Scientific and regulatory considerations on dermal PBPK modeling for virtual bioequivalence assessments and decision-making

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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CDER | U.S. FDA

September 30, 2021

Disclaimer

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

Overview

Bioequivalence (BE) of dermatological drug products

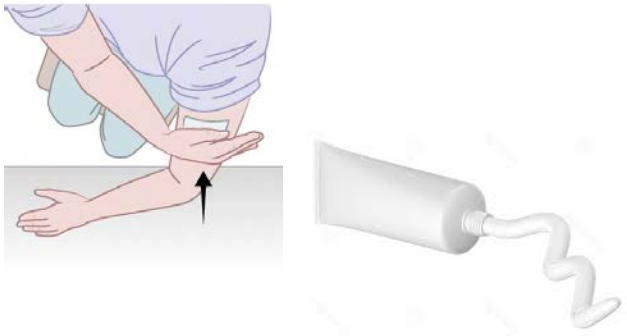
Physiologically-based pharmacokinetic (PBPK) modeling supporting the approval of dermatological products (dermal PBPK)

- Case example: approved Abbreviated New Drug Application (ANDA) for a diclofenac topical gel, 1%

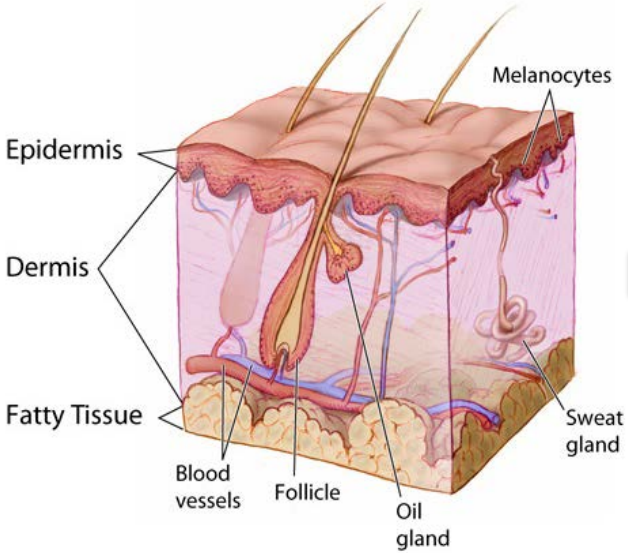
  Considerations on:

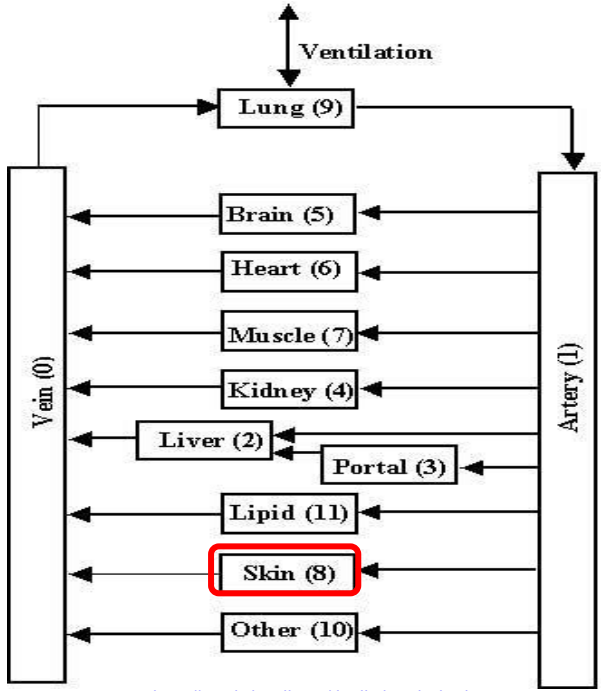
  - Model development
  - Model performance assessment
  - Virtual bioequivalence (VBE) studies
  - Reporting and documentation

  Conclusions/take home messages



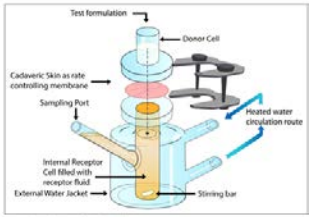
Modeling skin bioavailability by implementing dermal PBPK modeling and simulation approaches

