

# Enhanced Understanding of Structure Performance Relationship Using Modeling and Simulation – A Case Study with Dapsone Topical Gel

**Advancing Generic Drug Development 2024:  
Translating Science to Approval**

*Day 1, Session 2: Research to Support Guidance Development for Topical Drug Products*

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# Learning objectives

- Discuss in silico methodologies for topical products applied on the skin
- Explain the data requirements and scientific considerations when building and validating a dermal physiologically based pharmacokinetic (PBPK) model for dapsona topical gels
- Recognize how in silico models can be used to support regulatory decision making

# Outline

- Product-specific guidance (PSG) development
  - Considerations
- In silico methodologies for topicals
- Case study: Dapsone topical gel PSG
  - PBPK analysis: objective, model development, validation, application
  - Conclusions

# PSGs for topical products



- contain harmonized recommendations in alignment with the relevant general guidances
  - *Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in ANDAs*
  - *In Vitro Release Test (IVRT) Studies for Topical Drug Products Submitted in ANDAs*
  - *In Vitro Permeation Test (IVPT) Studies for Topical Drug Products Submitted in ANDAs*
- when they contain recommendations within a characterization-based bioequivalence (BE) approach, these BE recommendations are product-specific and are based on an understanding of the microstructure and performance of the drug product
- BE recommendations may include in vivo BE studies with PK endpoints or comparative clinical endpoint studies

# February 2024 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

**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**

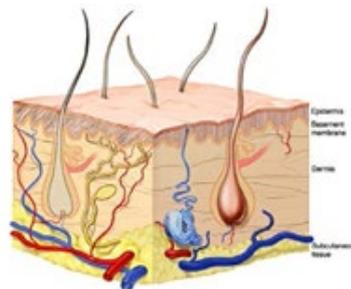
- “No significance difference” criterion
- same physicochemical and structural (Q3) attributes
- IVRT

**II. Option 2: One comparative clinical endpoint bioequivalence study**

### PSG revision was supported by modeling and simulation

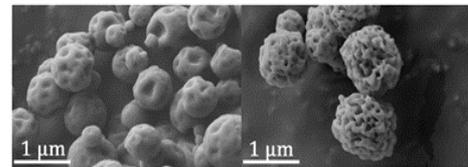
- Elucidated the relationship between drug product quality attributes and in vivo performance
- Established a link between systemic and local dapsone exposure

# In silico methodologies for skin drug products



Human Physiology  
in Individuals/Populations

Drug Product  
Characterization



In vitro Product Performance

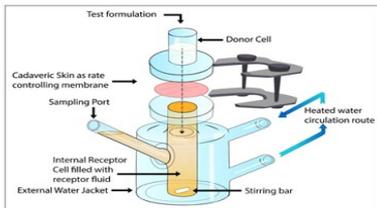
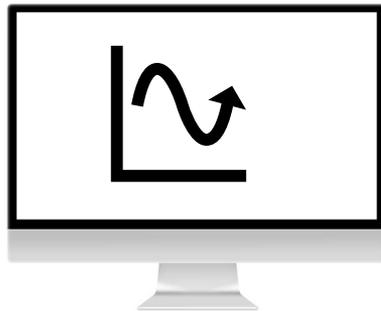


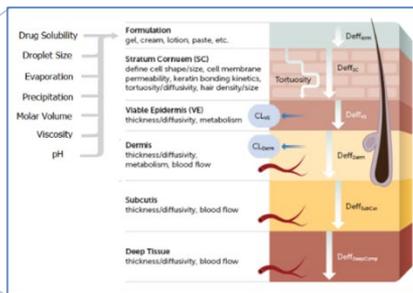
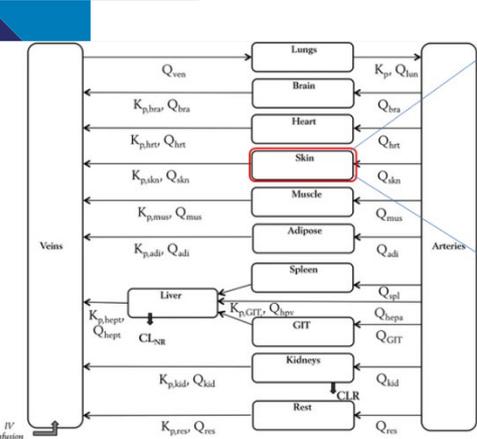
Figure 1. Schematic diagram of a static diffusion cell used in in vitro permeation tests.



