

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

Eleftheria Tsakalozou, PhD

Lead Pharmacologist
CDER/OGD/ORS/DQMM

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Outline

Mechanistic models of skin absorption

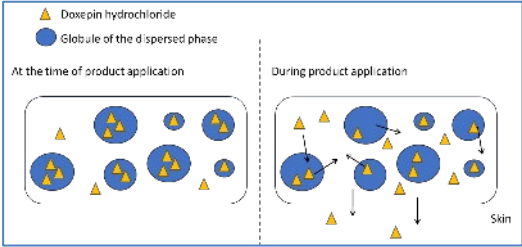
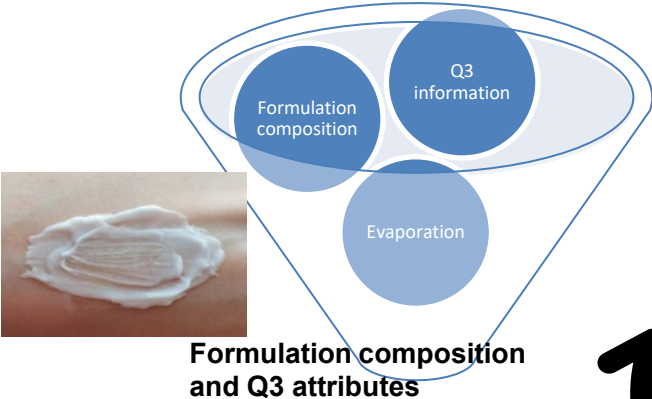
Dermal Physiologically Based Pharmacokinetic (PBPK) models

- Building blocks
- Evolution

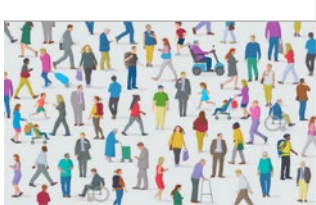
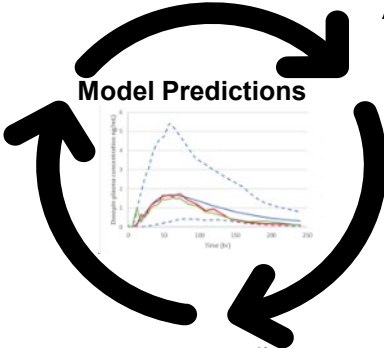
Case Studies

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

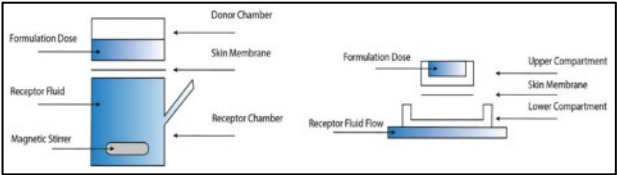
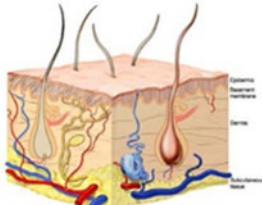
Development of Drug Product Specific PBPK Models



API distribution in the cream



Skin physiology and population variability



IVPT study data

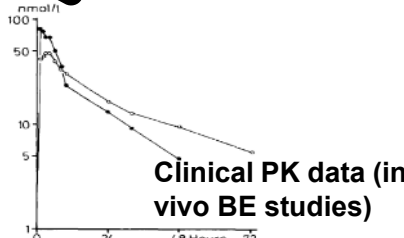


Fig. 1. Serum decay curves of doxepin (●) and dimethyldoxepin (○) in subject J. L. after an oral dose of 50 mg doxepin.