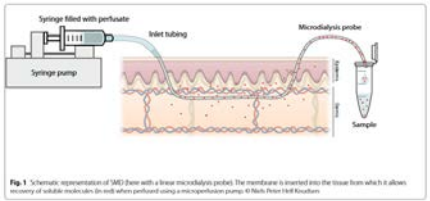




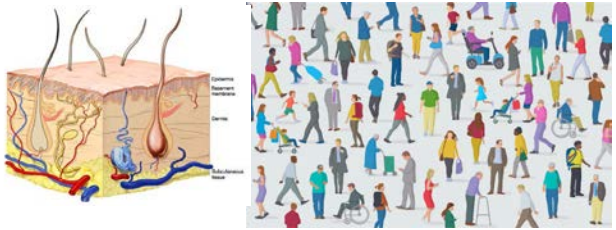
https://openi.nlm.nih.gov/detailedresult.php?img=PMC126244_1472-6904-2-5-1&req=4
https://visualsonline.cancer.gov/details.cfm?imageid=4604

Implement in silico methodologies for generic dermatological drug products

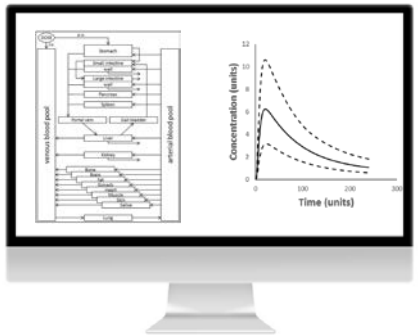




Skin Bioavailability



Skin Physiology in Individuals/Populations



Drug Product Characterization

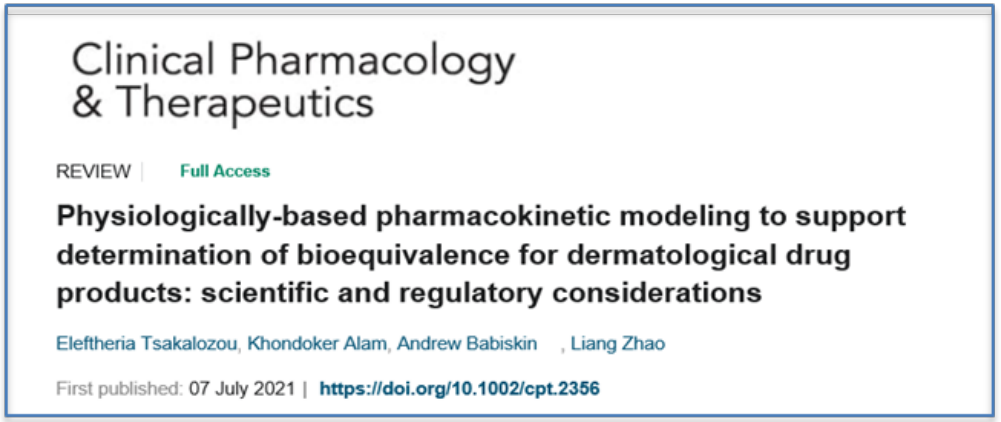
Ther Innov Regul Sci. 2019 Oct 3; In Vitro Skin Permeation Methodology for Over-The-Counter Topical Dermatologic Products. Luke Oh, Sojeong Yi, Da Zhang, Soo Hyeon Shin, Edward Bashaw.
Skin microdialysis: methods, applications and future opportunities-an EAACI position paper.
Modified from Front Pharmacol. 2012 May 21;3:92

Lessons learnt on developing dermal PBPK models for regulatory decision-making

Physiologically-based pharmacokinetic modeling to support bioequivalence and approval of generic products: A case for diclofenac sodium topical gel, 1%

Eleftheria Tsakalozou | Andrew Babiskin | Liang Zhao

CPT Pharmacometrics Syst Pharmacol. 2021 May;10(5):399-411.



