Challenges and Considerations with Model-based Virtual Bioequivalence Assessments for Generic Dermatological Products

SBIA 2021: Advancing Generic Drug Development: Translating Science to Approval

Day 2, Session 3: Topical Products (Part 2)

Eleftheria Tsakalozou, PhD
Pharmacologist

Khondoker Alam, PhD
Pharmacologist

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

CDER | U.S. FDA

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Overview: Part-2

1. General expectation on dermal PBPK model and/or modeling platform

2. Product-specific challenges and considerations in VBE approach

    - Case study-1: Clindamycin Phosphate Topical Lotion (Cleocin T®), eq 1% base
    - Case study-2: Low skin permeability active pharmaceutical ingredient (API) in topical cream

General Expectation on Dermal PBPK Model and/or Modeling Platform

Skin physiology

The PBPK model/modeling platform reasonably describes the skin physiology

Formulation attributes

The formulation attributes (i.e., Q3 characteristics) are accurately captured

Model parameterization

Informative datasets [e.g., clinical and/or in vitro permeation testing (IVPT) study] are leveraged towards informing key model parameters

Model assumption

The model has reasonable assumptions on input parameters when reliable method is not available to obtain the parameter value experimentally

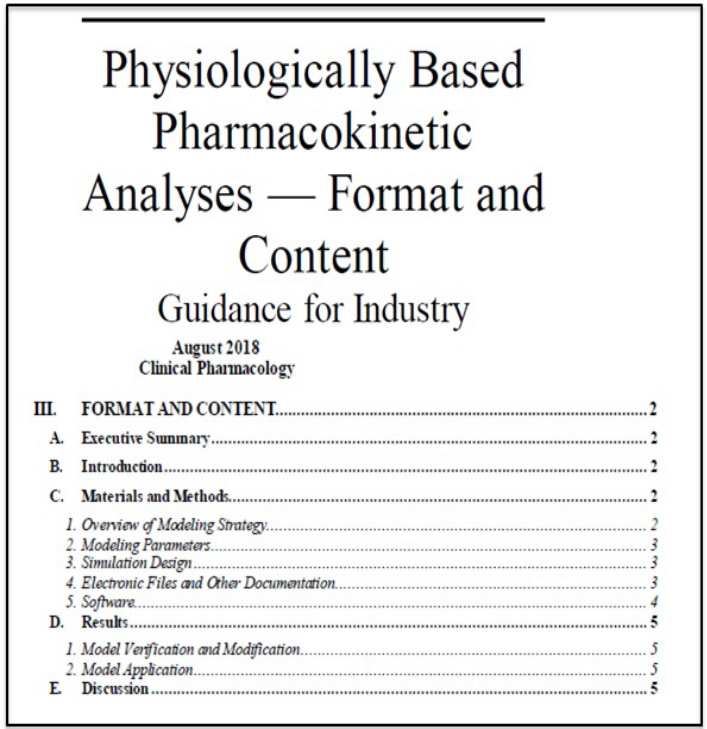
Model/platform validation

The predictive performance of PBPK model/platform is assessed by wide range of topical drug products and different topical dosage forms of reference drug (if available)

Mechanistic dermal PBPK model

General Expectation on Dermal PBPK Model and/or Modeling Platform

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

www.fda.gov

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

CPT: Pharmacometrics & Systems Pharmacology

REVIEW | Open Access

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

First published: 06 February 2021 | https://doi.org/10.1002/psp4.12600 | Citations: 2

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

Case Study-1: Clindamycin Phosphate Topical Lotion (Cleocin T®), Eq 1% Base

Pharmaceutical form: oil-in-water (o/w) emulsion

Indication: treatment of acne vulgaris

Current PSG recommendation: Comparative clinical endpoint BE study

Comparative clinical endpoint BE study

- Relatively insensitive in detecting formulation differences
- Large variability in the observed response
- Relatively costly as it requires higher subject number
- Drug development to approval time is long

