Physiologically-based Pharmacokinetic Modeling to Guide Study Design and Product Development for Generic Dermatological Products

SBIA 2020: Advancing Innovative Science in Generic Drug Development Workshop

Session 3: Future Directions, Emerging Technology, and Current Thinking on Alternative BE Approaches

Topic 3: Emerging Use of Modeling and Simulation for Bioequivalence

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Office of Generic Drugs| CDER | U.S. FDA

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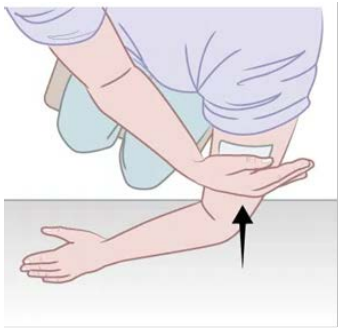
Disclaimer

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

Learning Objectives

- Understand the considerations for establishing bioequivalence (BE) for generic dermatological drug products
- Introduce physiologically-based pharmacokinetic (PBPK) modeling for generic dermatological products
- Explore how PBPK modeling can be used to support decisions over the entire life-cycle of a generic drug product: from development to approval

Overview



Dermatological drug products

- Challenges in generic drug product development and establishing BE

Role for PBPK modeling and simulation approaches

- Case example 1: inform design for cutaneous pharmacokinetics (PK) studies
- Case example 2: establish a “safe space” for drug product attributes

Take home messages

BE for generic dermatological drug products: A challenge

Comparative clinical endpoint BE studies

- Not sensitive in detecting formulation differences
- Large variability in the observed response
- Modest clinical efficacy

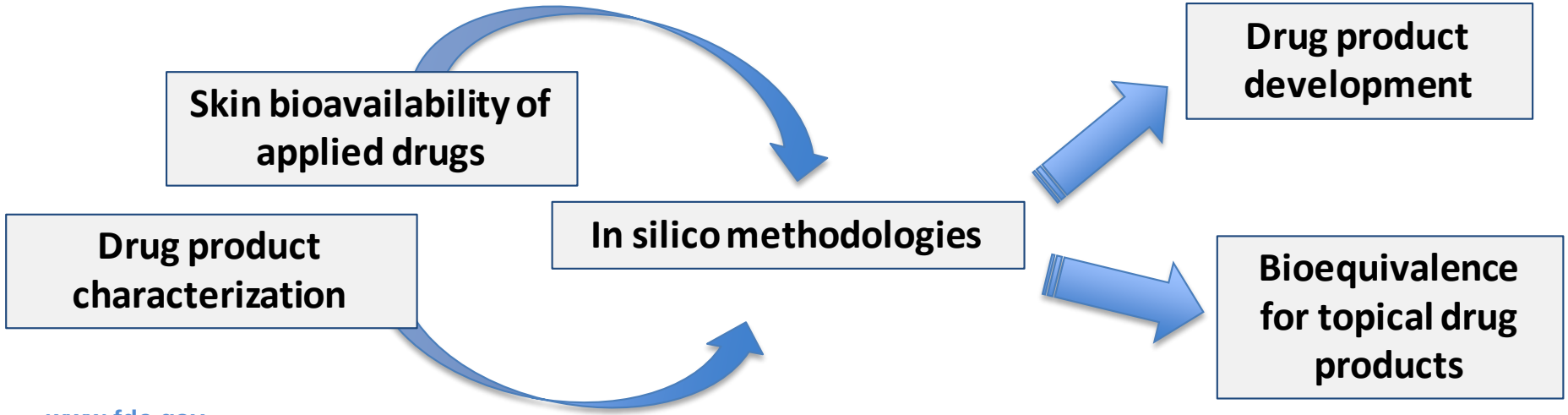
BE studies with PK endpoints

- Semisolid dosage forms: typically non-detectable systemic exposure
- Systemic exposure may not reflect local concentrations