Clinical Pharmacology & Therapeutics

REVIEW | Full Access

Physiologically-based pharmacokinetic modeling to support determination of bioequivalence for dermatological drug products: scientific and regulatory considerations

Eleftheria Tsakalozou, Khondoker Alam, Andrew Babiskin , Liang Zhao

First published: 07 July 2021 | https://doi.org/10.1002/cpt.2356

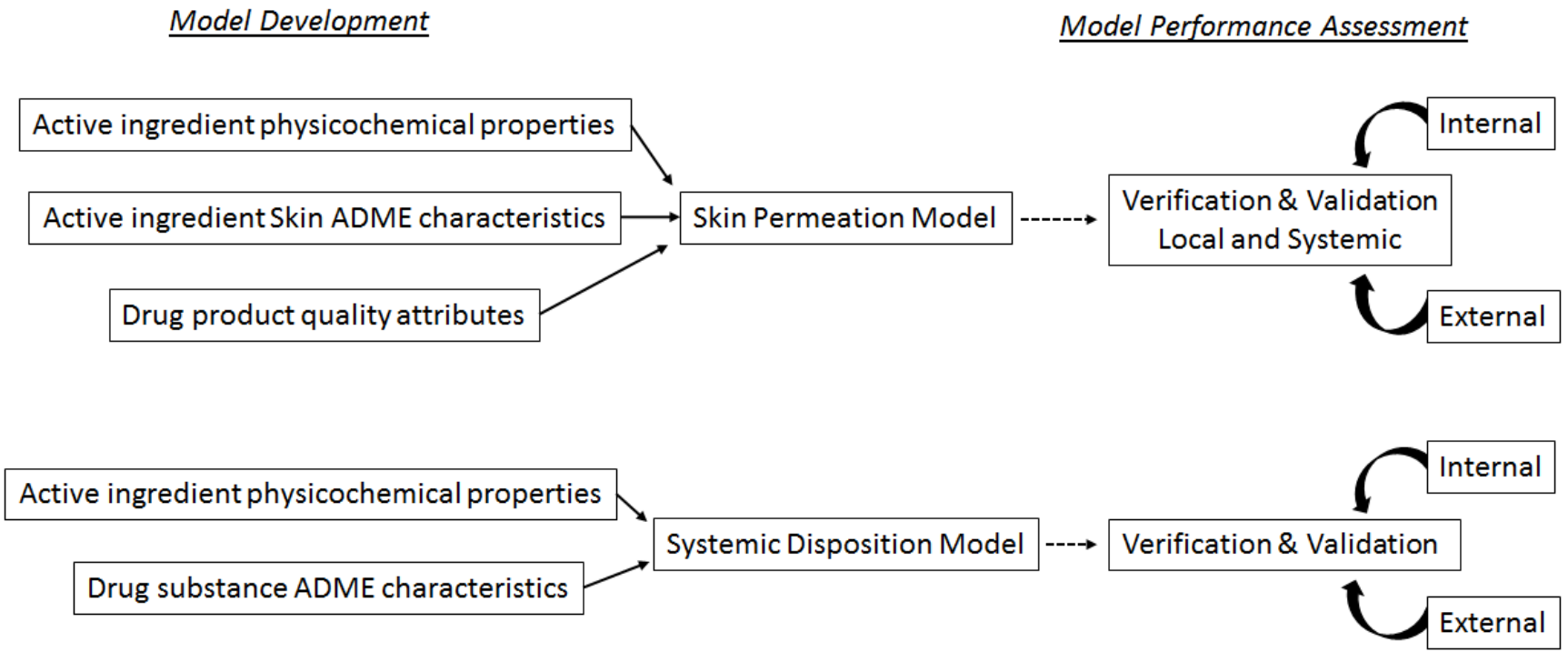
Tsakalozou, E et al. CPT Pharmacometrics Syst Pharmacol. 2021 May;10(5):399-411.
Tsakalozou, E et al. Clin Pharmacol Ther. 2021 Jul 7. doi: 10.1002/cpt.2356.

