Physiologically-based pharmacokinetic modeling and simulation used in assessing bioequivalence for generic dermatological products

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Overview

- Bioequivalence of locally-acting drug products
- Dermal physiologically-based pharmacokinetic (PBPK) modeling
  - Regulatory utility and challenges
  - Modeling strategies and approaches
  - Model performance evaluation
  - Virtual bioequivalence studies
- GDUFA-funded research
- Future directions

Regulatory utility of dermal PBPK models

Utilize dermal PBPK modeling in:

- Product-specific guidance development
- Generic drug approval
  - Support alternative approaches for demonstrating bioequivalence (BE)
    - Comparative clinical endpoint BE studies may not be sensitive to formulation differences
    - In vitro testing for BE assessment for Q1/Q2 formulations
  - Define a safe space for critical attributes of dermatological products
    - Risk assessments on the impact of critical quality product attributes on in vivo drug product performance
  - Extrapolate BE assessments from healthy to diseased subpopulations

Challenges of dermal PBPK models for regulatory decision making

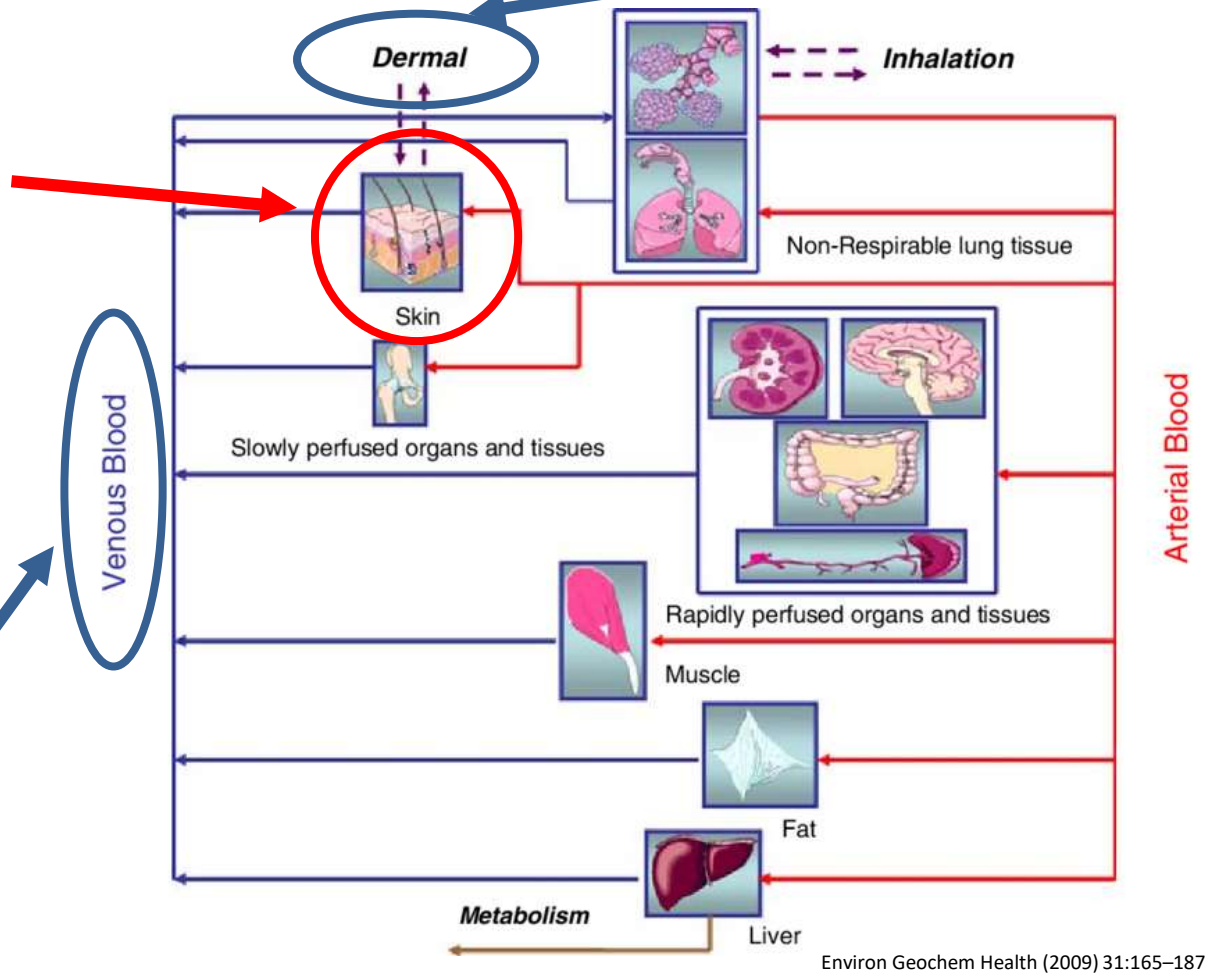
- Verify dermal PBPK models via observed skin and systemic concentrations
  - Not feasible or ethical to determine local concentrations
  - No correlation noted in multiple cases
- Develop and refine quantitative modeling tools to describe formulation attributes, active ingredient properties and skin states
  - Knowledge gaps exist
- Verify dermal PBPK models that capture inter- and intra-subject variability
  - Leverage data on local concentrations from research sources

