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

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Disclaimer

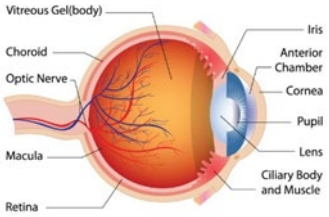
This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

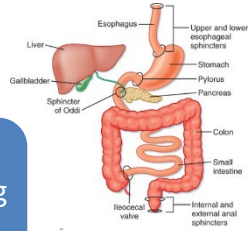
Outline

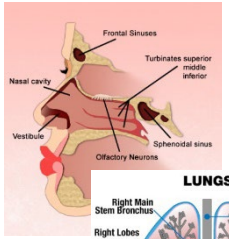
- Non-orally administered drug products
- Types of mechanistic models supporting modeling and simulation (M&S) approaches
- Scientific and Regulatory Expectations on Workflow: How to develop a mechanistic model for generic non-orally administered drug products?
  - Model assessment framework
  - Model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

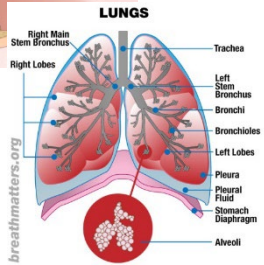
Non-orally administered drug products

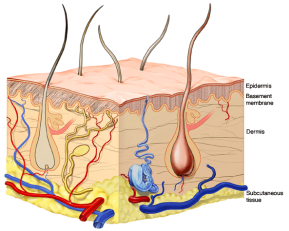
- GI locally acting drug products
- Applied on the skin (topicals, topical delivery systems and transdermal delivery systems)
- Ocular and Otic drug products
- Oral cavity drug products
- Orally inhaled and nasal drug products
- Long acting injectables and complex intravenous injectables
- Rectal, vaginal, intrauterine drug products

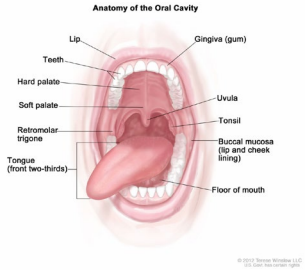


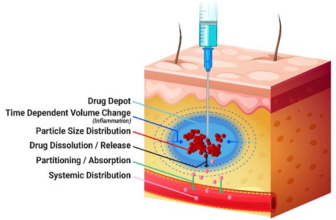








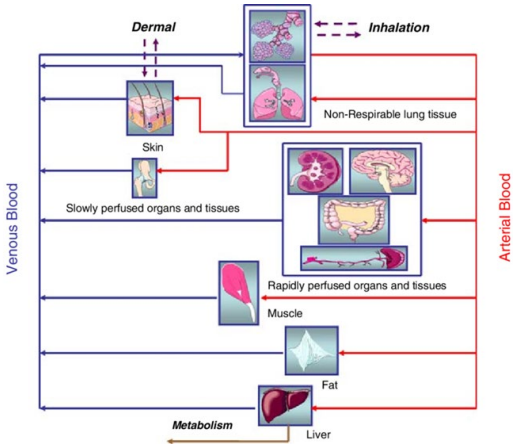


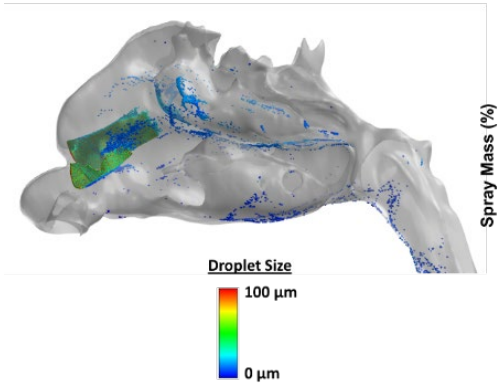


Based on the publication by Jiang W, Kim S, Zhang X, Lionberger RA, Davit BM, Conner DP, Yu LX. Int J Pharm. 2011 Oct 14;418(2):151-60.

https://pubmed.ncbi.nlm.nih.gov/38675213/ , Definition of buccal mucosa - NCI Dictionary of Cancer Terms – NCI

