CERTARA

Leveraging dermal physiologically-based pharmacokinetic modeling and simulation approaches for the approval of a generic diclofenac sodium topical gel

Eleftheria Tsakalozou, PhD (U.S. FDA)

Wednesday 8th December 2021

Welcome to the Simcyp Scientific Webinar Series

The session will begin at 11am EST (4pm GMT, 5pm CET). Please ensure you are muted. If you wish to ask a question, please type in the chat box and we can unmute you.

Today's Speaker

Eleftheria Tsakalozou, PhD

- Bio:

  Dr. Tsakalozou is currently a Staff Fellow at the Division of Quantitative Methods and Modeling at the Office of Research and Standards/Office of Generic Drugs/Center for Drug Evaluation and Research. She obtained her PhD in Pharmaceutical Sciences at the University of Kentucky in 2013 and completed a two-year Fellowship in Clinical Pharmacokinetics and Pharmacodynamics at the University of North Carolina at Chapel Hill.

  Her research interests include dermal physiologically-based pharmacokinetic modeling, interactions between excipients and molecular targets including gut transporters and development of quantitative modeling and simulation tools to support bioequivalence assessments.

- Title of todays talk:

  Leveraging dermal physiologically-based pharmacokinetic modeling and simulation approaches for the approval of a generic diclofenac sodium topical gel

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Leveraging dermal physiologically-based pharmacokinetic modeling and simulation approaches for the approval of a generic diclofenac sodium topical gel

Simcyp Scientific Webinar Series

Eleftheria Tsakalozou, PhD

Pharmacologist

Division of Quantitative Methods and Modeling, Office of Research and Standards,
Office of Generic Drugs

CDER | U.S. FDA

December 08, 2021

Disclaimer

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

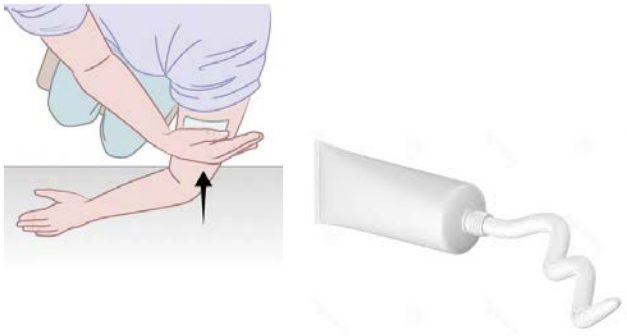
Overview

- 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



BE for generic dermatological drug products: current recommendations

Comparative clinical endpoint BE studies

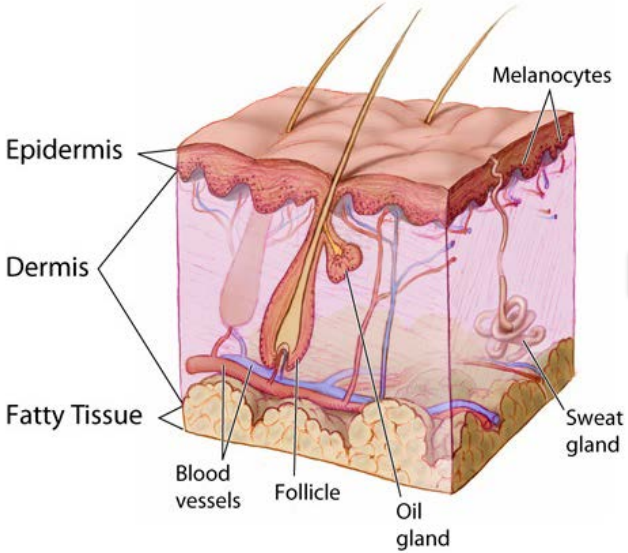
- Relatively insensitive in detecting formulation differences
- Large variability in the observed response
- Modest clinical efficacy

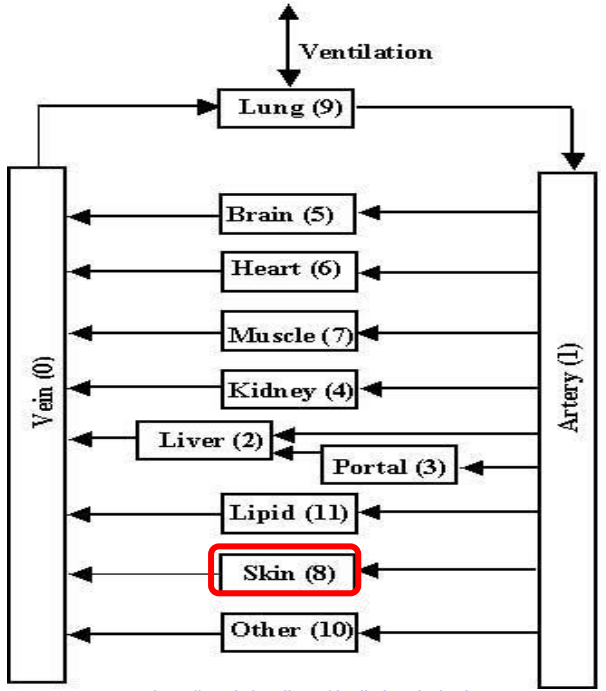
BE studies with PK endpoints

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

Drug product characterization studies

Modeling skin bioavailability by implementing dermal PBPK modeling and simulation approaches