Dermal PBPK modeling relates what we want to know to what we can measure

What we can measure:
-Formulation in vitro performance

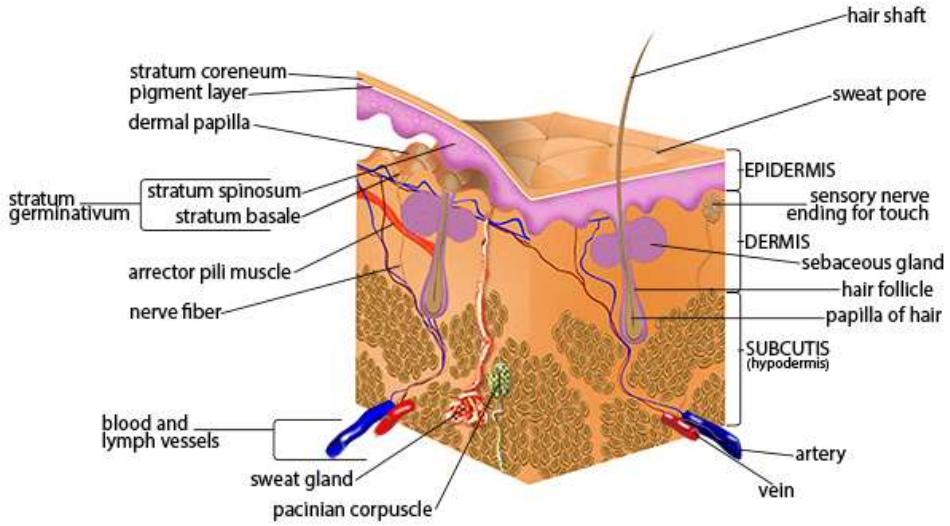
What we would like to know:
-local drug concentrations

