

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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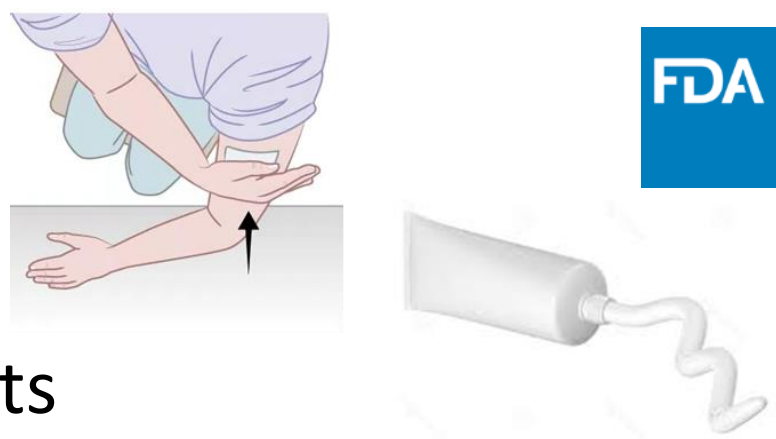
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Learning Objectives

- 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

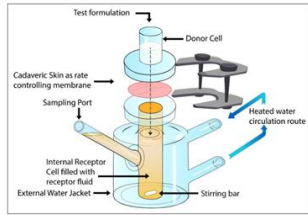
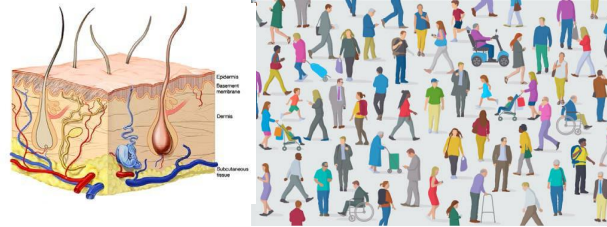


Figure 1. Schematic diagram of a static diffusion cell used in vitro permeation test.



Skin Physiology in Individuals/Populations



Drug Product Characterization

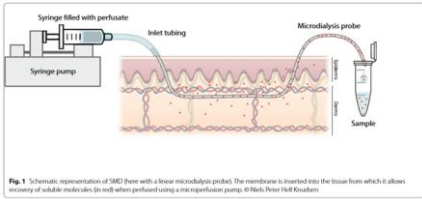
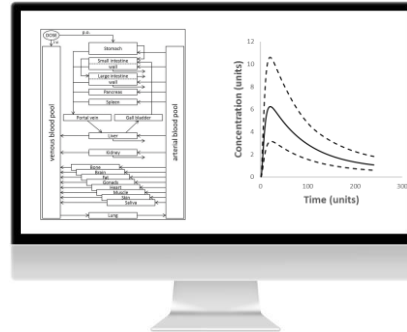
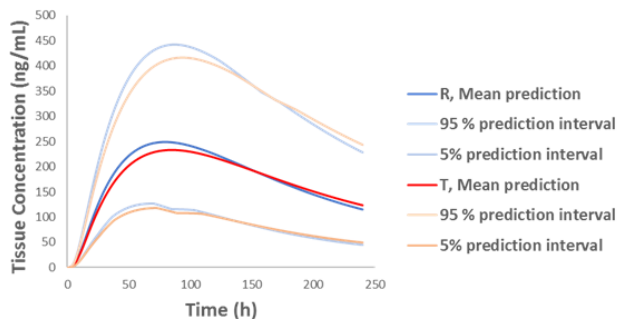
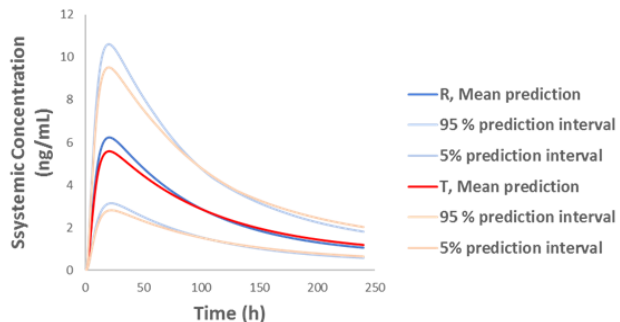


