Physiologically-based Pharmacokinetic Modeling for the Development of Dermatological Drug Products and its Regulatory Impact

ASCPT 2019 Pre-Conference:

PBPK Modeling for the Development and Approval of Locally Acting Drug Products

March 13th, 2019

Session 4: Dermal Drug Delivery

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CDER | US FDA

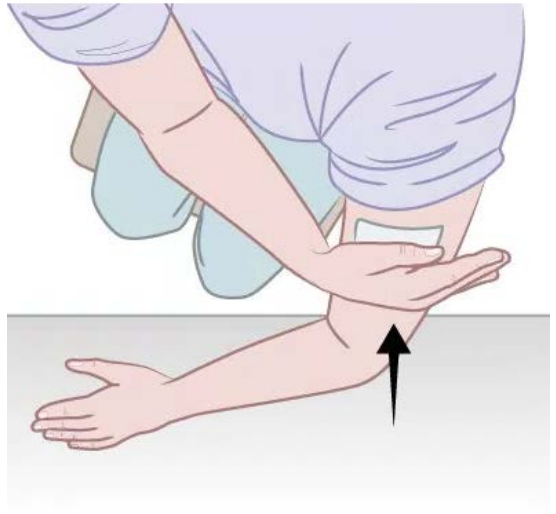
Disclaimer: My remarks today do not necessarily reflect the official views of the FDA

Overview

- Drug development of locally-acting drug products
  - Dermal physiologically-based pharmacokinetic (PBPK) modeling
- Regulatory utility of dermal PBPK modeling
  - Case studies
  - Challenges
- GDUFA-funded research
- Future directions

Dermatological Drug products

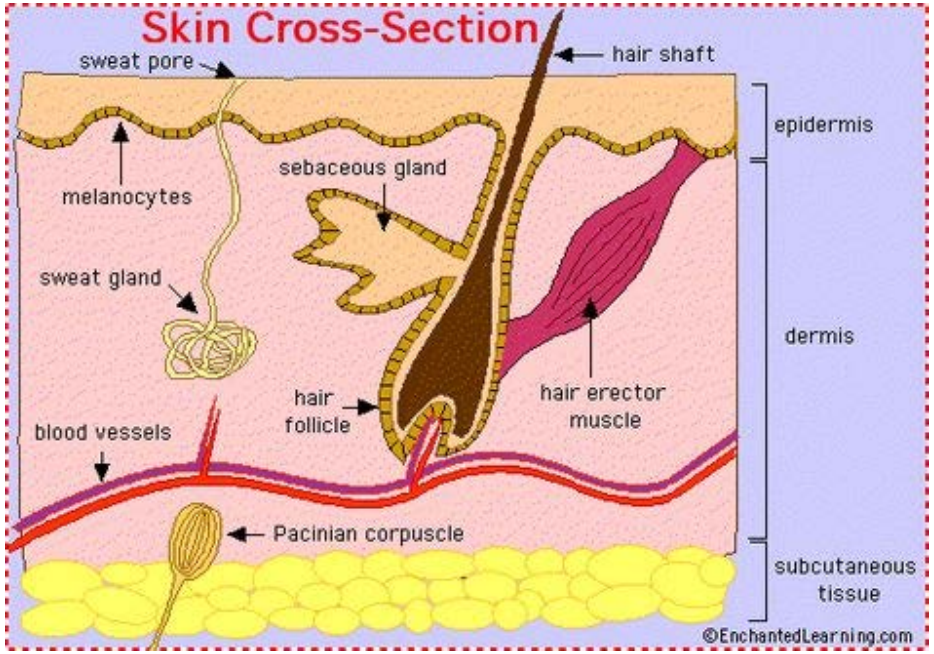
- Transdermal delivery systems (TDS)



- Semisolid Topicals
  - Creams
  - Ointments
  - Lotions
  - Gels

- Solution-based Topicals
  - Solutions
  - Swab
  - Foam aerosols

Modeling Skin Bioavailability …



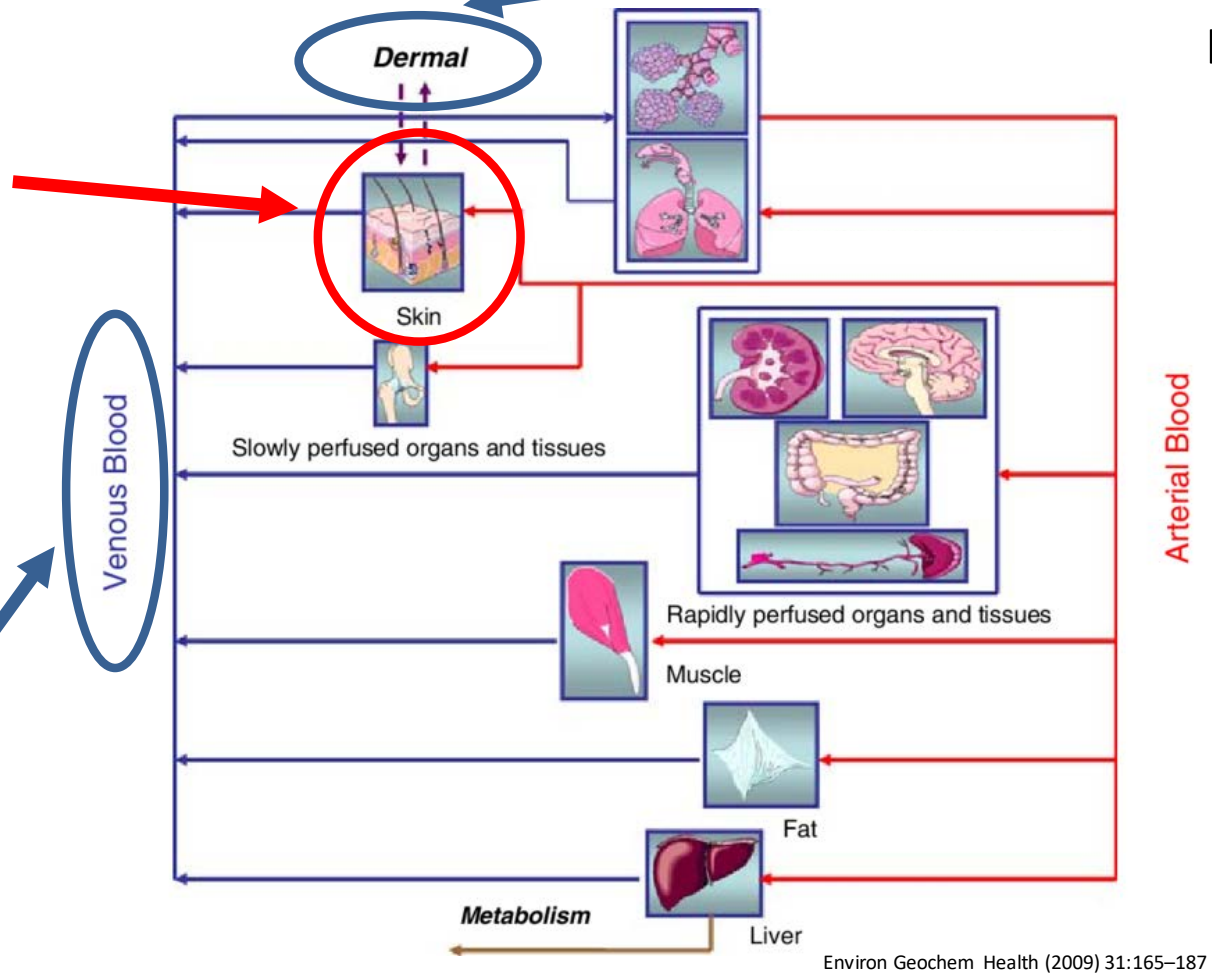
- QSAR models: hydrophobicity, MW, hydrogen bonding
- Mathematical models: diffusion-based or compartmental models
- Computational Fluid Dynamics models: fluid and particle transport based on realistic geometries
- Mechanistic PBPK models: API, formulation and human/animal physiology (variability and population)