What we can measure:
-Systemic drug exposure

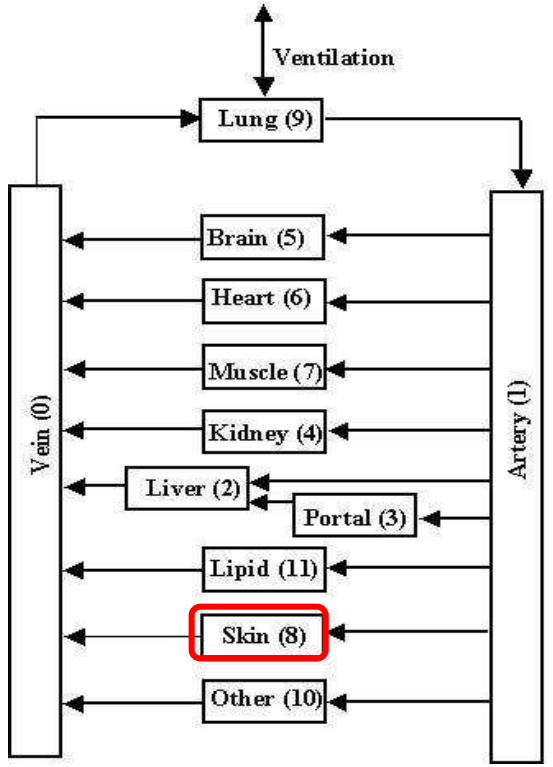


Environ Geochem Health (2009) 31:165–187

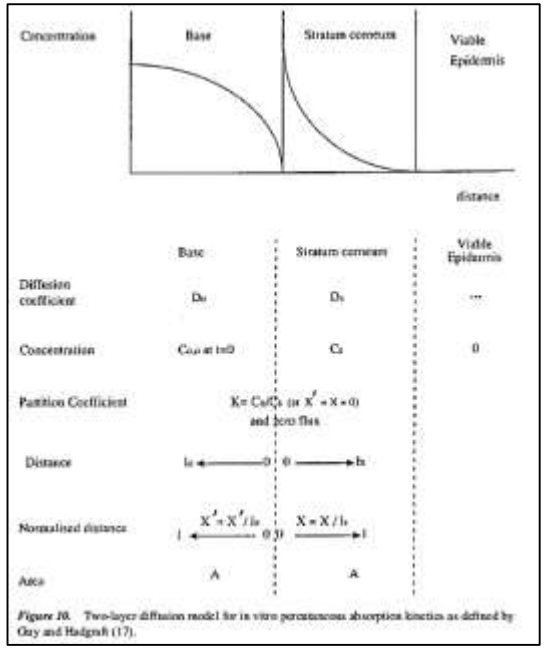
Modeling skin bioavailability…



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



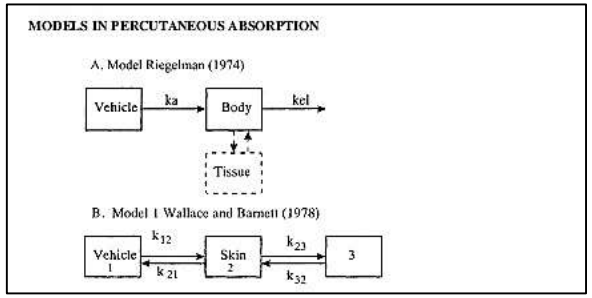
Mathematical models:
diffusion-based or compartmental models



QSAR models:
hydrophobicity, MW, hydrogen bonding

$$\text{Log } K_p = -0.626\ \Sigma Ca - 23.8\ \Sigma(Q+)/\alpha - 0.289\ SsssCH - 0.0357\ SsOH - 0.482\ I_B + 0.405\ B_R + 0.834 \quad (8)$$

$n = 91 \quad r^2 = 0.832 \quad s = 0.563 \quad F = 69.2$



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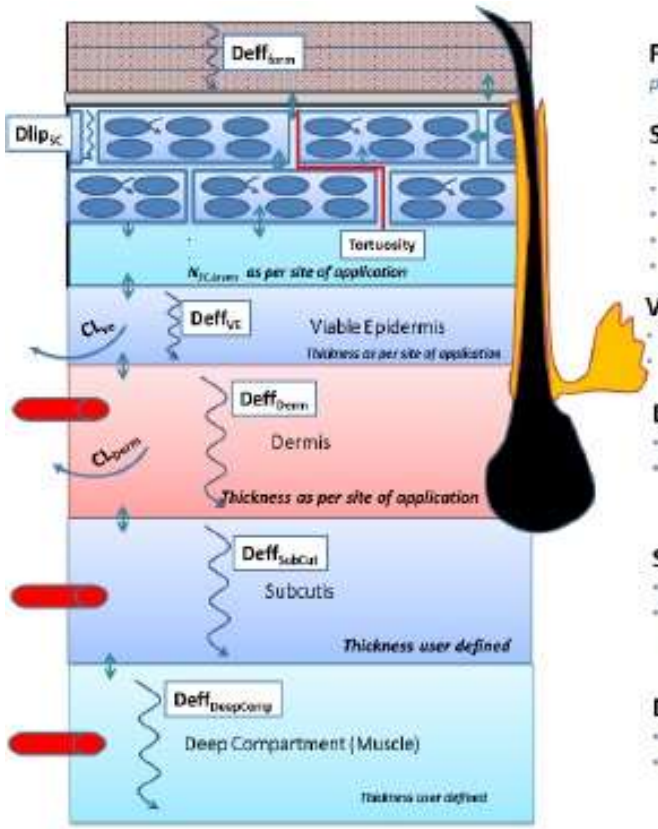
Melanoma Res. 2001 Aug;11(4):423-31.
https://training.seer.cancer.gov/melanoma/anatomy/
https://openi.nlm.nih.gov/detailedresult.php?img=PMC126244_1472-6904-2-5-1&req=4

