Mechanistic Modeling Supporting Regulatory Assessment for Generic Tazarotene Cream

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

Session 1: Current Recommendations, Challenges and Opportunities for Topical Products

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September 10th, 2026

Outline

Mechanistic models of skin absorption

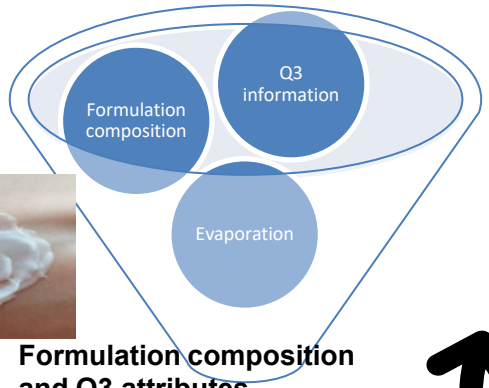
Dermal Physiologically Based Pharmacokinetic (PBPK) models

- Building blocks
- Evolution

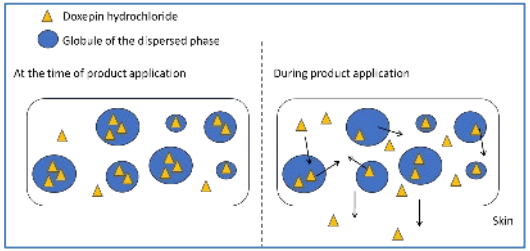
Case Studies

- Diclofenac sodium topical **gel**, 1%
- Tazarotene topical **cream**, 0.05%

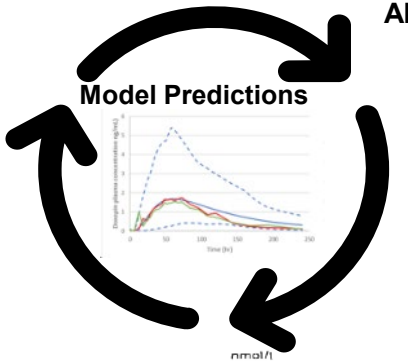
Development of Drug Product Specific PBPK Models

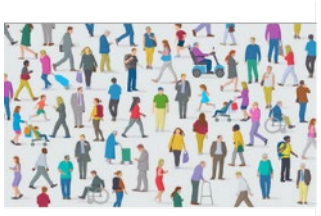


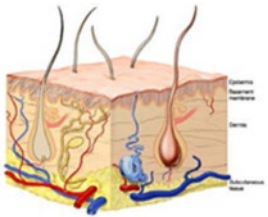
Formulation composition and Q3 attributes



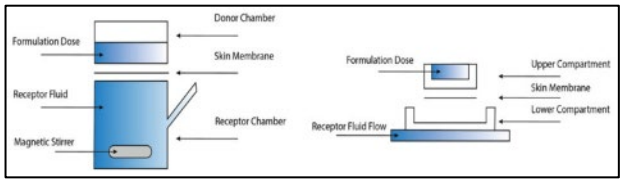
API distribution in the cream







Skin physiology and population variability



IVPT study data

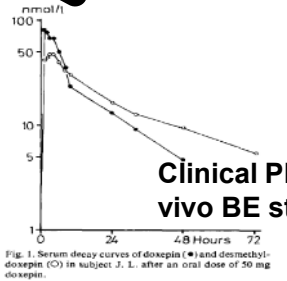


Fig. 1. Serum decay curves of doxepin (●) and desmethyl-doxepin (○) in subject J. L. after an oral dose of 50 mg doxepin.

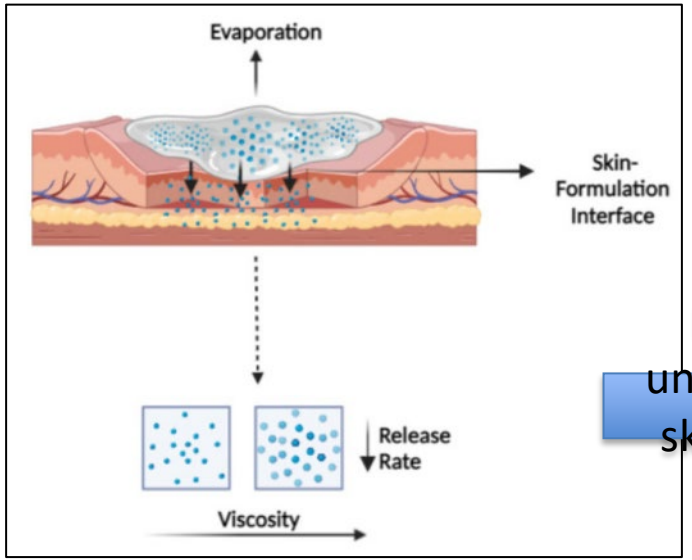
Clinical PK data (in vivo BE studies)