Drug product characterization studies

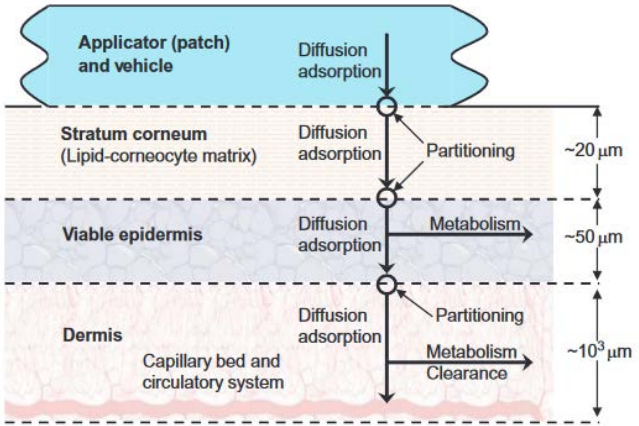
Implement in silico methodologies for generic dermatological drug products: A challenge

"for a drug that is not intended to be absorbed into the bloodstream" the Agency may consider establishing "alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect"

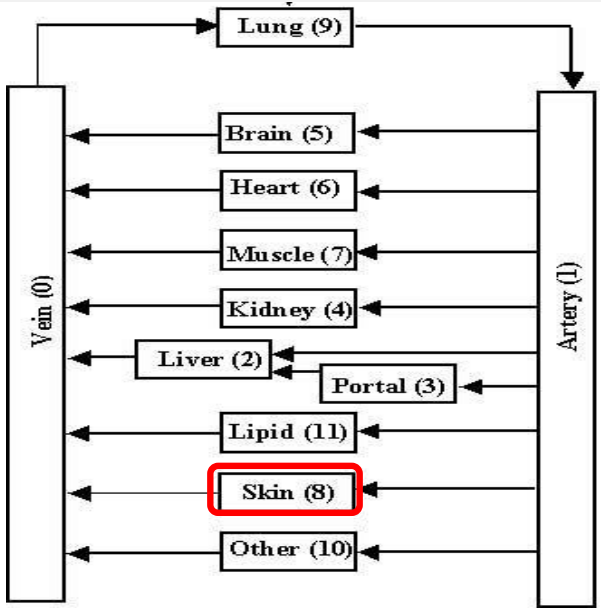


United States Food and Drug Administration, 21CFR320.23, accessed on 08/13/2020, https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=320.23

Modeling skin bioavailability…



Mechanistic PBPK models:
API, formulation and human/animal physiology (variability and population)



API: Active Pharmaceutical Ingredient

BMC Clin Pharmacol. 2002 Aug 15;2:5. PKQuest: a general physiologically based pharmacokinetic model. Introduction and application to propranolol. David G Levitt.
Skin models for the testing of transdermal drugs. Abd E, Yousef SA, Pastore MN, Telaprolu K, Mohammed YH, Namjoshi S, Grice JE, Roberts MS. Clin Pharmacol. 2016 Oct 19;8:163-176.
https://reader.elsevier.com/reader/sd/pii/B9780124080775000109?token=7B6390B968A5B97902A420B977D483BD3FDCA4A2581F89FE99F66732BA808D0E8F0BF98B6BA263D3F277D2A0725D9441

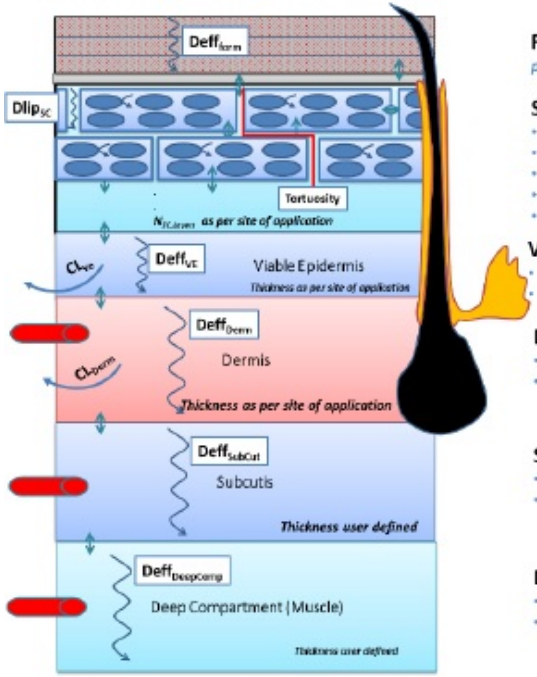
PBPK modeling and simulation applications:

- Alternative BE approaches for product approval
  - Diclofenac topical gel, 1%, ANDA 211253