Fig. 1 Schematic representation of SMD (with a linear microdialysis probe). The membrane is inserted into the tissue from which it allows recovery of soluble molecules (in cell) when perfused using a microperfusion pump. © Melli Peter Hoff Kruehler

Skin Bioavailability

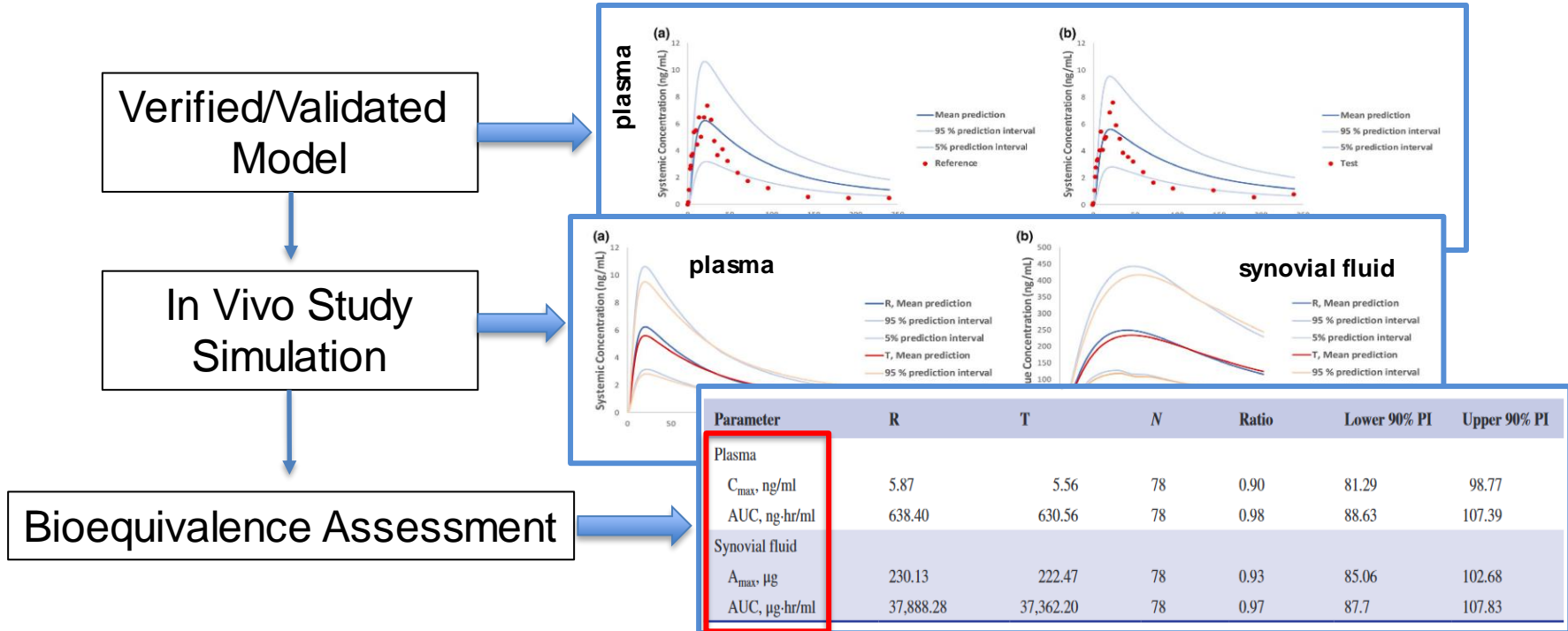


Dermal PBPK model supporting ANDA 211253 approval

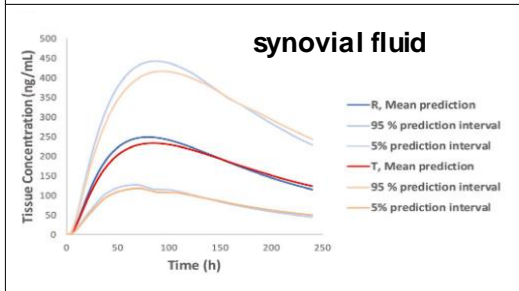
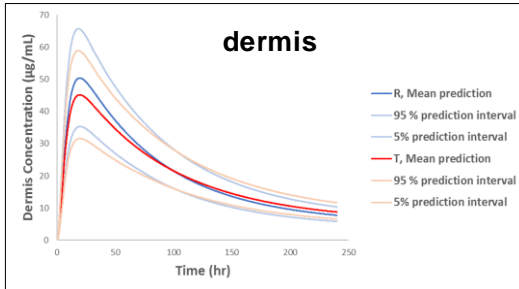


- Diclofenac sodium topical gel, 1%
- Dermal PBPK model to support an alternative BE approach for the Q1/Q2/Q3 formulation
- The alternative BE approach did not include the PSG-recommended in vivo comparative clinical endpoint BE study
- Dermal PBPK model leveraged for virtual BE assessments on predicted systemic and local exposure

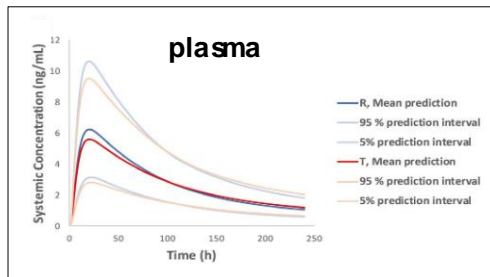
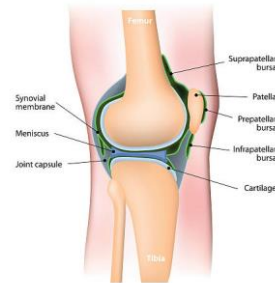
Proposed workflow of VBE implementation



