Mechanistic Modelling to Streamline PSG Recommendations and Reduce Regulatory Burden

Advancing Generic Drug Development: Modernizing Bioequivalence Approaches for Topical & Transdermal Products

Session 2: Using Research to Support and Streamline Product Specific Guidances (PSG) for Topical Products

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Outline

Product specific guidances

Mechanistic models of skin absorption

[dermal Physiologically Based Pharmacokinetic (PBPK) models]

- Building blocks
- Evolution

Case Studies

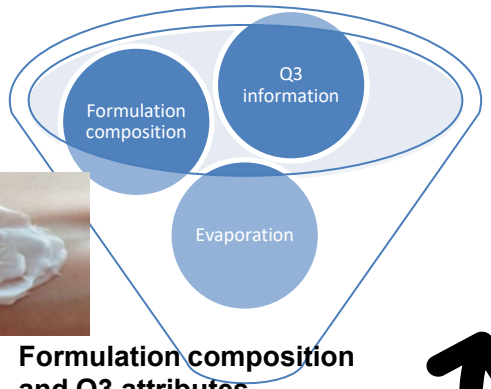
- PSG revision: Dapsone topical **gel**, 7.5% and 5%
- PSG revision: Doxepin hydrochloride topical **cream**, 5%

Conclusions

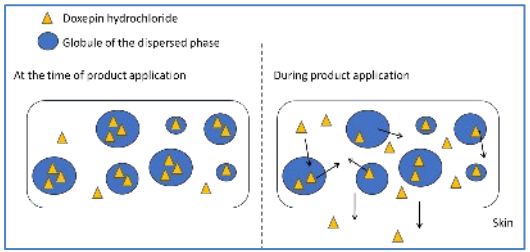
"product-specific guidances describing the agency's current thinking and expectations on how to develop generic drug products therapeutically equivalent to specific reference listed drugs"

- The agency routinely posts and revises product-specific guidances.
- There are over 2400 published PSGs and growing
- Regulatory research provides **new tools** for FDA and industry to evaluate generic drug equivalence, to enable more efficient development of generic drugs and thus improve access

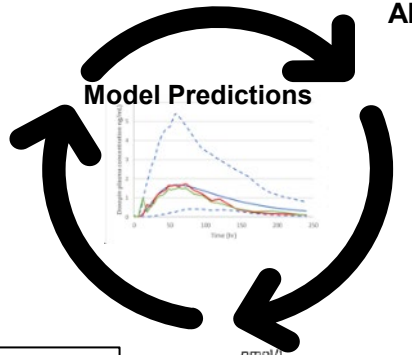
Development of PBPK Models for Products Applied on the Skin

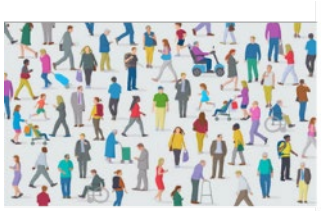


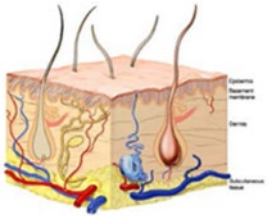
Formulation composition and Q3 attributes



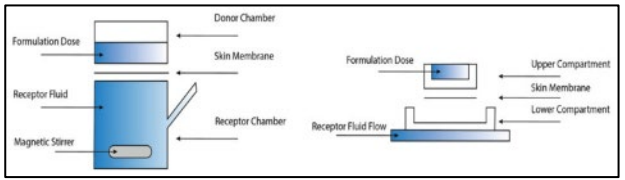
API distribution in the cream







Skin physiology and population variability



IVPT study data

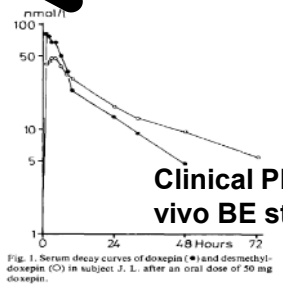


Fig. 1. Serum decay curves of doxepin (●) and desmethyldoxepin (○) in subject J. L. after an oral dose of 50 mg doxepin.

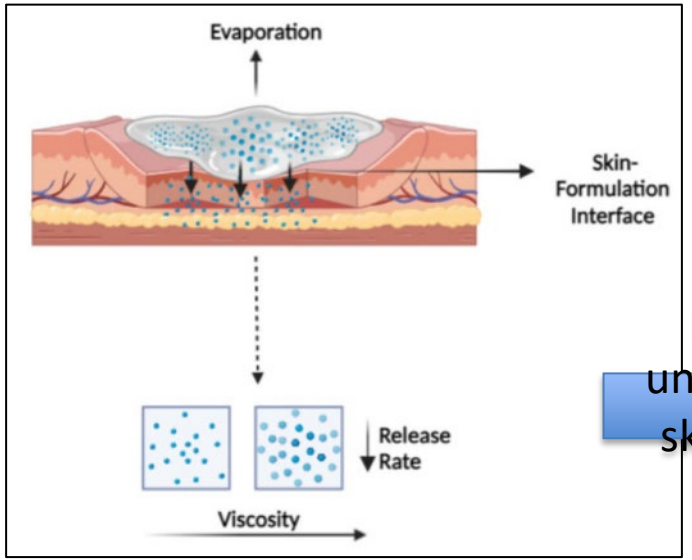
Clinical PK data (in vivo BE studies)