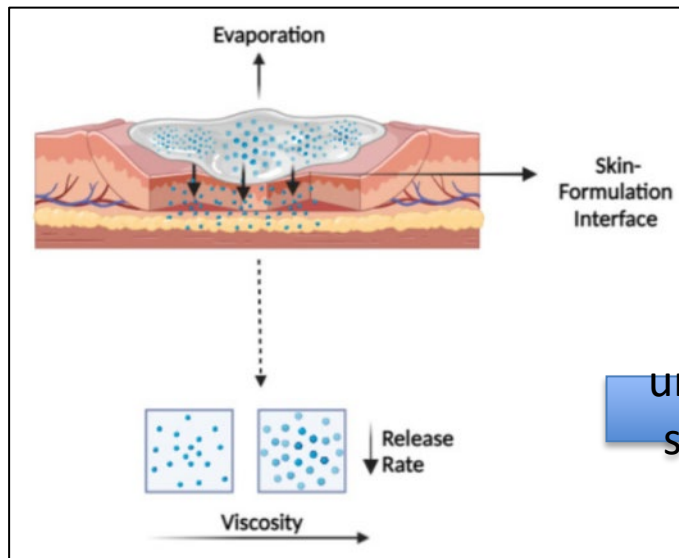
API: active pharmaceutical ingredient
 IVPT: in vitro permeation testing
 Q3: physicochemical and structural properties
 BE: bioequivalence