# Model objectives

- Understand the factors governing the permeation of dapsonone through the skin.
- Identify drug product quality attributes for dapsonone topical gels, that may impact local and systemic bioavailability.
- Perform virtual bioequivalence assessments to evaluate the impact of formulation differences on BE outcomes.
  - Virtual in vivo BE studies
  - Virtual IVPT studies

# Basic principles of dermal PBPK modeling



Simcyp simulator v22, MPML MechDerma

## Development and Validation

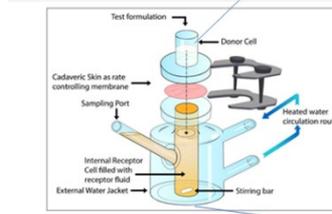
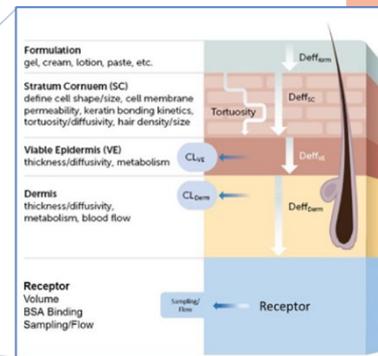


Figure 1. Schematic diagram of a static diffusion cell used in in vitro permeation tests.



Simcyp Simulator v22, IVPT Model

# Workflow

## Dapsone topical gel, 7.5%

Systemic disposition model for dapsone (literature)

Dermal PBPK model for dapsone topical gel, 7.5% using ANDA 1 data (internal validation)

Validation with IVPT data

External validation with ANDAs 2, 3, and 4 data

The validated dermal PBPK models were applied for VBE assessments for ANDAs 1, 2, 3, 4 in skin (SC and dermis) and plasma

## Dapsone topical gel, 5%

Systemic disposition model for dapsone (literature)

Dermal PBPK model for dapsone topical gel, 5% using ANDA 1, 2, 3 (external validation)

The validated dermal PBPK models were applied for VBE assessments for ANDAs 1, 2, 3 in skin (SC and dermis) and plasma

# Workflow

## Dapsone topical gel, 7.5%

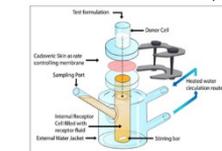


Figure 1. Schematic diagram of a skin absorption cell used in in vitro permeation tests.

In silico IVPT model for dapsone topical gel, 7.5% using the ANDA 1 data (internal validation)

Used the partially validated in silico IVPT model for VBE assessment for ANDAs 1, 2, 3 and 4 in skin (SC) and receptor media



Systemic disposition model for dapsone (literature)

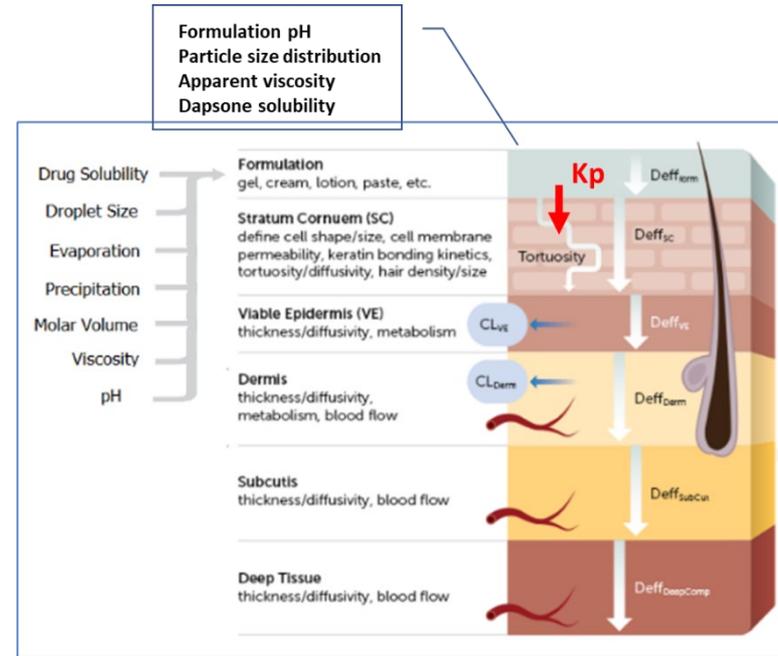
Dermal PBPK model for dapsone topical gel, 7.5% using ANDA 1 data (internal validation)

