obtain more biorelevant in vitro data for model development. Another area would be to continue utilizing preclinical models to better understand the formulation CQAs. Altogether, continuous efforts will advance the model-integrated alternative BE approaches to support generic drug product development and regulatory decision making.

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CONFLICT OF INTEREST STATEMENT

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