Dermal PBPK modeling: a case study

Multi-phase Multi-layer MechDermA model: Development, verification and application of a PBPK-PD model of dermal absorption for transdermal product assessment

CERTARA Simcyp

Frederico Martins[1], Nikunjkumar Patel[1], Farzaneh Salem[1], Masoud Jamei[1], Sebastian Polak[1,2]
[1]Simcyp (a Certara company), Sheffield, United Kingdom, [2]Jagiellonian University Medical College, Kraków, Poland



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

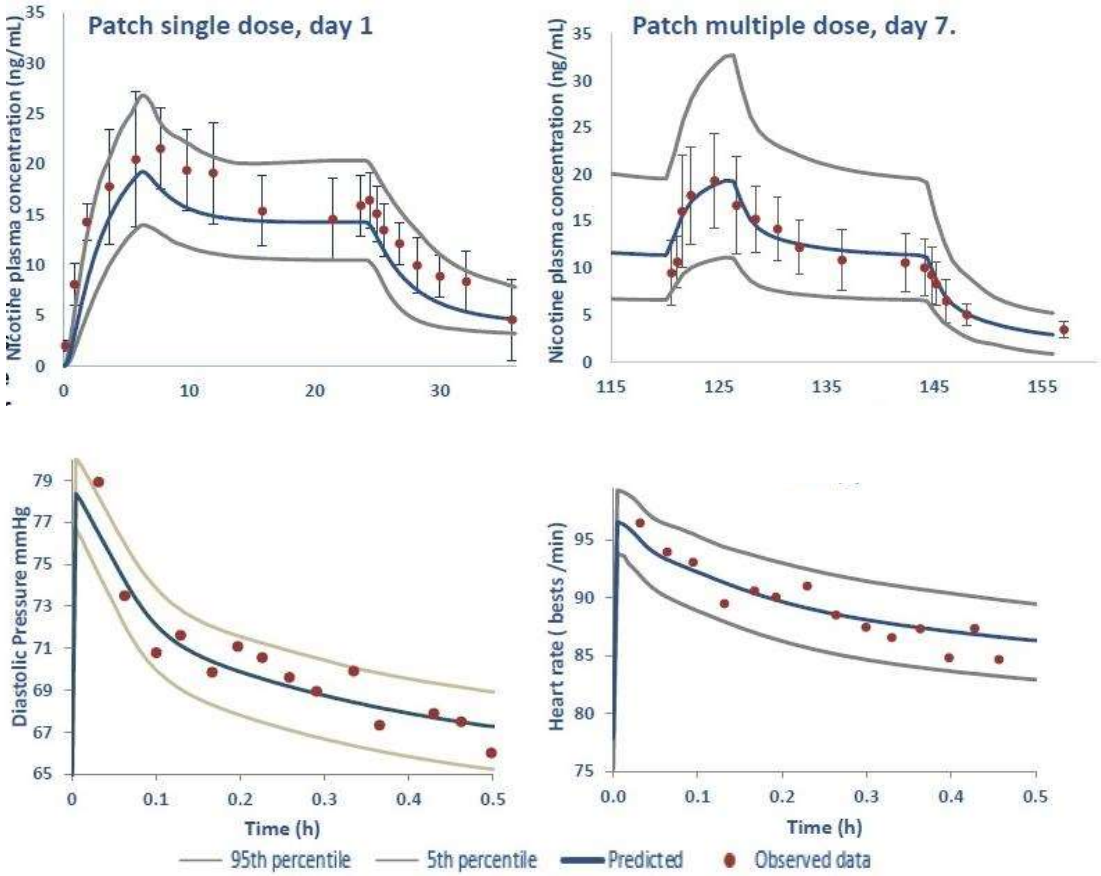
Stratum Corneum (SC)
- *Define cell shape and size*
- *Cell membrane permeability*
- *Keratin bonding kinetics*
- *Tortuosity and diffusivity*
- *Hair follicle density and size*