Modeling Drug Product Application: Guiding Principles

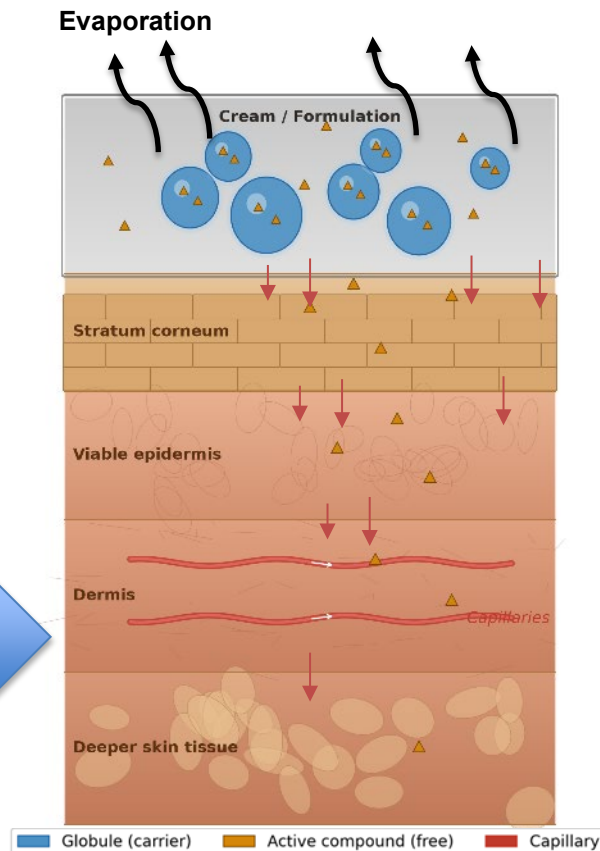


“In use” product conditions

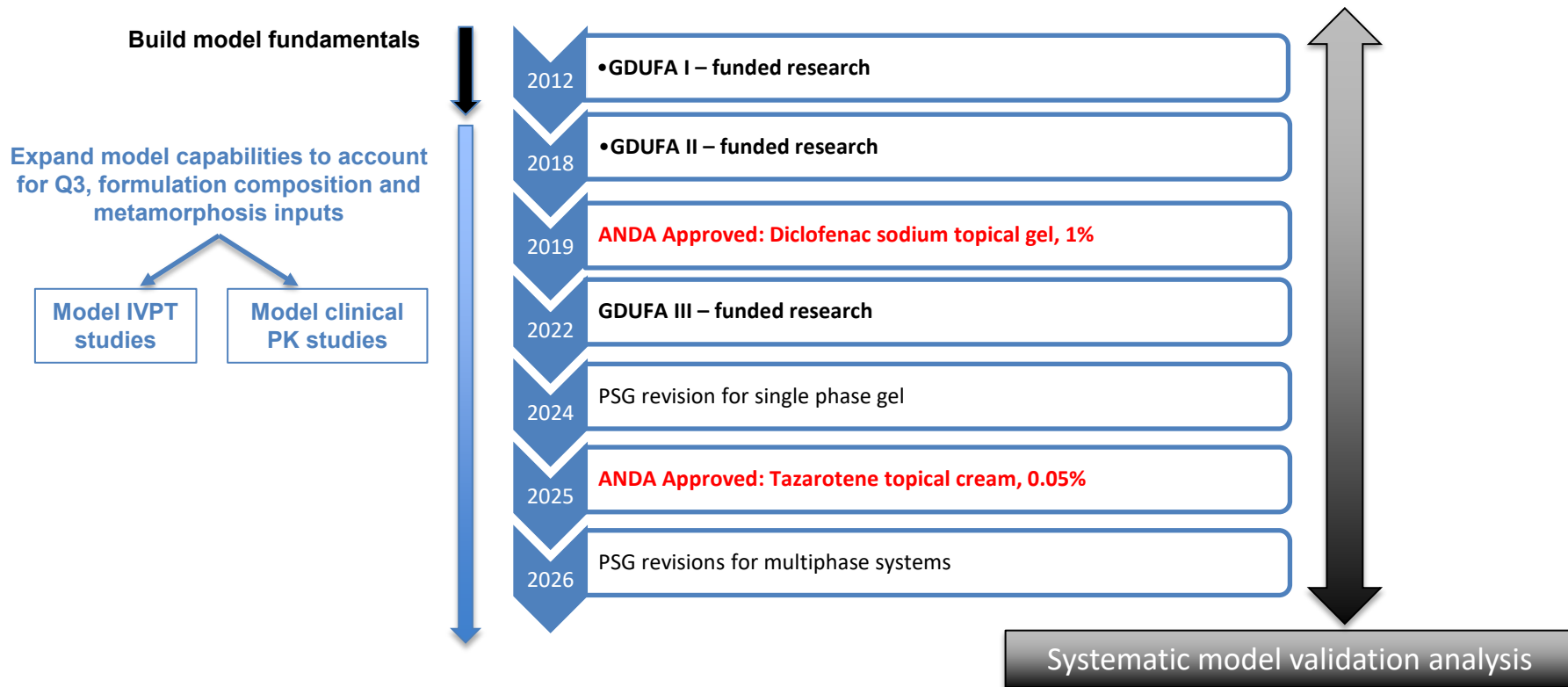
Drug product metamorphosis: evaporation, supersaturation and crystallization, changes in thermodynamic activity



Mechanistic understanding in skin absorption models



Evolution of Mechanistic Skin Absorption Models for Generics





Case studies

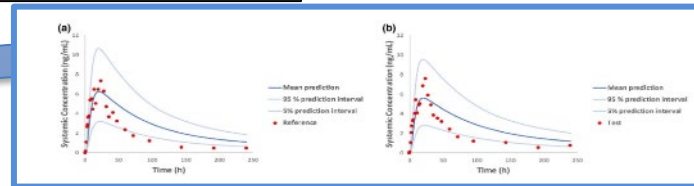
1. Diclofenac sodium topical gel, 1%

Regulatory Approval Supported by Modeling and Simulation

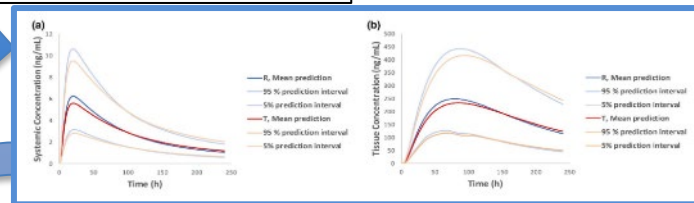


- Generic diclofenac sodium topical gel, 1% referencing Voltaren® (diclofenac sodium) topical gel, 1% (NDA 022122)
- PSG recommendation:
 - comparative clinical endpoint BE study
 - BE study with PK endpoints
- Alternative BE approach for a Q1/Q2/Q3 same formulation: dermal PBPK model **in lieu of an 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} pg	240.13	222.47	78	0.93	85.06	102.68
AUC, μ g-hr/ml	37,888.28	37,362.20	78	0.97	87.7	107.83