- Development of a drug product prior to approval
  - Inform study design: in vivo BE studies with PK endpoints, **IVPT, percutaneous PK studies**
  - Justify deviations on formulation attributes (Q3 characterization) – define "safe space"

IVPT: In Vitro Permeation Testing

Dermal PBPK model supporting ANDA 211253 approval



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*

- Diclofenac sodium topical gel, 1%
- Dermal PBPK model to support an alternative BE approach for the Q1/Q2/Q3 formulation
- The alternative BE approach did not include the PSG-recommended in vivo comparative clinical endpoint BE study
- Dermal PBPK model leveraged for virtual BE assessments on predicted systemic and local exposure

PSG: Product-Specific Guidance

Tsakalozou, E. Physiologically-based pharmacokinetic modeling and simulation approaches: best practices for regulatory applications related to locally-acting generic drugs. Presented at Regulatory Education for Industry: 2019 Complex Generic Drug Product Development Workshop, Maryland, USA.

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Methods on studying percutaneous PK

Dermal microdialysis

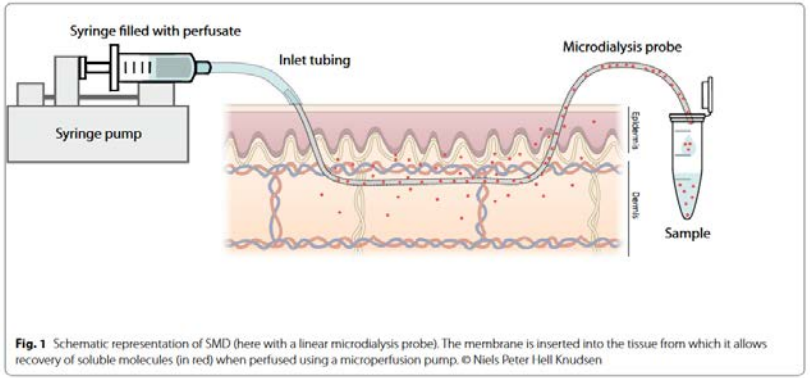
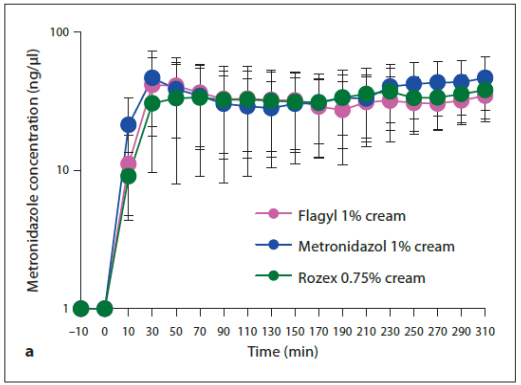


Fig. 1 Schematic representation of SMD (here with a linear microdialysis probe). The membrane is inserted into the tissue from which it allows recovery of soluble molecules (in red) when perfused using a microperfusion pump. © Niels Peter Hell Knudsen



Dermal open flow microperfusion

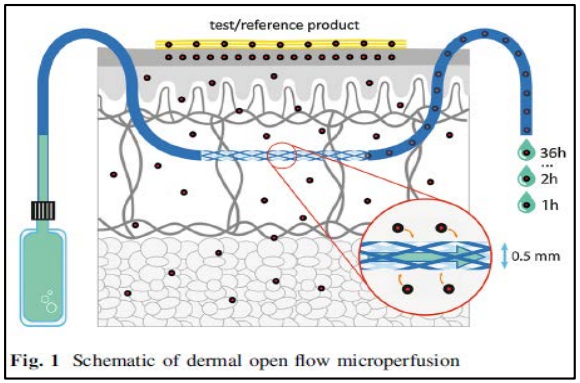
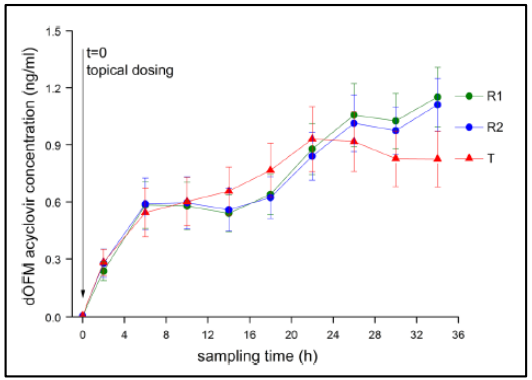