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

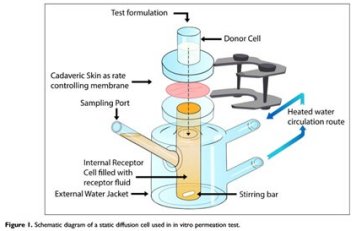


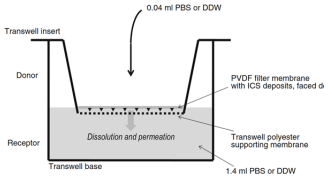


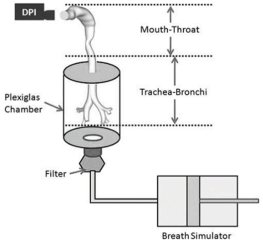
- ***Physiologically based pharmacokinetic (PBPK) modeling***
  - Predictions of local and systemic active pharmaceutical ingredient (API) exposure
  - Integration of information on physiology, drug and drug product
  - Validated with in vitro or in vivo data
- ***Computational fluid dynamics (CFD) Modeling***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

Environ Geochem Health (2009) 31:165–187. J Aerosol Med PulmDrug Deliv. 2017;30(3):18-19. International journal for numerical methods in biomedical engineering. 2018;34(5):e2955.

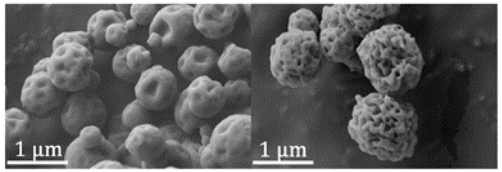
Mechanistic Modeling and Simulation Tools: “Building Blocks”



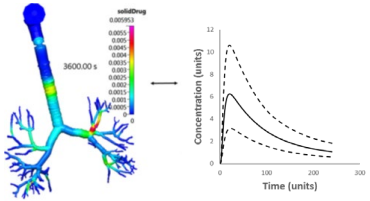




In vitro Product Performance



Drug Product Characterization



Human Physiology in Individuals/Populations

Ther Innov Regul Sci. 2020 May;54(3):693-700. Pharmaceutical research. 2010;27(5):786-95. Journal of Aerosol Medicine and Pulmonary Drug Delivery. 2013;26(3):138-44. International Journal of Pharmaceutics. 2017;520(1-2):207-15. International journal for numerical methods in biomedical engineering. 2018;34(5):e2955.

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

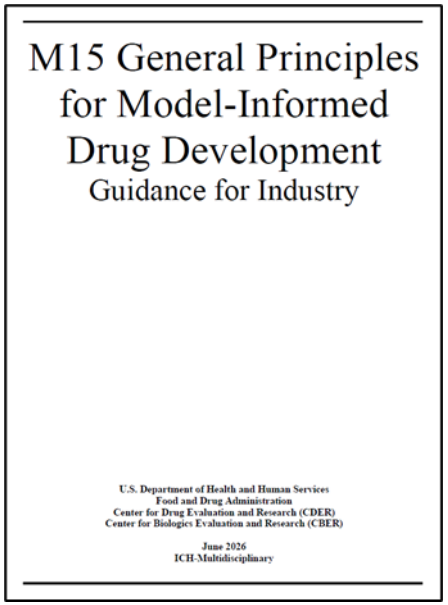
Critical to understand for the role of the M&S approach in a regulatory submission in the pre-submission or submission stage:

✓ Improve quality of interactions during industry meetings

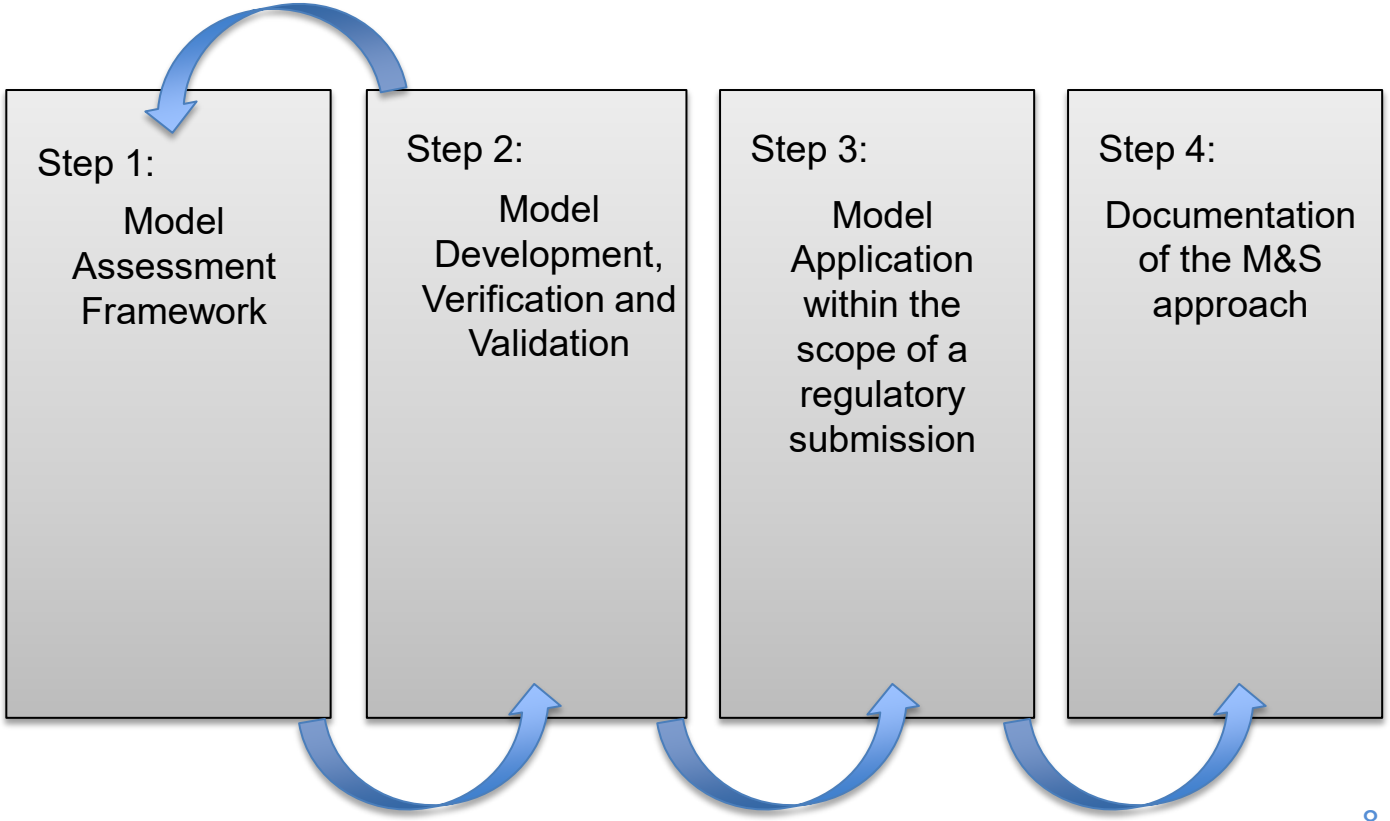
✓ Improve quality of submissions to FDA

✓ Streamline regulatory assessment process

✓ Reduce potential IRs and major deficiencies



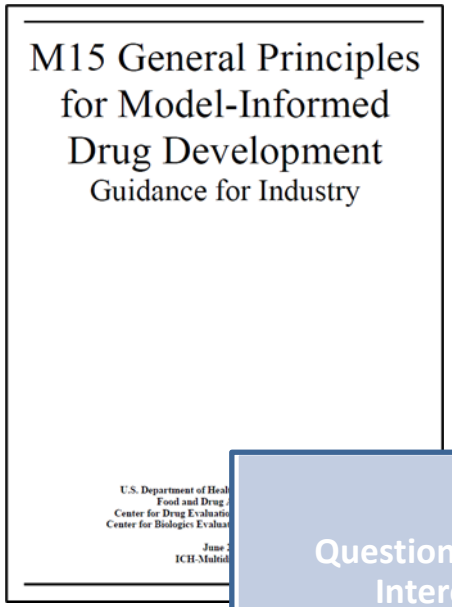
Workflow: How to Develop a Mechanistic Model