Synovial joint of the knee





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



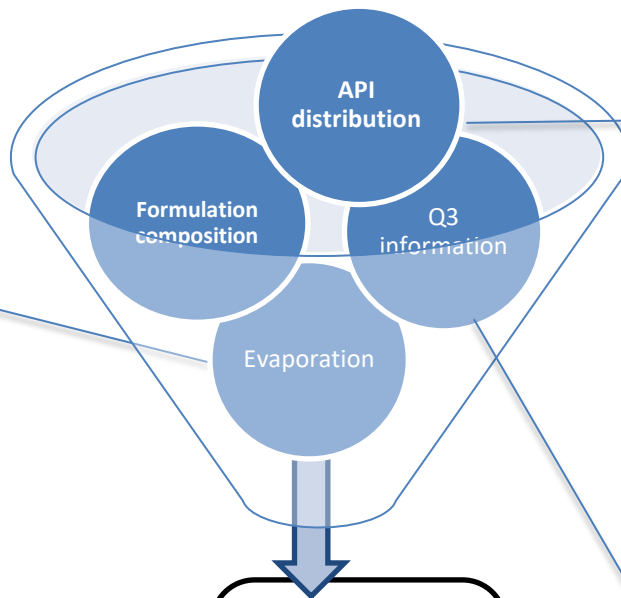
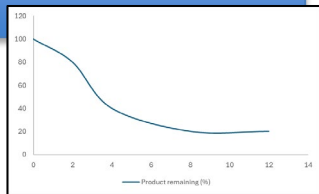
M&S Approach Overview



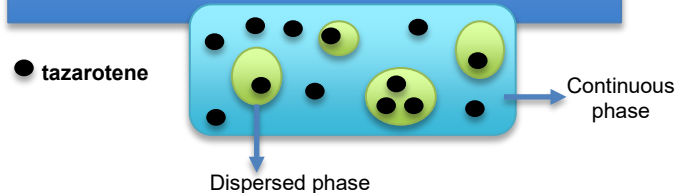
M&S Approach: Model Building

Model development
with Q1/Q2/Q3 data

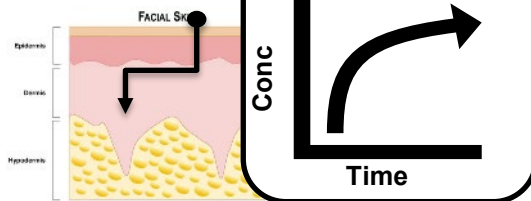
Metamorphosis: loss on drying



Tazarotene amounts measured in the
phases of the product



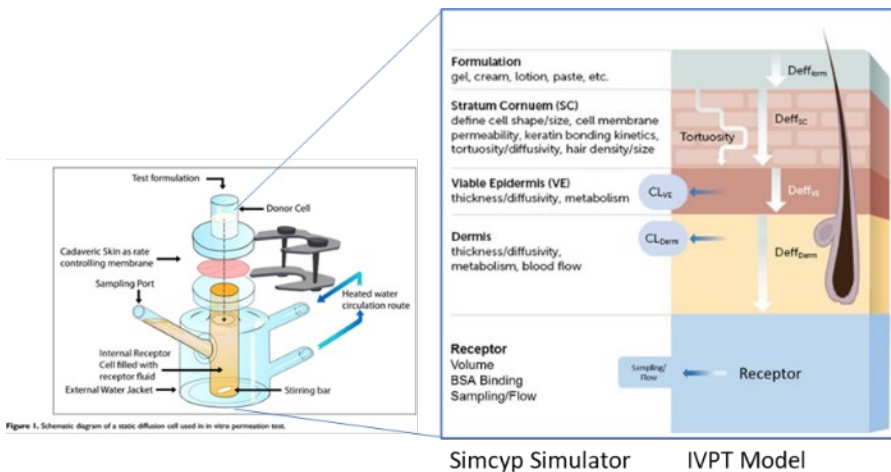
In vitro characterization studies
Globule size distribution, Formulation
pH, Apparent viscosity



M&S Approach: Model Building

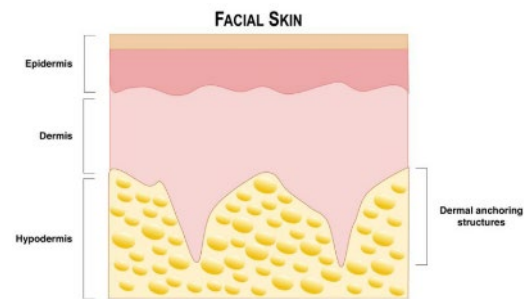
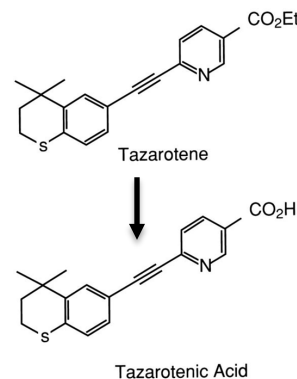
- ✓ IVPT study 1 and 2: 4-6 donors and 3-4 replicates
- ✓ IVPT method validated for its intended purpose
- ✓ Mass balance studies on tazarotene and tazarotenic acid