API: active pharmaceutical ingredient
IVPT: in vitro permeation testing
Q3: physicochemical and structural properties
BE: bioequivalence

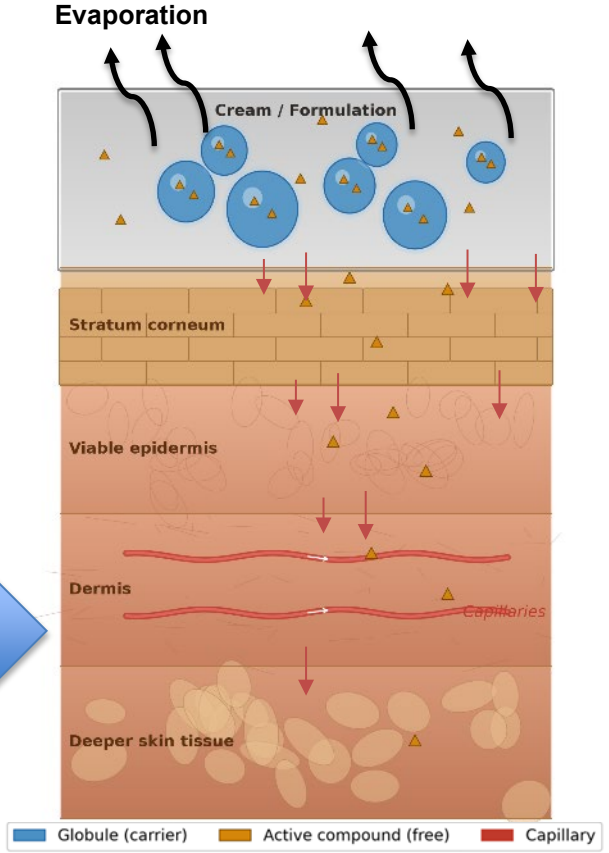
Modeling Drug Product Application: Guiding Principles

"In use" product conditions

Drug product metamorphosis: evaporation, supersaturation and crystallization, changes in thermodynamic activity

