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 1)

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Learning Objectives

- Describe virtual bioequivalence (VBE) assessment and its applications towards supporting product development and approval of generic dermatological products
- Explain the considerations for employing in silico methodologies and performing VBE assessments for generic dermatological drug products
- Discuss the challenges when performing VBE assessments and future directions
- Discuss the general factors to be considered in dermal physiologically-based pharmacokinetic (PBPK) model
- Discuss two case studies of VBE approach: Product specific challenges and model development process

Overview

- Dermatological drug products
- In silico methodologies and VBE assessment
  - Case example
- Considerations and challenges in implementing VBE
- VBE for dermatological drug products
- Take home messages

BE for generic dermatological drug products: current recommendations

Comparative clinical endpoint BE studies

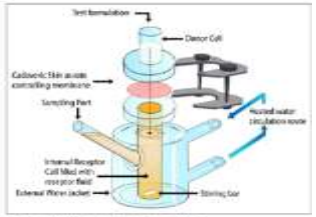
- Relatively insensitive in detecting formulation differences
- Large variability in the observed response
- Modest clinical efficacy

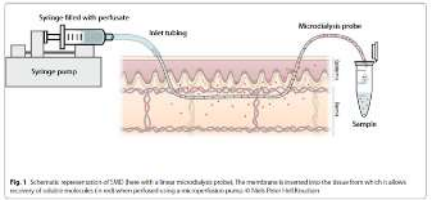
BE studies with PK endpoints

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

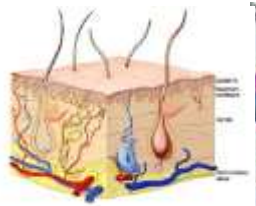
Drug product characterization studies

Implement in silico methodologies for generic dermatological drug products

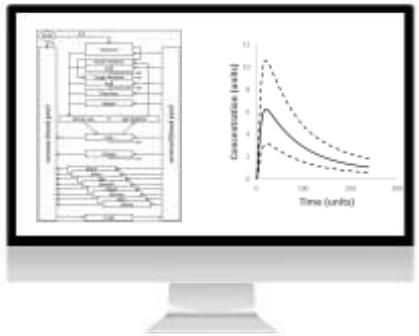




Skin Bioavailability



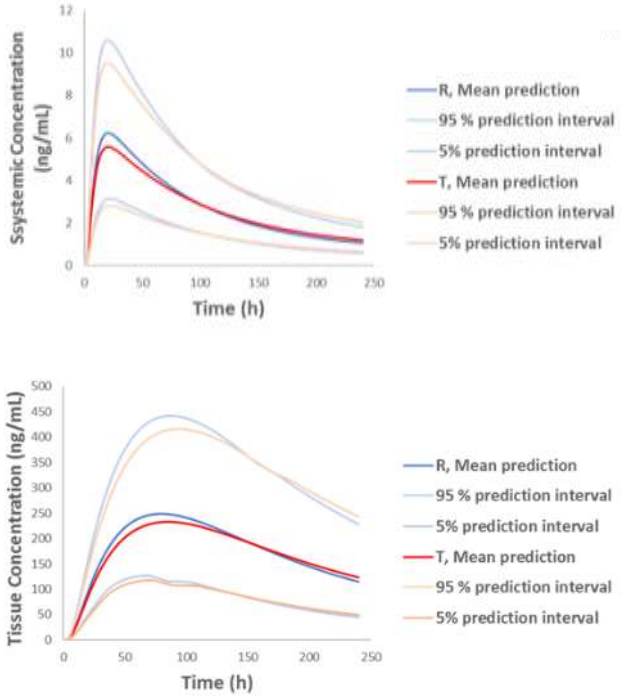
Skin Physiology in Individuals/Populations