EnvToxicol In Vitro. 2002 Jun;16(3):299-317.
Melanoma Res. 2001 Aug;11(4):423-31.
https://training.seer.cancer.gov/melanoma/anatomy/
https://openi.nlm.nih.gov/detailedresult.php?img=PMC126244_1472-6904-2-5-1&req=4

Dermal PBPK Modeling Relates What we Want to Know to What we can Measure

What we can measure:
-Formulation in vitro performance

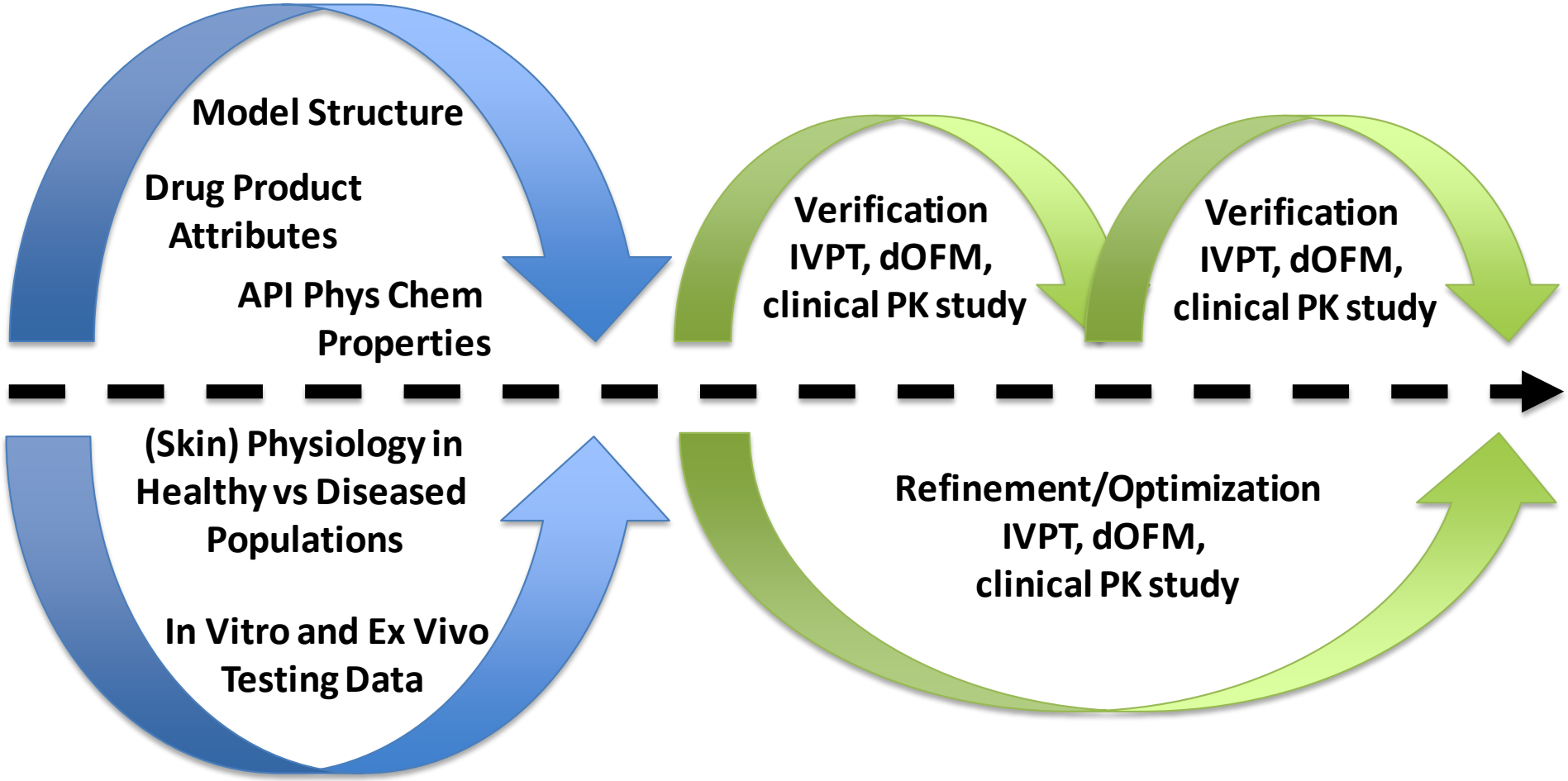
What we would like to know:
-local drug concentrations



What we can measure:
-Systemic drug exposure

Environ Geochem Health (2009) 31:165–187

Dermal PBPK Model Development Process



IVPT: In Vitro Permeation Testing, dOFM: dermal open-flow microperfusion, PK: Pharmacokinetic