Considerations in implementing a VBE assessment



Synovial joint of the knee



- Comparison of simulated PK profiles between R and T drug products
 - Application site/skin layers
 - Site of pharmacological action (target site)
 - Systemic circulation
- PK metrics 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



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

Challenges in performing a VBE assessment



Accurate representation of the study design

- Parallel
- Crossover
- Fully or partial replicated

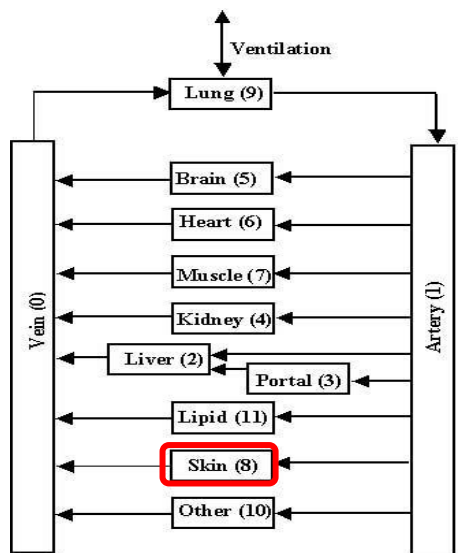
Accurate representation of the study population

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

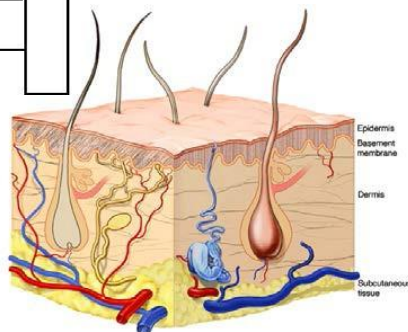


Challenges in performing a VBE assessment

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



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 II¹.