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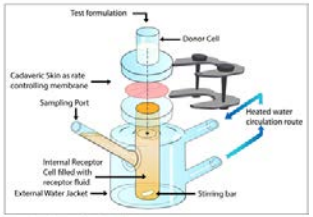
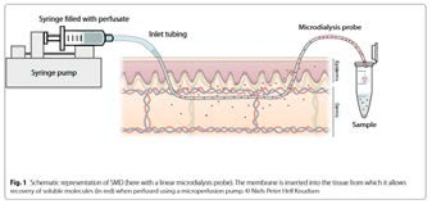
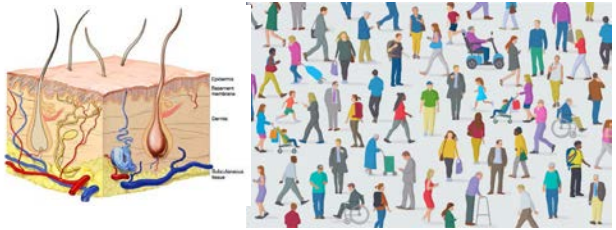
https://visualsonline.cancer.gov/details.cfm?imageid=4604

Implement in silico methodologies for generic dermatological drug products

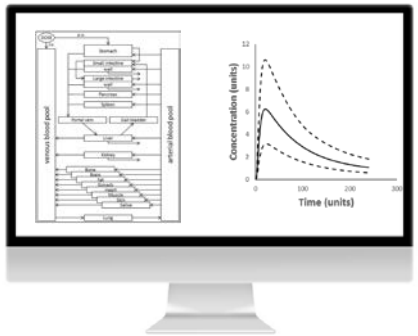




Skin Bioavailability



Skin Physiology in Individuals/Populations



Drug Product Characterization

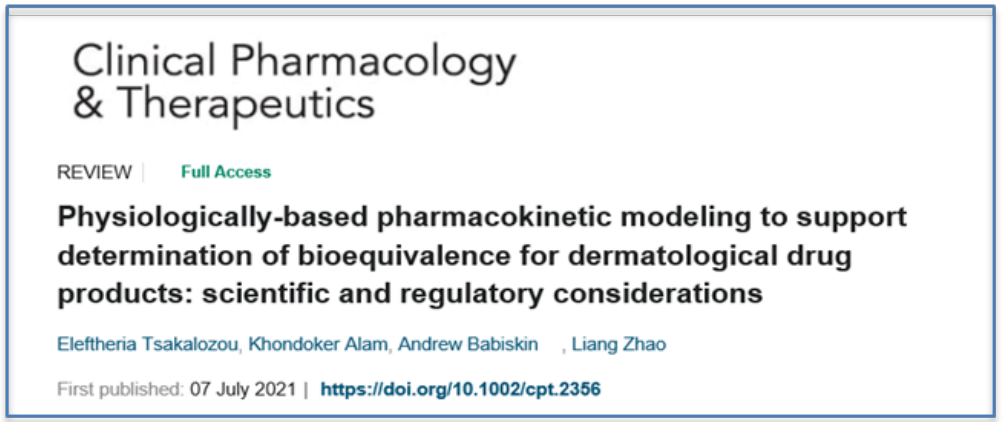
Ther Innov Regul Sci. 2019 Oct 3; In Vitro Skin Permeation Methodology for Over-The-Counter Topical Dermatologic Products. Luke Oh, Sojeong Yi, Da Zhang, Soo Hyeon Shin, Edward Bashaw.
Skin microdialysis: methods, applications and future opportunities-an EAACI position paper.
Modified from Front Pharmacol.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

Lessons learned 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

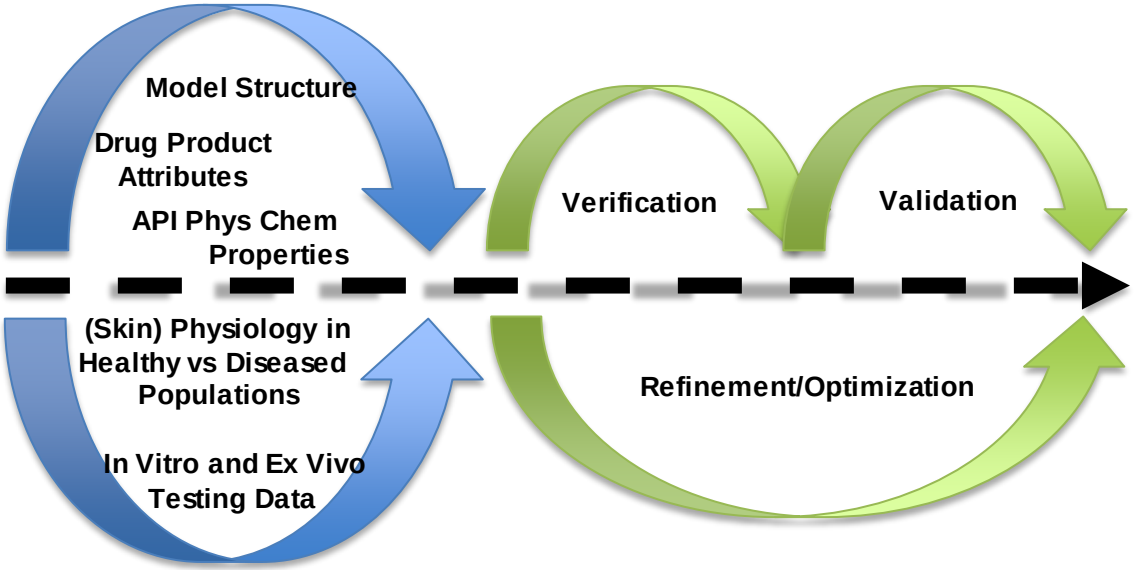
Physiologically-based pharmacokinetic modeling to support determination of bioequivalence for dermatological drug products: scientific and regulatory considerations