Fig. 1 Schematic of dermal open flow microperfusion



Clin Pharmacokinet 2017 Jan;56(1):91-98. Open Flow Microperfusion as a Dermal Pharmacokinetic Approach to Evaluate Topical Bioequivalence. Bodenlenz M, Tiffner KI, Raml R, Augustin T, Dragatin C, Birngruber T, Schimek D, Schwagerle G, Pieber TR, Raney SG, Kanfer I, Sinner F.
Skin microdialysis: methods, applications and future opportunities-an EAACI position paper.
Baumann KY, Church MK, Clough GF, Quist SR, Schmelz M, Skov PS, Anderson CD, Tannert LK, Giménez-Arnau AM, Frischbutter S, Scheffel J, Maurer M. Clin Transl Allergy. 2019 Apr 10;9:24.
U01FD004946, U01FD005861, PI: F Sinner, U01FD005862, PI: G. Stangi.

PBPK modeling used to predict dermis exposure

Metronidazole topical gel

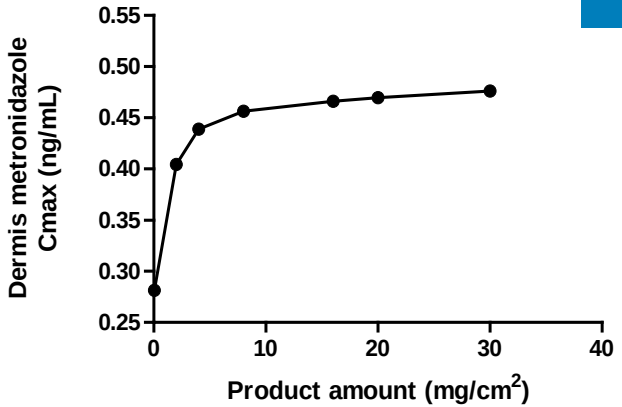
Simcyp v18 Simulator, MPML MechDermA Model

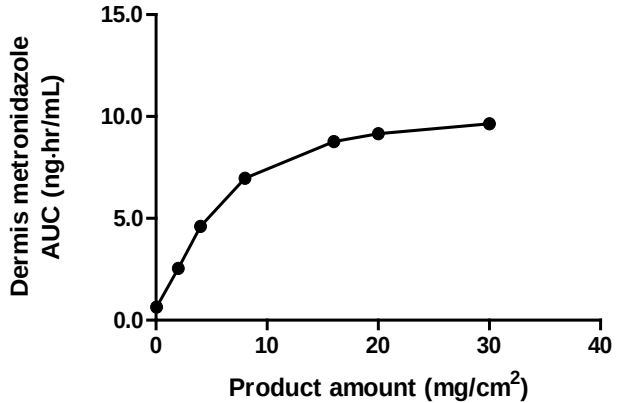
- Minimal PBPK model
- Skin absorption parameters informed by QSAR models and optimized based on systemic PK data
- Formulation attributes
  - Q3 characterization
  - Vehicle evaporation (GDUFA-funded research, 1U01FD005223)
- Model performance assessment
  - Systemic exposure data (in-house data)
  - Redistribution from the systemic circulation to the dermis: literature data
  - Additional metronidazole topical drug products

Validation of dermis model predictions

pilot study

(not performed for the present example)





QSAR: Quantitative Structure-Activity Relationship

PBPK modeling used to predict dermis exposure: considerations

- Inform study design and answer “what if” scenarios
  - Study protocol (application methodology, (non)occlusion, sampling scheme, dose and application duration)
  - Positive and negative controls
  - Population (healthy/patients, male/female)
- Identify appropriate PK parameters for BE assessment in the dermis
- Determine an appropriate dose range for the applied drug product with discriminatory capability for test and reference products