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
thinkstockphotos.com

Dermal PBPK model supporting ANDA 211253 approval



- 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

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

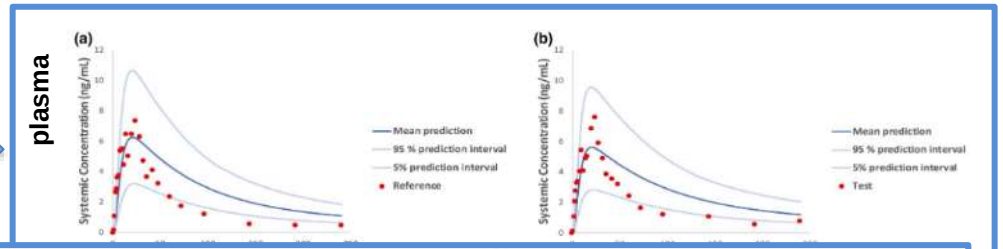
Q1: qualitative, Q2: quantitative, Q3: physicochemical and structural characteristics , PSG: Product-Specific Guidance

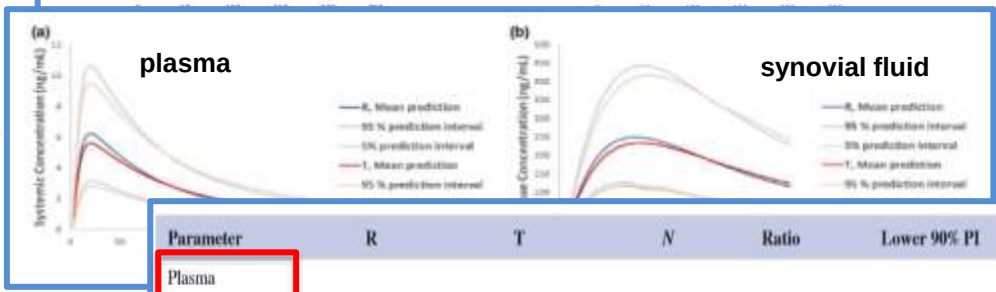
Proposed workflow of VBE implementation

Verified/Validated Model

In Vivo Study Simulation

Bioequivalence Assessment

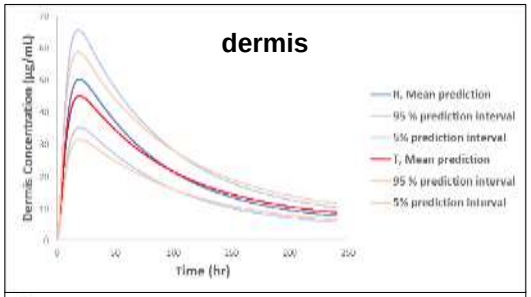


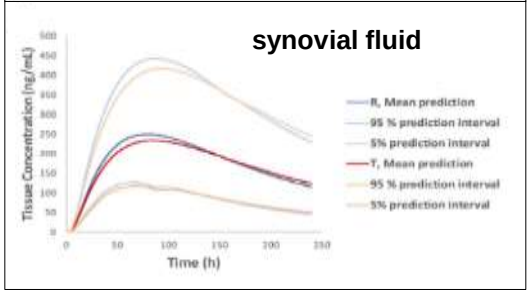


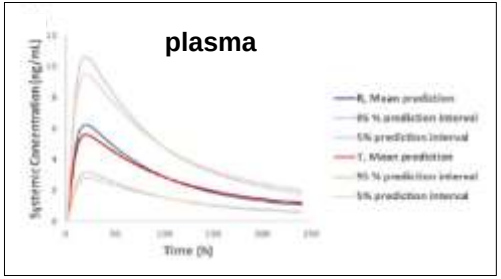
Parameter	R	T	N	Ratio	Lower 90% PI	Upper 90% PI
Plasma						
C_{max}, ng/ml	5.87	5.56	78	0.90	81.29	98.77
AUC, ng·hr/ml	638.40	630.56	78	0.98	88.63	107.39
Synovial fluid						
A_{max}, µg	230.13	222.47	78	0.93	85.06	102.68
AUC, µg·hr/ml	37,888.28	37,362.20	78	0.97	87.7	107.83

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

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
- PK metrices for BE statistical analysis
  - Cmax (Amax)
  - AUC
- Overall shape of PK curve (Tmax, absorption and elimination phase) is considered

R: reference drug product, T: test drug product, Cmax: maximum plasma concentration, Amax: maximum amount, AUC: area under the concentration versus time curve