Dermal PBPK model supporting ANDA 211253 approval

- Generic diclofenac sodium topical gel, 1% for Voltaren® (diclofenac sodium) topical gel, 1% (NDA 022122, reference product)
- Approved on May 16, 2019
- PSG recommendation:
  - comparative clinical endpoint BE study
  - BE study with PK endpoints
- Alternative BE approach for a Q1/Q2/Q3 formulation: dermal PBPK model in lieu of an in vivo comparative clinical endpoint BE study

PSG: product-specific guidance

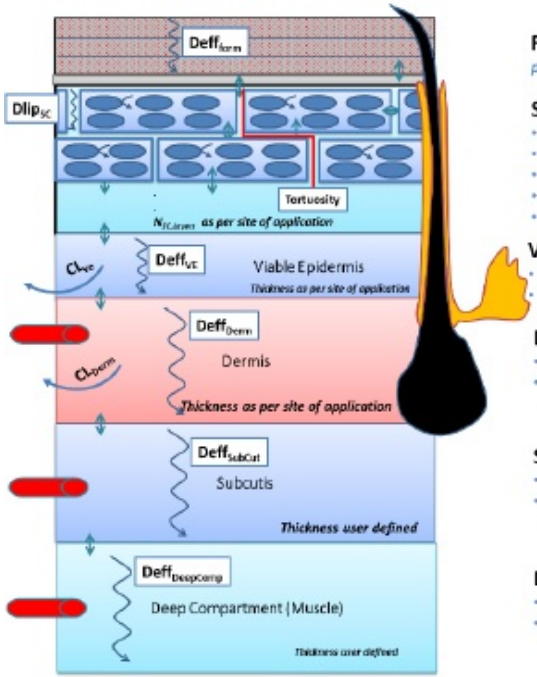
Overview of model development, verification and validation



ADME: absorption, distribution, metabolism, elimination

Tsakalozou, E et al. Clin Pharmacol Ther. 2021 Jul 7. doi: 10.1002/cpt.2356.

Dermal PBPK model supporting ANDA 211253 approval: development



Formulation *(Gel, cream, lotions, paste, patch, ointments, etc.)*

Stratum Corneum (SC)
- *Define cell shape and size*
- *Cell membrane permeability*
- *Keratin bonding kinetics*
- *Tortuosity and diffusivity*
- *Hair follicle density and size*

Viable Epidermis (VE)
- *Thickness, diffusivity*
- *Metabolism*

Dermis
- *Thickness, diffusivity*
- *Metabolism, blood flow*

Subcutis
- *Thickness, diffusivity*
- *Blood flow*

Deep Tissue
- *Thickness, diffusivity*
- *Blood flow*

Model developed on a commercially available platform:

- API physicochemical properties
- API ADME properties
- Formulation attributes for R and T drug products (viscosity, globule size, pH)
- Inter- and intra-subject variability (gender, race, age, skin anatomical location)
- Deep tissue compartment was modified to simulate the synovial fluid (volume)

API: active pharmaceutical ingredient, ADME: absorption, distribution, metabolism, elimination, R: reference, T: test

Dermal PBPK model supporting ANDA 211253 approval: performance assessment

Platform

- >10 dermal PBPK models for TDS and topical products
  - Multiple doses/product strengths and dosing regiments, age and anatomical locations
  - Systemic and local bioavailability (skin biopsy, IVPT, dermal microdialysis) data
  - Satisfactory model performance