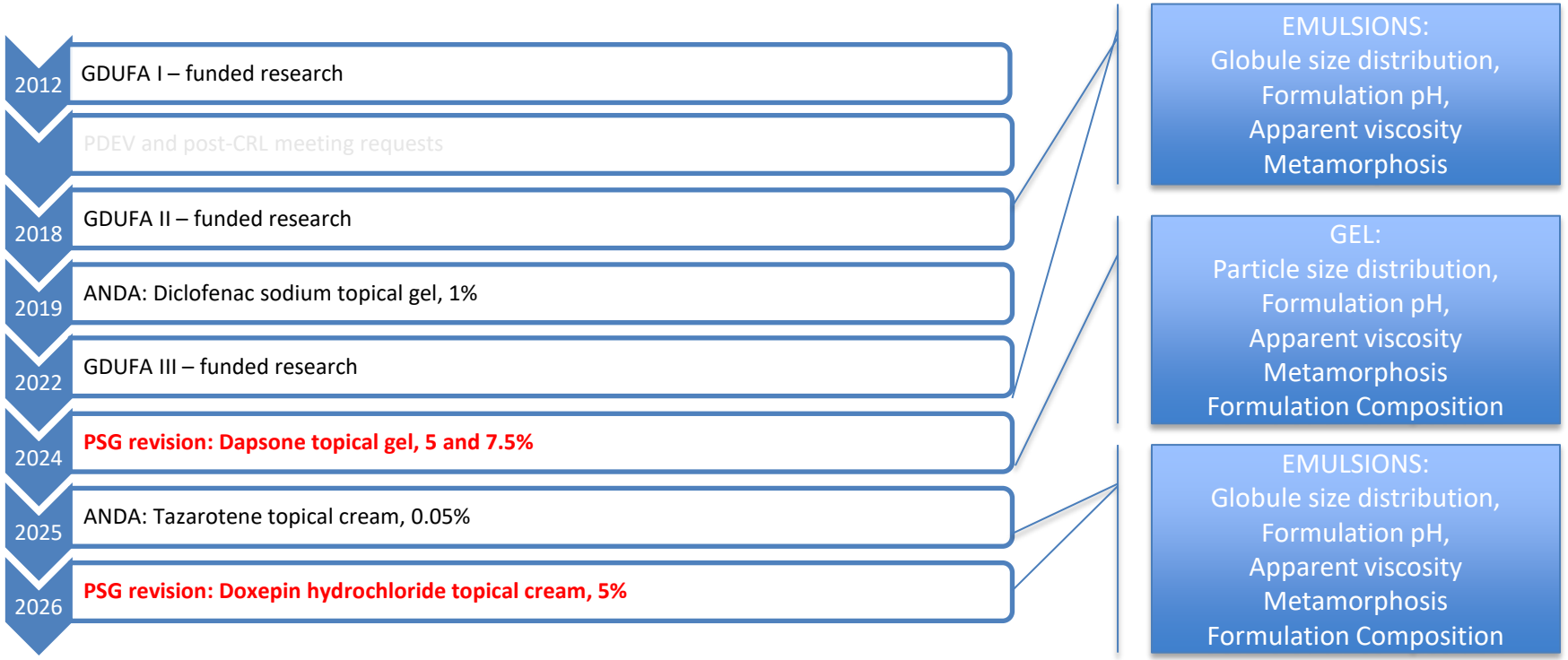


Mechanistic understanding in skin absorption models

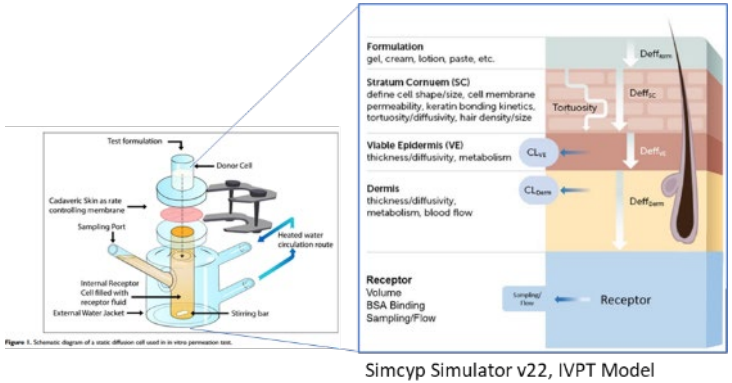


https://pmc.ncbi.nlm.nih.gov/articles/PMC9692522/

Evolution of Mechanistic Skin Absorption Models for Generics

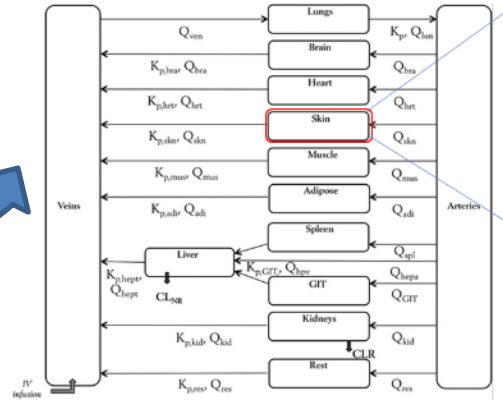


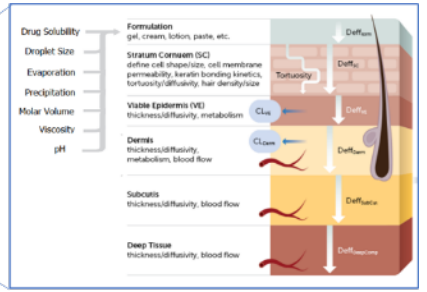
Basic principles of dermal PBPK modeling



