

Mechanistic Models for Generic Non-orally Administered Drug Products: Maximizing the Regulatory Impact Through MIE submissions

Eleftheria Tsakalozou, PhD

Lead Pharmacologist

DQMM | ORS | OGD | CDER

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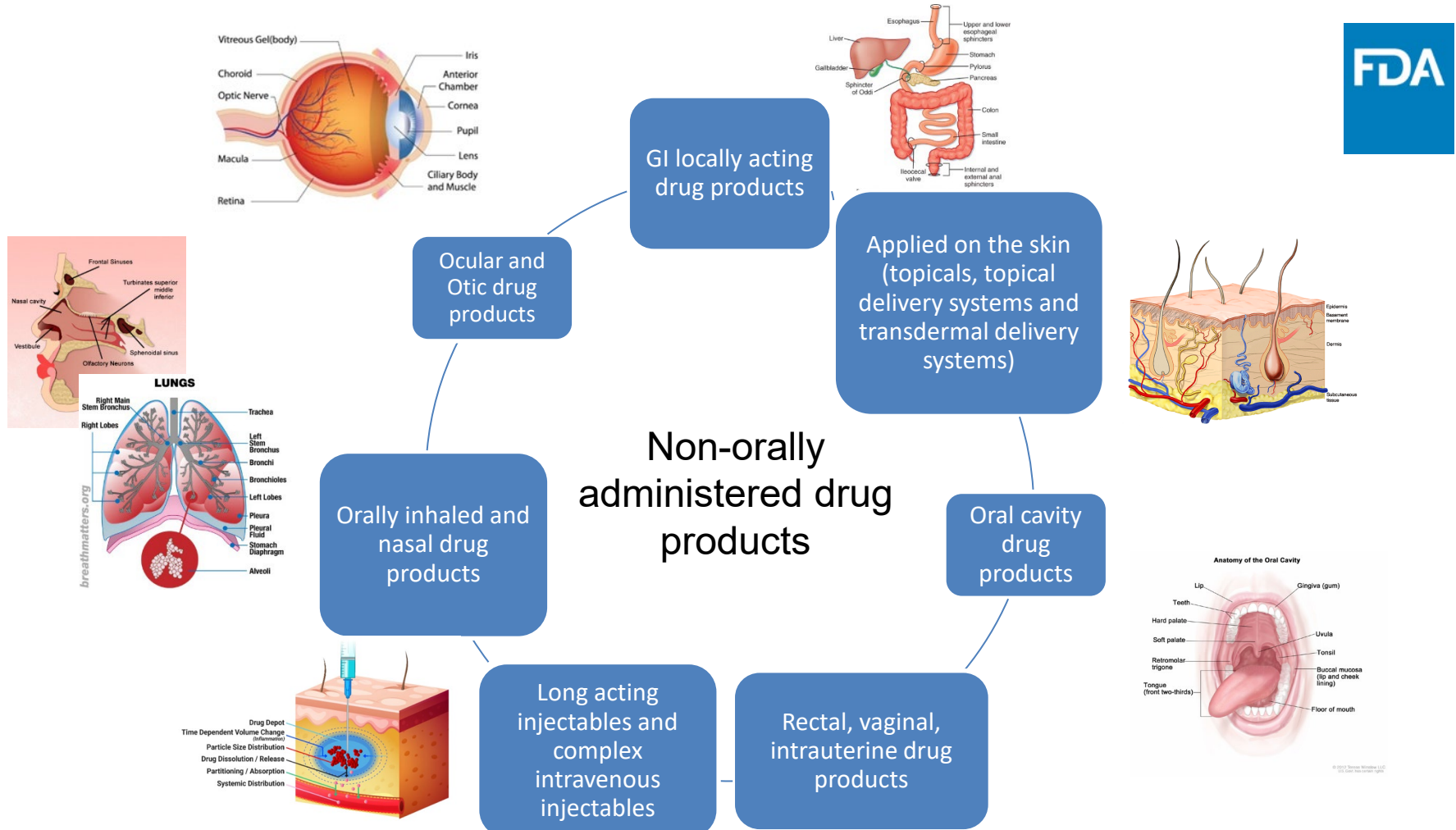
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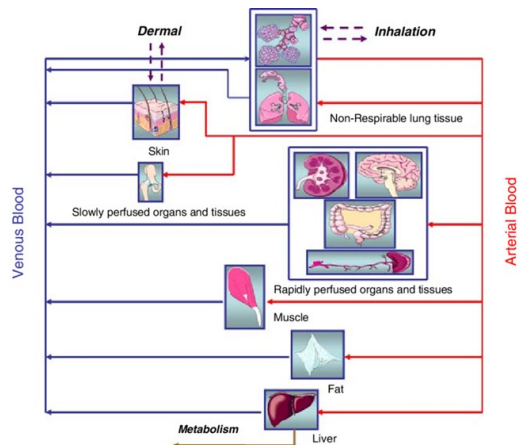
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Outline