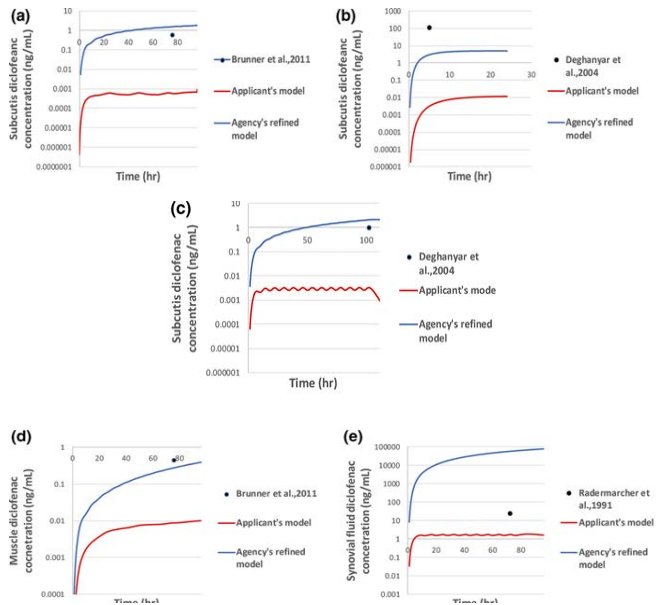
Suitably validated platform

Model

- Model verification
  - Code
  - Biological plausibility
- Model validation
  - Dermal PBPK models for diclofenac sodium topical products (solution, gel/emulsion)
    - Literature and application data on doses, product strengths, dosing regiments, routes of administration and local/systemic exposure data
  - Dermal PBPK models for the R and T products