Virtual BE study

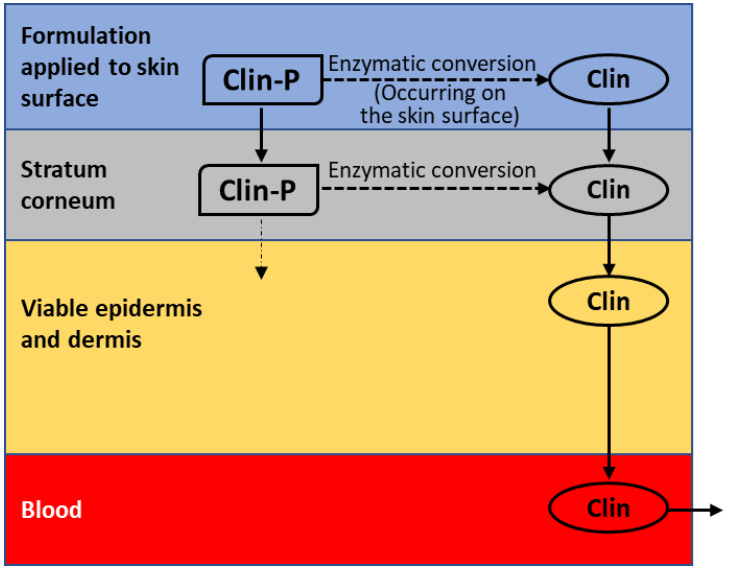
- Agency welcomes innovative approach if the proposed approach satisfies requirements of applicable statues and regulations
- Bioavailability in local tissues can be compared between test and reference drug products
- Cost effective and faster drug development

Case Study-1: Clindamycin Phosphate Topical Lotion (Cleocin T®), Eq 1% Base

Product-specific challenges and considerations in VBE approach:

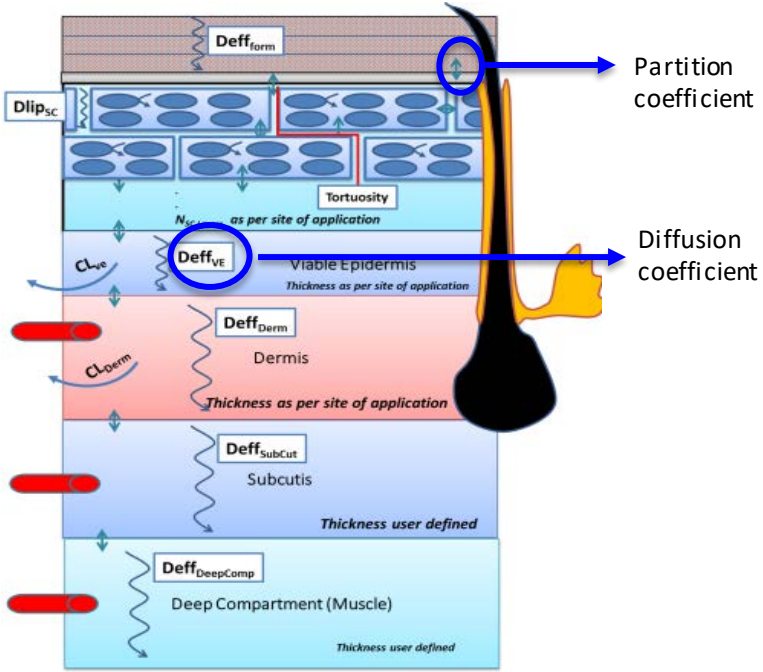
Following topical application of the lotion, clindamycin phosphate is hydrolyzed to clindamycin base by esterases/phosphatases on the skin surface and within the skin

- The proposed model structure should capture this hydrolysis process



Case Study-1: Clindamycin Phosphate Topical Lotion (Cleocin T®), Eq 1% Base

Product-specific challenges and considerations in VBE approach:



Partition coefficients between two layers (e.g., formulation and stratum corneum; two adjacent skin layers) and diffusion coefficients within skin layers govern the permeation of API through skin

→ Model structure should capture the dynamic permeation process

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The values of partition and diffusion coefficient may be informed by IVPT study or other suitable form of experiment