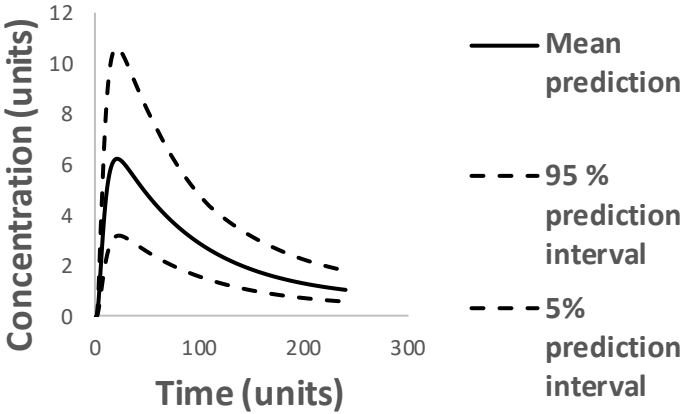
Eleftheria Tsakalozou, Khondoker Alam, Andrew Babiskin , Liang Zhao

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.

PBPK modeling for locally-acting drug products



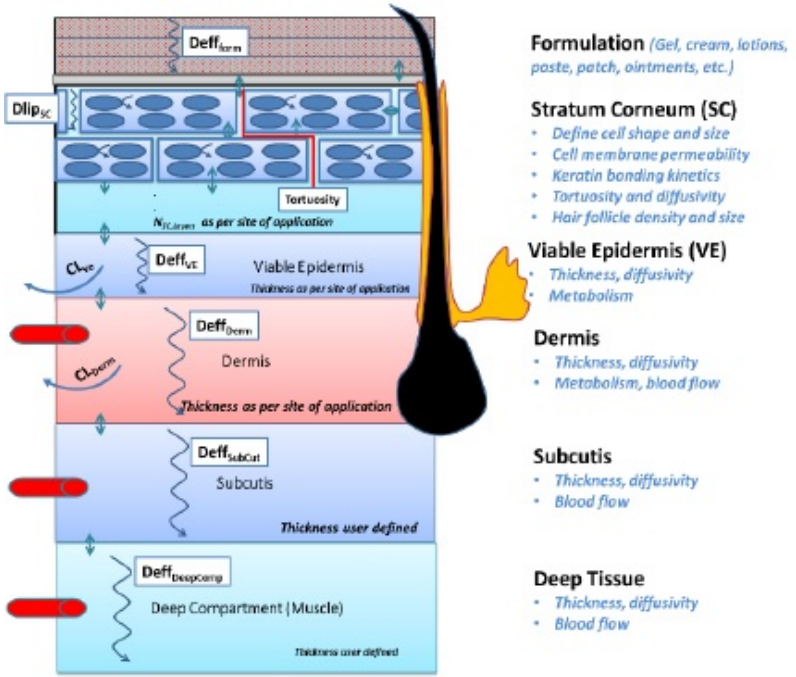


Dermal PBPK model supporting ANDA approval

- Generic diclofenac sodium topical gel, 1% for Voltaren® (diclofenac sodium) topical gel, 1% (NDA 022122, reference listed drug)
- 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, qualitative (Q1) and quantitative (Q2) Sameness of inactive ingredient components and quantitative composition between reference and generic products, Q3: Physical & Structural Characterization as relevant to the nature of the product

Dermal PBPK model supporting ANDA 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*

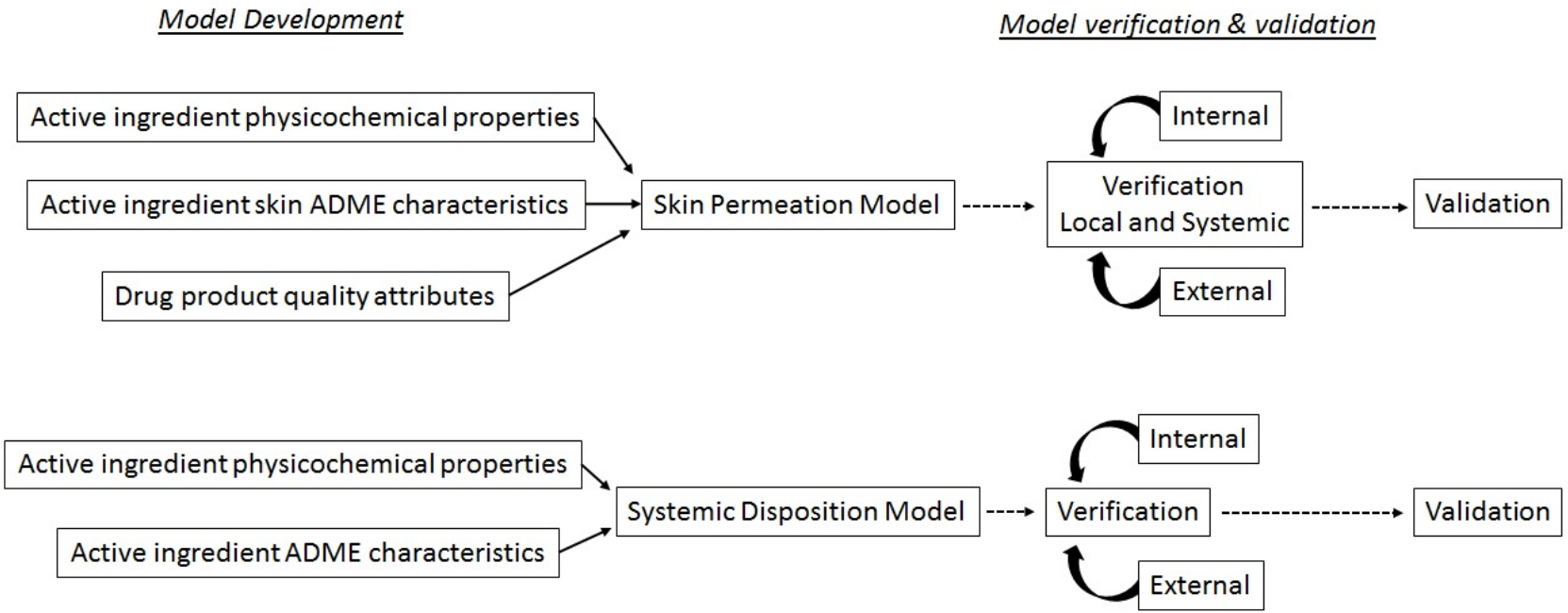
Deep Tissue
- *Thickness, diffusivity*
- *Blood flow*