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

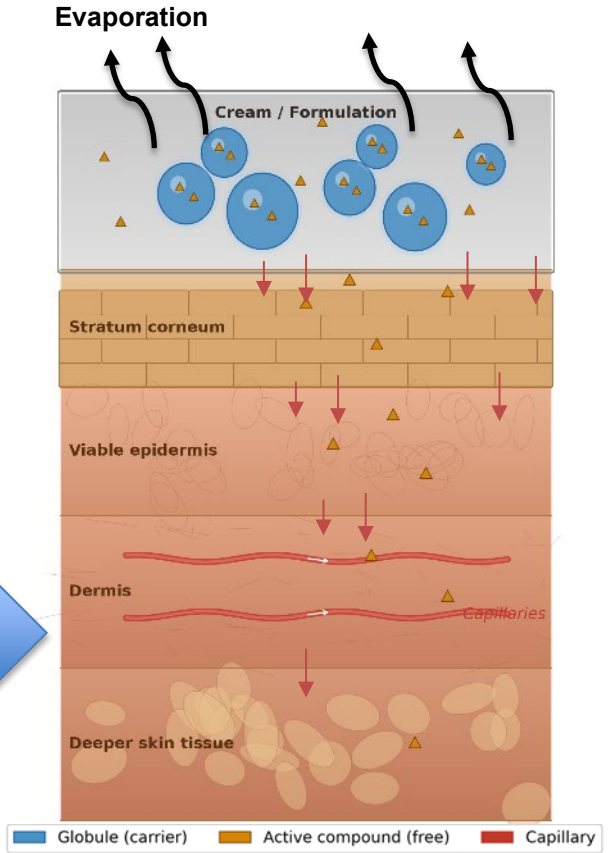
Modeling Drug Product Application: Guiding Principles