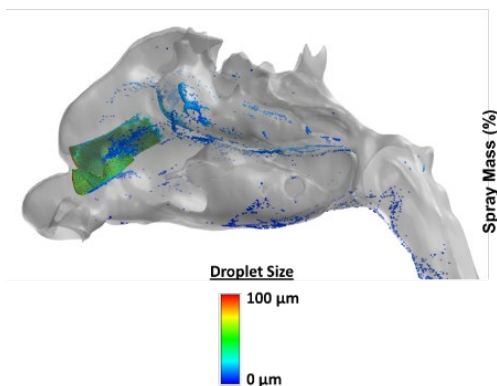
- Non-orally administered drug products
- Types of mechanistic models supporting modeling and simulation (M&S) approaches
- Scientific and Regulatory Expectations on Workflow: How to develop a mechanistic model for generic non-orally administered drug products?
 - Model assessment framework
 - Model development, verification, validation and application
- Documentation of M&S approach
- Checklist



Mechanistic Modeling and Simulation Tools For Non-Orally Administered Drug Products



- ***Physiologically based pharmacokinetic (PBPK) modeling***
 - Predictions of local and systemic active pharmaceutical ingredient (API) exposure
 - Integration of information on physiology, drug and drug product
 - Validated with in vitro or in vivo data
- ***Computational fluid dynamics (CFD) Modeling***
 - Prediction of fluid and particle transport
 - Allows for consideration of realistic geometries
 - Validated with in vitro or in vivo data



Mechanistic Modeling and Simulation Tools: “Building Blocks”

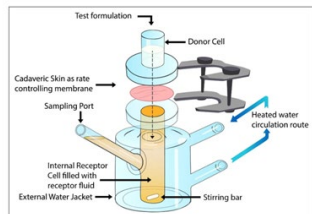
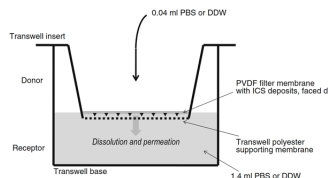
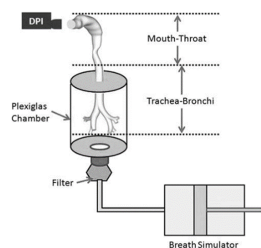


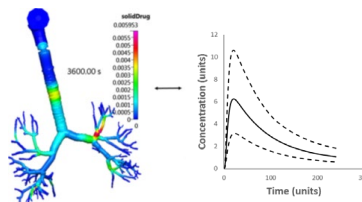
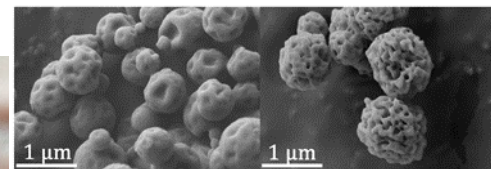
Figure 1. Schematic diagram of a static diffusion cell used in vitro permeation test.



In vitro Product Performance



Drug Product Characterization



Human Physiology in Individuals/Populations

M&S in Regulatory Space for Complex Generics

- Establishing bioequivalence (BE) for complex generics may be challenging
- Alternative BE approaches that contain M&S approaches are explored by applicants for complex generics

Critical to understand for the role of the M&S approach in a regulatory submission in the pre-submission or submission stage:



- ✓ Improve quality of interactions during industry meetings
 - ✓ Improve quality of submissions to FDA
 - ✓ Streamline regulatory assessment process
 - ✓ Reduce potential IRs and major deficiencies