External validation with ANDAs 2, 3, and 4 data

The validated dermal PBPK models were applied for VBE assessments for ANDAs 1, 2, 3, 4 in skin (SC and dermis) and plasma

# PBPK analysis

- Model Development and Validation
- Formulation composition
- Drug product quality (Q3 in vitro characterization studies)
- In vivo systemic PK and IVPT study data
- Assumptions
  - Evaporation/drying rate
  - No rubbing post application



# PBPK analysis



- VBE assessment
- 10 Virtual BE trials
  - Population demographics matched
  - Sample size
  - Study design
  - Application conditions (dosing, anatomical site(s), duration of application)
  - BE for C<sub>max</sub> and AUC in SC, dermis, plasma
- IVPT virtual BE studies
  - Donor demographics
  - Donor replicates
  - Dosing conditions
  - Experimental conditions (IVPT study)
  - BE for PK metrics in SC (A<sub>max</sub> and AUC), receptor solution (AMT and J<sub>max</sub>)

# Dermal PBPK model for dapsons topical gel, 7.5%



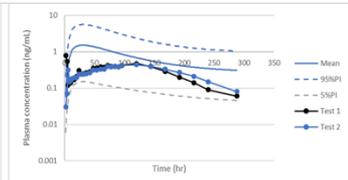
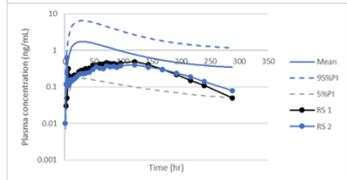
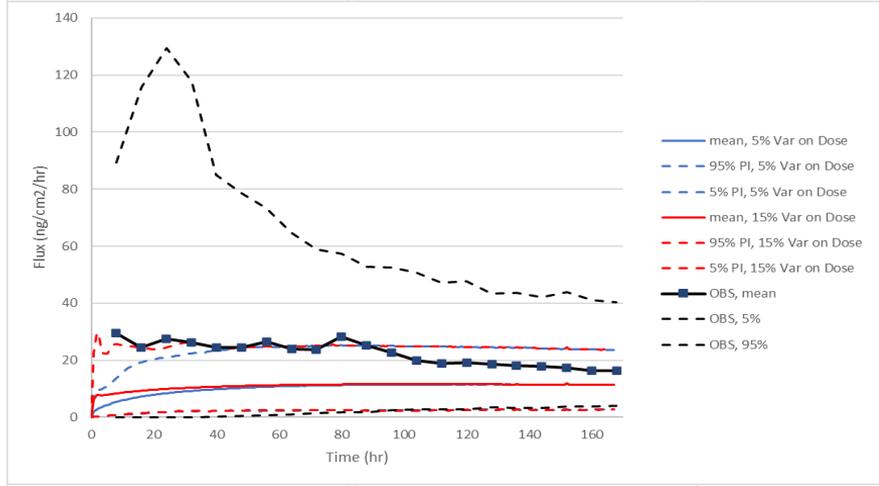
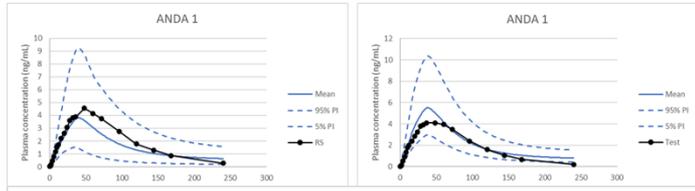
Systemic disposition model for dapsons (literature)

Dermal PBPK model for dapsons topical gel, 7.5% using ANDA 1 data (internal validation)

Validation with IVPT data

External validation with ANDAs 2, 3, and 4 data

The validated dermal PBPK models were applied for VBE assessments for ANDAs 1, 2, 3, 4 in skin (SC and dermis) and plasma