TDS: Transdermal Delivery Systems, IVPT: in vitro permeation testing

Dermal PBPK model supporting ANDA 211253 approval: model refinement

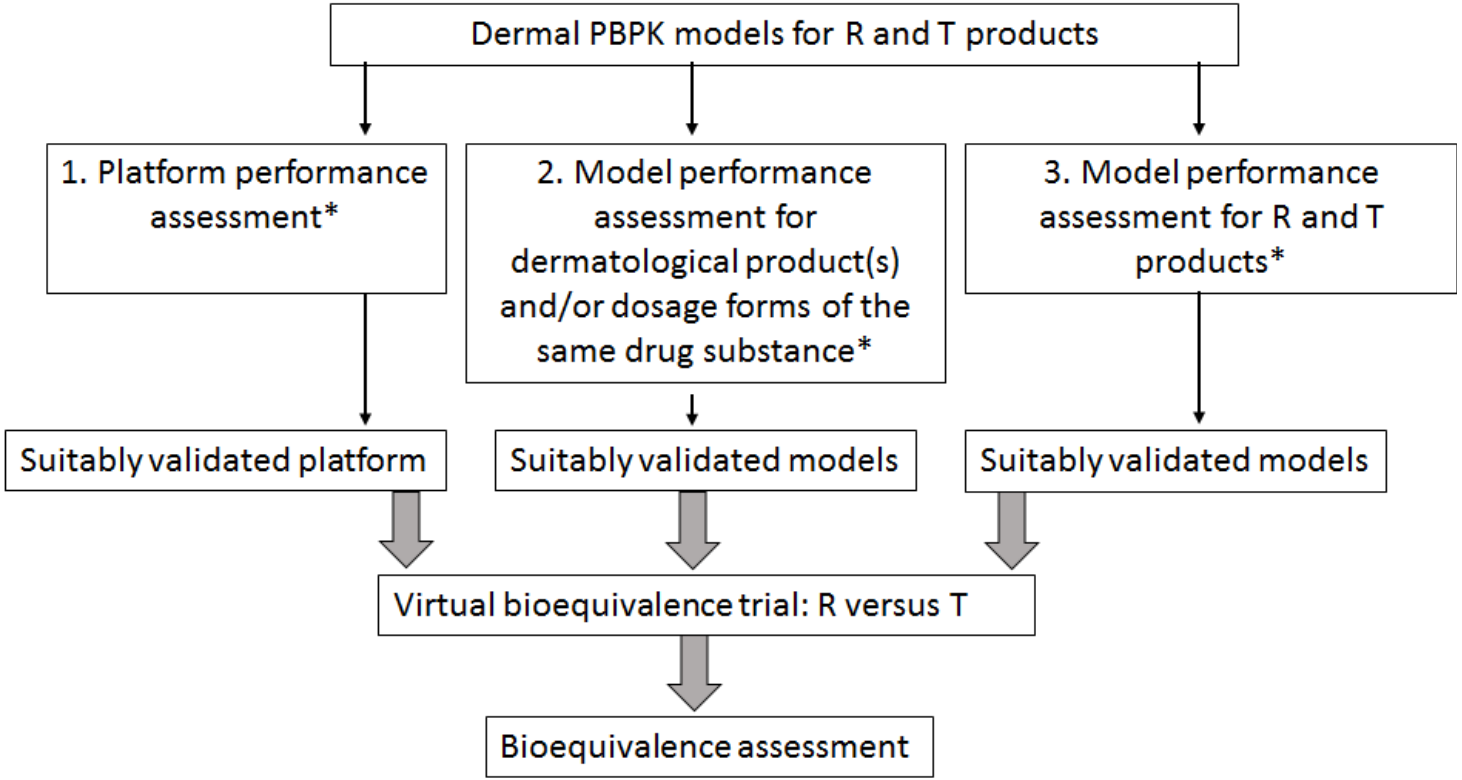


- Agency refined the applicant's model to improve local exposure predictions
  - Protein binding in all skin layers
  - Drug product attributes updated
  - Partition coefficients modified
- Validation leveraging microdialysis and skin biopsy data (literature)
- Model structural and numerical identifiability considered
- Satisfactory model performance

Suitably validated model

Tsakalozou, E et al. CPT Pharmacometrics Syst Pharmacol. 2021 May;10(5):399-411.

V&V methodology in support of fit-for-purpose dermal PBPK models



Tsakalozou, E et al. Clin Pharmacol Ther. 2021 Jul 7. doi: 10.1002/cpt.2356.

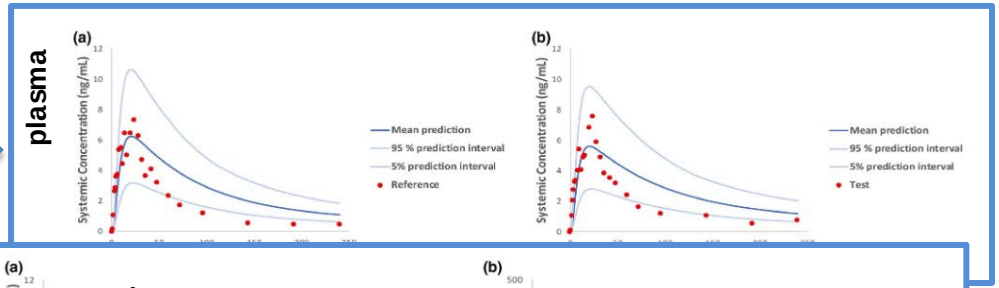
* Simulations in healthy or diseased population, V&V: verification and validation

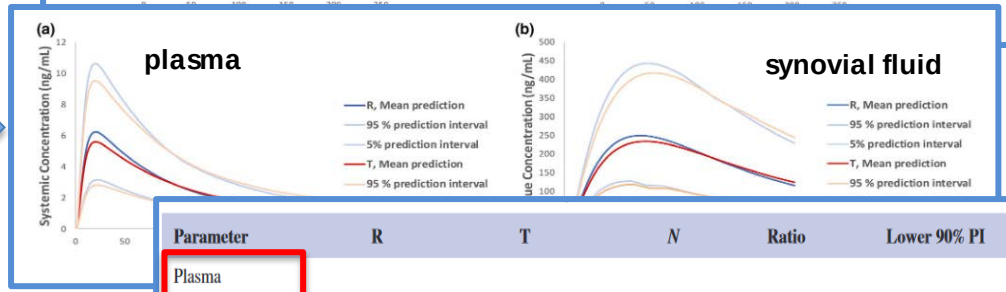
Implemented VBE Workflow

Verified/Validated Model

In Vivo Study Simulation

Bioequivalence Assessment





Parameter	R	T	N	Ratio	Lower 90% PI	Upper 90% PI
Plasma						
C_{max}, ng/ml	5.87	5.56	78	0.90	81.29	98.77
AUC, ng·hr/ml	638.40	630.56	78	0.98	88.63	107.39
Synovial fluid						
A_{max}, µg	230.13	222.47	78	0.93	85.06	102.68
AUC, µg·hr/ml	37,888.28	37,362.20	78	0.97	87.7	107.83

