Research overview and regulatory experience on mechanistic modeling for generic dermatological drug products

2021 CRCG PBPK workshop
Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches
Day 1, Session 2: Modeling of Dermal Drug Products

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Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA’s views or policies.
Overview

• Scope of mechanistic physiologically-based pharmacokinetic (PBPK) modeling for alternative bioequivalence (BE) approaches for generic dermatological drug products

• Research roadmap towards developing mechanistic dermal PBPK models

• Use of dermal PBPK modeling and simulation approaches in regulatory space
General BE Study Recommendations for Topical Dermatological Drug Products

• In Vitro characterization based BE approach
  – Qualitative (Q1) and Quantitative (Q2) Sameness or ‘No Difference’
  – Physicochemical and Structural (Q3) Sameness/Similarity
  – IVRT (In Vitro Release Test)
  – IVPT (In Vitro Permeation Test)

• In Vivo study to demonstrate BE
  1. In vivo comparative clinical endpoint BE study
  2. Other in vivo studies -
     A. BE study with PK endpoints
     B. Vasoconstrictor study
     C. Adhesion study
     D. Skin irritation and sensitization study
Use of Mechanistic Modeling to Establish BE of Topical Dermatological Drug Products

Comparative clinical endpoint BE study

- Relatively insensitive in detecting formulation differences
- Large variability in the observed response
- Relatively costly as it requires higher subject number
- Drug development to approval time is long

Model-integrated virtual BE study

- Agency welcomes innovative approach if the proposed approach satisfies requirements of applicable statues and regulations
- Bioavailability in local tissues can be compared between test and reference drug products
- Cost effective and allows faster drug development process
Mechanistic Dermal Physiologically-based Pharmacokinetic (PBPK) Modeling

Skin physiology
- Individual layer thickness and complexity
- Partition coefficient
- Diffusion coefficient

Formulation attributes
- Rheological properties
- pH, specific gravity
- Physicochemical properties
- Metamorphosis

Informing model parameters
- IVPT studies
- Skin biopsy
- Microdialysis
- Systemic PK data
Dermal PBPK modeling to predict local and systemic bioavailability: Overview

Formulation attributes
- API Phys Chemical Properties
- (Skin) Physiology in Healthy vs Diseased Populations
- In Vivo, In Vitro and Ex Vivo Testing Data

Model Structure

Verification
Validation
Refinement/Optimization

Virtual BE of topical drug products

API = Active pharmaceutical ingredient

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Research Roadmap towards Developing Mechanistic Dermal PBPK Model

Major research focus:

• Realistic description of skin physiology
• Incorporating formulation attributes
• Virtual BE of topical drug products
Generic Drug User Fee Amendments (GDUFA)-Funded Research is Aimed to Close Knowledge Gaps

• Realistic description of skin physiology in in silico tools
  — Improve understanding on skin physiology in healthy and diseased populations
  — Develop and validate in silico healthy and diseased skin models

• Identify drug product-specific informative formulation attributes for semi-solid dosage forms
  — In vitro characterization of selected drug products
  — Incorporate formulation attributes in in silico tools
  — Define a safe space for drug product quality attributes

• Improve our understanding on interplay between skin physiology and drug product quality attributes

• Develop and validate in vitro, ex vivo, and in vivo methodologies that can be used to assess the in vitro and in vivo performance of drug products applied on the skin

• Develop and validate in silico tools
  — To establish in vitro-in vivo relationships (IVIVR) that can be used to predict unknown scenarios
  — To perform virtual BE assessment for topical drug products
## Generic Drug User Fee Amendments (GDUFA):
### Regulatory Science/Research

<table>
<thead>
<tr>
<th>Grant</th>
<th>Grant Duration</th>
<th>Institute</th>
<th>Grant No.</th>
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<tr>
<td>Development and validation of dermal PBPK modelling platform towards virtual bioequivalence assessment considering population variability</td>
<td>2014-2018</td>
<td>Simcyp, Ltd</td>
<td>1U01FD005225</td>
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<td>Physiologically based biopharmaceutics and pharmacokinetics of drug products for dermal absorption in humans</td>
<td>2014-2019</td>
<td>University of South Australia</td>
<td>1U01FD005232</td>
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<td>Characterization of key system parameters of mechanistic dermal PBPK models in various skin diseases and performance verification of the model using observed local and systemic concentrations</td>
<td>2018-2020</td>
<td>Simcyp, Ltd</td>
<td>1U01FD006521</td>
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<td>Assessment of Transdermal Drug Product Quality and Performance Attributes via Enhanced Virtual Bioequivalence Simulations</td>
<td>2018-2020</td>
<td>SimulationsPlus, Inc</td>
<td>1U01FD006526</td>
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<td>Formulation drug product quality attributes in dermal physiologically-based pharmacokinetic models for topical dermatological drug products and transdermal delivery systems</td>
<td>2018-2020</td>
<td>University of Queensland</td>
<td>1U01FD006522</td>
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<td>PBPK and Population Modeling Seamlessly Linked to Clinical Trial Simulation in an Open-Source Software Platform</td>
<td>2018-2021</td>
<td>Children’s Hospital of Los Angeles</td>
<td>1U01FD006549</td>
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<td>progressing integration of in vitro topical formulation characterisation, release and permeation data to the next level - PBPK based extrapolation to bioequivalence assessment in virtual populations</td>
<td>2021-2023</td>
<td>Certara UK,Ltd</td>
<td>1U01FD007323</td>
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<td>Dermal Drug Product Quality and Bioequivalence Assessment through Advanced MAM and PBPK Simulation</td>
<td>2021-2023</td>
<td>SimulationsPlus, Inc</td>
<td>1U01FD007320</td>
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Research Aiming to Develop Mechanistic Dermal PBPK model