"In use" product conditions

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

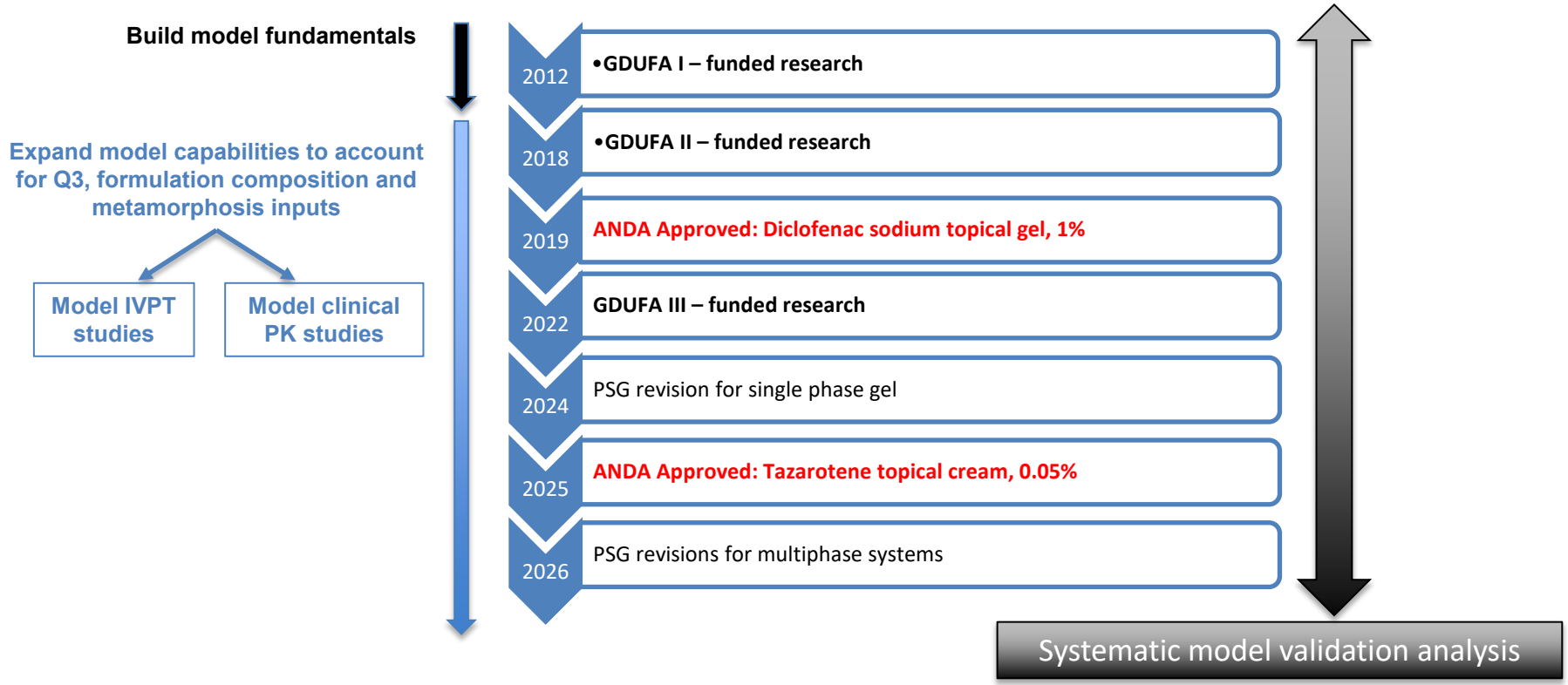


Mechanistic understanding in skin absorption models



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

Evolution of Mechanistic Skin Absorption Models for Generics



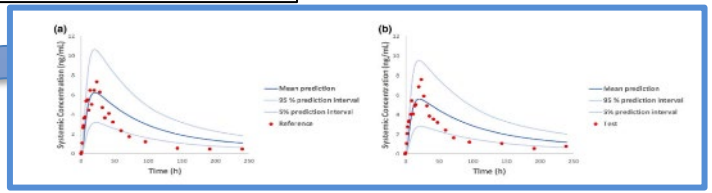
Case studies

1. Diclofenac sodium topical gel, 1%

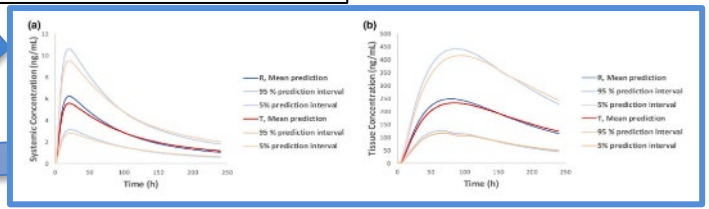
Regulatory Approval Supported by Modeling and Simulation

- Generic diclofenac sodium topical gel, 1% referencing Voltaren® (diclofenac sodium) topical gel, 1% (NDA 022122)
- PSG recommendation:
  - comparative clinical endpoint BE study
  - BE study with PK endpoints
- Alternative BE approach for a Q1/Q2/Q3 same formulation: dermal PBPK model **in lieu of an in vivo comparative clinical endpoint BE study**

Verified/Validated Model



In Vivo BE Study Simulation



Virtual Bioequivalence (VBE) 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

Synovial joint of the knee

PSG: product-specific guidance, qualitative (Q1) and quantitative (Q2) sameness of inactive ingredient components and quantitative composition between reference (R) and generic (T) products, Q3: Physical & Structural Characterization as relevant to the nature of the product, PI: prediction interval.