Simcyp Simulator v22, IVPT Model

Development and Validation





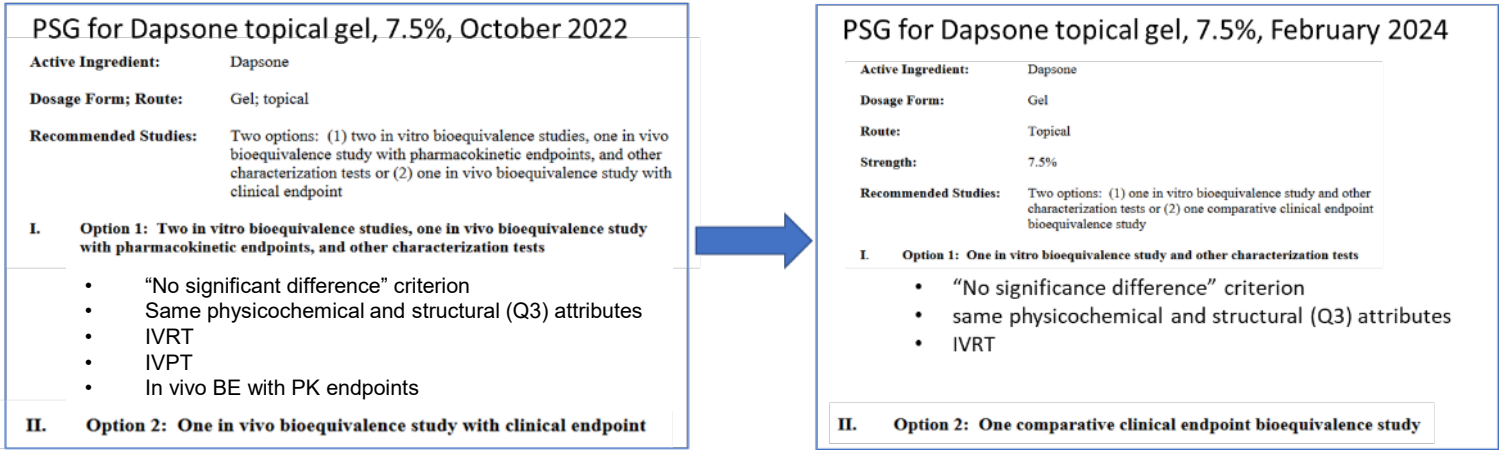
Simcyp simulator v22, MPML MechDermA

https://www.fda.gov/media/164843/download#page=70
https://www.certara.com/app/uploads/2021/04/WP_Demonstrating_Virtual_Bioequivalence.pdf
https://link.springer.com/article/10.1007/s10928-016-9486-9/figures/1

Case studies

1. PSG revision: Dapsone topical gel, 5% and 7.5%

Dapsone Gel, 5% and 7.5% PSG Revisions



PSG for Dapsone topical gel, 7.5%, October 2022

Active Ingredient: Dapsone

Dosage Form; Route: Gel; topical

Recommended Studies: Two options: (1) two in vitro bioequivalence studies, one in vivo bioequivalence study with pharmacokinetic endpoints, and other characterization tests or (2) one in vivo bioequivalence study with clinical endpoint

I. Option 1: Two in vitro bioequivalence studies, one in vivo bioequivalence study with pharmacokinetic endpoints, and other characterization tests

- "No significant difference" criterion
- Same physicochemical and structural (Q3) attributes
- IVRT
- IVPT
- In vivo BE with PK endpoints

II. Option 2: One in vivo bioequivalence study with clinical endpoint

PSG for Dapsone topical gel, 7.5%, February 2024

Active Ingredient: Dapsone

Dosage Form: Gel

Route: Topical

Strength: 7.5%

Recommended Studies: Two options: (1) one in vitro bioequivalence study and other characterization tests or (2) one comparative clinical endpoint bioequivalence study

I. Option 1: One in vitro bioequivalence study and other characterization tests

- "No significance difference" criterion
- same physicochemical and structural (Q3) attributes
- IVRT

II. Option 2: One comparative clinical endpoint bioequivalence study

PSG revision was supported by modeling and simulation

- Elucidated the relationship between drug product quality attributes and in vivo performance
- Established a link between systemic and local dapsone exposure

GEL:
Particle size distribution,
Formulation pH,
Apparent viscosity
Metamorphosis
Formulation Composition

Case studies

2. PSG revision: Doxepin hydrochloride topical cream, 5%

Doxepin Hydrochloride Topical Cream, 5%

BE recommendations no longer include an in vivo BE study with PK endpoints

Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Doxepin Hydrochloride

May 2026

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient:	Doxepin hydrochloride
Dosage Form	Cream
Route:	Topical
Strength:	5%
Reference Listed Drug:	NDA 020126
Recommended Studies:	In vitro bioequivalence studies and other characterization tests

Eligibility: To demonstrate bioequivalence for doxepin hydrochloride topical cream, 5% using in vitro studies, the test product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference standard (RS) that may significantly affect the local or systemic availability of the active ingredient. For example, if the test product and RS are qualitatively (Q1) and quantitatively (Q2) the same, as defined in the guidance for industry *ANDA Submissions – Refuse-to-Receive Standards*[a], and the criteria below are also satisfied, the bioequivalence of the test product may be established using a characterization-based bioequivalence approach.

Class of study: Comparative characterization
Type of study: Characterization studies for the following physicochemical and structural (Q3) attributes:

1. Visual appearance and texture
2. Structural organization of matter (microscopic examination, globule size distribution)
3. Rheological behavior
4. pH
5. Specific gravity

1. Class of study: Bioequivalence
   Type of study: In vitro release test (IVRT)
   Design: Single-dose, two-treatment, parallel, multiple-replicate per treatment group study design using an occluded pseudo-infinite dose, in vitro