Challenge: high variability



Simcyp Simulator

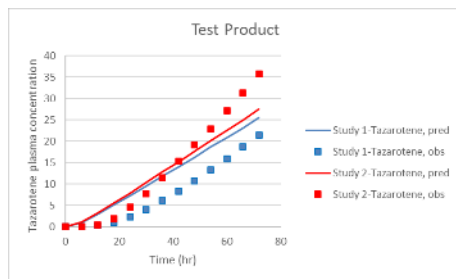
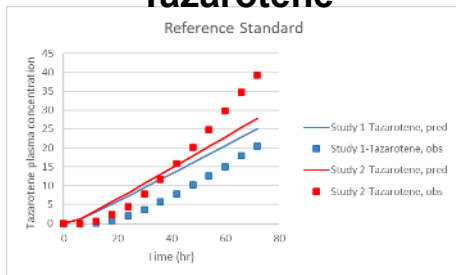
IVPT Model



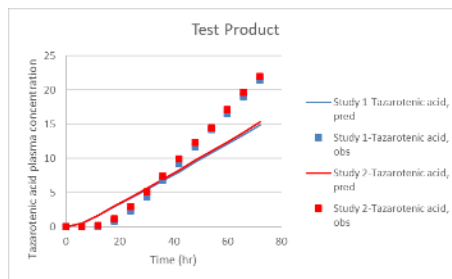
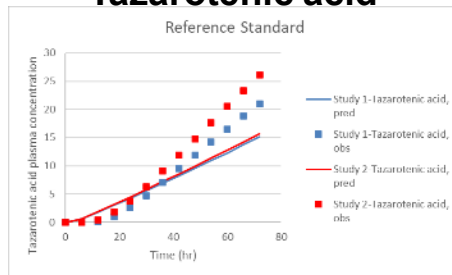
M&S Approach: Model Building and Internal Validation



Tazarotene



Tazarotenic acid



Overall acceptable IVPT model performance based on

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

M&S Approach Overview: Model Validation

Model validation with IVPT study data

Model validation with
in vivo clinical PK data
(literature)

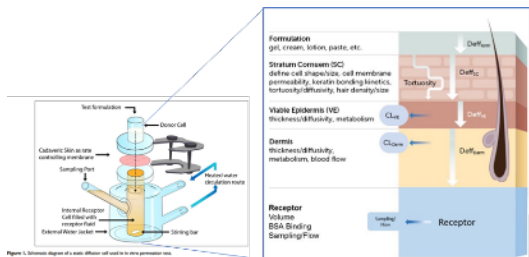
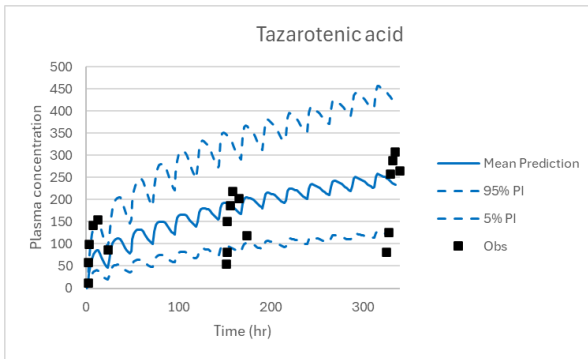
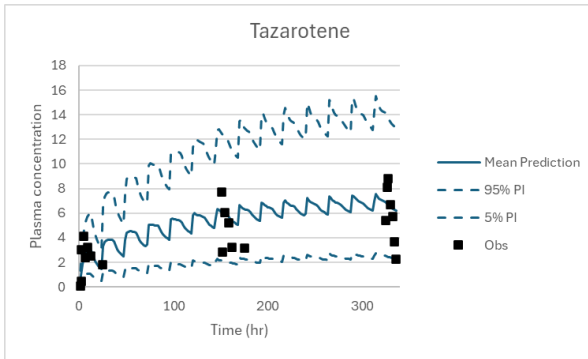


Figure 1. Schematic diagram of a static diffuser cell used in *in vitro* permeation tests.