PMID: 33547863

Case studies

2. Tazarotene topical cream, 0.05%

Regulatory Approval Supported by Modeling and Simulation

- TAZORAC® Cream 0.05% (NDA 021184) indicated for plaque psoriasis

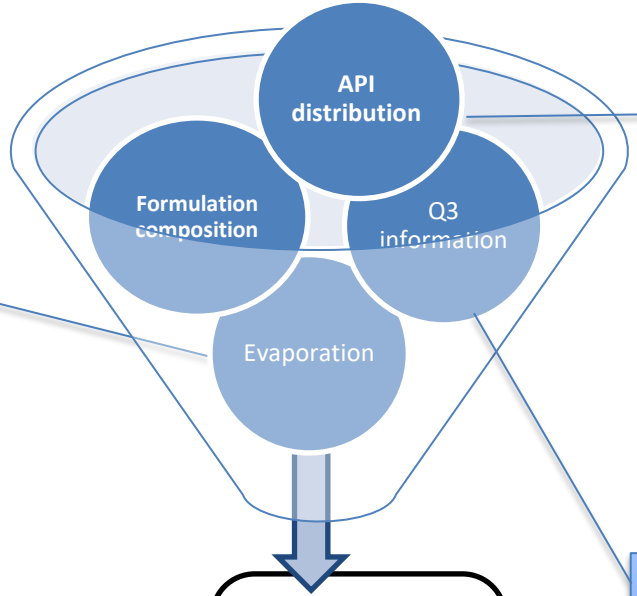
Product Specific Guidance Bioequivalence Recommendations	Alternative Bioequivalence Approach
T product that has the **same inactive ingredients and at the same amounts** present in their formulation as the RS	✓
T product that has the **same physicochemical and structural (Q3) characteristics** as the RS	✓
RS and T product show equivalent rate of tazarotene release based upon an acceptable **in vitro release test (IVRT) bioequivalence study**	✓
RS and T product show equivalent rate and extent of tazarotene permeation through excised human skin based upon an acceptable **in vitro permeation test (IVPT) bioequivalence study**	Modeling and simulation approach to demonstrate bioequivalence for the T product and RS in the skin and the plasma in virtual subjects

NSD: no significant difference, RS: Reference Standard

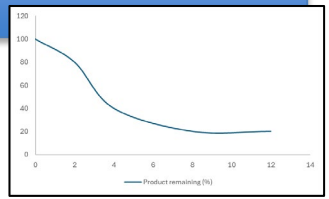
M&S Approach Overview

Model development with Q1/Q2/Q3 data

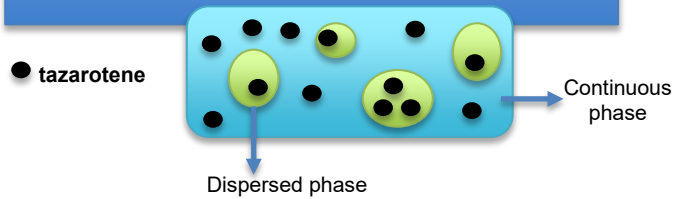
M&S Approach: Model Building

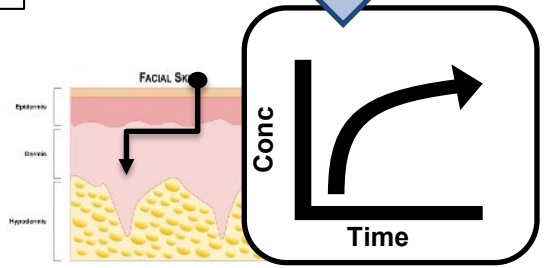


Metamorphosis: loss on drying



Tazarotene amounts measured in the phases of the product

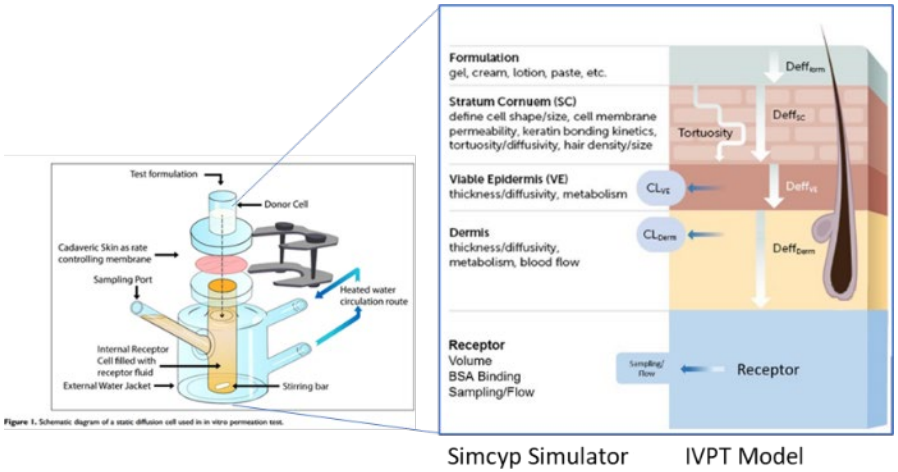




In vitro characterization studies

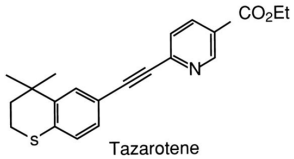
Globule size distribution, Formulation pH, Apparent viscosity