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 (sex, race, age, skin anatomical location)
- Deep tissue compartment was modified to simulate the synovial fluid (volume)

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

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.

Overview of model development, verification and validation

TABLE 1 Data sources and key information considered for the development and validation of the PBPK model for diclofenac sodium topical gel, 1%, developed in MPML MechDermA within the Simcyp Simulator, version 17

Data source	Model development		Model validation	
	Systemic disposition	Skin permeation	Systemic disposition	Skin permeation
Drug substance				
Physicochemical properties (MW, lipophilicity, ionization status, etc.)	X	X		
ADME properties (protein binding, blood to plasma ratio, tissue distribution, and elimination)	X			
Skin ADME properties (protein binding, tissue distribution and sequestration, metabolism, and handling by transporter proteins)		X		
Clinical PK (plasma/blood) profiles following intravenous administration[a]	X		X	
Drug product				
In vitro physicochemical characterization of the drug product		X		
Formulation pH, API solubility (aqueous or oil phase), droplet size, rheological properties (viscosity)		X		
Formulation composition		X		
Evaporation (drying rate or vehicle volume loss profile)[b]		X		
In vivo percutaneous PK studies (dMD)		X[c]		X
Synovial fluid sampling		X[c]		X
Clinical (plasma/blood) PK profiles following skin application			X	

Abbreviations: ADME, absorption, distribution, metabolism, elimination; API, active pharmaceutical ingredient; dMD, dermal microdialysis; MPML, multi-phase multi-layer; MW, molecular weight; PBPK, physiologically-based pharmacokinetic; PK, pharmacokinetic.

[a]If not available, clinical PK profiles following oral administration may be considered.

[b]Not included in the current model.

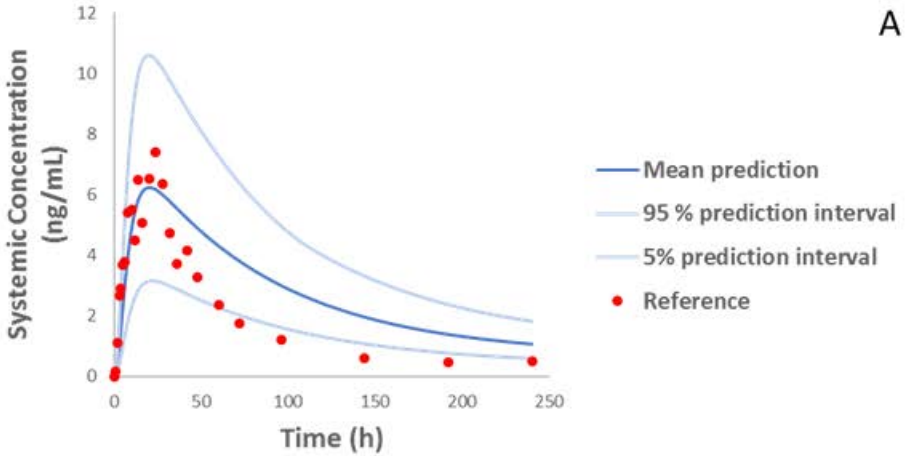
[c]Model refinement by the Agency.

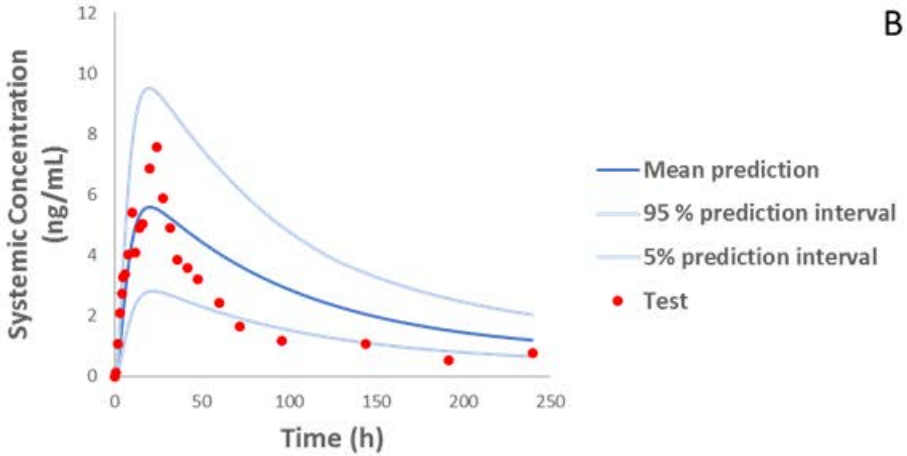
Tsakalozou, E et al. CPT Pharmacometrics Syst Pharmacol. 2021 May;10(5):399-411.