Regulatory Utility of Dermal PBPK Models

Model-integrated evidence for generic drug development and approval

- Support alternative bioequivalence (BE) approaches
  - Comparative clinical endpoint BE studies not sensitive to formulation differences
  - In vitro testing for Q1/Q2 same formulations
- Define a safe space for critical attributes
- Extrapolate BA predictions and BE assessments from healthy to diseased populations

Conduct virtual BE studies

Product-specific guidance (PSG) development

Zhao et al., Clin Pharmacol Ther. 2018 Nov 10 doi: 10.1002/cpt.1282

Regulatory Utility of Dermal PBPK Models today's discussion

- Office of Generic Drugs → Alternative BE approaches proposed by applicants
- FDA Internal Research → Design a safe space for formulation attributes based on BE assessments
  - Case Study 1: Nicotine, TDS
  - Case Study 2: Lidocaine, topical cream
- GDUFA-funded Research → Predict BA and perform BE assessments in diseased populations

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Dermal PBPK Modeling to Support Alternative BE Approaches

- Pre-ANDA meeting requests/ANDAs on dermatological drug products (yrs 2017-2018)
- PSG recommendations include in vivo BE studies

  Applicants' proposals:

  Dermal PBPK modeling in support of not conducting in vivo BE studies (comparative clinical endpoint or pharmacokinetic endpoint studies)

  - Q1/Q2 same and Q3 similar drug products, IVRT and/or IVPT
  - Suitably verified dermal PBPK model to predict local and systemic drug amounts
  - Virtual bioequivalence study and bioequivalence assessment

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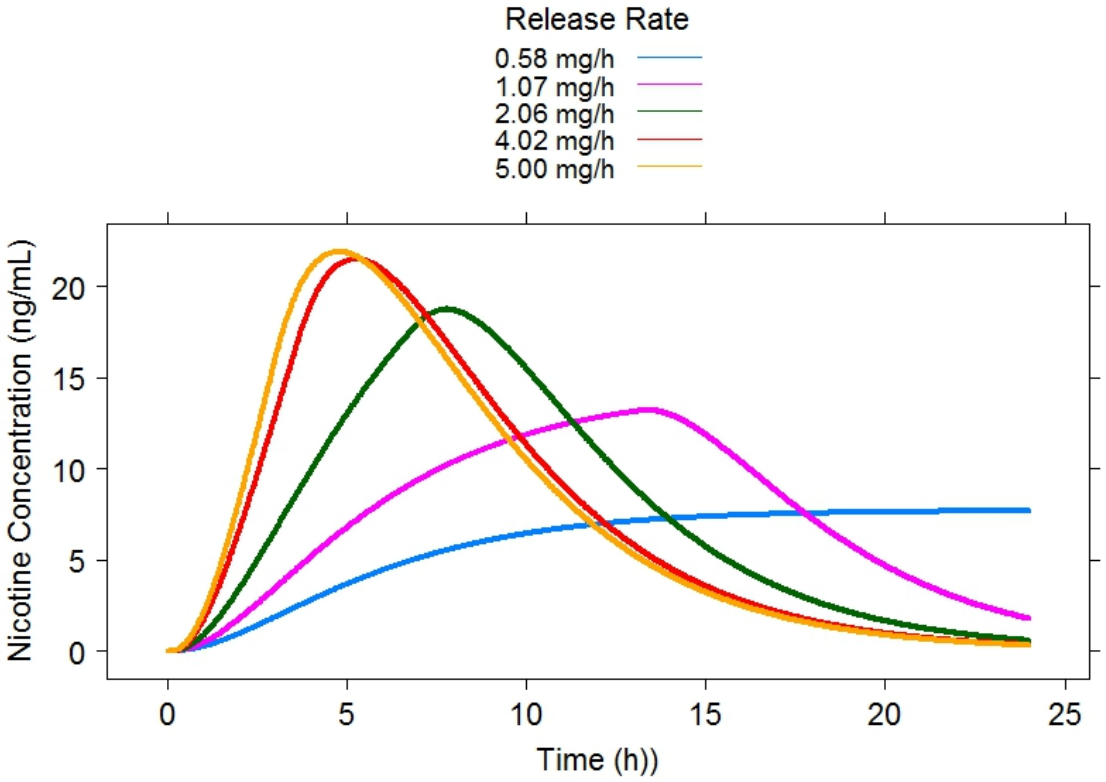
Predict Systemic Bioavailability Based on the Release Rate for a Nicotine TDS

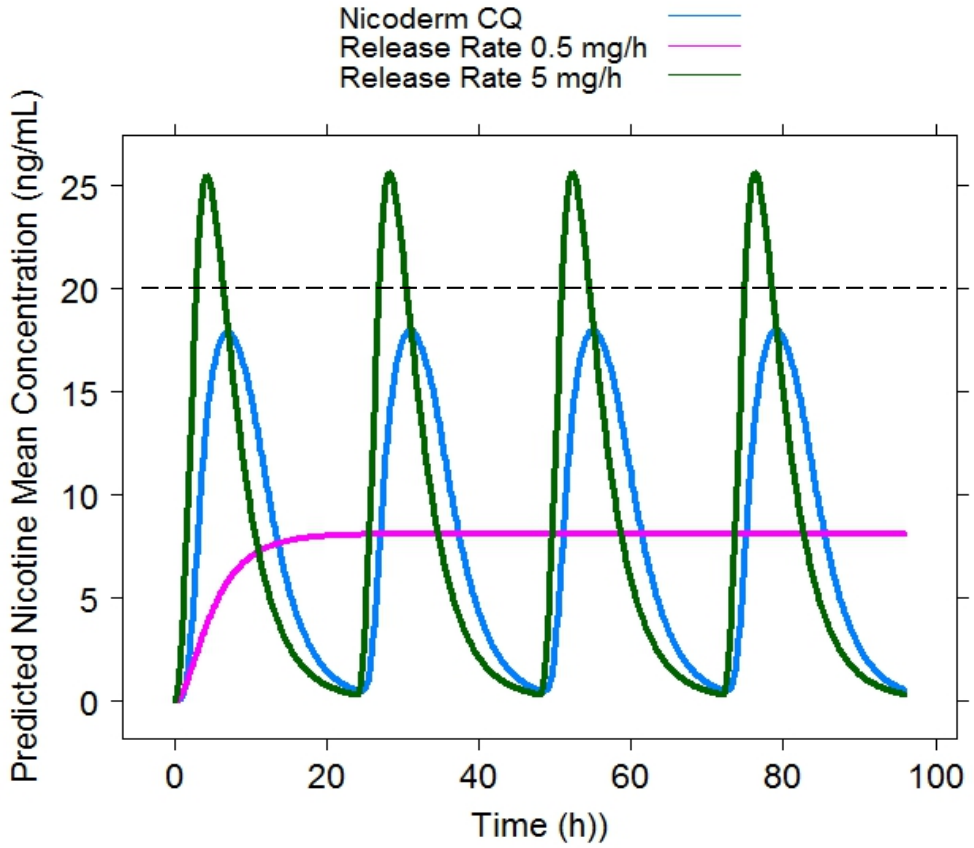
- Nicoderm CQ®, Nicotine TDS, 21 mg/24 hours, extended release patch
- Simcyp Simulator (v17), MPML MechDermA Model
- Nicotine: monoprotic base, minimal PBPK model[1]
- Default skin absorption parameters
- Formulation attributes
  - Dermal patch, controlled release profile from IVPT data[2] or zero order release rate[3]
- Model verification
  - Systemic exposure[2,3]