M&S Approach: Model Building

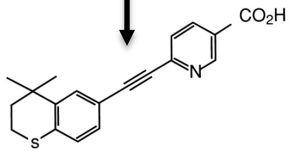


- ✓ IVPT study 1 and 2: 4-6 donors and 3-4 replicates
- ✓ IVPT method validated for its intended purpose
- ✓ Mass balance studies on tazarotene and tazarotenic acid

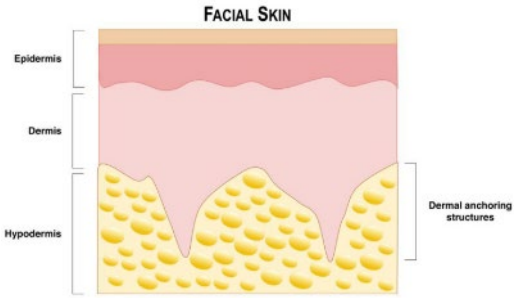
Challenge: high variability



Tazarotene



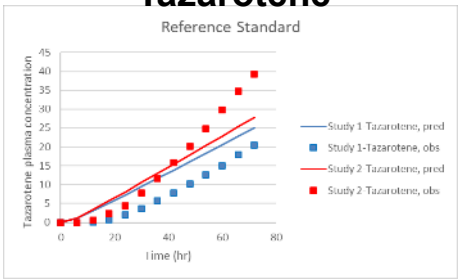
Tazarotenic Acid

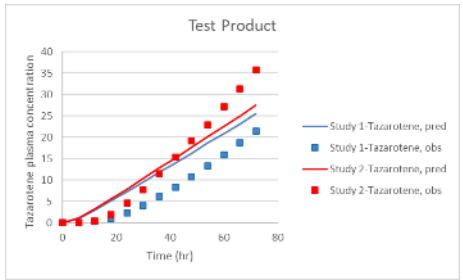


IVIVE: in vitro-in vivo extrapolation

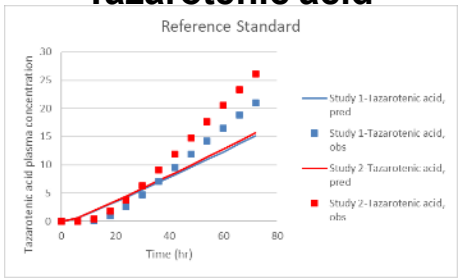
M&S Approach: Model Building and Internal Validation

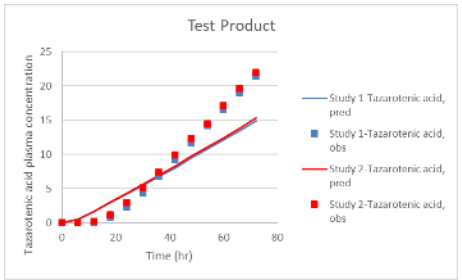
Tazarotene





Tazarotenic acid





Overall acceptable IVPT model performance based on

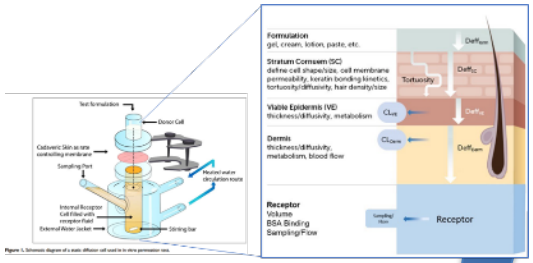
- ✓ 2 IVPT studies
- ✓ Mass balance data
- ✓ Additional IVPT study datasets

IVIVE: in vitro-in vivo extrapolation

M&S Approach Overview: Model Validation

Model validation with IVPT study data

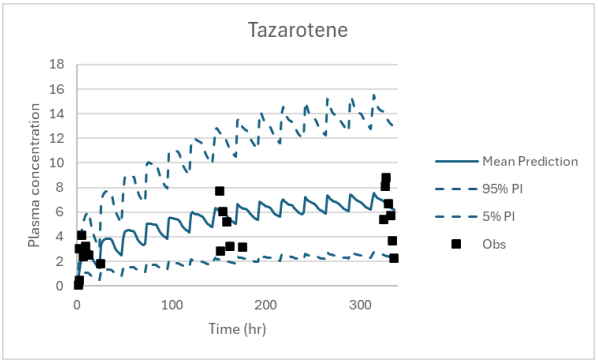
Model validation with in vivo clinical PK data (literature)