Dermal PBPK model supporting ANDA approval: model performance assessment

- 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

Dermal PBPK model supporting ANDA approval: model performance assessment





✓ The proposed model described the observed data reasonably well

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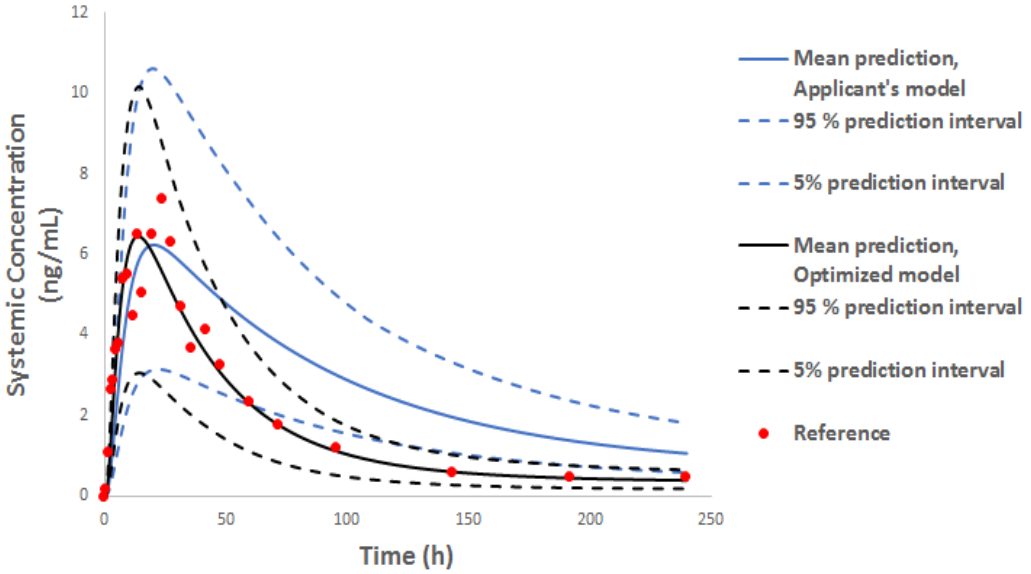
R: Reference, T: Test

Dermal PBPK model supporting ANDA approval: model refinement



- ✓ "bottom-up approach"
- ✓ Sensitivity analysis-guided parameter optimization may have resulted in improved model predictions
- ✓ No impact on BE outcome

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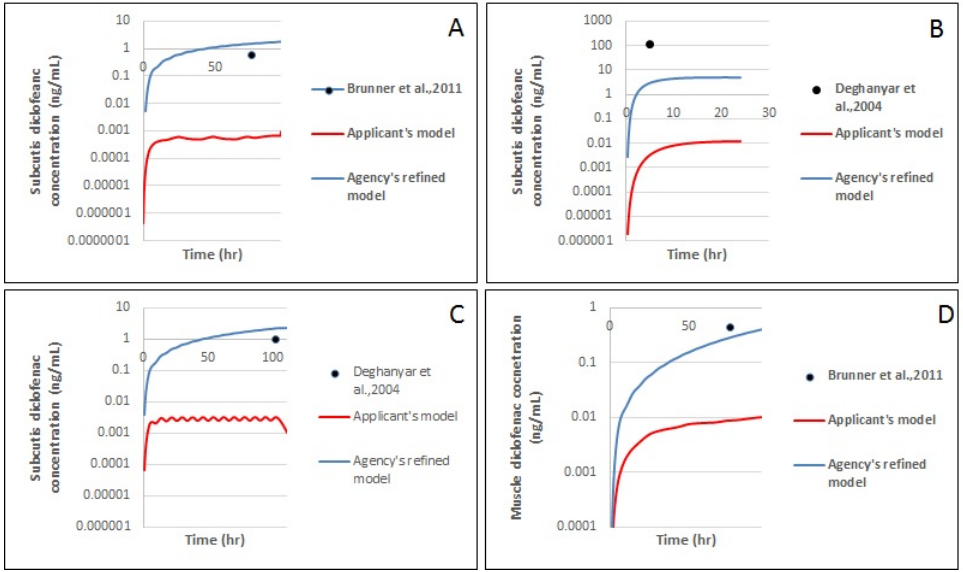
Dermal PBPK model supporting ANDA approval: model refinement