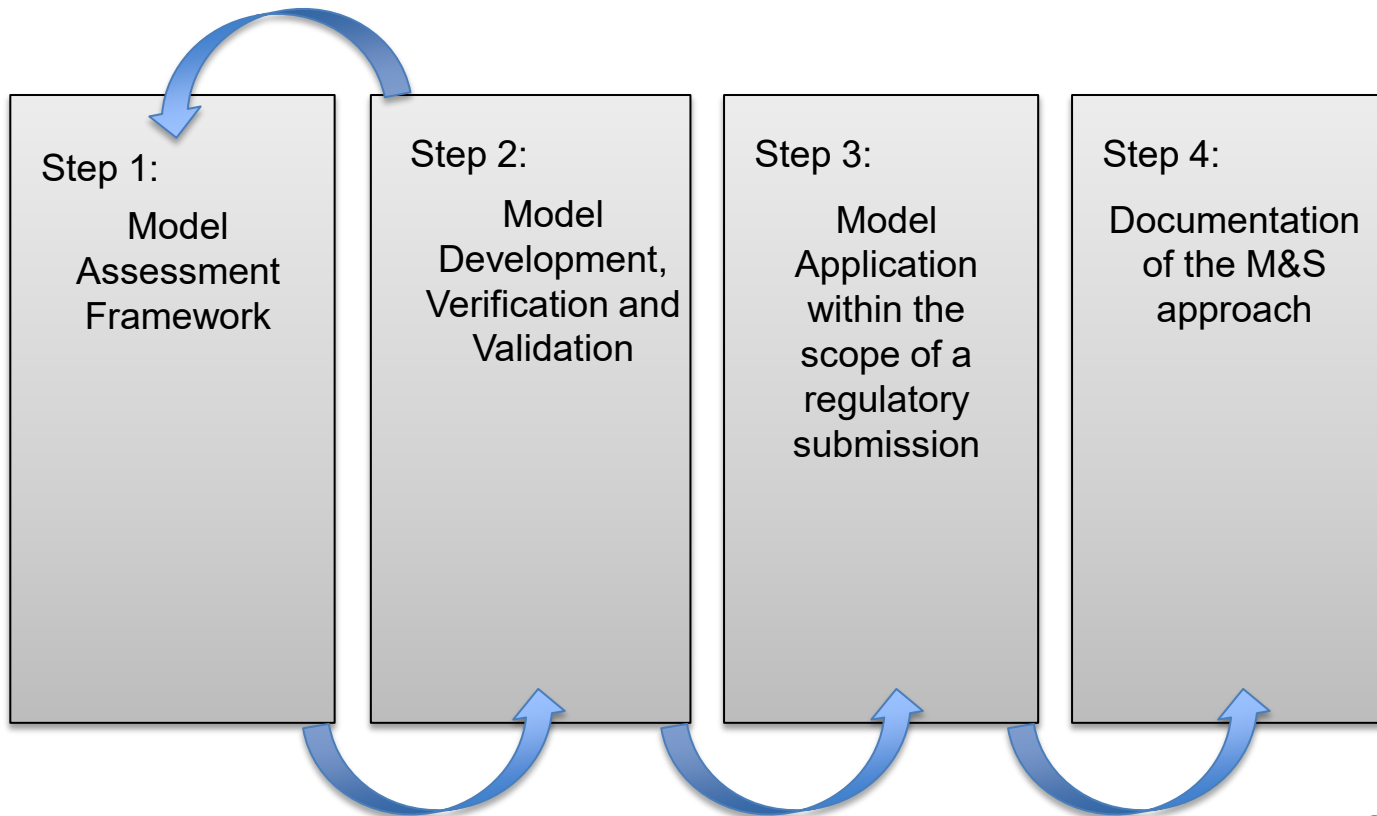
M15 General Principles
for Model-Informed
Drug Development
Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

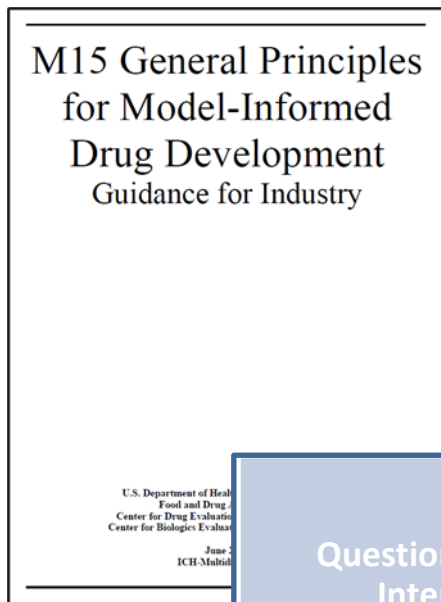
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Workflow: How to Develop a Mechanistic Model



