FDA's Perspective on the Physiologically Based Pharmacokinetic (PBPK) Analyses for Biopharmaceutics Applications

Banu Zolnik, Ph.D.
Division of Biopharmaceutics/ONDP/OPQ/CDER/FDA

March 4, 2021

Model Informed Drug Development MIDD+

Outline

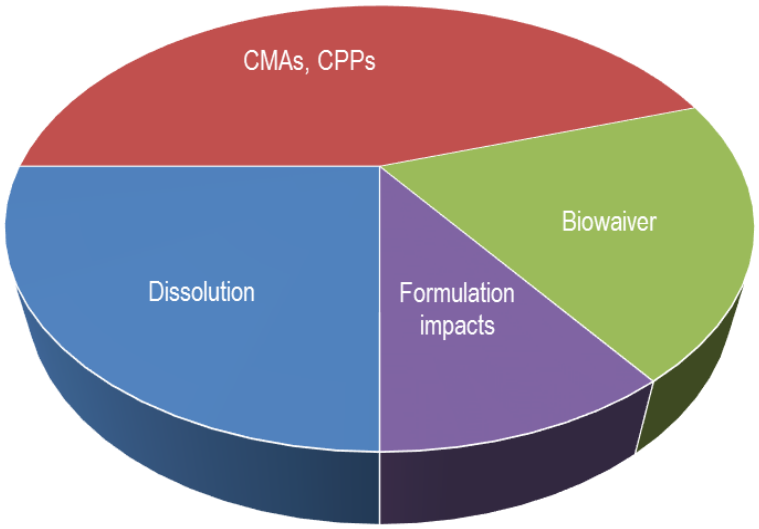
- The Biopharmaceutics Applications supported by PBPK analyses
- Current Regulatory Landscape
- General Considerations for Model Development and Evaluation
- PBPK Study Report for Biopharmaceutics Applications for Regulatory Submission
- Case Study
- Conclusions

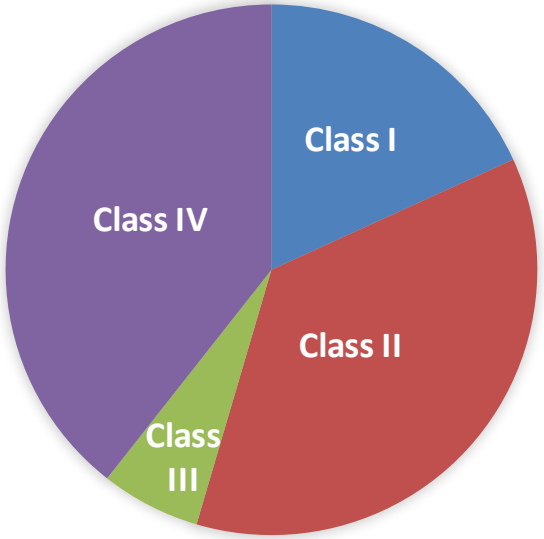
The Biopharmaceutics Applications Supported by Physiologically-Based Pharmacokinetic Analyses

- To link dissolution or other in vitro testing inputs to in vivo drug exposure via PBPK modeling
- Examples of categories of applications:
  - Formulation development
  - Establish clinically relevant product specifications
  - Quality risk assessment
  - Drug product life cycle management
- Potentially reduces the number of in vivo BA/BE studies