- 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

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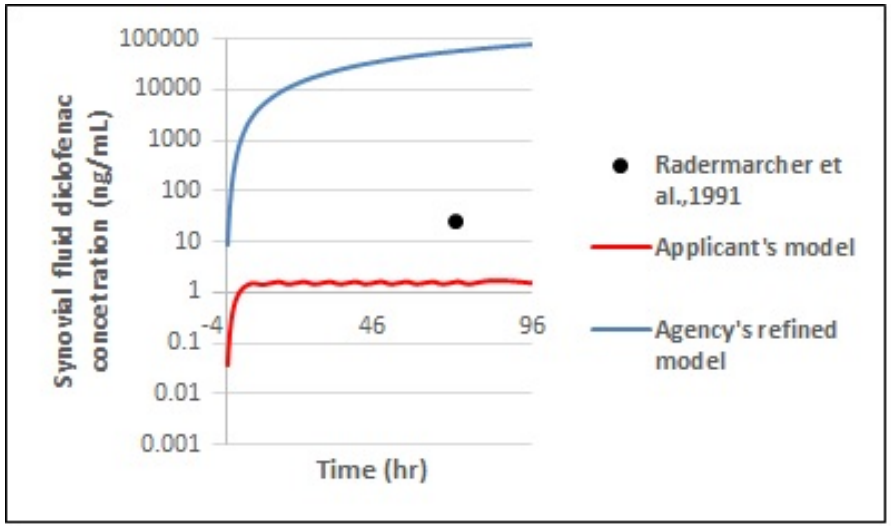
Dermal PBPK model supporting ANDA approval: model refinement



- Model refinement did not improve model predictions in the synovial fluid
  - Protein expression, diclofenac partitioning and diffusion into the synovial fluid, extent of vascularization different than muscle
  - Disease state: data from osteoarthritis patients

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Dermal PBPK model supporting ANDA approval: platform performance assessment

TABLE 3 Overview of the platform performance assessment conducted by the applicant in support of the dermal PBPK model for diclofenac sodium topical gel, 1%, developed in MPML MechDermA within the Simcyp Simulator, version 17

Active ingredient[a]	1	2	3	4	5	6	7	8	9	10	11
Dosage form/products[b]	TDS	TDS	TDS	Solution	TDS	Cream	Gel ointment cream	TDS cream	Gel Solution Nanoparticles TDS	Gel	Solution
Verification matrix	Plasma	Plasma	Plasma	Plasma	Plasma	IVPT	Plasma	Plasma	Plasma Synovial fluid Subcutis Muscle Dermis Stratum corneum	Plasma Synovial fluid	Skin biopsy (stratum corneum, viable epidermis, dermis)
Number of literature sources for validation of the systemic disposition PBPK model	4	1	1	c	1	c	3	c	4	2	c
Number of literature sources for validation of the dermal PBPK model	8	2	1	1	1	1	1/1/1	1/1	6/1/1/1	2	1

Abbreviations: IVPT, in vitro permeation testing; MPML, multi-phase multi-layer; PBPK, physiologically-based pharmacokinetic; TDS, transdermal delivery system.

[a]The selected active ingredients differed in terms of their physicochemical properties (lipophilicity and ionization potential) and pharmacokinetic characteristics (protein binding, extent of distribution in the human body, route of elimination, and blood-to-plasma partitioning among others). More specifically, the molecular weight, logP (lipophilicity), blood to plasma ratio, fraction unbound in plasma, volume of distribution at steady-state and total systemic clearance of the selected active pharmaceutical ingredients ranged from 162 to 468 g/mol, from −1.6 to 6.4, from 0.55 to 1.107, from 0.003 to 0.95, from 0.123 L/Kg to 48.8 L/Kg and from 1.6 L/h to 71.5 L/h, respectively. The selected active ingredients were acids, bases, and ampholytes.

[b]Product-specific dermal PBPK models were developed for each of these dosage forms.

[c]Not provided in the submission or refers to a drug substance that is not given by other than the topical route.

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Dermal PBPK model supporting ANDA approval: platform performance assessment

>10 dermal PBPK models for TDS and topical products

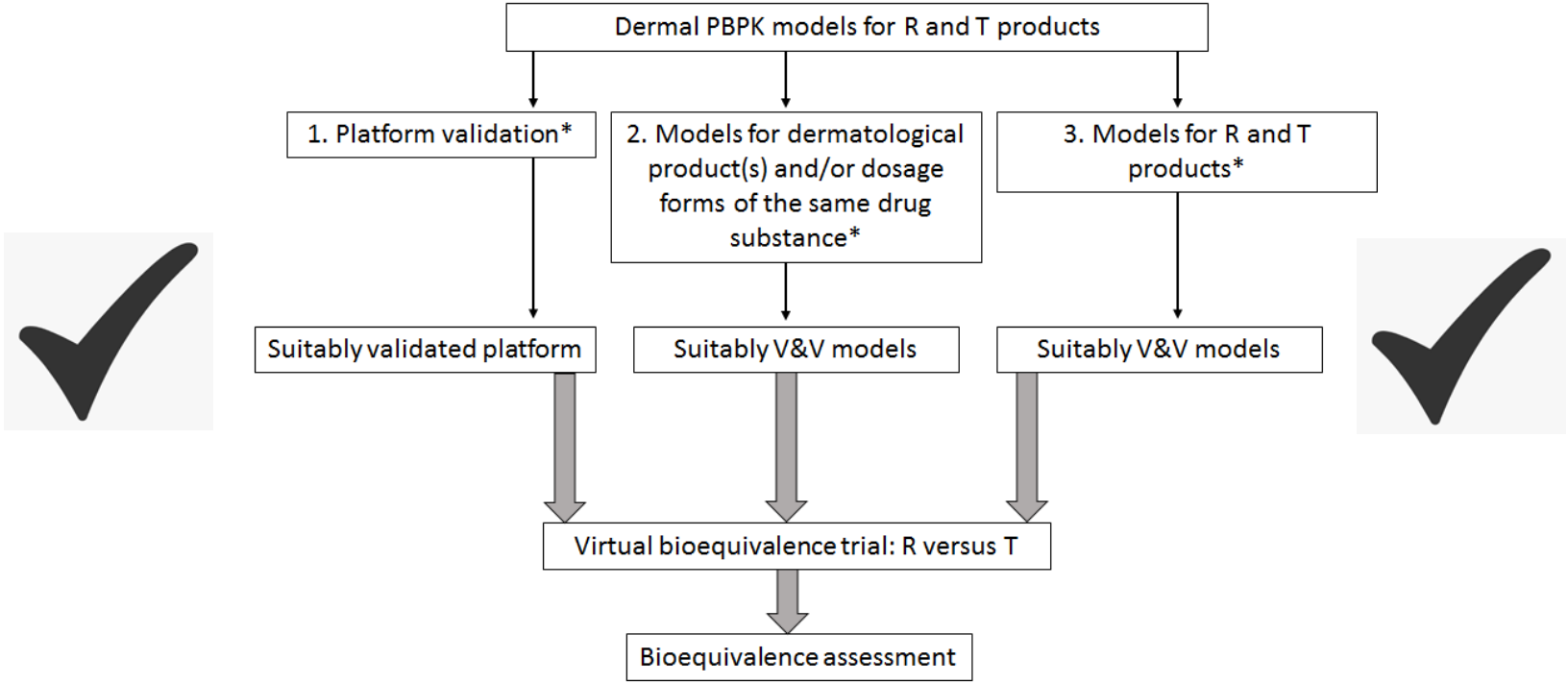
- Multiple doses/product strengths and dosing regiments, age and anatomical locations
- Systemic and local bioavailability (skin biopsy, IVPT, dermal microdialysis) data
- Satisfactory model performance