Model Assessment Framework



Question of
Interest

Model Assessment

Consequence of
Wrong Decision

Context of
Use

Model
Influence

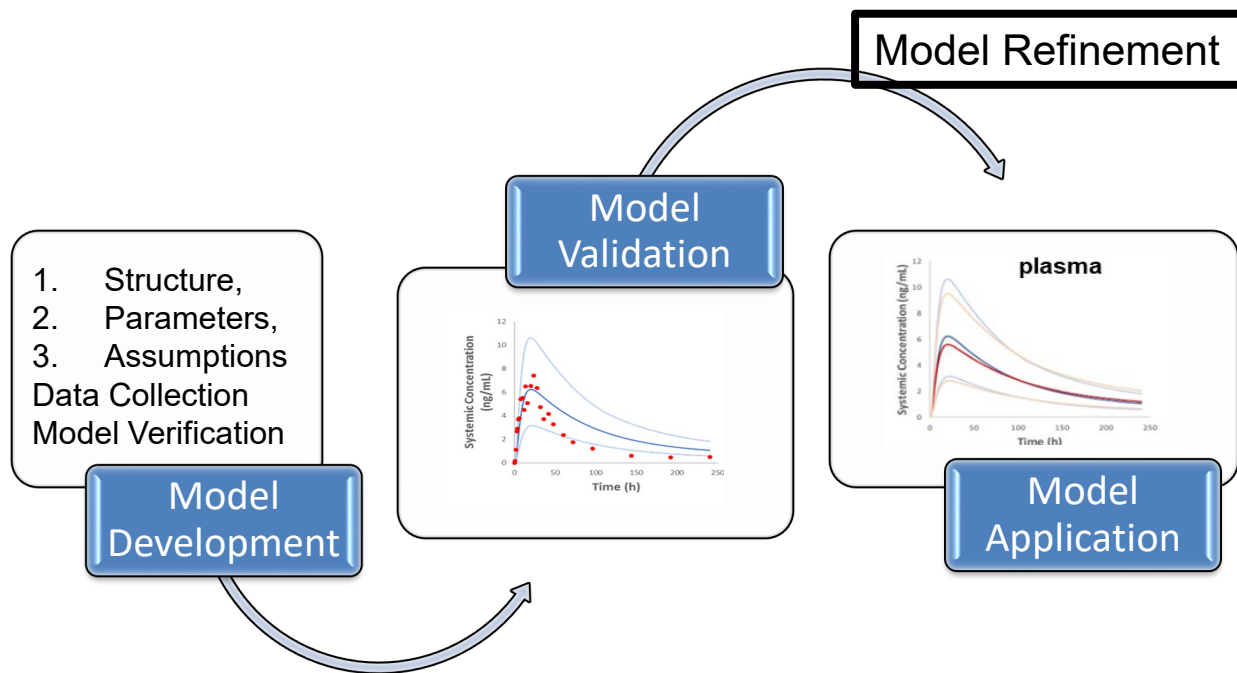
Model Risk

Q: What is the role/scope of
the M&S approach in the
regulatory submission?

Q: Model in the “Totality of evidence” approach

Regulatory Expectations

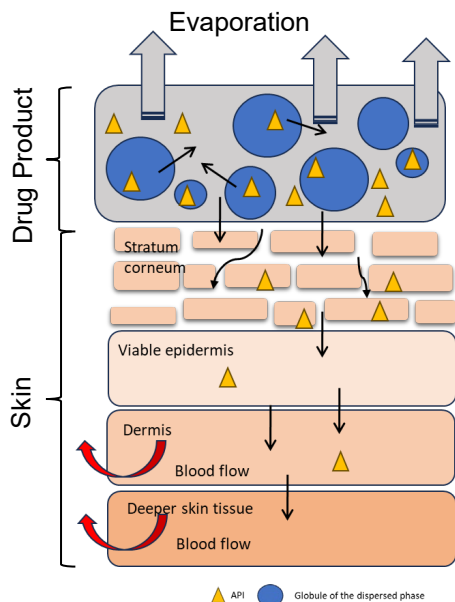
Mechanistic Modeling and Simulation Tools for Drug Products



Applicants are encouraged to follow best practices for M&S approaches in regulatory submissions



Mock Example: Development of a Skin Absorption Model



Model Structure: Organ/tissue physiology and formulation attributes

- The PBPK model reasonably describes the skin physiology
- The formulation attributes are experimentally determined and accurately captured