[1]Svensson. Clin Pharmacokinetics. 1987, 12: 30-40
[2]Shin et al., 2015 AAPS Annual Meeting and Exposition, Orlando, FL.
[3]Benowitz et al., Clin Pharmacol Ther. 1991 Sep;50(3):286-93

Transdermal Patch Development Leveraging the Nicotine Dermal PBPK Model

Patch release rate impacts systemic exposure





Smoking[1,2]

Formulation selection based on simulated single dose and steady state scenarios

www.fda.gov

[1] Benowitz et al., Handb Exp Pharmacol. 2009;(192):29-60, [2] Jiloha. Indian J Psychiatry. 2014 Jan;56(1):87-95

Predict Systemic and Skin Bioavailability Based on Formulation Attributes for a Lidocaine Cream

- EMLA® Cream (lidocaine 2.5 %/prilocaine 2.5 %)
- Simcyp v17 Simulator, MPML MechDermA Model
- Lidocaine: monoprotic base, minimal PBPK model[1]
- Skin absorption parameters modified based on systemic exposure data[2]
- Formulation attributes[3]
  - Emulsion
  - Vehicle evaporation
- Model verification
  - Systemic exposure data[2]
  - Dermal open-flow microperfusion (dOFM) data[4]

[1] Benowitz et al.. Clin Pharmacokinetics. 1978, May-Jun;3(3):177-201
[2] EMLA® CREAM, label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/019941s021lbl.pdf
[3] Rangappa et al., 2018 AAPS Annual Meeting and Exposition, Washington, D.C.
[4] Tiffner et al., 2018 AAPS Annual Meeting and Exposition, Washington, D.C.

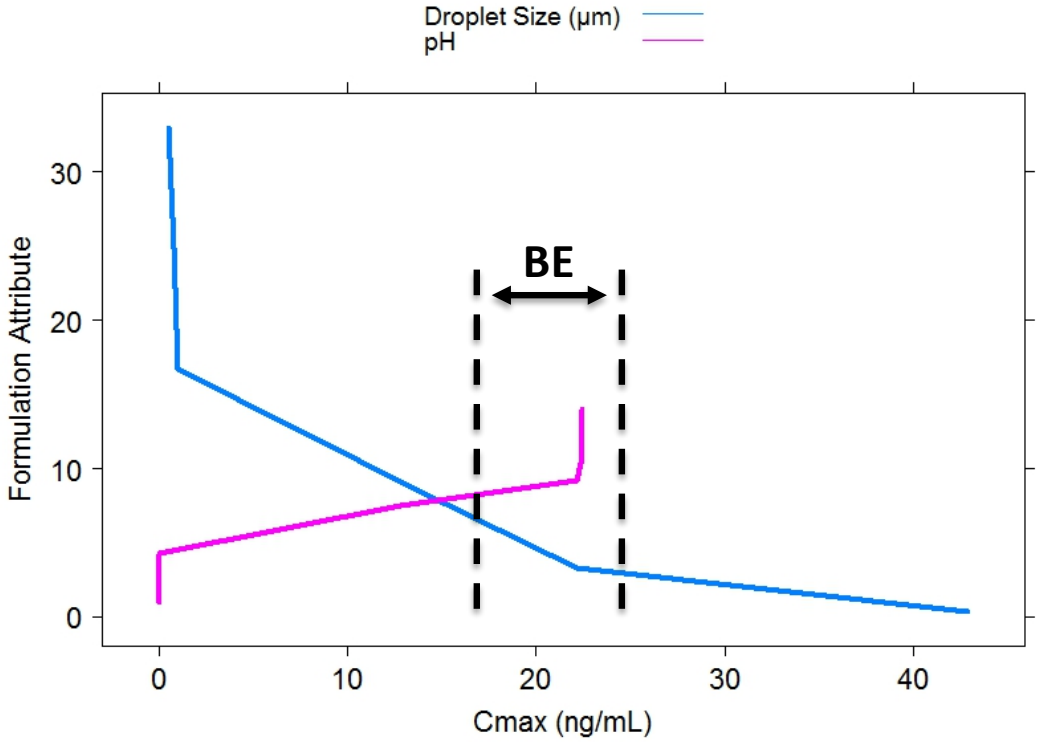
Identify Formulation Attributes Impacting Systemic and Local Lidocaine Exposure

Parameter sensitivity analysis using the lidocaine dermal PBPK model

- Formulation pH → systemic + dermis exposure
- Evaporation rate ✗
- Droplet size → systemic + dermis exposure
- Droplet number ✗
- Viscosity ✗
- Solubility ratio (dispersed/continuous phase) → dermis exposure