Current Regulatory Landscape

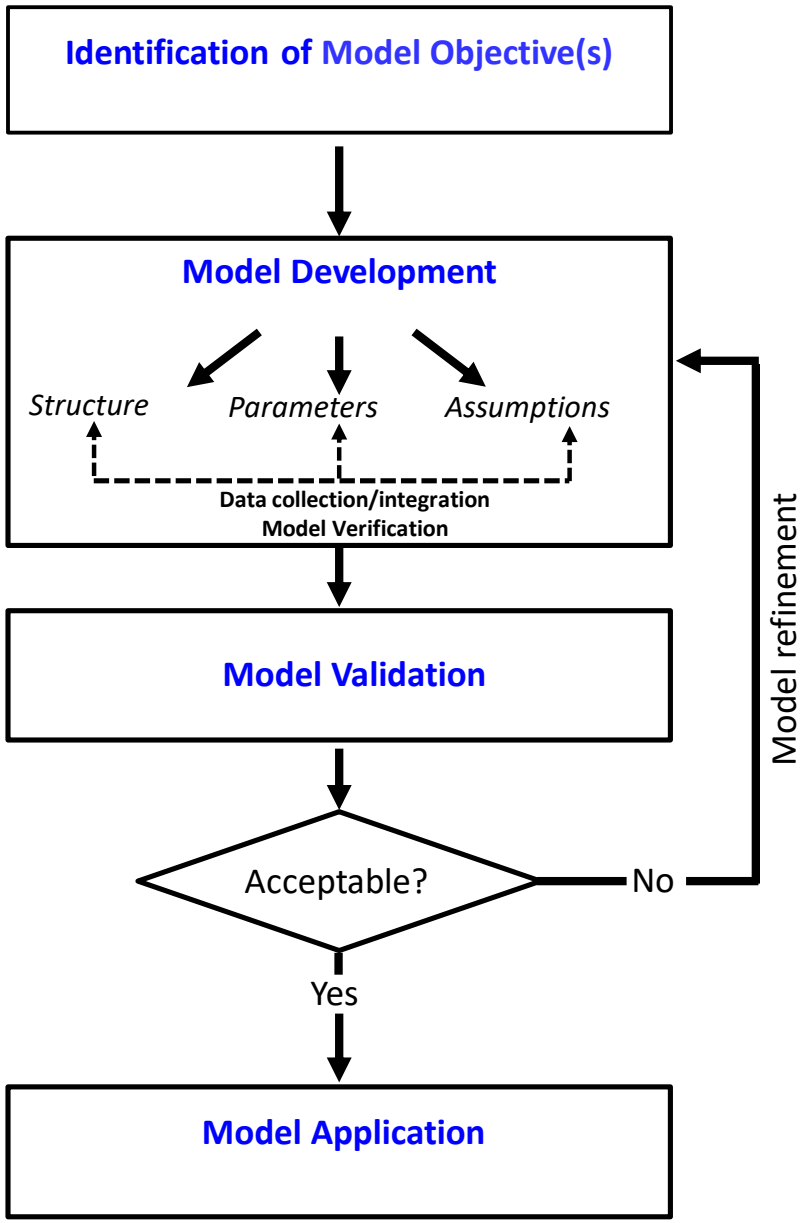
- FDA Draft Guidance: The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls was issued in October 2020.
  https://www.fda.gov/media/142500/download





A total of 36 submissions included in INDs, NDAs and ANDAs from 2008-2020.
32 submissions out of 36 submitted in the last 5 years.

General Workflow



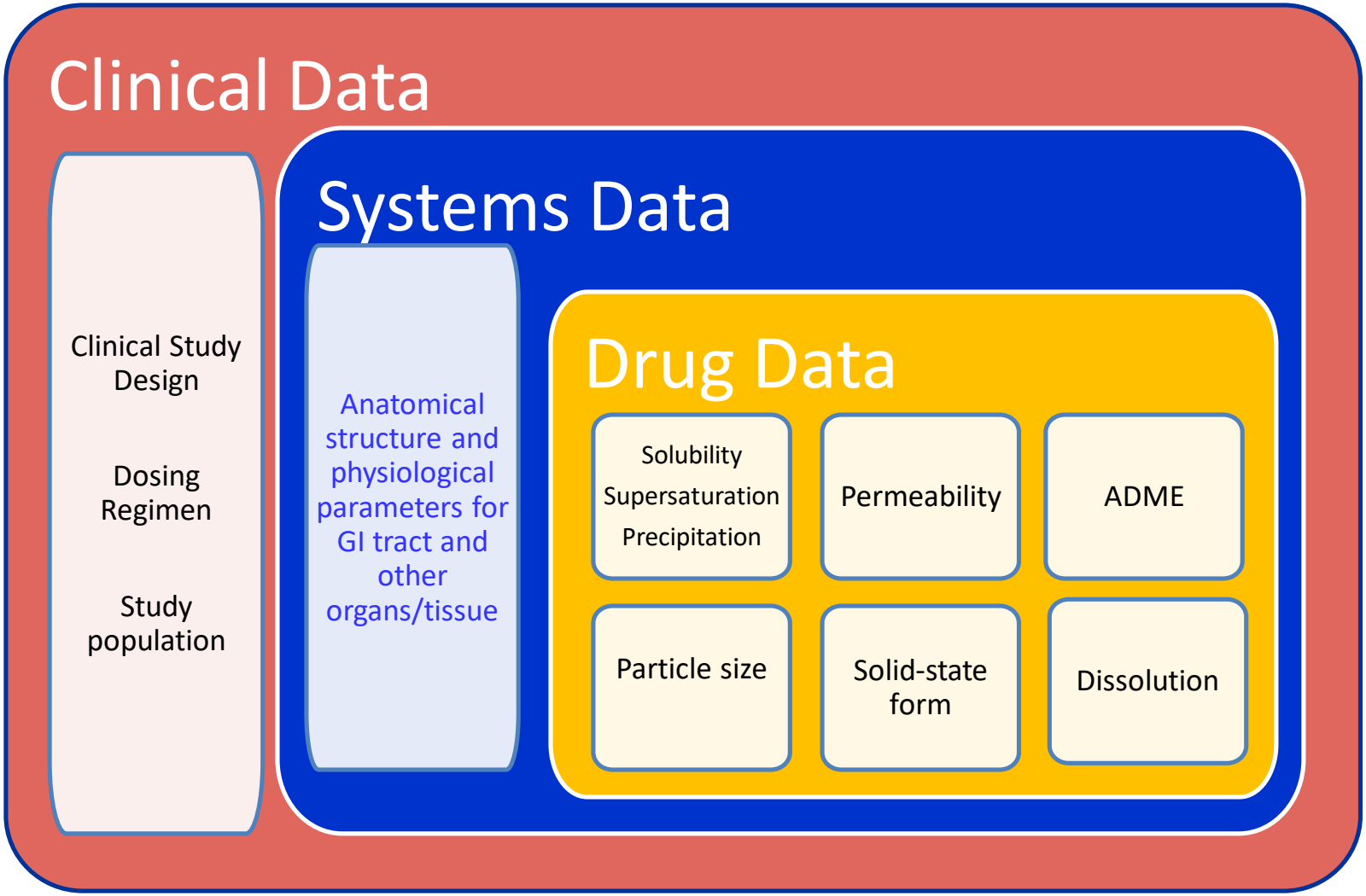
Ref: Draft Guidance: https://www.fda.gov/media/142500/download