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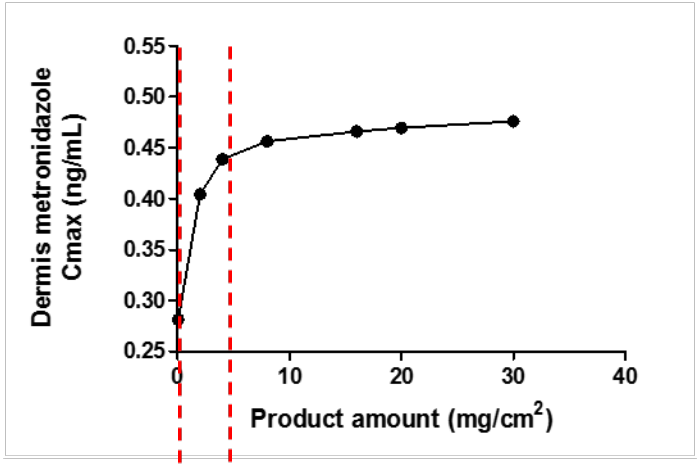

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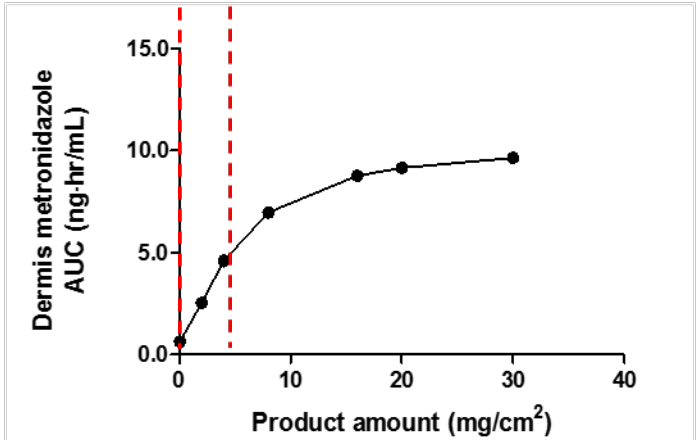


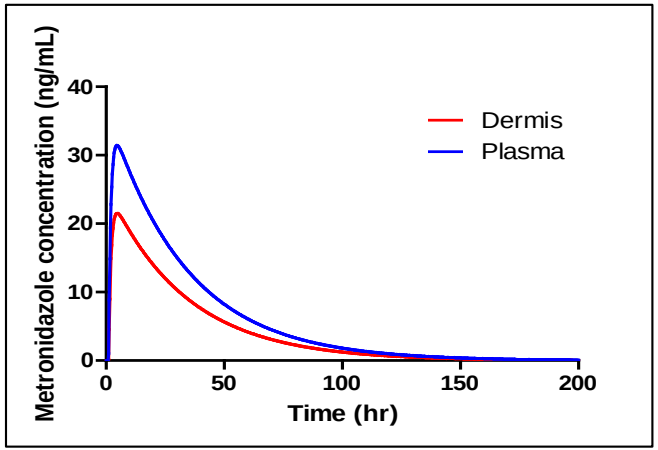
PBPK modeling used to predict dermis exposure: considerations

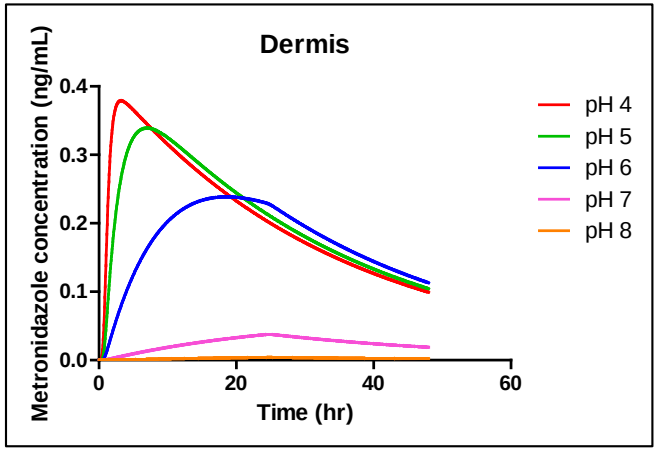
Assessment of extent of redistribution from plasma to dermis

- Model validation
- Potentially critical for local BE assessments

Identify formulation attributes that may impact local and systemic exposure

- Sensitivity analysis





PBPK modeling and simulation applications:

- Alternative BE approaches for product approval
  - Diclofenac topical gel, 1%, ANDA 211253

- Development of a drug product prior to approval
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  - Justify **deviations on formulation attributes (Q3** characterization) – define "safe space"