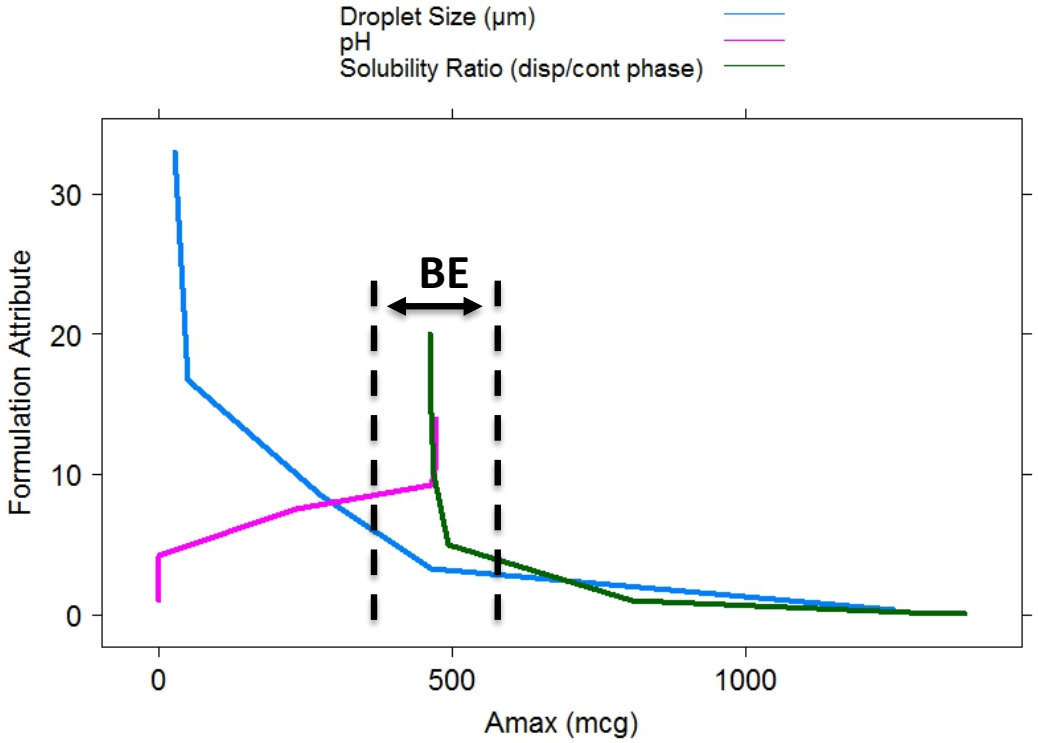
Define Safe Space Criteria for Formulation Attributes Leveraging the Lidocaine Dermal PBPK Model

Systemic Exposure



Dermatological Products with:
Therapeutic effect involves partitioning into the blood
Safety concerns

Skin Bioavailability



Dermatological Products with:
Therapeutic effect related to local exposure

Regulatory Utility of Dermal PBPK Models today's discussion

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Predict Caffeine Skin Bioavailability in Psoriatic Patients

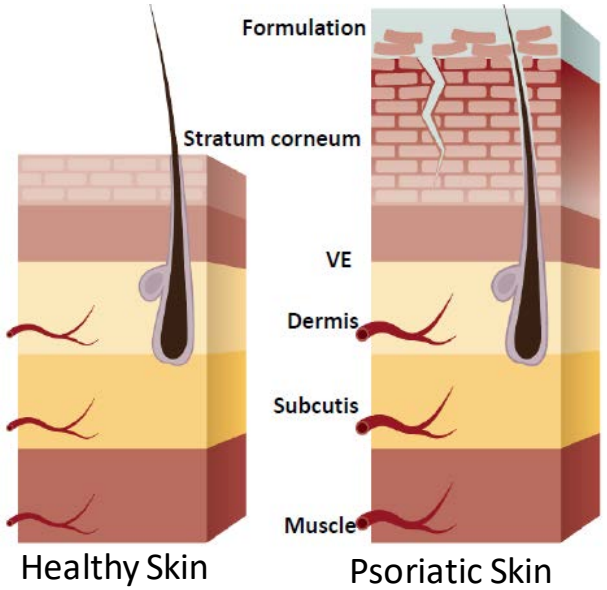
Perspectives in Percutaneous Penetration 2018, 12th International Conference, La Grande Motte, France

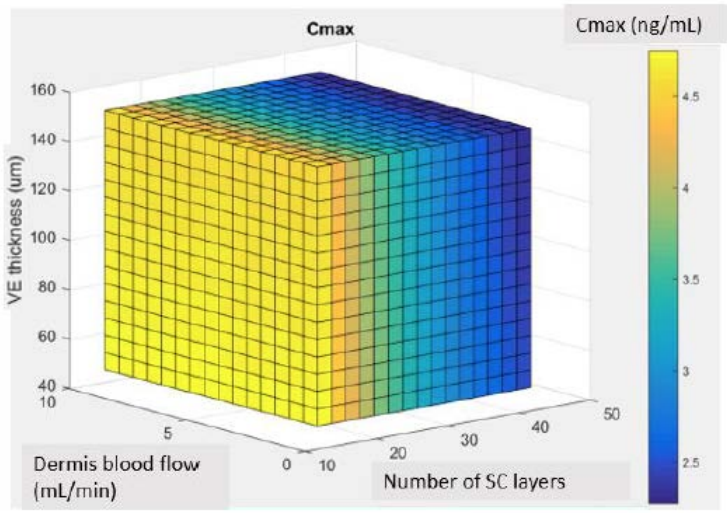
Mechanistic Physiologically-Based Pharmacokinetic Modelling for Prediction of Dermal Absorption in Psoriatic Patients

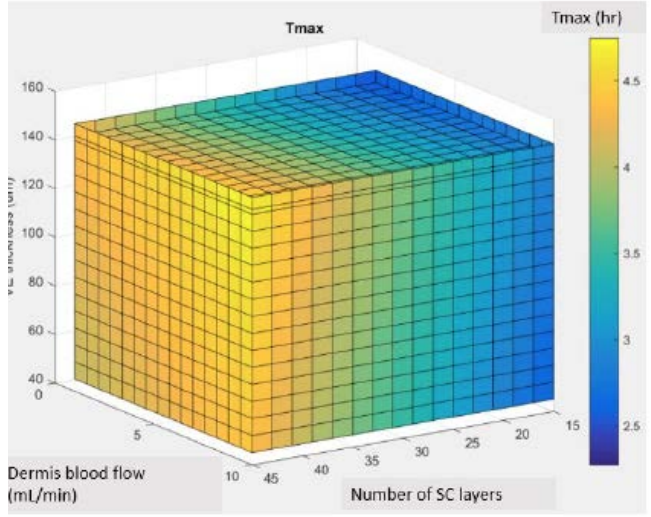
CERTARA Simcyp

F MARTINS[1], N PATEL[1], M. JAMEI[1] and S POLAK[1,2]
[1]Simcyp Limited, UK; [2]Faculty of Pharmacy, Jagiellonian University Medical College, Poland