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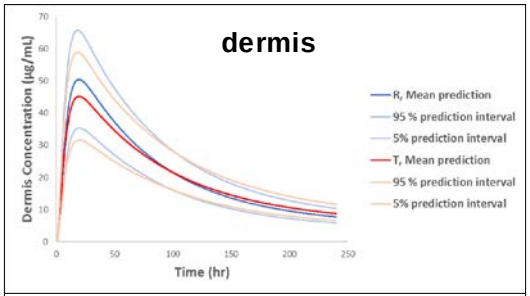
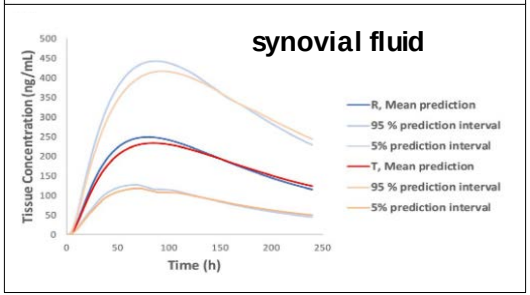
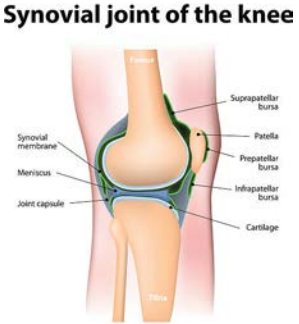
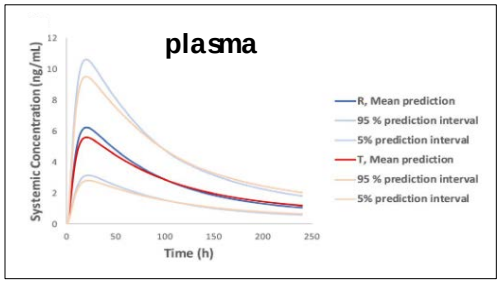
Considerations in implementing a VBE assessment









- Comparison of simulated PK profiles between R and T drug products
  - Application site/skin layers
  - Site of pharmacological action (target site)
  - Systemic circulation
- Accounting for all sources of intra and inter-subject variability
  - skin physiology parameters (skin layer thickness, pH, and blood flow)
  - application sites (arm, leg, head, abdomen, and back)
  - virtual population (sex, race, and age)
  - drug product characteristics and their impact on local bioavailability
- PK metrices for BE statistical analysis
  - Cmax (Amax)
  - AUC
- Overall shape of PK curve (Tmax, absorption and elimination phase) is considered

Cmax: maximum plasma concentration, Amax: maximum amount, AUC: area under the concentration versus time curve

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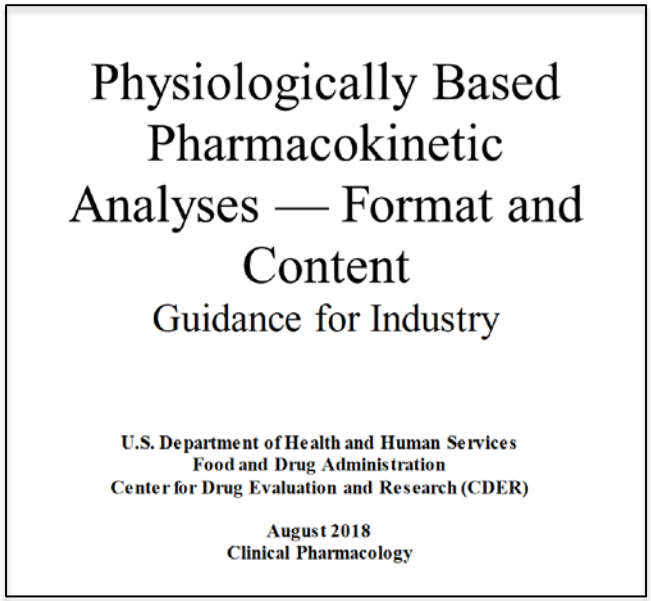
Applicants are encouraged to follow best practices when developing dermal PBPK models for regulatory submissions