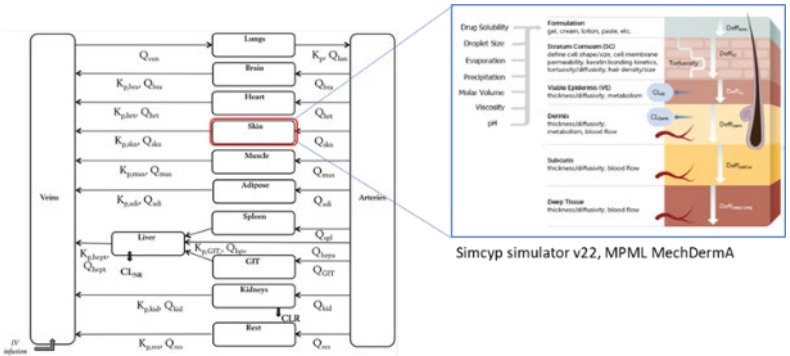
2. Type of study: In vitro permeation test (IVPT)
   Design: Single-dose, two-treatment, parallel, multiple-replicate per treatment group study design using an unoccluded finite dose, in vitro

- Applicants may propose an alternative approach (e.g., a bioequivalence (BE) study with pharmacokinetic (PK) endpoints in lieu of the IVPT study) for a formulation that meets the no significant difference criteria.

Meeting recommendations: Applicants intending to propose an alternative approach by which to demonstrate bioequivalence should refer to the guidance for industry *Controlled Correspondence Related to Generic Drug Development*[a] and the guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*[a] for additional information describing the procedures on how to clarify regulatory expectations regarding your individual drug development program.

Recommended Nov 2018; Revised Nov 2019, Oct 2022, May 2026

Objectives of the Mechanistic M&S Approach



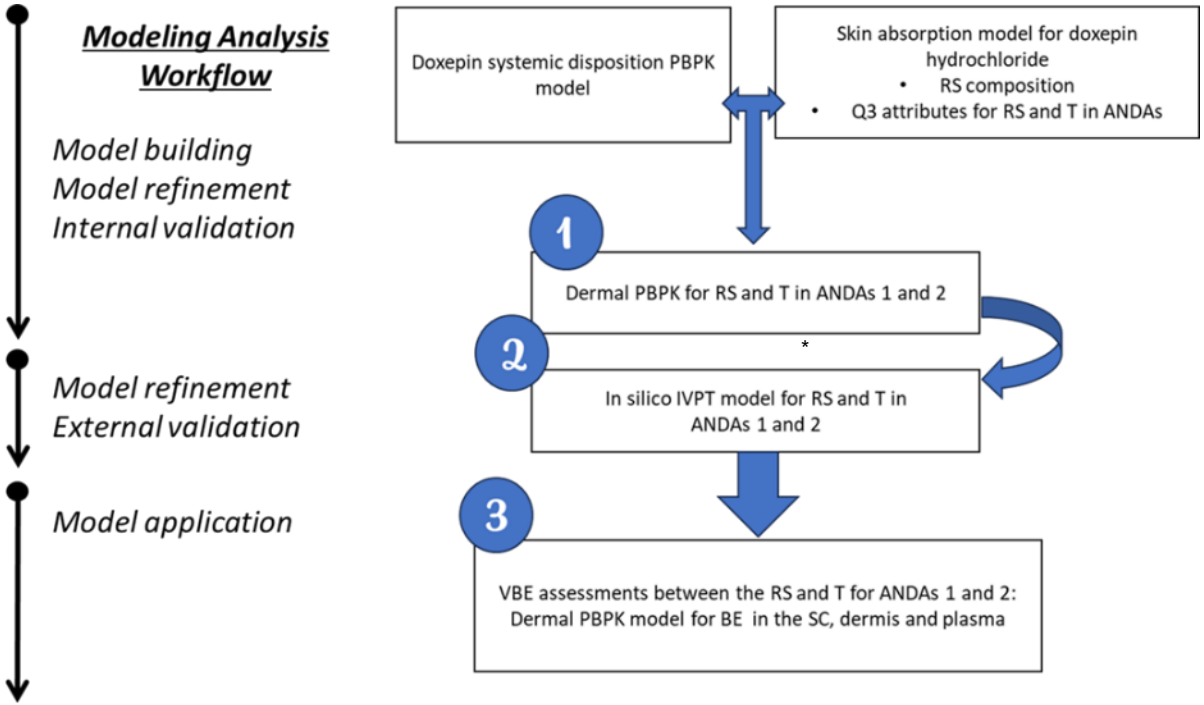
Simcyp simulator v22, MPML MechDermA

Develop and validate a mechanistic PBPK model to:

- Understand the factors governing the permeation of doxepin through the skin
- Identify drug product quality attributes for the product that may impact local and systemic bioavailability
- Virtually assess bioequivalence in the skin and the systemic circulation between the T and RS that meet the NSD criterion