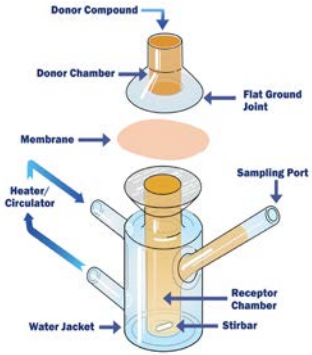


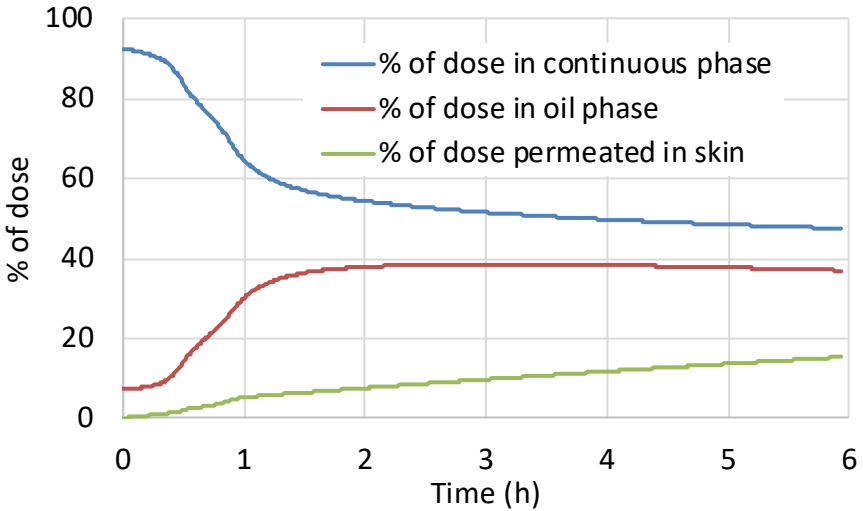
Image courtesy of PermeGear

www.fda.gov https://www.certara.com/app/uploads/Resources/Posters/Martins_2016_DMDG_dermal.pdf

Case Study-1: Clindamycin Phosphate Topical Lotion (Cleocin T®), Eq 1% Base

Product-specific challenges and considerations in VBE approach:

Effect of **vehicle evaporation** on phase distribution and skin permeability of drug molecule



Vehicle of clindamycin phosphate lotion evaporates rapidly from skin surface

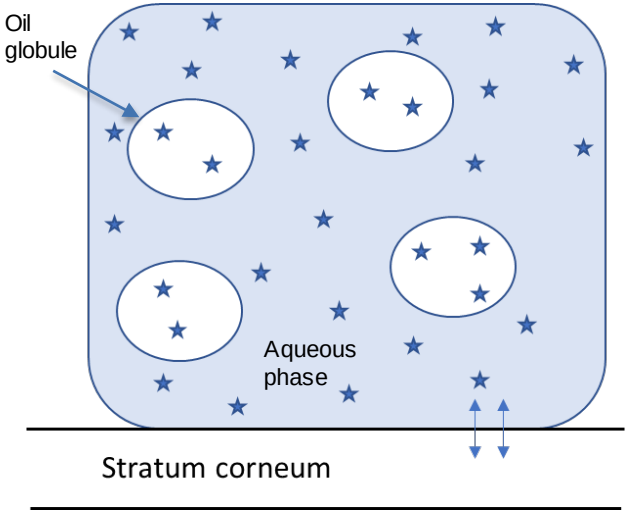
This may change the extent of phase distribution of API and skin permeability by increasing the thermodynamic activity of drug molecule

- Model structure should capture this dynamic process
- Model predictions can be validated by IVPT data collected under occluded and non-occluded conditions.