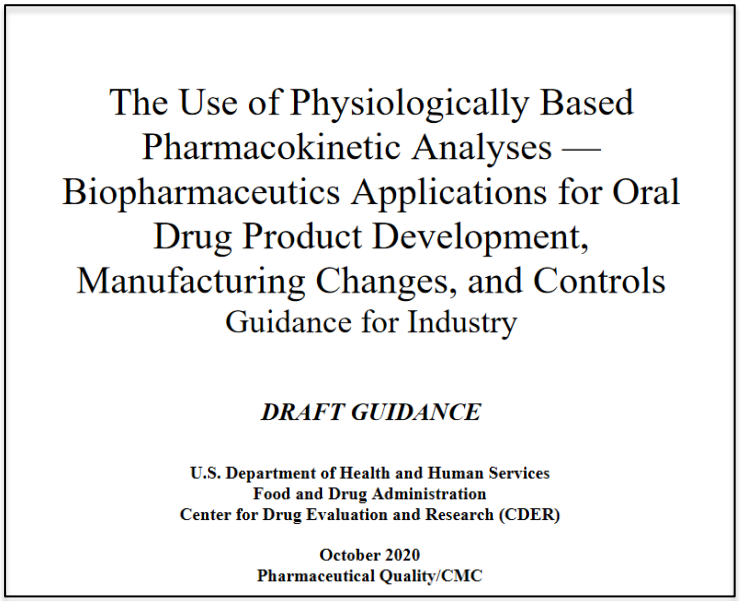


Physiologically Based Pharmacokinetic Analyses — Format and Content

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

August 2018
Clinical Pharmacology



The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls

Guidance for Industry

DRAFT GUIDANCE

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2020
Pharmaceutical Quality/CMC

https://www.fda.gov/media/101469/download

Take home messages

- PBPK models for dermatological drug products can be used to support:
  - Development of a drug product prior approval
  - Alternative BE approaches for product approval
- Model development is an intense and resource-demanding process:
  - Complexity of the models and the drug products (remote target site)
  - Limitations in data availability in model development and validation
- PBPK modeling supporting an ANDA: early interaction between industry and regulatory agency should be initiated - pre-ANDA meeting request program, GDUFA II

Generic Drug User Fee Amendments: Regulatory Science/Research

Grant	Grant Duration	Institute	Grant No.
Development and validation of dermal PBPK modelling platform towards virtual bioequivalence assessment considering population variability	2014-2018	Simcyp, Ltd	1U01FD005225
Physiologically based biopharmaceutics and pharmacokinetics of drug products for dermal absorption in humans	2014-2019	University of South Australia	1U01FD005232
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	2018-2020	Simcyp, Ltd	1U01FD006521
Assessment of Transdermal Drug Product Quality and Performance Attributes via Enhanced Virtual Bioequivalence Simulations	2018-2020	SimulationsPlus, Inc	1U01FD006526
Formulation drug product quality attributes in dermal physiologically-based pharmacokinetic models for topical dermatological drug products and transdermal delivery systems	2018-2020	University of Queensland	1U01FD006522
PBPK and Population Modeling Seamlessly Linked to Clinical Trial Simulation in an Open-Source Software Platform	2018-2021	Children's Hospital of Los Angeles	1U01FD006549
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	2021-2023	Certara UK, Ltd	1U01FD007323
Dermal Drug Product Quality and Bioequivalence Assessment through Advanced MAM and PBPK Simulation	2021-2023	SimulationsPlus, Inc	1U01FD007320

Acknowledgments

FDA/CDER

OGD/ORS/DQMM

Andrew Babiskin
Khondoker Alam
Ross Walenga
Mingliang Tan
Lucy Fang
Liang Zhao

OGD/ORS/DTP I

Priyanka Ghosh
Tannaz Ramezanli
Mengmeng Niu
Markham Luke

OGD/ORS-IO

Lei Zhang
Robert Lionberger
Sam Raney

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Questions?

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