Suitably validated platform

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

Zhao et al. CPT Pharmacometrics Syst Pharmacol. 2019 Jun;8(6):347-351.
Tsakalozou, E et al. Clin Pharmacol Ther. 2021 Jul 7. doi: 10.1002/cpt.2356.

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.

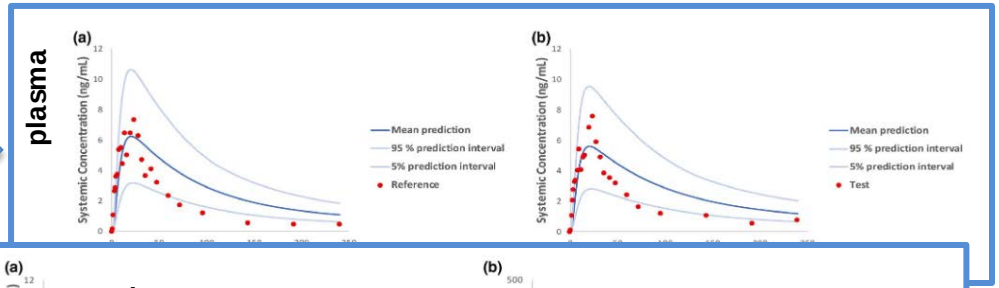
* Simulations in healthy or diseased population, V&V: verification and validation