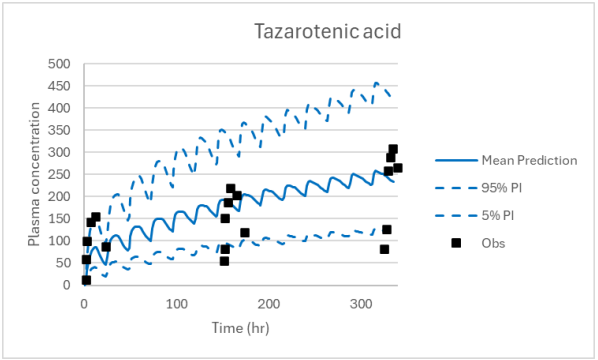


Simcyp Simulator v22, IVPT Model

IVIVE

Literature: 10 simulated trials

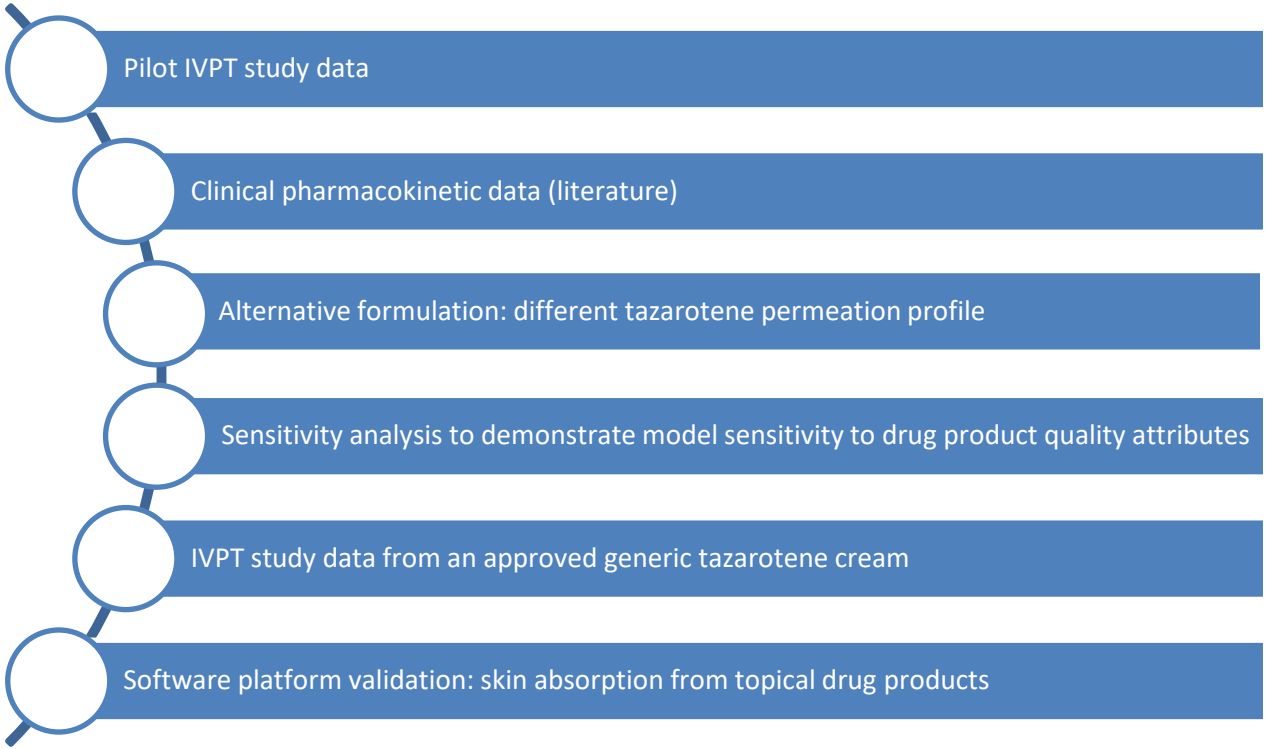




IVIVE: in vitro-in vivo extrapolation

M&S Approach: Model Validation

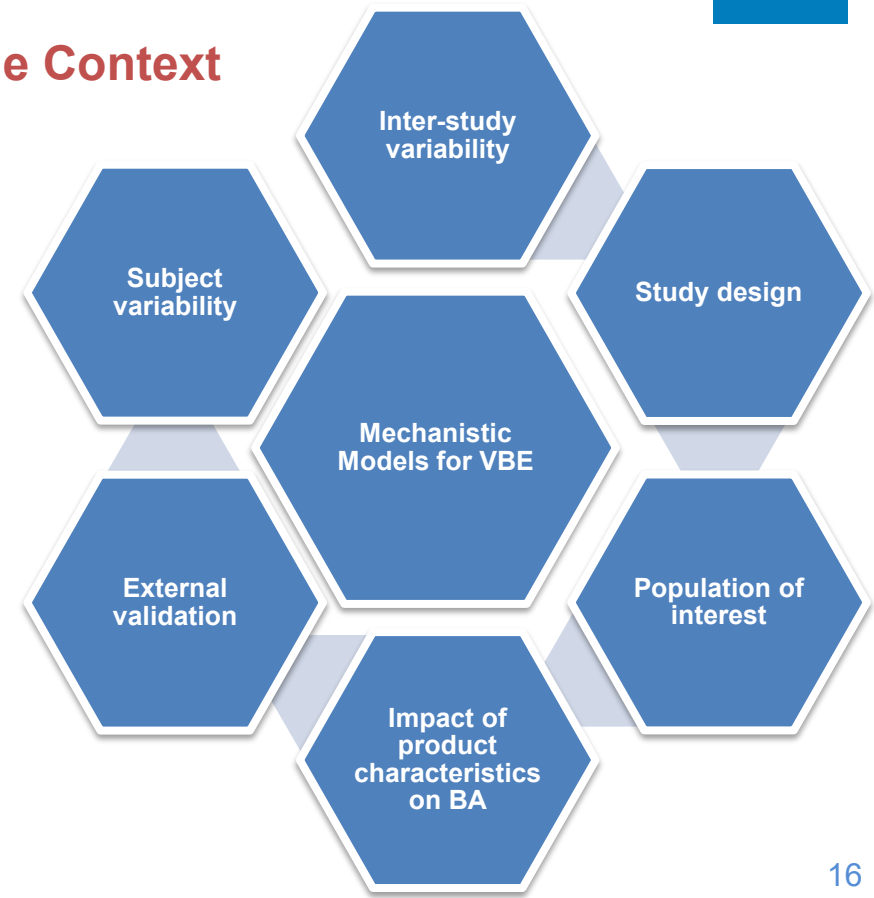
Multi-layered Model Validation Strategy



IVIVE: in vitro-in vivo extrapolation

M&S Approach: Model Validation

Model Validation Strategy considering the Context of Use:
Virtual Bioequivalence Assessment



M&S Approach: VBE Assessment

Face as application site: VBE assessments with the validated PBPK model by the applicant