In Vitro Permeation Testing

Vertical Diffusion cell

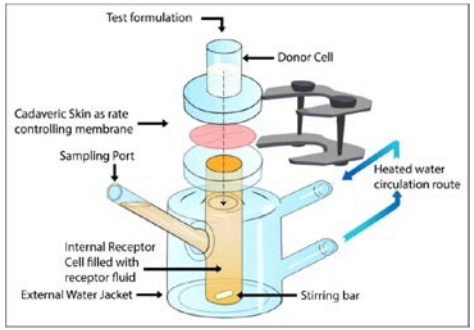
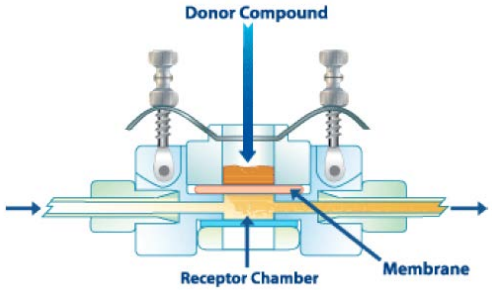
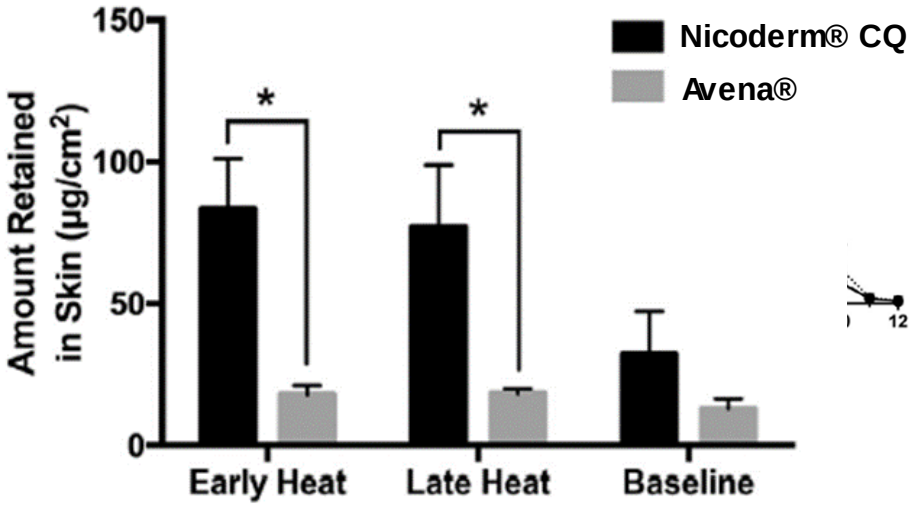


Figure 1. Schematic diagram of a static diffusion cell used in in vitro permeation test.