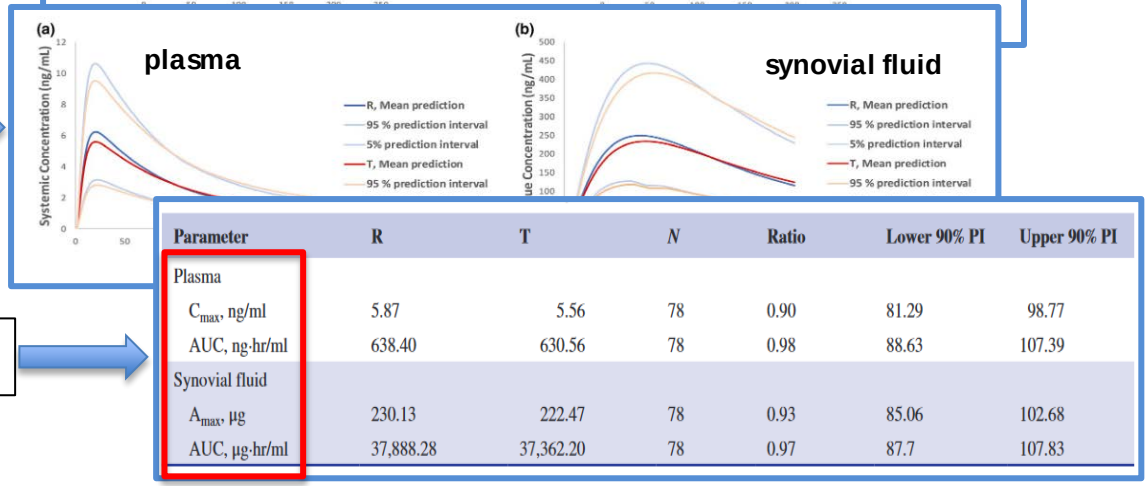
Implemented VBE Workflow

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

VBE: virtual bioequivalence

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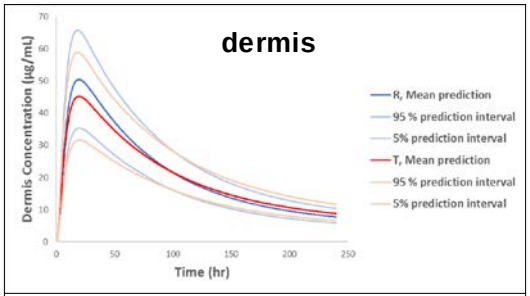
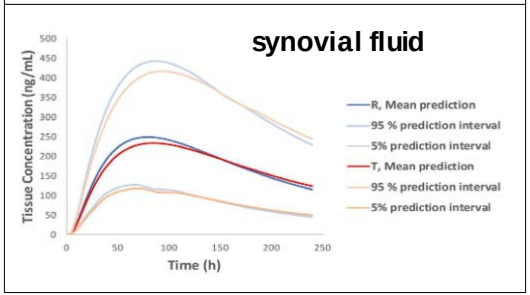
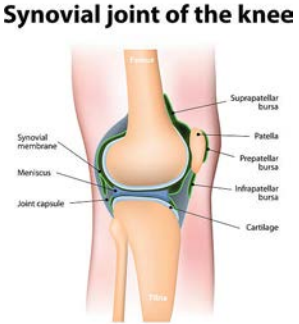
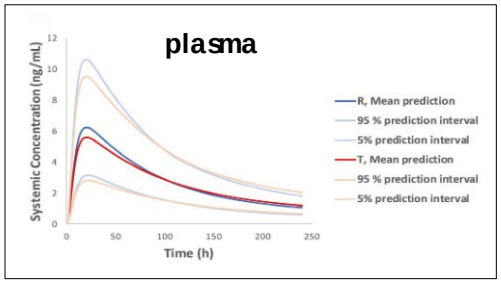
Considerations in implementing a VBE assessment









- 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 metrics 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, Tmax: time at Cmax

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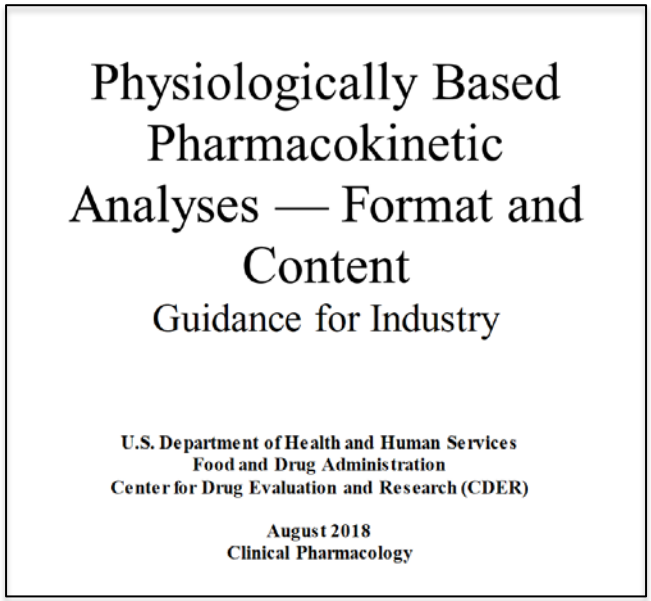
Applicants are encouraged to follow best practices when developing dermal PBPK models for regulatory submissions

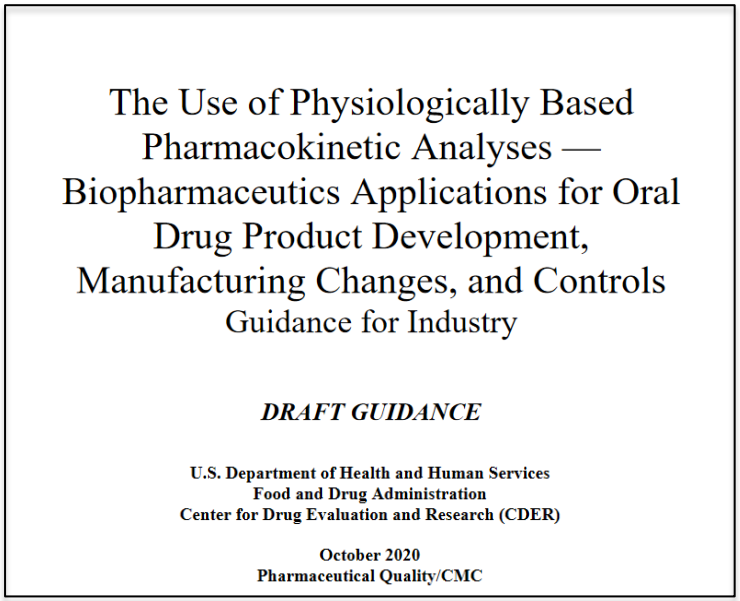


Physiologically Based Pharmacokinetic Analyses — Format and Content

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/regulatory-information/search-fda-guidance-documents

Take home messages - 1

- A dermal PBPK model for diclofenac sodium topical gel, 1% supported the ANDA approval
- The developed model was used to bridge drug product quality attributes with local bioavailability and BE considerations for the test drug product
- A novel V&V was proposed and successfully implemented by the applicant resulting in increased confidence on model predictions
- The dermal PBPK model coupled with a virtual BE assessment component demonstrated that the R and T products were BE in the systemic circulation AND the presumed site of action

Take home messages - 2

- PBPK models for dermatological drug products can be used to support:
  - Development of a drug product prior to approval
  - Alternative BE approaches for product development and regulatory 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 interactions between industry and regulatory agency should be initiated - pre-ANDA meeting program, GDUFA II and controlled correspondence

GDUFA: Generic Drug User Fee Amendments

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
Quantitative Expression and Inter-Individual Variability of Skin Proteins Involved in Drug and Excipient Metabolism and Transporters Using Targeted and Label Free LC MS/MS Proteomics	2021-2023	University of Manchester	1U01FD007348

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