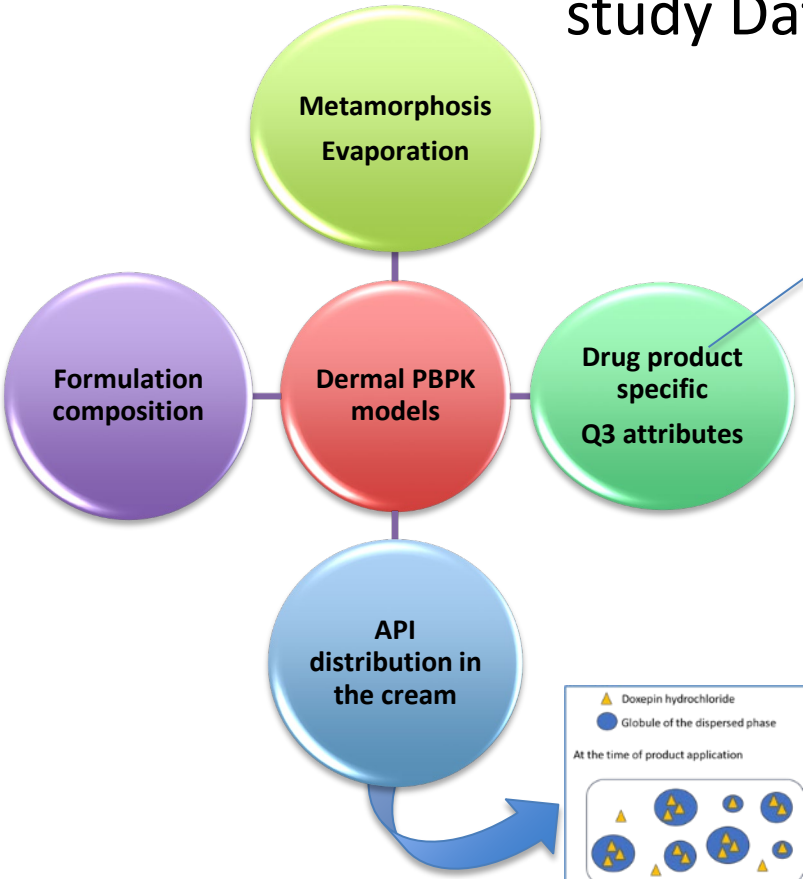
NSD: no significant difference

Modeling Analysis Workflow



*ANDAs 1 and 2 met the NSD criterion based on the submitted IVPT BE and in vivo BE studies supporting their regulatory submissions

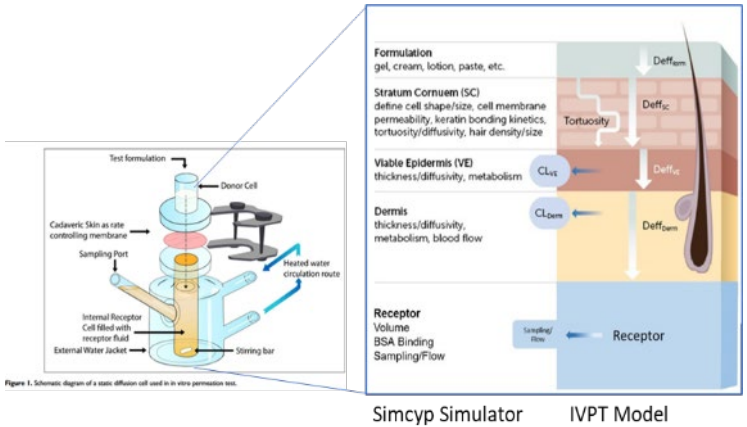
Model Development Leveraging In vitro Characterization study Data