In-line Flow cell



Amount in Skin

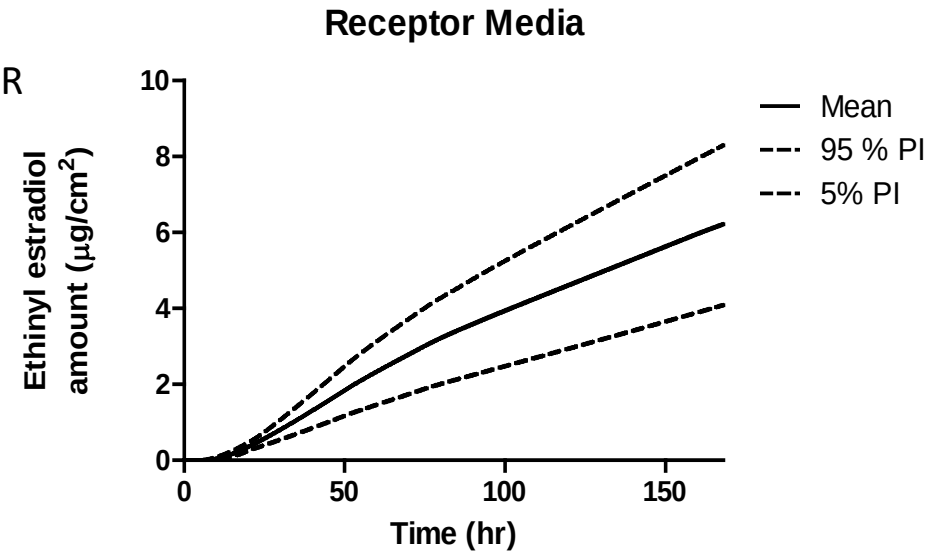


Ther Innov Regul Sci. 2019 Oct 3; In Vitro Skin Permeation Methodology for Over-The-Counter Topical Dermatologic Products. Luke Oh, Sojeong Yi, Da Zhang, Soo Hyeon Shin, Edward Bashaw.
https://permegear.com/
In vitro-in vivo correlations for nicotine transdermal delivery systems evaluated by both in vitro skin permeation (IVPT) and in vivo serum pharmacokinetics under the influence of transient heat application. Shin SH, Thomas S, Raney SG, Ghosh P, Hammell DC, El-Kamary SS, Chen WH, Billington MM, Hassan HE, Stinchcomb AL. J Control Release. 2018 Jan 28;270:76-88.

PBPK modeling used to define “safe space”

Ethinyl estradiol, Transdermal Delivery System (TDS)
Simcyp v19 Simulator, MPML MechDermA Model

- Minimal PBPK model
- Skin absorption parameters informed by QSAR models and optimized based on systemic PK data
- Formulation attributes
  - Loaded dose
  - Application area
  - Application site
- Model performance assessment
  - Systemic exposure data



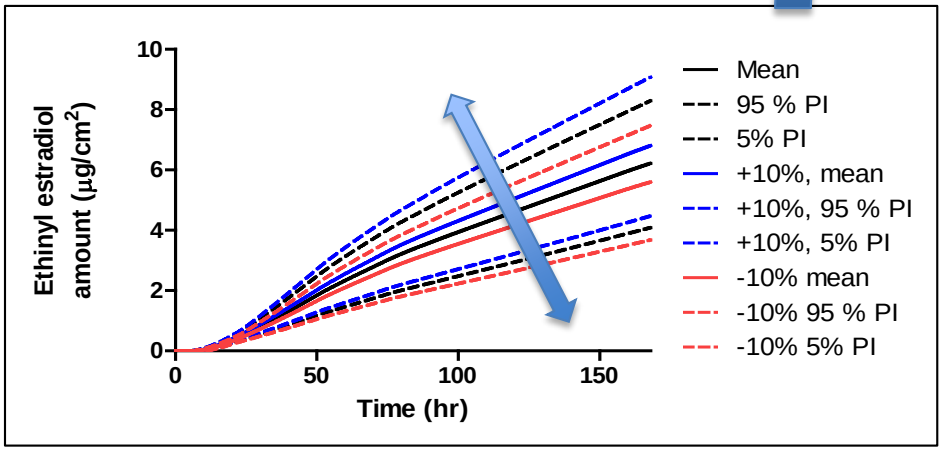
Validation of IVPT model predictions pilot study (not performed for the present example)

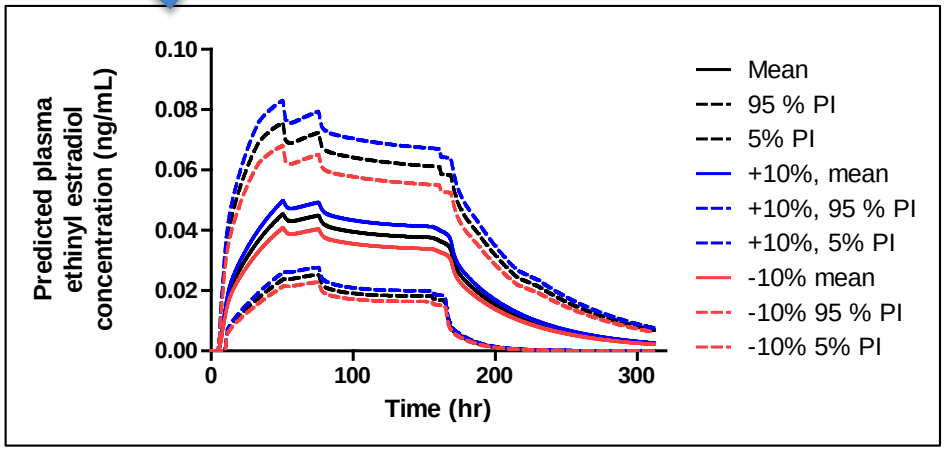
PBPK modeling used to define “safe space”