Step 1:

Model Assessment Framework

Model Assessment Framework



Question of Interest

Model Assessment

Consequence of Wrong Decision

Context of Use

Model Influence

Model Risk

Regulatory Expectations

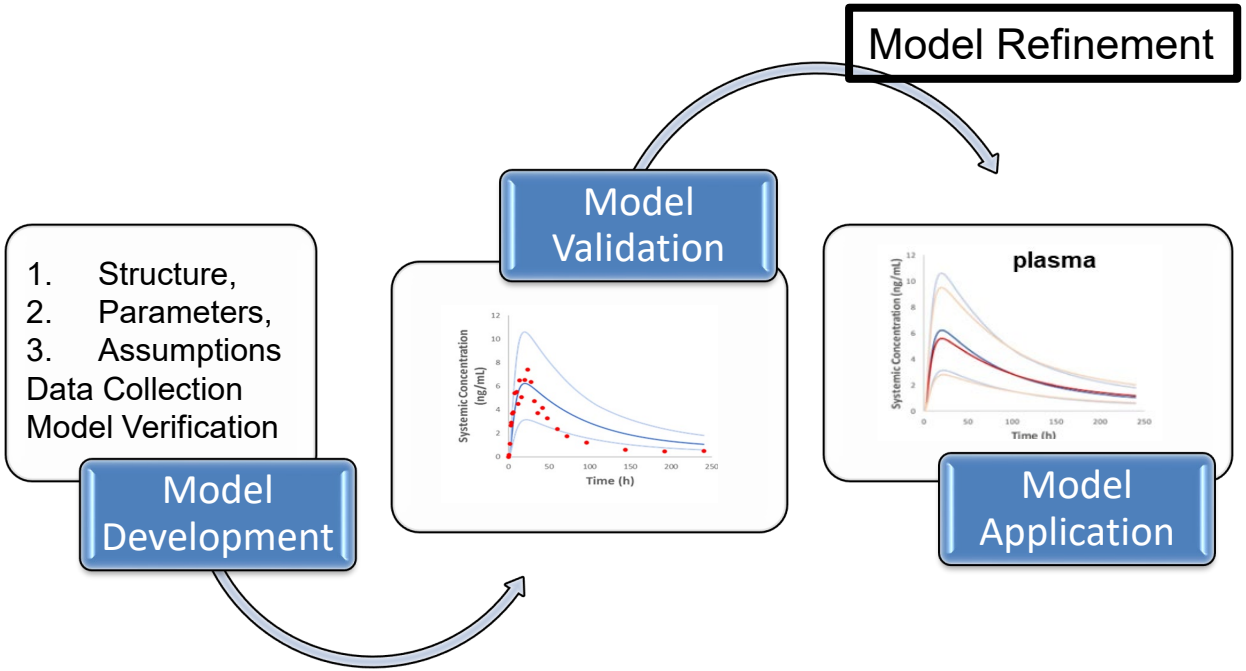
Q: What is the role/scope of the M&S approach in the regulatory submission?

Q: Model in the “Totality of evidence” approach

Step 2:

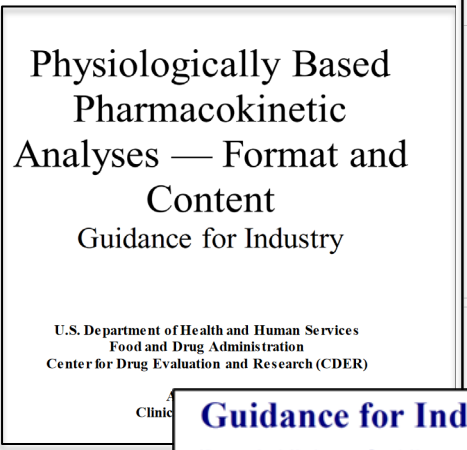
Model Development, Verification and Validation