- Simcyp v17 Simulator, Psoriasis Dermal population
- Caffeine, solution gel







- Number of cracks, skin pH and SC hydration affect percutaneous absorption
- Performance verification

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Dermal PBPK modeling: Challenges

- Assessing model performance
  - Data availability: preclinical species, verification/qualification
  - Verification standards
- Proper documentation for model building and model performance
  - Model assumptions and limitations
  - Parameter optimization/sensitivity analyses
  - Verification and qualification outcomes
- Virtual bioequivalence studies
  - Drug product attributes, API characteristics and species physiology, intra- and inter-subject variability

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

Towards Developing Reliable Dermal PBPK Models For Regulatory Decision-making …

Dermal PBPK modeling is a powerful approach that can be used to

- Explore relationships between systemic and local drug exposure
- Support alternative BE approaches
- Define a safe space for formulation attributes
- Extrapolate BA predictions/BE assessments from healthy to diseased populations
- Conduct virtual BE studies
- PSG development

Acknowledgments

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Priyanka Ghosh

Tannaz Ramezanli

OGD/ORS-IO

Lei K. Zhang

Robert Lionberger

OTS/OCP

Xinyuan Zhang

Grantees

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Simcyp Ltd, Grant #: 1U01FD005225, 1U01FD006521

University of Queensland, Grant # 1U01FD006522

SimulationsPlus, Inc, Grant # 1U01FD006526

Children's Hospital of Los Angeles, Grant # 1U01FD006549

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Towards developing reliable dermal PBPK models…

Moving forward it is **important to engage all stakeholders** to

- improve software tools that adequately describe formulation and drug substance properties and skin physiology/disease states
- leverage data on local drug concentrations to develop and qualify dermal PBPK models that capture inter- and intra-subject variability
  - literature sources
  - FDA-funded research sources

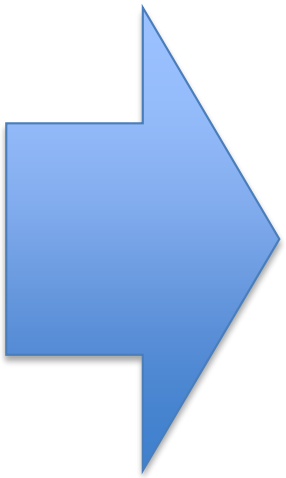
GDUFA-funded research is set to close knowledge gaps

Local drug concentrations
dOFM, skin stripping, dermal microdialysis
In vitro permeation testing

Formulation
Product quality attributes of semisolid dosage forms

API
Variety of physicochemical properties and pharmacokinetics

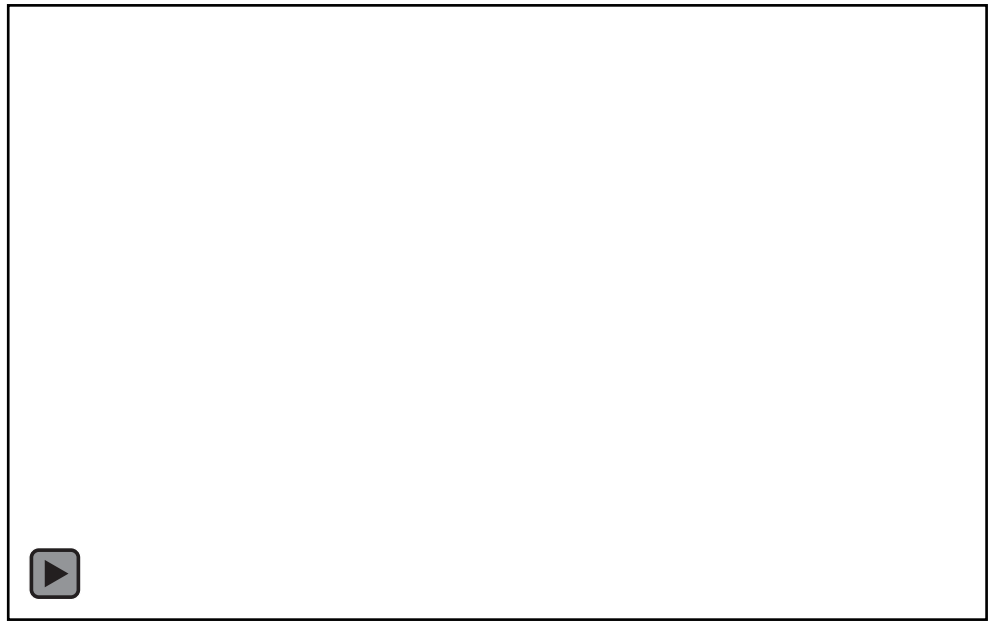
Systemic drug exposure
Individual drug concentration-time profiles



Increase model predictability in regards to local drug concentrations

In vitro-in vivo correlations to predict local drug concentrations based on key formulation characteristics