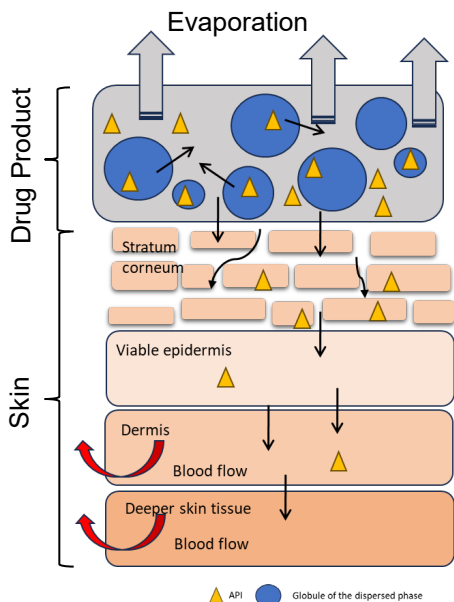
Model parameterization

- Informative datasets are leveraged towards informing key model parameters

Model assumptions and limitations

- Reasonable assumptions on structure and input parameters when reliable method is not available to obtain the parameter value experimentally
- Limitations are acknowledged and justification or additional evidence is provided

Mock Example: Validation of a Skin Absorption Model



Model validation

- Informative datasets
- Datasets not used previously for model development
- Validation in accordance with the credibility assessment framework
- Predefined model performance acceptance criteria
- Numerical and graphical comparisons of PK metrics, population variability

Model/platform validation

- The predictive performance of PBPK model/platform is assessed by wide range of topical drug products and different topical dosage forms of reference drug (if available)

Mock Example: Model Application for Virtual BE Assessment

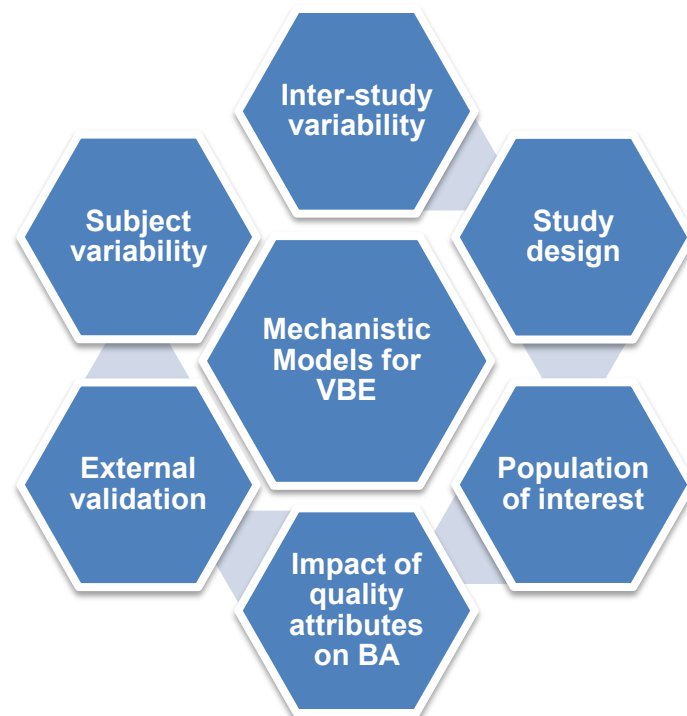


Model Validation Against Context Of Use:

- Model sensitivity to product quality attributes
- Population and study variability captured in the model
- Type I error analysis

Model application:

- Complete, detailed and comprehensive description of virtual BE studies, i.e., study design, sample size, population, trial number.
- Interpret simulation outcomes (i.e., VBE assessment)
- Describe the model-based answer to the Question Of Interest





Documentation of the M&S

- Modeling Analysis Plan (MAP) or Modeling Analysis Report (MAR)
 - Steps 1-4 in a detail, comprehensive, clear manner
- Orientation file
 - Supporting material and their role in the submission/M&S approach
- Model files, relevant datasets, literature
- Version control for MAR/MAP, model files and other supporting material

Mechanistic Modeling Checklist:

- ☐ Is the Question of Interest clearly stated, and the Context of Use clearly defined regarding the proposed model?
 - Is the role/scope of the M&S approach clearly outlined in the regulatory submission?
 - Is Model Risk determined within the totality of evidence proposed for this submission?
- ☐ Is a credibility assessment framework developed for the proposed M&S approach?
- ☐ Is the model developed and validated following regulatory guidances and best practices against the Context Of Use and predefined model risk?
- ☐ Are the model results interpreted within the model's Context Of Use?
- ☐ Is the model answering the Question Of Interest within the proposed totality of evidence approach?
- ☐ Are the developed MAP/MAR a detailed, comprehensive, clear and concise representation of Steps 1-4 of the M&S approach?
- ☐ Is FDA feedback received during previous interactions for (similar) products been considered throughout the process?

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Questions?