RS and T were found BE in the SC, dermis and plasma

Abdomen as application site: VBE assessments with the validated PBPK model by the assessor

RS and T were found BE in the SC, dermis and plasma

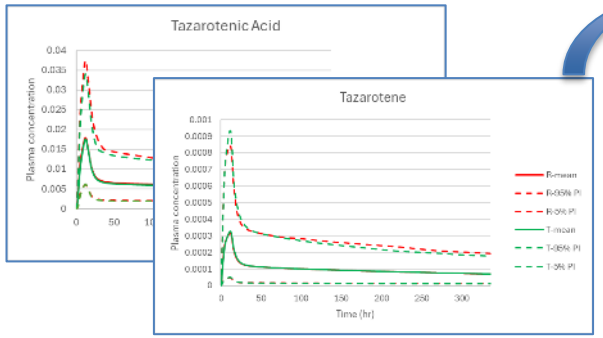
SC: stratum corneum, VE: viable epidermis

M&S Approach: VBE Assessment

Model application for VBE assessments for RS and T products

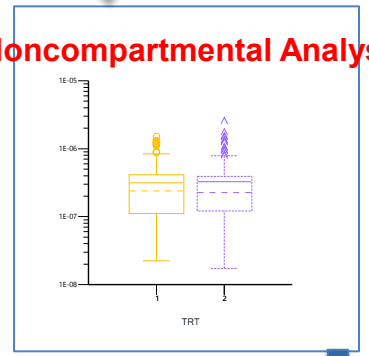
- ✓ Validated dermal PBPK models for RS and T
- ✓ BE simulated trials (10 crossover trials, sample size informed by population variability)
- ✓ BE statistical assessment in skin (SC, dermis) and plasma