API distribution in the cream

M&S Approach: IVPT Model Building

IVPT Studies Inform Model Parameterization

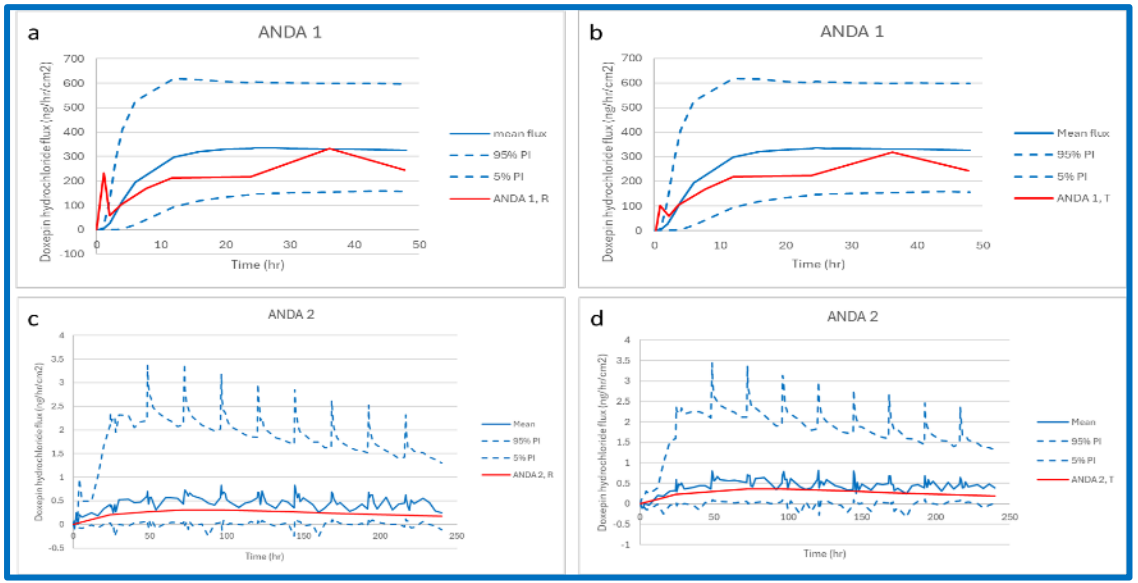


Simcyp Simulator IVPT Model

- **Formulation composition**
  - impact of inactive ingredients on doxepin thermodynamic activity during and post application on permeation
- **Drug product characteristics**
  - impact of physicochemical and structural characteristics on bioavailability
- **Metamorphosis process**
  - impact of evaporation on permeation

Modeling Analysis: Model Validation and Application

- In silico IVPT PBPK model



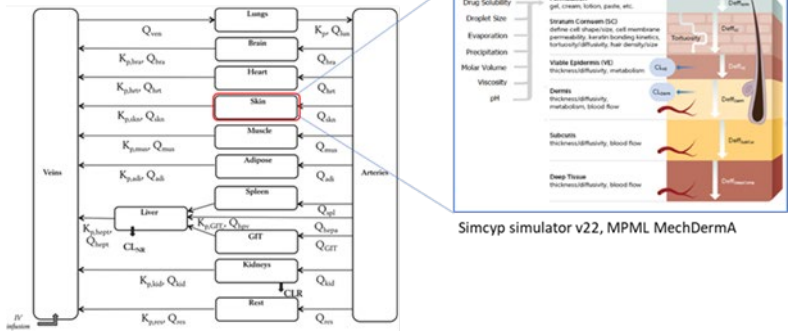
✓ Acceptable model performance

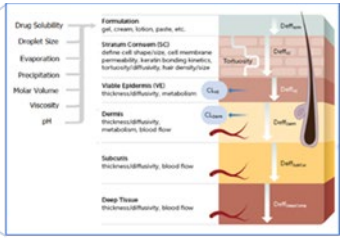
Modeling Analysis: Model Validation and Application

- In vivo dermal PBPK model

IVPT Model

IVIVE





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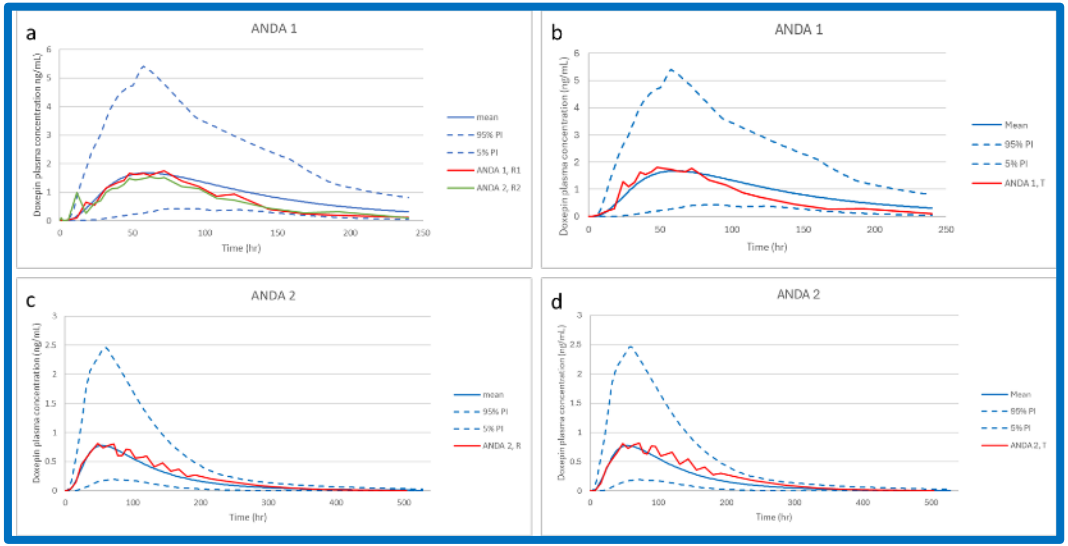


✓ Acceptable model performance

Modeling Analysis: VBE Assessment

Steps for implementing a VBE assessment:

1. Validated dermal PBPK models for RS and T
2. BE simulated trials (10 crossover trials, sample size informed by population variability)
3. BE statistical assessment in skin (SC, dermis) and plasma

VBE outcomes for 10 virtual BE studies with PK endpoints		
Matrix	ANDA 1	ANDA 2
SC	Pass (100%)	Pass (100%)
Dermis	Pass (100%)	Pass (100%)
Plasma	Pass (100%)	Pass (100%)

RS and T products are found to be bioequivalent

Conclusions

Predictions of skin permeation and absorption were informed by formulation composition, Q3 characterization and IVPT studies.