Impact of deviations on loading dose on product performance

- Scenario 1: +10%
- Scenario 2: -10%

IVIVE





PBPK modeling used to define “safe space”: considerations

- Experimental conditions captured properly in the IVPT model
  - Static or flow through cell / sampling methodology
  - Receptor solution solubility (protein, surfactants)
  - Excised skin (thickness, preparation, storage)
- IVPT study design captured properly in the IVPT model
  - Demographics: male/female, age
  - Application site
  - Donor and replicates
  - Population variability
- IVPT model validation
  - IVPT study design is sensitive to drug product differences
  - Model predictions are sensitive to drug product differences

Take home messages

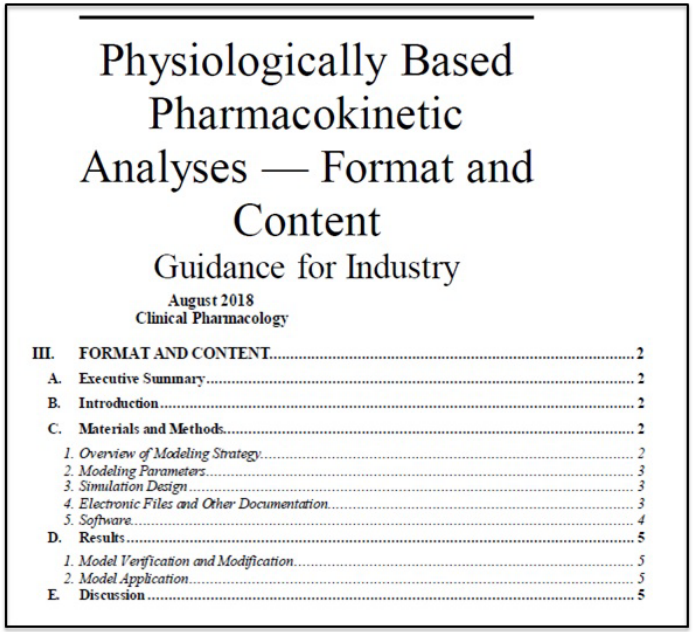
- PBPK models for generic dermatological drug products can be used to support:
  - Development of a drug product prior approval (study design, deviations on Q1/Q2/Q3 attributes)
  - Alternative BE approaches for product approval

- PBPK modeling supporting an ANDA: early interactions between industry and regulatory agency should be initiated – e.g., pre-ANDA meeting program under GDUFA II

- Model development is an intense and resource-demanding process due to:
  - Complexity of models and drug products (remote target site)
  - Limitations in data availability in model development and validation

Take home messages

- Applicants are encouraged to follow best practices when developing (dermal) PBPK models



Physiologically Based Pharmacokinetic Analyses — Format and Content

Guidance for Industry

August 2018
Clinical Pharmacology

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

Acknowledgments

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OGD/ORS/DTP

Sam Raney & Team

OGD/ORS-IO

Lei Zhang
Robert Lionberger

www.fda.gov/GDUFARegScience

Generic Drug User Fee Amendments: Regulatory science research

Grant/Contract	Institute	Grant or Contract No.
An integrated multiscale-multiphysics modeling framework for evaluation of generic ophthalmic drug products	CFD Research Corporation	HHSF223201810151C
GastroPlus OCAT model extension and validation	SimulationsPlus, Inc	HHSF223201810255P
A Multiscale Computational Framework for Bioequivalence of Orally Inhaled Drugs	CFD Research Corporation	HHS223201810182C
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	Simcyp, Ltd	1U01FD006521
Assessment of Transdermal Drug Product Quality and Performance Attributes via Enhanced Virtual Bioequivalence Simulations	SimulationsPlus, Inc	1U01FD006526
Formulation drug product quality attributes in dermal physiologically-based pharmacokinetic models for topical dermatological drug products and transdermal delivery systems	University of Queensland	1U01FD006522
PBPK and Population Modeling Seamlessly Linked to Clinical Trial Simulation in an Open-Source Software Platform	Children's Hospital of Los Angeles	1U01FD006549

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Questions?

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Challenge Question #1

PBPK models for generic dermatological drug products can be used to support:

A. Development of a drug product prior to approval

B. Alternative BE approaches for product approval

C. Both A and B

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PBPK models for generic dermatological drug products can be used to support:

A. Development of a drug product prior to approval

B. Alternative BE approaches for product approval

C. Both A and B