Model Objective Examples

Dissolution	• Development of Clinically Relevant Dissolution Specification (Method and Acceptance Criteria
Other Specifications	• Particle size • Polymorphic form
Bridging	• Clinical batches to the to-be-marketed commercial product
Biowaiver	• Biowaiver for post approval changes

The Model Objective should be clearly specified!

Model Development and Verification



The assumptions should be clearly presented!

Model Validation

- The model's validation acceptance criteria, should be established a priori.

- Independent datasets not used in model development are recommended to evaluate the predictive performance of the model

Virtual Bioequivalence (vBE) Studies

- Use of a model to predict the outcome
- The number of subjects in vBE should be estimated based on the specific intra-subject variability using a power-analysis.
- 90% CI is within the 80-125% BE limits for the geometric mean ratio of AUC and Cmax.
- Exposure-response data can also be used if data falls outside the BE limits.

PBPK Study Report for Biopharmaceutics Applications for Regulatory Submission

The following information should be included but are not limited to:

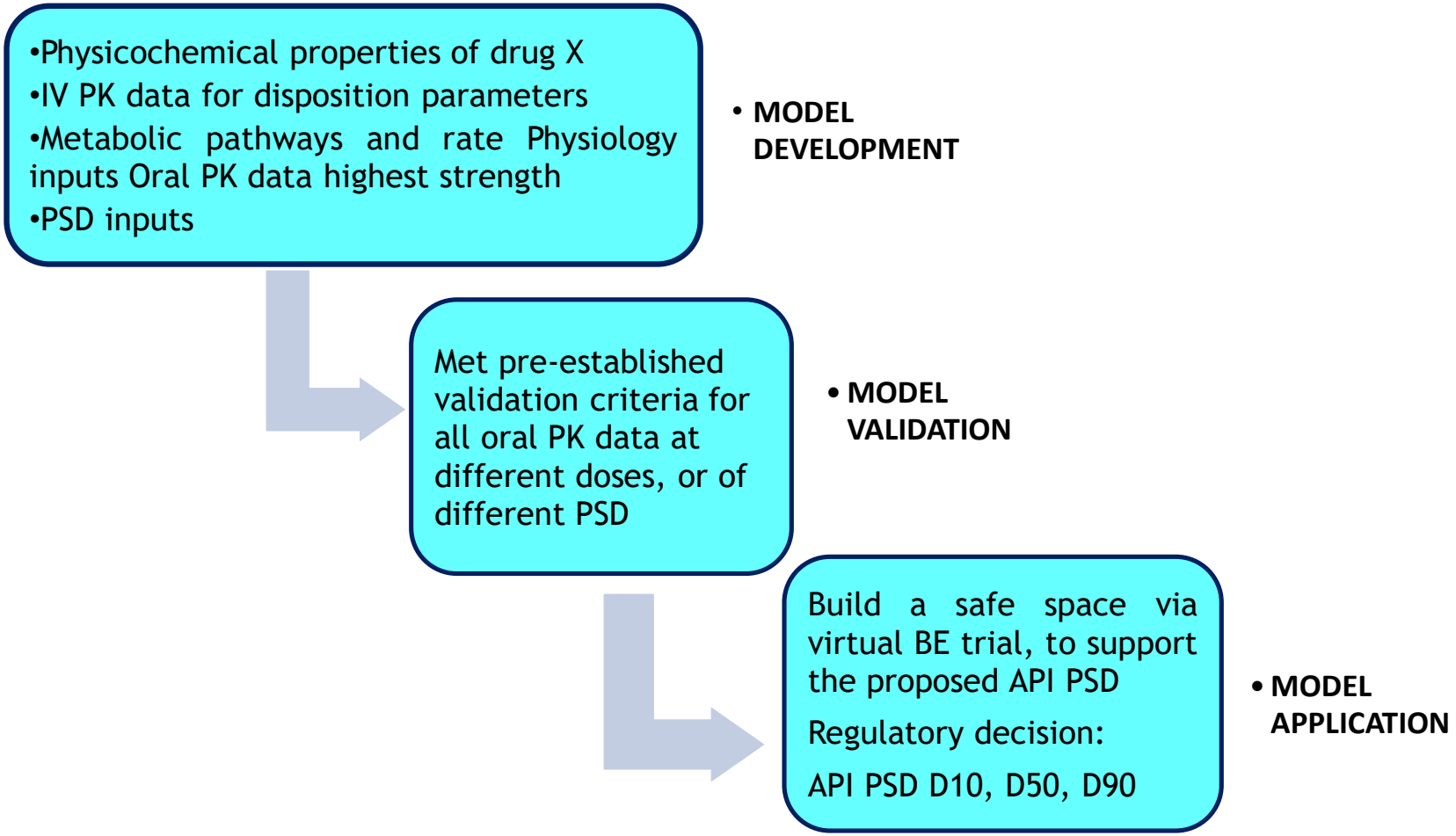
- A modeling summary report elaborating modeling strategy
- The objective of the model
- Modeling flow chart covering model development, verification and validation
- Rationale and supportive information on model parameters
- Formulations and in vitro dissolution
- Clinical study:
  - Study design and subject numbers
  - In vivo concentration profile data
  - Non-BE data preferred
- Virtual BE trials:
  - Description of intra- and inter- subject variability
  - Justification of the number of subjects and trials used in virtual BE trials

Case Study 1

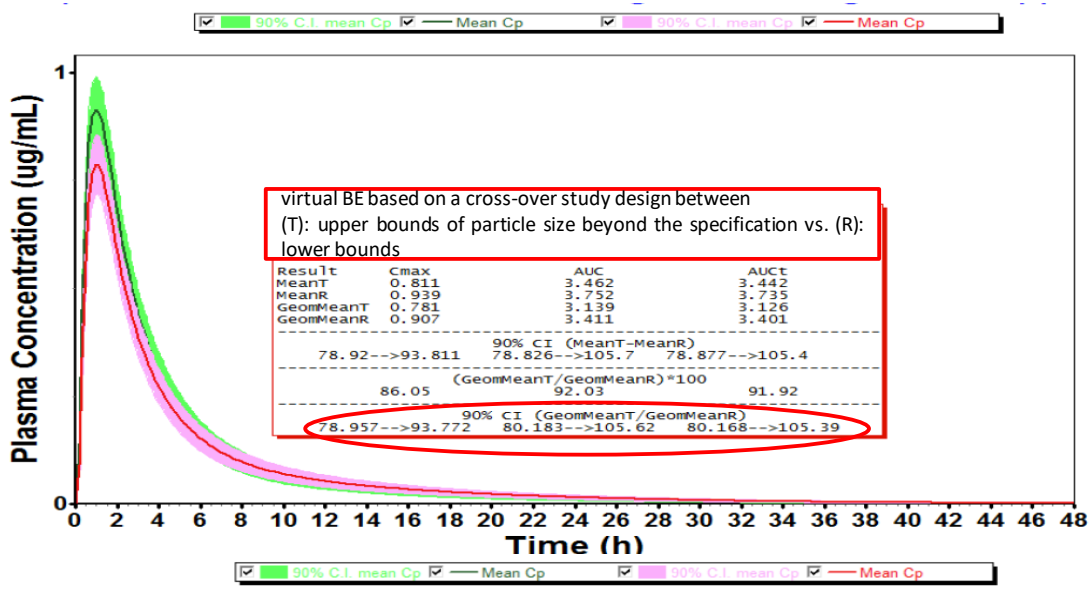
- Model Objective:
  - To support the selection of API particle size distribution
- API:
  - BCS Class 4, weakly basic
- Drug Product:

  Immediate release capsule
- Model Development:
  - Experimental data are used for API related input parameters
  - Default physiology parameters are used
  - IV data, and additional clinical studies are used to develop the model
- Model Validation:
  - Another set of clinical data which are not part of the model development are used
- Model Application:
  - Final drug substance particle size specification was selected based parameter sensitivity analysis and the Virtual Bioequivalence studies.

Model's Flow Chart

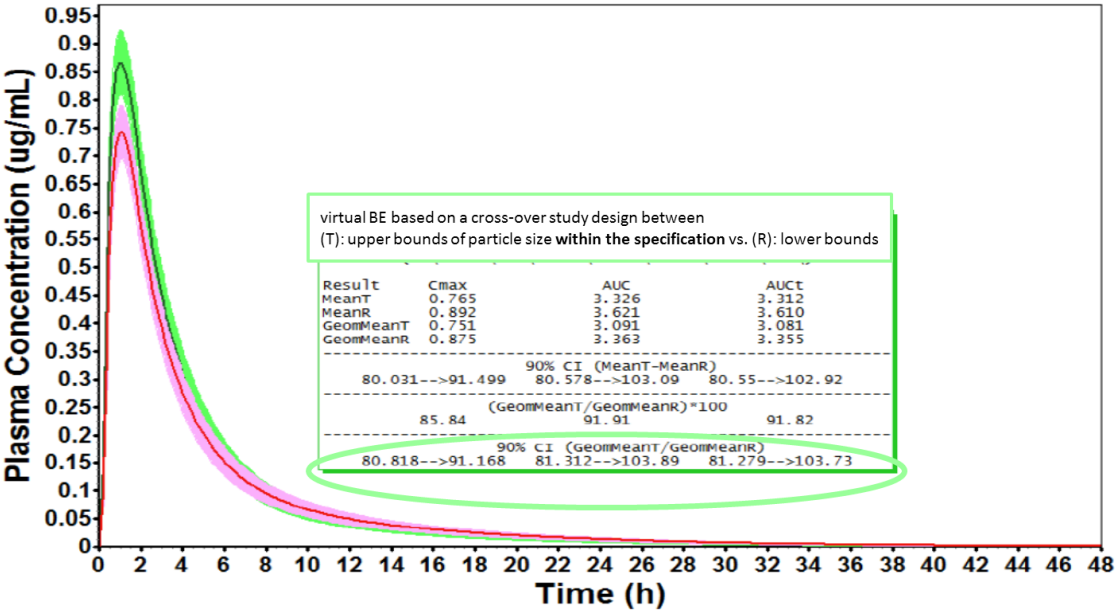


Virtual BE Results



Cross-over virtual BE simulation

Virtual batch with particle size **outside** the PSD specification **fails** the BE criteria



Virtual batch with particle size **within the PSD specification passes** the BE criteria

Conclusions

- The use of Physiologically-Based Pharmacokinetic Analyses for Biopharmaceutics Applications:
  - Establishes a link between in vitro and in vivo
  - Provides regulatory flexibility
  - Potentially reduces the number of in vivo BA/BE studies.
- FDA supports innovative and data driven mechanistic modeling approaches.
- Early interaction with FDA with regards of using modeling approaches is encouraged.

Acknowledgements

Dr. Paul Seo

Dr. Angelica Dorantes

ONDP Biopharmaceutics PBPK for Biopharmaceutics Committee:

Drs. Om Anand, Min Kang, Vidula Kolhatkar, Min Li

Dr. Yang Zhao

Division of Biopharmaceutics

FDA U.S. FOOD & DRUG ADMINISTRATION

Thank you!