Simcyp Simulator v22, IVPT Model

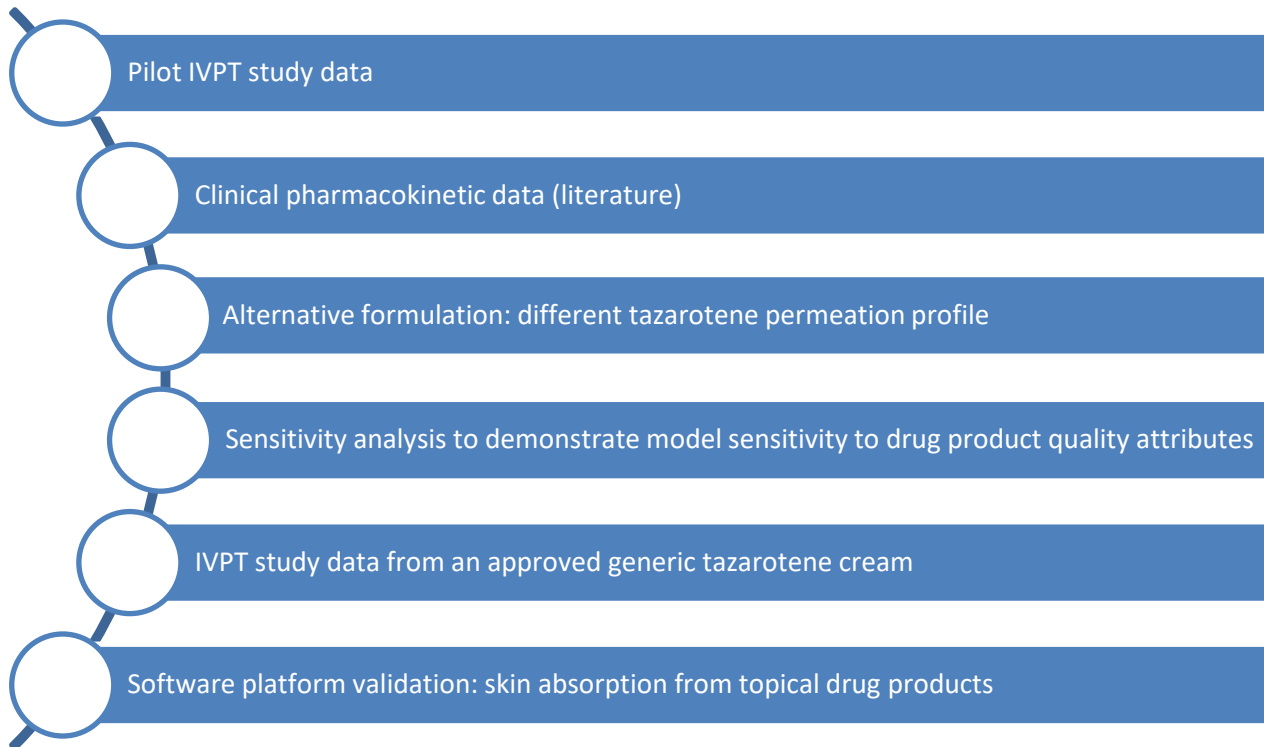
IVIVE

Literature: 10 simulated trials



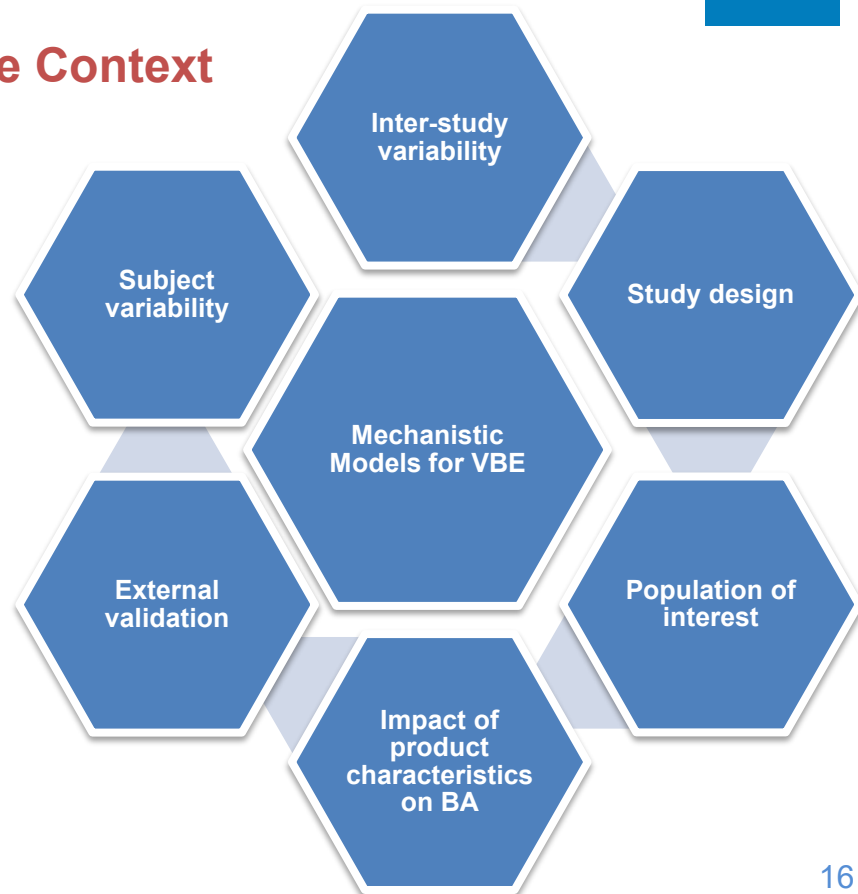
M&S Approach: Model Validation

Multi-layered Model Validation Strategy

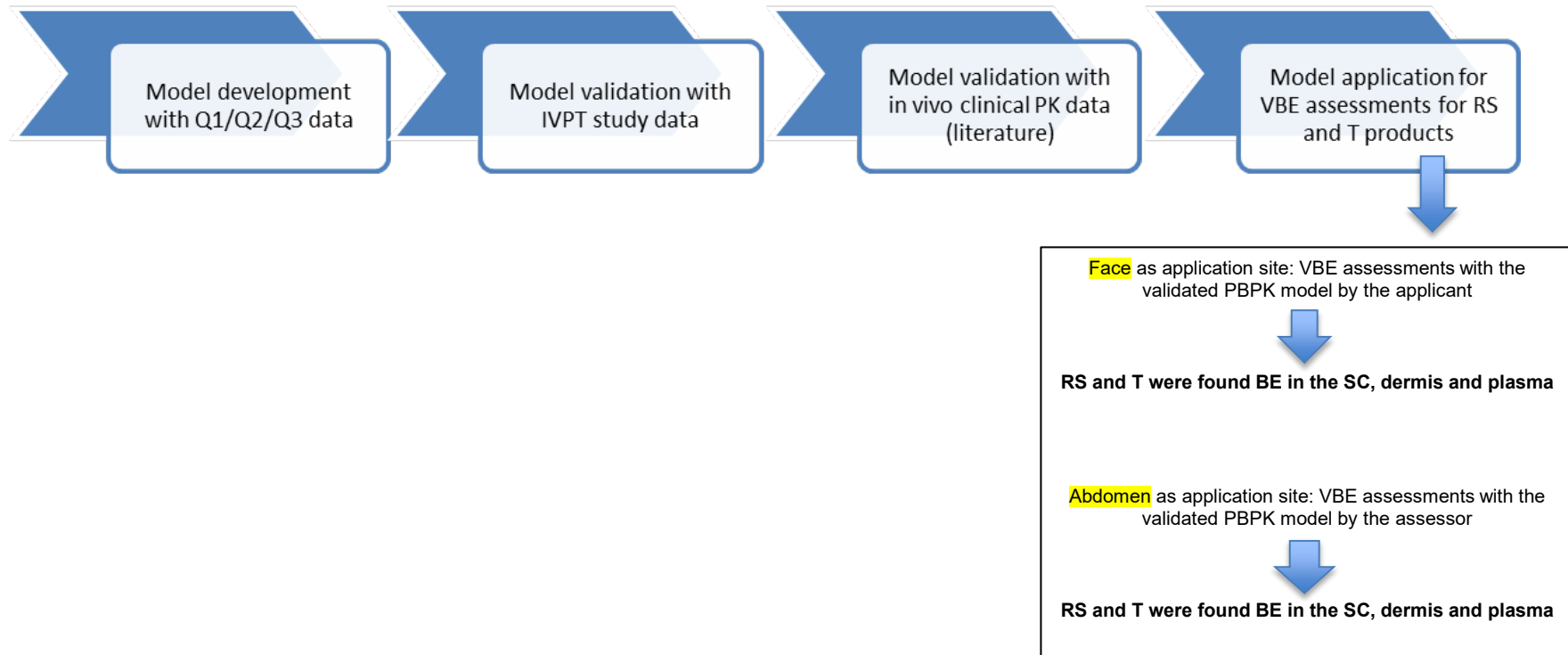


M&S Approach: Model Validation

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



M&S Approach: VBE Assessment

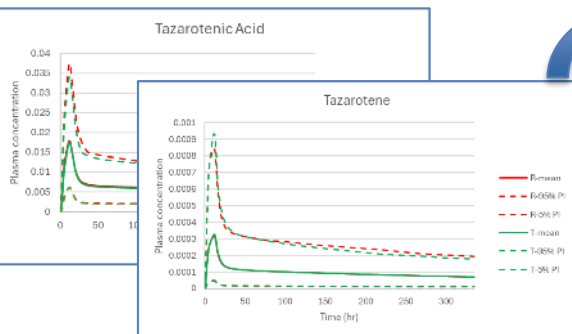