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

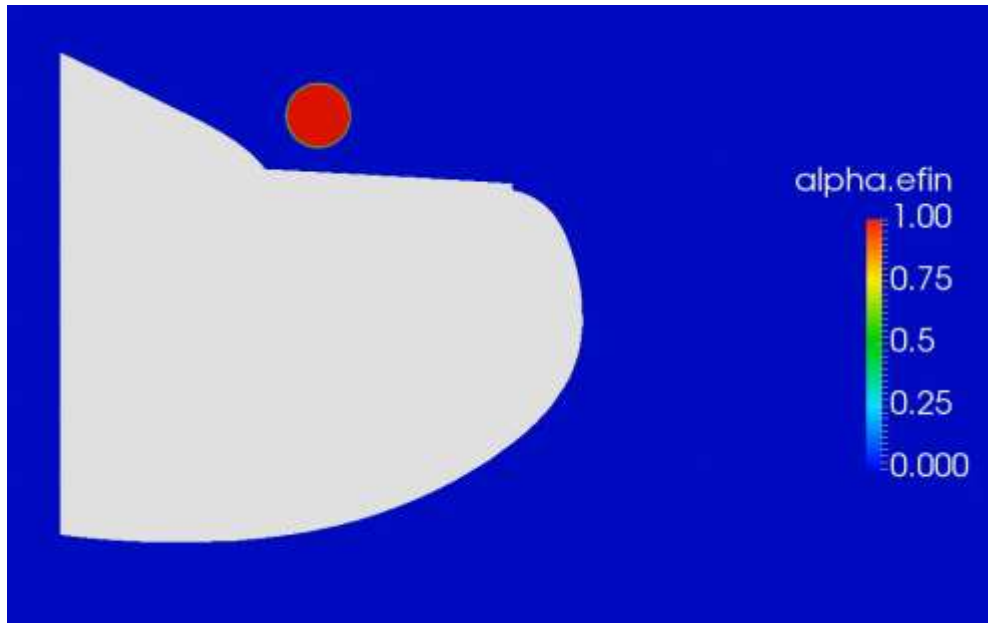
Dermis
- *Thickness, diffusivity*
- *Metabolism, blood flow*

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

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



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

Dermal PBPK modeling and virtual bioequivalence studies: challenges

- ❑ Satisfactory model performance
  - Agreement between observed and predicted data

- ❑ Proper documentation of the model building and qualification process
  - Model assumptions and limitations
  - Parameter optimization/refinement
  - Sensitivity analysis, verification and qualification outcomes

- ❑ Virtual bioequivalence studies
  - Formulation critical quality attributes, API characteristics and skin physiology captured
  - Intra- and inter-subject variability captured in the model
    - Directly related to reliable predictions and prediction intervals
    - Essential in establishing BE criteria for dermal products

Ultimate goal:

Development of a Universal Model for Dermatological Products that requires minimal verification

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM531207.pdf

Generic Drug User Fee Amendments: Regulatory Science/Research

Awarded in 2014:

- Physiologically based biopharmaceutics and pharmacokinetics of drug products for dermal absorption in humans, University of South Australia
  - Site PI: Michael Roberts, Grant #: 1U01FD005232-01
- Development and validation of dermal PBPK modelling platform towards virtual bioequivalence assessment considering population variability, Simcyp Ltd
  - Site PI: Sebastian Polak, Grant #: 1U01FD005225-01

Awarded in 2018:

- RFA-FD-18-017: Characterize skin physiology parameters utilized in dermal physiologically-based pharmacokinetic model development across different skin disease states.
- RFA-FD-18-019: Formulation drug product quality attributes in dermal physiologically-based pharmacokinetic models for topical dermatological drug products and transdermal delivery systems.

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

Towards developing reliable dermal PBPK models…

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

- explore relationships between systemic and local drug exposure
- predict in vivo performance of dermatological drug products when only product critical quality attributes are available
- conduct risk assessment on the impact of product critical quality attributes on the in vivo drug product performance of reference and test drug products

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

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www.fda.gov/GDUFARegScience


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