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

VBE for dermatological drug products

- Assess exposure locally and systemically using modeling and simulation approaches for R and T products
  - Biological samples cannot be collected (not ethical, not feasible, costly)
  - Virtual healthy or diseased populations
- Bridge drug product quality and BE
  - Define a “safe space” for clinically relevant quality attributes
  - Justify deviations on quality between R and T products
- Inform decisions throughout the entire life cycle of a drug product

R: reference drug product, T: test drug product

Challenges in performing a VBE assessment

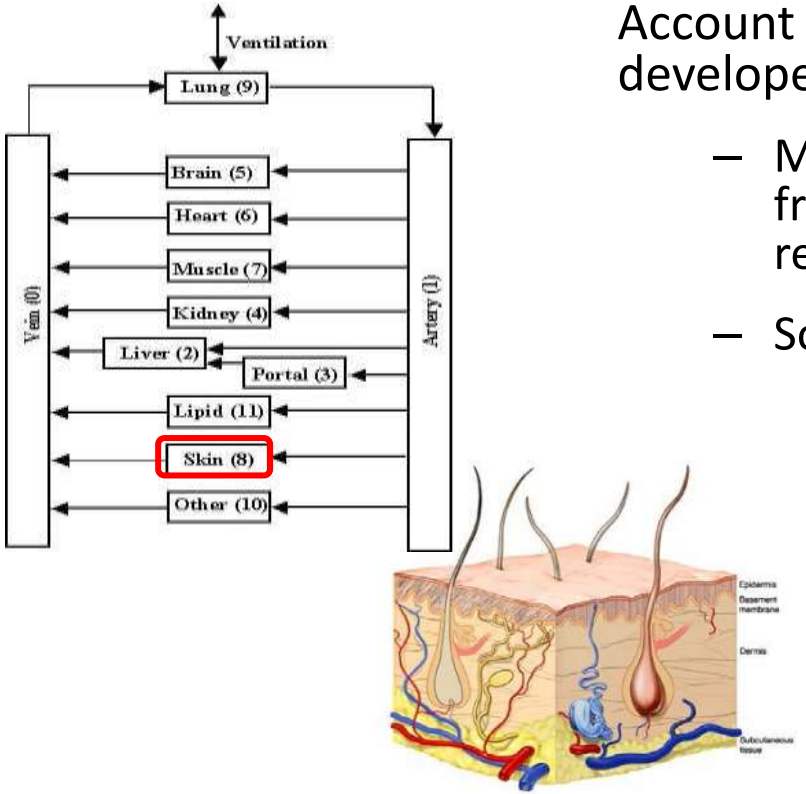
Accurate representation of the study design

- Parallel
- Crossover
- Fully or partial replicated

Accurate representation of the study population

- Age, gender, race
- Special populations
- Disease or healthy virtual subjects
- Sample size

Challenges in performing a VBE assessment



Account for inter- and intra-subject variability in developed models

- Mechanistic modeling approaches provide a framework for rationally assigning variability to relevant model parameters
- Sources of 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

BMC Clin Pharmacol. 2002 Aug 15;2:5. PKQuest: a general physiologically based pharmacokinetic model. Introduction and application to propranolol. David G Levitt.
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.

Approaches towards accounting for variability

- Differentiate from uncertainty (unknown origin, associated with bioanalytical methodology)
- Sufficiently verified/validated models for their intended purpose
- Identify and adequately characterize sources of variability
  - Understanding of biological processes is necessary
  - Experimentally study relevant sources of variability
  - May not always be feasible to characterize
- Sensitivity analysis to identify impactful parameters and assign variability
  - Key assumption: model misspecification

Take home messages-Part 1

- Modeling and simulation approaches with a VBE assessment component can be used to support product development and approval for dermatological drug products.
  - Impact of drug product attributes on local bioavailability
- Challenges in the implementation of VBE assessments were recognized and discussed. Research and collaboration among academia, industry and regulatory agencies is necessary to tackle those issues.
- Modeling and simulation approaches coupled with a VBE assessment supporting an Abbreviated New Drug Application (ANDA):
  - early interaction between industry and regulatory agency should be initiated through the pre-ANDA meeting request program, GDUFA II[1].

[1] Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA Guidance for Industry, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/formal-meetings-between-fda-and-anda-applicants-complex-products-under-gdufa-guidance-industry