Efinaconazole topical solution

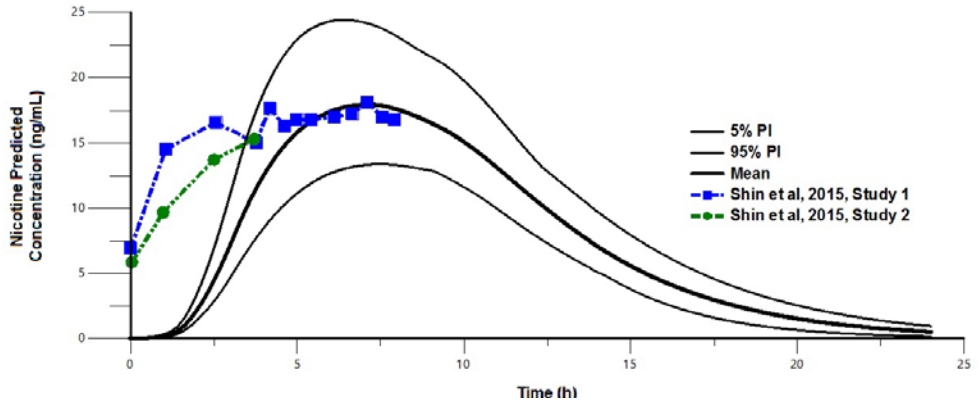


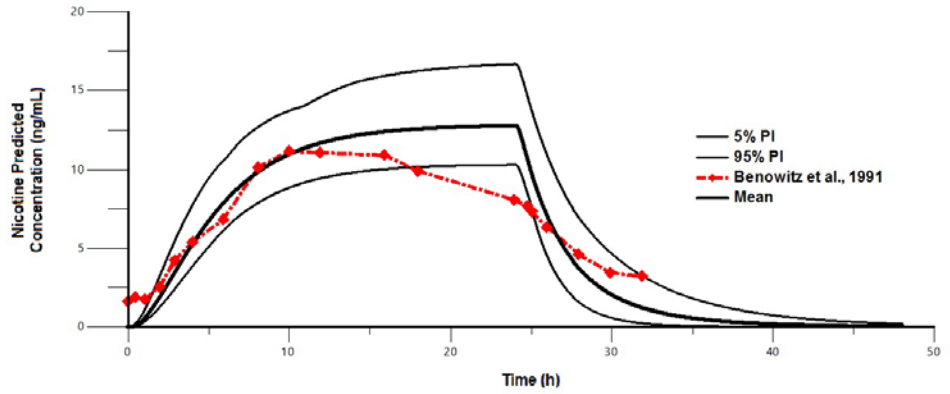
Spreadability of brand name product
viscosity and surface tension

- Indicated for toenail fungal infections
- Computational fluid dynamics (CFD)
- Spreadability, penetrability, absorption of non-Q1/Q2 formulations

Prediction of Systemic Bioavailability Based on Nicoderm CQ patch Release Rate

- Nicoderm CQ®, Nicotine Transdermal System 21 mg Delivered over 24 hours, extended release patch
- Simcyp Simulator (V17), MPML MechDermA Model
- Nicotine: monoprotic base, minimal PBPK model: Vd=3 L/Kg, CL=72 L/h
- Default skin absorption parameters
- Formulation attributes: Dermal patch, Controlled release profile from IVPT data (Shin et al., 2015) or zero order release rate (Benowitz et al., 1991)



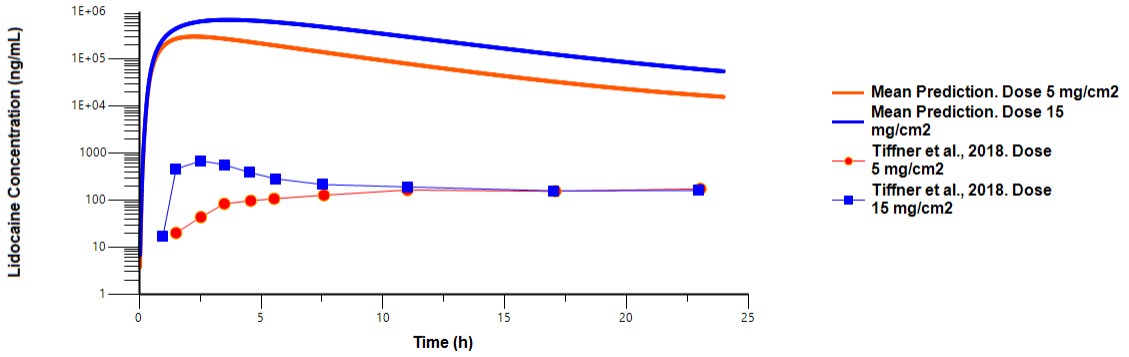


Model Verification

Prediction of Systemic and Skin Bioavailability Based on EMLA® Cream Formulation Attributes

EMLA® Cream (lidocaine 2.5 %/prilocaine 2.5 %)
Simcyp Simulator (V17), MPML MechDermA Model
Lidocaine: monoprotic base, minimal PBPK model: Vd=1.5 L/Kg, CL=60 L/h
Skin absorption parameters were modified based on systemic exposure data[1]
Formulation attributes: emulsion, vehicle evaporation was assumed (Rangapa et al., 2018, AAPS) for verification of the dOFM data (Tiffner et al., 2018, AAPS)

EMLA, package insert		Predicted		Ratio	
Cmax (µg/mL)	Tmax (h)	Cmax (µg/mL)	Tmax (h)	Cmax	Tmax
280	10	317	8.62	1.13	0.86



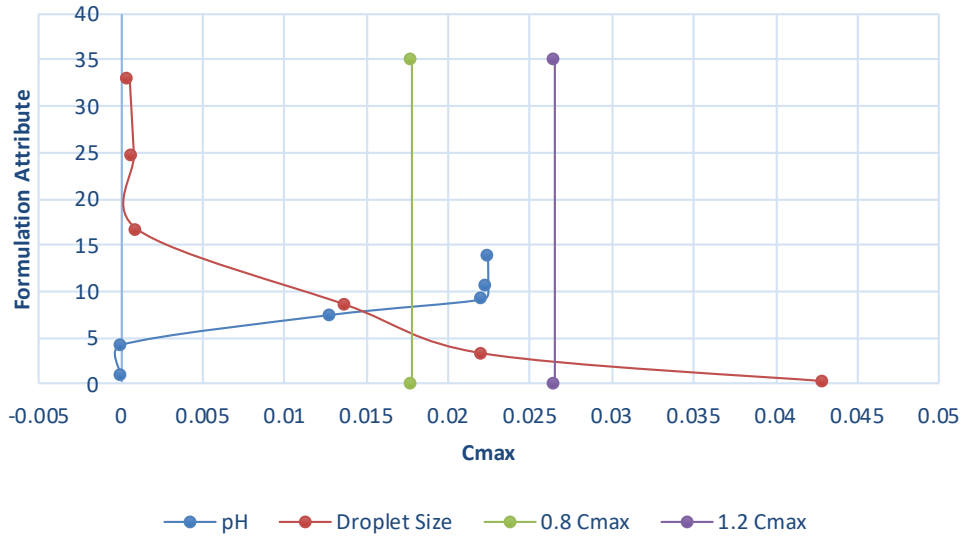
	Ratio	
	Cmax	Tmax
5 mg/cm2 dose	1719	0.10
15 mg/cm2 dose	988	1.44