Grants:
• 1U01FD005225
• 1U01FD006521
• 1U01FD006522

In collaboration with –
• University of Queensland
• University of South Australia

Grant: 1U01FD005232
In collaboration with Goethe University Frankfurt

Grant: 1U01FD006526
In collaboration with industry partners

Grant: 1U01FD006496
In collaboration with University of Surrey

Grant: 1U01FD006549
In collaboration with –
• University of Waterloo
• Children’s Hospital of Los Angeles
Key Outcomes From GDUFA-Funded Research

• Development of mechanistic dermal PBPK model: skin physiology and formulation attributes

• Development of skin disease model, e.g., acne/comedone, atopic dermatitis, psoriasis

• Developing IVPT module: model IVPT study results

• Developing vasodilation model: vasodilation/constriction in the dermis

• Enabling “Two Sites” for the application of drug product to resemble real life scenarios, e.g., apply topical product to face and shoulder simultaneously

• Incorporating inter- and intra-subject variabilities

To improve the predictive power of dermal PBPK model

To increase confidence on the model to perform virtual BE assessments
Dermal PBPK Modeling: Research Focus in FY21

RFA-FD-21-019
Dermal Physiologically-based Pharmacokinetic (PBPK) Models Accounting for the Absorption and Evaporation of Vehicle/Co-solvent following the Application of Generic Dermatological Products (U01)

Absorption: Change in skin physiology and its effect on API permeability
Evaporation: Metamorphosis of formulation

RFA-FD-21-018
Quantify the expression of metabolizing enzymes and transporter proteins in lung, eye and skin tissue in relevant animal models and humans (U01)

RFA-FD-21-013
Physiologically-based pharmacokinetic (PBPK) models to aid the development of generic dermatological products (U01)

To improve existing dermal PBPK model/platform

Mechanistically describe skin permeation of active and inactive ingredients. Enable model integrating in vitro and in vivo data obtained experimentally.

* RFA = Request for Applications
Use of Dermal PBPK Model in Regulatory Space

- Model-integrated evidence for generic drug development and approval
  - Support alternative bioequivalence (BE) approaches, e.g., virtual BE studies
  - Define a safe space for critical attributes
  - Extrapolate bioavailability predictions and BE assessments from healthy to diseased populations
- Making informed regulatory decision in the review of ANDA, preANDA, controlled correspondence, citizen petition etc.
- Product-specific guidance (PSG) development and other regulatory research

![Dermal PBPK Model Since 2017]

* still ongoing
Summary of FY2020 Activities

One of the main objectives of this research is to continue to work with external experts to develop and advance mechanistic-based modeling, such as physiologically-based pharmacokinetic (PBPK) modeling and computational fluid dynamics (CFD), in order to better understand the role that product properties play on local bioavailability. In total, modeling specific to locally-acting product modeling andplatform advances was part of 8 separate external projects (i.e., contracts and grants) in FY2020 – 4 of which were initiated in FY2019 or at the end of FY2018. Among these four projects:

- In the complex injectable area new FY2020 GDUFA Science and Research Report: complex injectables, formulations, and Nanomaterials, a new contract (15/HO1/R12036) was awarded that aims to utilize a model-informed drug development approach (Figure 1) for evaluating target site bioequivalence of drug products that incorporate nanomaterials (e.g., nanoparticle drug products). The contract intends to develop an in silico systems-based multiscale models to capture various biological and physicochemical events that affect the transport and residence of nanoparticles (NPs) and its cargo active pharmaceutical ingredient (API).

- Articles, posters, presentations

- Summary of research activities
- Research projects and collaborations
  - New, continuing and completed grants/contracts
  - Active FDA research
Take home messages

• PBPK model-based virtual BE is an innovative alternative approach for the approval of dermal drug products

• GDUFA-funded research is set for continuous improvement of dermal PBPK model or modeling platform –
  o To improve the predictive power of dermal PBPK model
  o To increase confidence on the model to perform virtual BE assessments

• Mechanistic dermal PBPK modeling is used -
  o by the applicants to support their drug development and approval process
  o by the Agency to make informed regulatory decisions

• Academia/industry/software developing companies are encouraged to follow ‘Notice of funding opportunity’ to work with the Agency to achieve critical mission of GDUFA
Acknowledgments

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Questions?

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