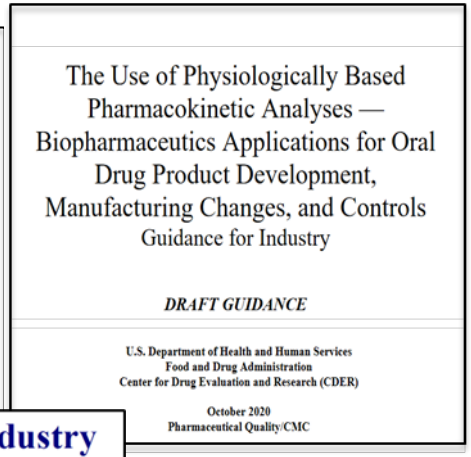
Mechanistic Modeling and Simulation Tools for Drug Products

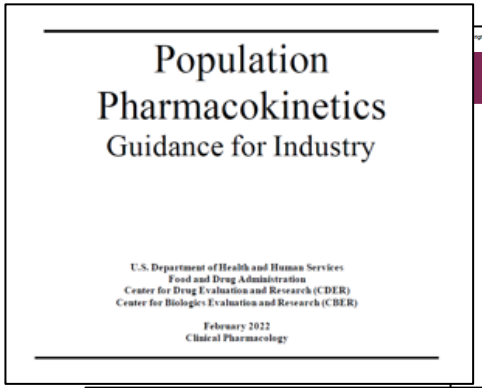


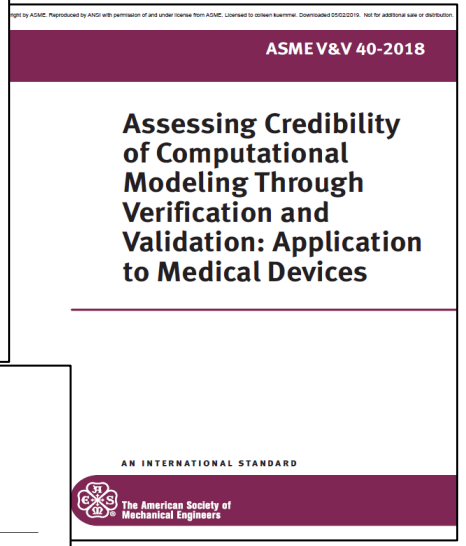
The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls Draft Guidance for Industry September 2020, https://www.fda.gov/media/142500/download

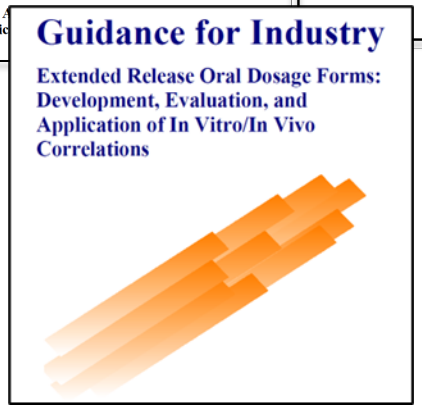
Applicants are encouraged to follow best practices for M&S approaches in regulatory submissions