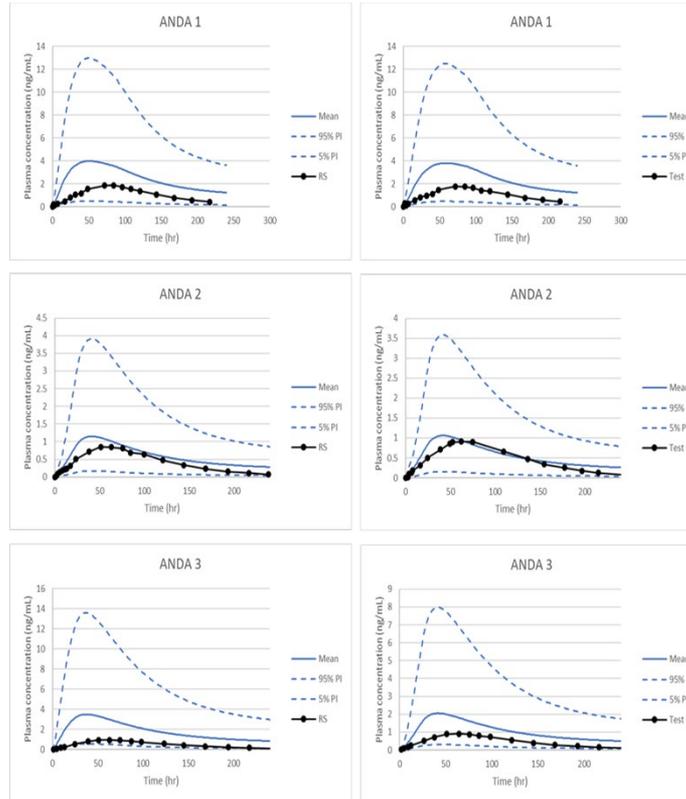
# Dermal PBPK model for dapsonsone topical gel, 5%



Systemic disposition model for dapsonsone (literature)

Dermal PBPK model for dapsonsone topical gel, 5% using ANDA 1, 2, 3 (external validation)

The validated dermal PBPK models were applied for VBE assessments for ANDAs 1, 2, 3 in skin (SC and dermis) and plasma



# Analysis on virtual BE trials



	Dapsone topical gel, 7.5%				Dapsone topical gel, 5%		
	ANDA 1	ANDA 2	ANDA 3	ANDA 4	ANDA 1	ANDA 2	ANDA 3
Matrix	VBE outcome						
SC	Pass	Pass	Pass	Pass	Pass	Pass	Pass
Dermis	Pass*	Pass	Pass*	Pass	Pass	Pass	Pass*
Plasma	Pass*	Pass	Pass	Pass	Pass	Pass	Pass*

\*The VBE analysis revealed dependency of the VBE outcome on particle size distribution and apparent viscosity and their interplay Simcyp simulator v22/VBE model

- For the studied ANDAs where the test product meets the “no significant difference criterion”, the M&S analysis showed that:
  - Q3 sameness between RS and test products leads to BE locally and systemically
  - Certain Q3 attributes such as particle size distribution and apparent viscosity may impact BE outcomes and should closely controlled

# Analysis on virtual IVPT studies



## In Vitro Permeation Test Studies for Topical Drug Products Submitted in ANDAs Guidance for Industry

*DRAFT GUIDANCE*

### VIII. IVPT PIVOTAL STUDY STATISTICAL ANALYSIS

- For the studied ANDAs where the test product meets the “no significant difference criterion”, the M&S analysis showed that:
  - Q3 sameness between RS and test products leads to BE locally and in the receptor solution

	Dapsonе topical gel, 7.5%			
	ANDA 1	ANDA 2	ANDA 3	ANDA 4
Matrix	VBE outcome			
SC	Pass	Pass	Pass	Pass
Receptor solution	Pass	Pass (Jmax SABE)	Pass	Pass

# Conclusions



- Enhanced understanding of the structure-performance relationship of dapsones gels gained through the PBPK modeling research
  - Apparent viscosity and particle size distribution appear to be Q3 quality attributes that may impact the local and systemic dapsones bioavailability.
  - For test products that meet the “no significant difference criterion”, Q3 sameness between RS and test products appears to lead to BE locally and systemically
- The developed dermal PBPK models can serve as tools supporting a risk-based BE assessment
- The compelling evidence from this PBPK modeling aligns with, and reinforces, the BE recommendations in the aforementioned draft PSGs for other topical gels

# Challenge Question #1



Which Q3 attributes were identified as impacting bioavailability based on the developed dermal PBPK model?

- A. Formulation pH
- B. Rheological properties, apparent viscosity
- C. Particle size distribution
- D. Droplet size distribution
- E. B and C.

# Challenge Question #2



Enhanced understanding of the structure-performance relationship of dapsones gels gained through the PBPK modeling research led to:

- A. A successful PDEV meeting for an applicant
- B. An ANDA approval
- C. A PSG revision

# Acknowledgements



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