Doxepin distribution in the product phases and drug product evaporation were critical model inputs.

The analysis showed that T and RS Q3 sameness AND comparable doxepin hydrochloride distribution in the cream result in demonstration of BE in the skin and the plasma of virtual subjects when T and RS meet the NSD criterion

Q3 sameness between the T and the RS especially regarding formulation pH should be demonstrated with qualified and robust methodologies

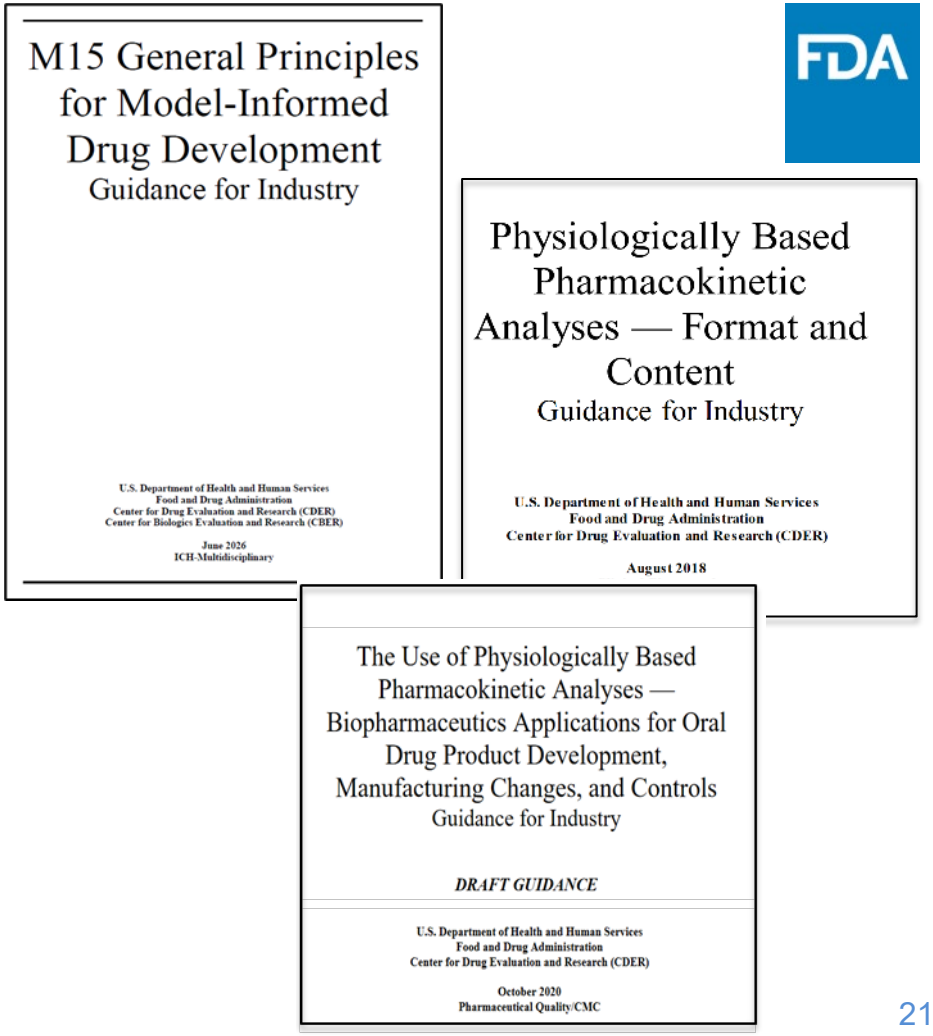
Overall Conclusions

1. The PBPK model described here provided a validated link between Q3 and bioavailability (local and systemic).
2. The PBPK model analysis results and additional understanding of the doxepin hydrochloride topical cream, 5% supported the revised BE recommendations of reduced testing and reduced burden for applicants.
3. Validated PBPK models can be used as risk-based assessment tools supporting lifecycle management of drug products such as the doxepin hydrochloride topical cream, 5%.

Closing thoughts…

How to get the FDA's Early Input on your alternative BE approaches that include M&S approaches?

- Formal Meeting
  - submit a Product Development meeting request with your questions
- Controlled correspondence
  - an option for further discussion



Acknowledgements

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CDER/OGD/ORS/IO
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- Lei K Zhang, PhD

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Questions?