Simulated BE Trial 1 …



Simulated BE Trials

Noncompartmental Analysis



Tazarotene						
	Cmax			AUC0-t		
Matrix	Ratio (%)	PI 90% lower	PI 90% upper	Ratio (%)	PI 90% lower	PI 90% upper
Plasma	100.85	88.61	114.77	98.00	86.10	111.53
SC	94.83	93.55	96.12	95.37	93.11	97.69
Dermis	99.07	90.03	109.01	96.35	88.14	105.32
Tazarotenic acid						
Plasma	96.84	86.58	108.32	94.99	85.49	105.56
SC	93.04	87.26	99.21	92.91	86.78	99.47
Dermis	98.51	90.97	106.67	96.01	89.19	103.34

Statistical Assessment

SC: stratum corneum, VE: viable epidermis

Conclusions

- The dermal PBPK models for RS and T product were built on information on composition, Q3 characterization and IVPT studies
- The dermal PBPK models leveraged data on product metamorphosis and API distribution in the product phases
- The dermal PBPK models were validated for their context of use
- The dermal PBPK models reduced the need for in vivo and in vitro studies in the complex generics space for products applied on the skin

Overall Conclusions

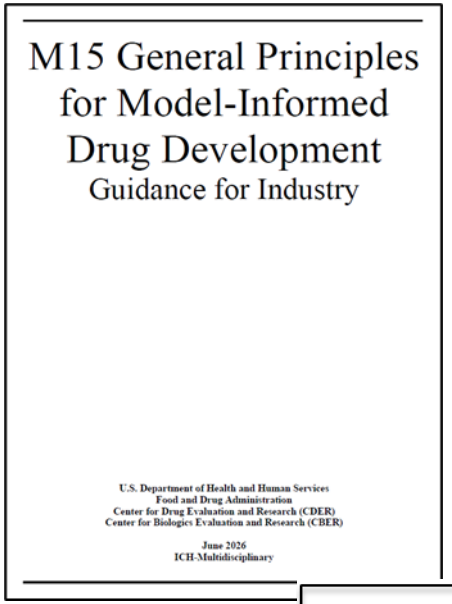
For generic products applied on the skin, PBPK models can

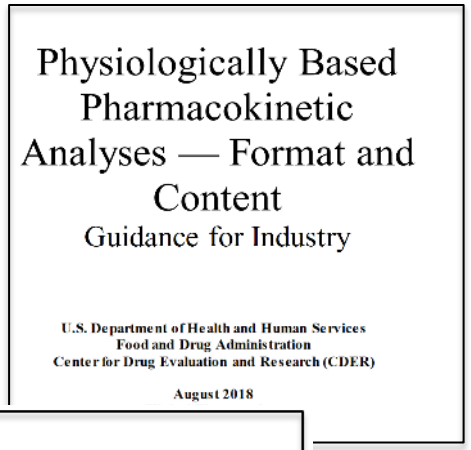
- be applied to mitigate the risk of not conducting in vivo and IVPT BE studies for a T product that meets the NSD criterion and is Q3 same to the RS
- be applied as risk-based assessment tools
  - drug product development
  - lifecycle management of the drug product
- be successfully integrated into the model integrated evidence paradigm

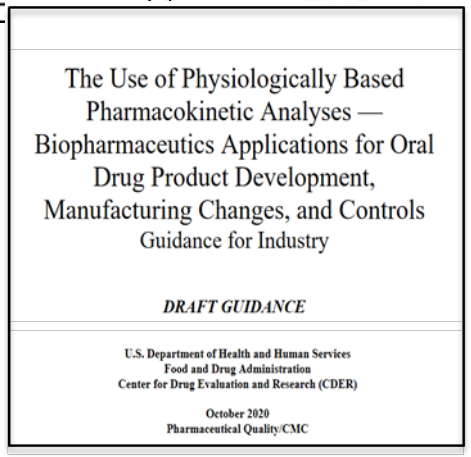
Closing thoughts…

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

CDER/OGD/ORS/DQMM
- Andrew Babiskin, PhD
- Lanyan (Lucy) Fang, PhD

CDER/OGD/ORS/DTPI
- Priyanka Ghosh, PhD
- Tannaz Ramezanli, PhD, PharmD
- Markham Luke, PhD, MD
- Sam Raney, PhD

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

CDER/OGD and CDER/OPQ review teams
- Usha Katragadda, PhD
- Wendy Cai, PhD
- Chunsheng Zhao, PhD
- Svetlana Cherstniakova, PhD
- April Braddy, PhD, RAC, SEP
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- Yoon Oh, PhD
- Kai Kwok, PhD

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Questions?