In-house PBPK model-based simulated data

Case Study-1: Clindamycin Phosphate Topical Lotion (Cleocin T®), Eq 1% Base

Product-specific challenges and considerations in VBE approach:



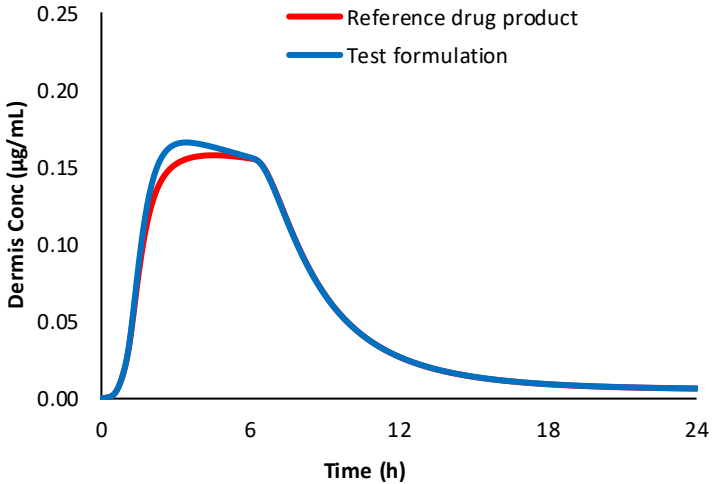
Size of emulsion globules and distribution of API in two phases may potentially impact the permeation of drug molecule into skin

→ Model parameter of globule size and phase distribution of API should be informed experimentally

Other model parameters relating to formulation attributes such as pH, apparent viscosity, specific gravity should also be informed experimentally.

Case Study-1: Clindamycin Phosphate Topical Lotion (Cleocin T®), Eq 1% Base

Establishing VBE between test and reference drug products



Once the dermal PBPK model of clindamycin phosphate lotion and/or PBPK platform is suitably validated, bioavailability of test and reference formulations can be compared in different layers of skin such as stratum corneum, viable epidermis, dermis as well as systemic compartment

Case Study-2: Low Skin Permeability API in Topical Cream

Pharmaceutical form: oil-in-water (o/w) emulsion

Presumed site of action: skin surface and outer skin layers

In vitro characterization studies:

- qualitatively (Q1) and quantitatively (Q2) the same
- physically and structurally similar based upon physicochemical characterization
- show equivalent rate of API release [e.g., in vitro release testing (IVRT) study]
- show equivalent rate and extent of API permeation through excised human skin (e.g., IVPT study)

Case Study-2: Low Skin Permeability API in Topical Cream

Relatively low permeability of API observed in IVPT study may pose some challenges to the in vitro characterization-based BE approach.

- Unexpected high cost associated with pivotal IVPT study to establish BE
- Delays drug development process

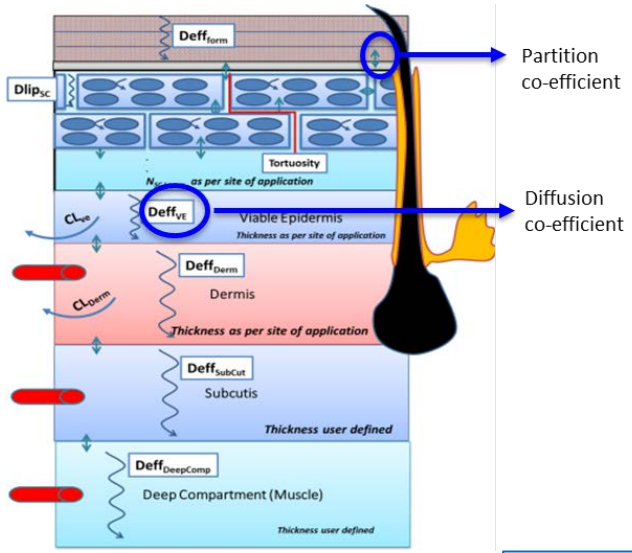
PBPK model based virtual BE study could be potential solution

As per Agency's current thinking on innovative approaches, alternative BE approach may involve:

1. In vitro characterization studies for R and T products that are:
   - Q1, Q2 the same
   - physically and structurally similar based upon physicochemical characterization
   - show equivalent rate of API in vitro release
2. PBPK model to perform a VBE locally (skin) and systemically between the R and T products

Case Study-2: Low Skin Permeability API in Topical Cream

Product-specific challenges and considerations in VBE approach:



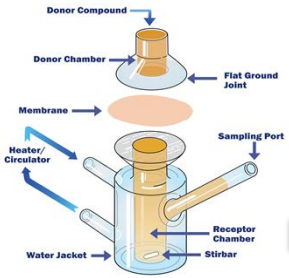
https://www.certara.com/app/uploads/Resources/Posters/Martins_2016_DMDG_dermal.pdf

- General expectations on dermal PBPK model and/or modeling platform is same as discussed under case study-1
- Model should capture any sensitive formulation attributes
  - Drug product metamorphosis post application
  - Distribution of API in two phases
  - Distribution of emulsion globules
  - pH, apparent viscosity, specific gravity etc.
- Important model parameters describing permeation through the skin may be informed by skin distribution or IVPT studies

Can IVPT study still be used to inform model parameters?

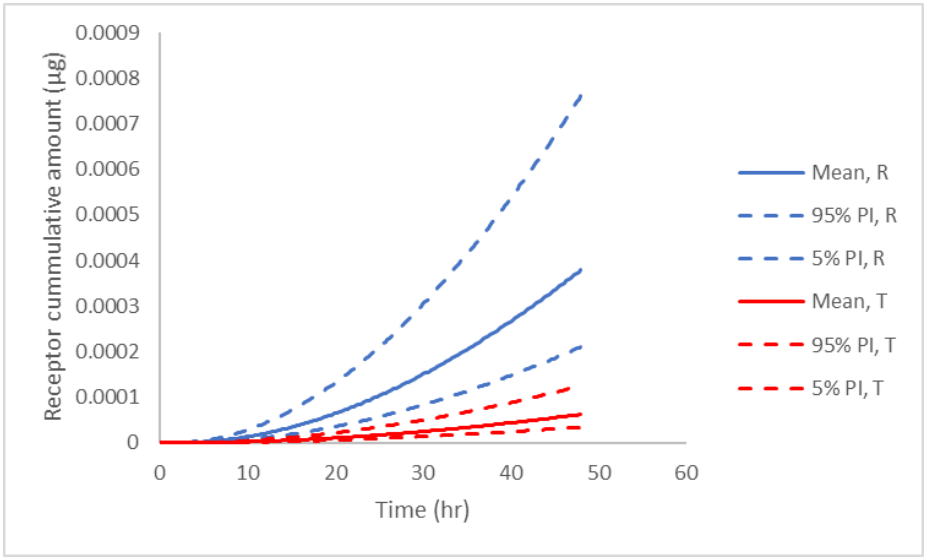
Yes. However, IVPT method should be validated.

Case Study-2: Low Skin Permeability API in Topical Cream



Model validation using IVPT study data

Formulation attributes for R and T products



Virtual IVPT profiles for 30 donors

Take Home Messages: Part -2

PBPK modeling and simulation approaches may be used to:

- Provide insight on the effect of important formulation attributes that may influence skin permeability of API
- Support alternative BE approaches developed to address challenges with IVPT studies

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Sam Raney

www.fda.gov/GDUFARegScience

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

Questions?

Eleftheria Tsakalozou, PhD
Eleftheria.Tsakalozou@fda.hhs.gov

Khondoker Alam, PhD
Khondoker.Alam@fda.hhs.gov

Division of Quantitative Methods and Modeling
Office of Research and Standards, Office of Generic Drugs
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Challenge Question #1

VBE for generic dermatological drug products can be used to support:

A. BE assessments between R and T drug products

B. Bridge BE and drug product quality

C. Inform decisions throughout the entire life cycle of a drug product

D. All of the above

Challenge Question #1

VBE for generic <u>dermatological drug products</u> can be used to support:

A. BE assessments between R and T drug products

B. Bridge BE and drug product quality

C. Inform decisions throughout the entire life cycle of a drug product

D. All of the above

Challenge Question #2

What factors should be considered towards developing a dermal PBPK model to be used in a VBE approach?

A. Model/modeling platform reasonably describes the skin physiology

B. Informative datasets such as clinical and/or IVPT study are leveraged towards informing key model parameters

C. The formulation attributes are accurately captured

D. The predictive performance of the PBPK model/platform is adequately assessed

E. All of the above

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