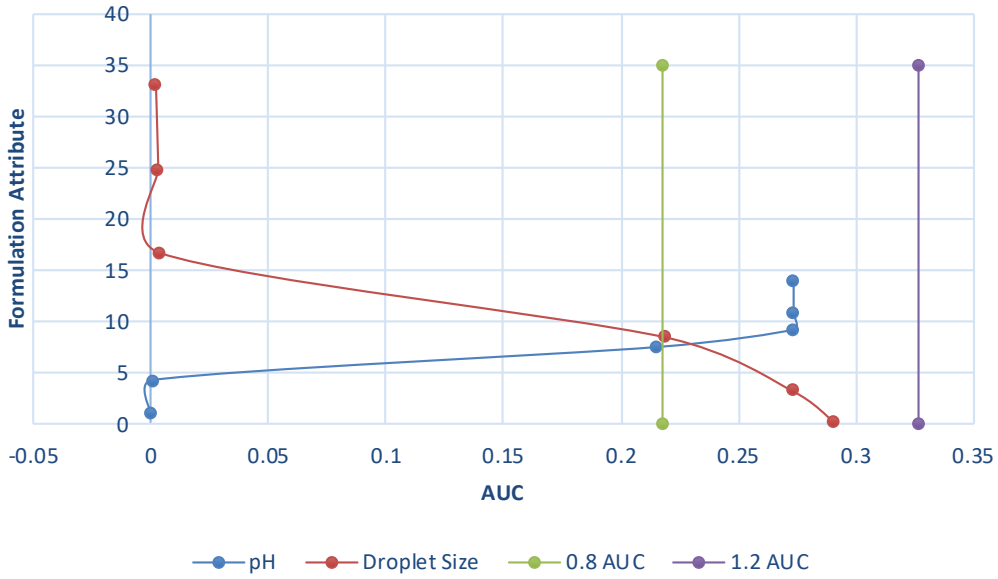
Model Verification

[1] Drug label

Define a Safe Space Criteria for Formulation Characteristics Based on Bioequivalence Assessment

Systemic Exposure



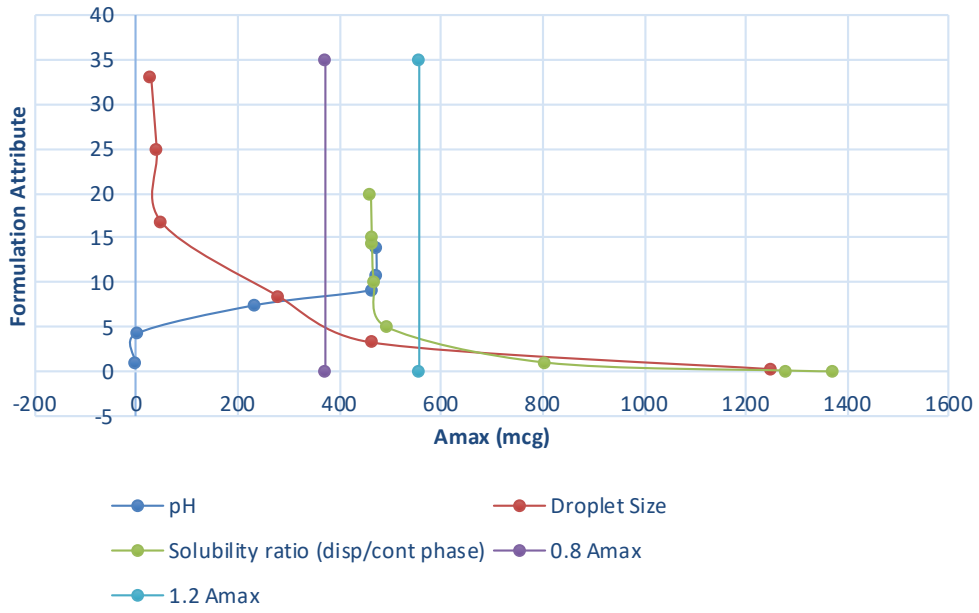


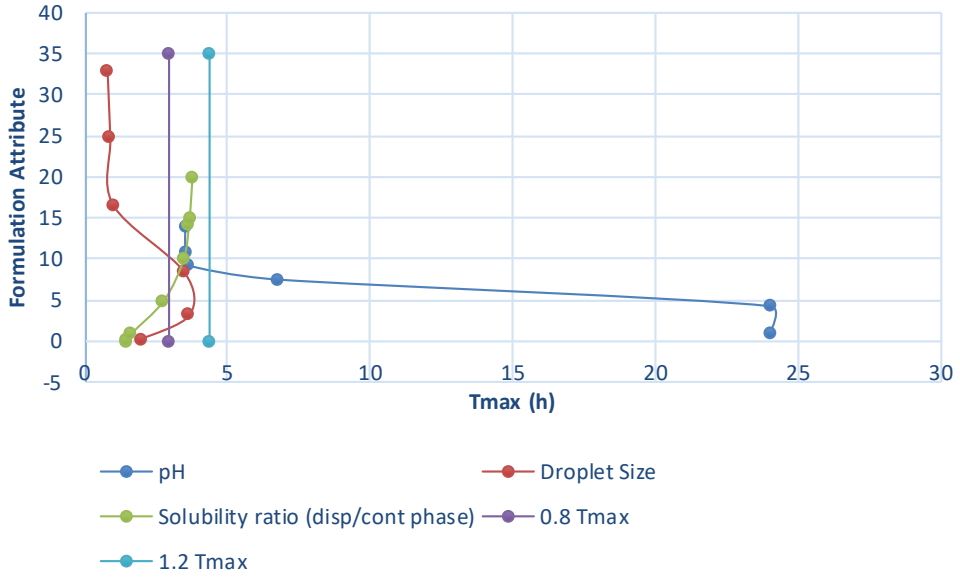
Dermatological Products with:

- ✓ Safety concerns
- ✓ Therapeutic effect involves partitioning into the blood

Define a Safe Space Criteria for Formulation Characteristics Based on Bioequivalence Assessment

Skin Bioavailability





Dermatological Products that:

- ✓ Act locally on the skin
- ✓ Therapeutic effect related to local exposure