M&S Approach: VBE Assessment

Model application for
VBE assessments for RS
and T products

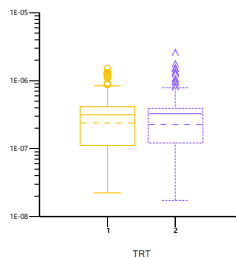
- ✓ Validated dermal PBPK models for RS and T
- ✓ BE simulated trials (10 crossover trials, sample size informed by population variability)
- ✓ BE statistical assessment in skin (SC, dermis) and plasma

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	100.8			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

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

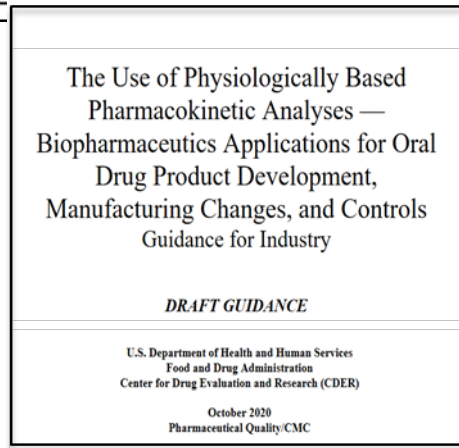
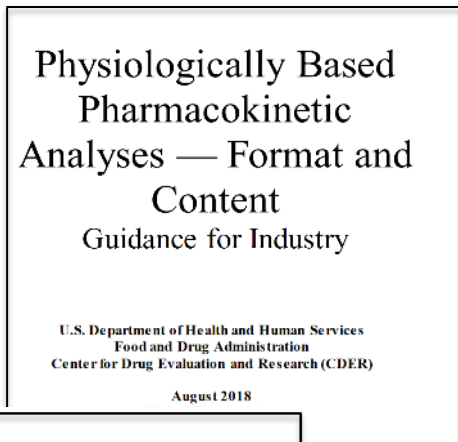
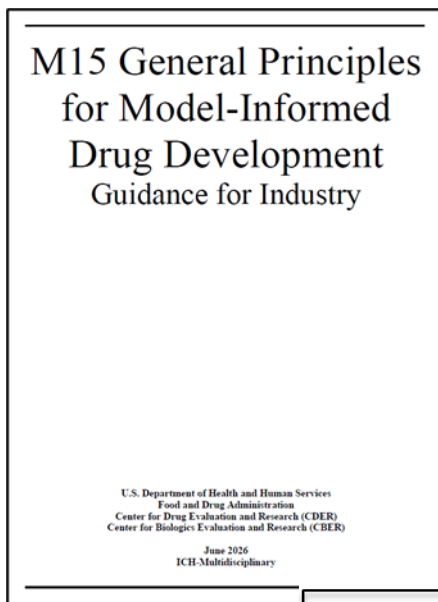
For generic products applied on the skin, PBPK models can

- 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



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Questions?