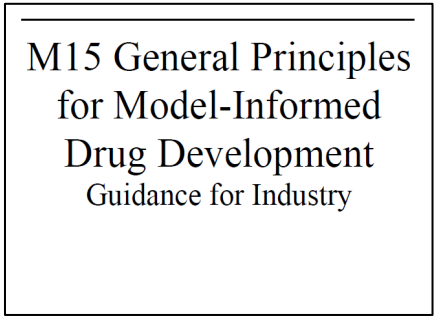


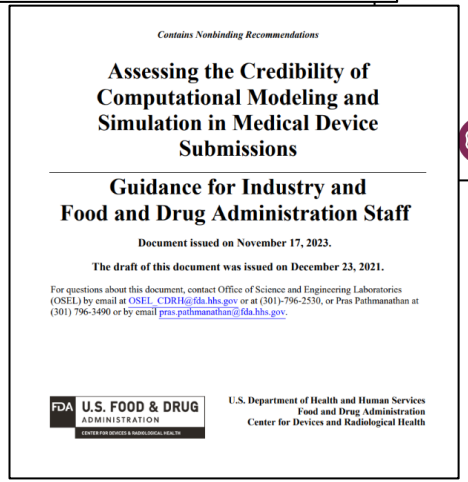








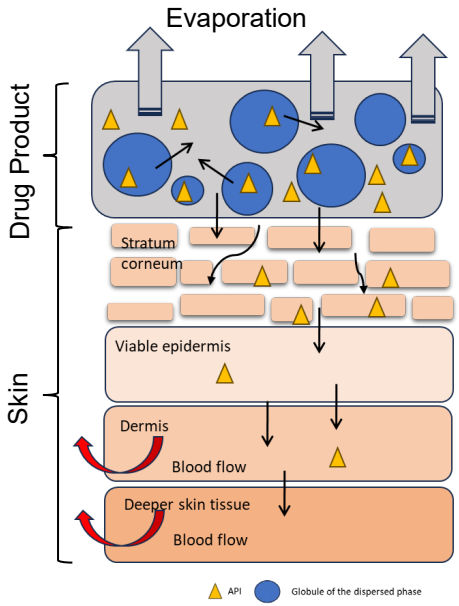




Step 2:

Model Development, Verification and Validation

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

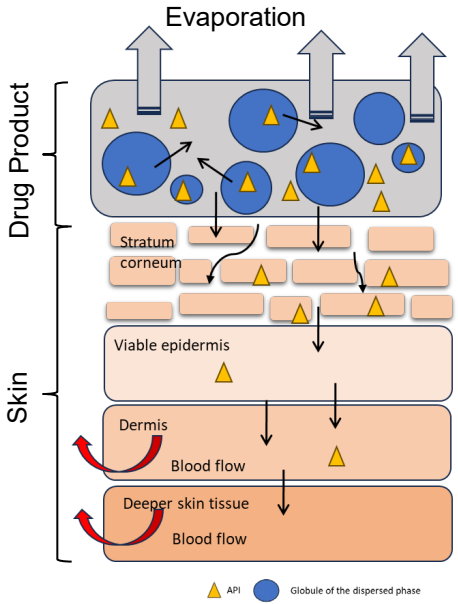
Model parameterization

- 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)

Step 3:

Model Application

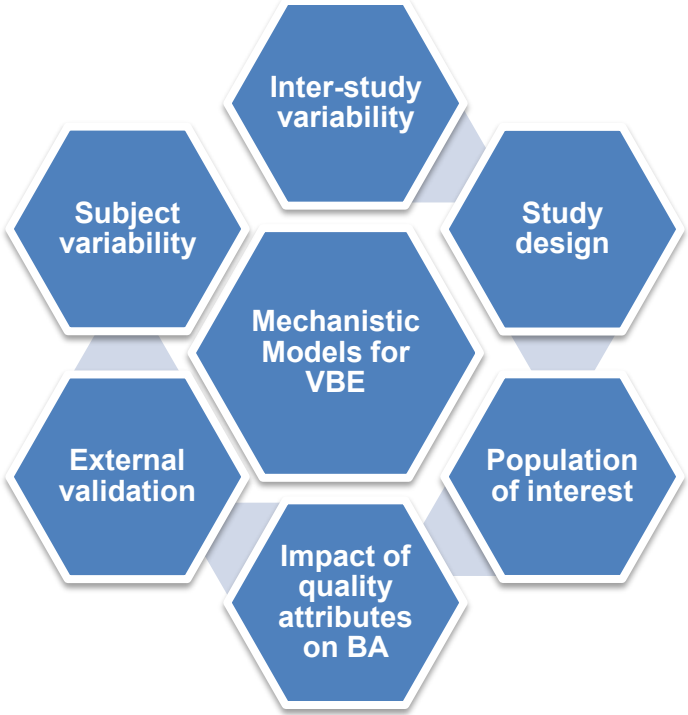
Mock Example: Model Application for Virtual BE Assessment

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



VBE: virtual bioequivalence, BA: bioavailability

Step 4:

Documentation

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?

Acknowledgements

FDA/CDER/OGD/ORS/DQMM
- Khondoker Alam
- Steven Chopski
- Mingliang Tan
- Ross Walenga
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- Alex Benet
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- Andrew Babiskin

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- Lei Zhang
- Robert Lionberger

U.S. FOOD & DRUG ADMINISTRATION

Questions?

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