Application of Physiologically Based Biopharmaceutics Modeling in Support of Drug Product Quality

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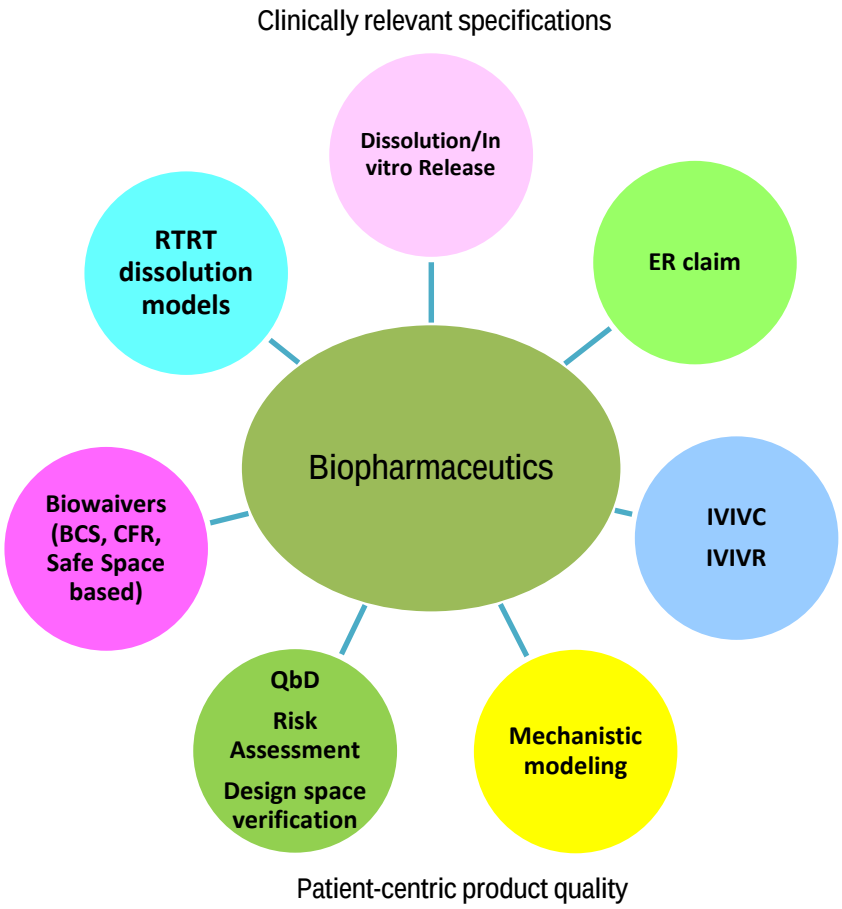
This presentation reflects the views of the presenter and should not be construed to represent the FDA's views or policies.

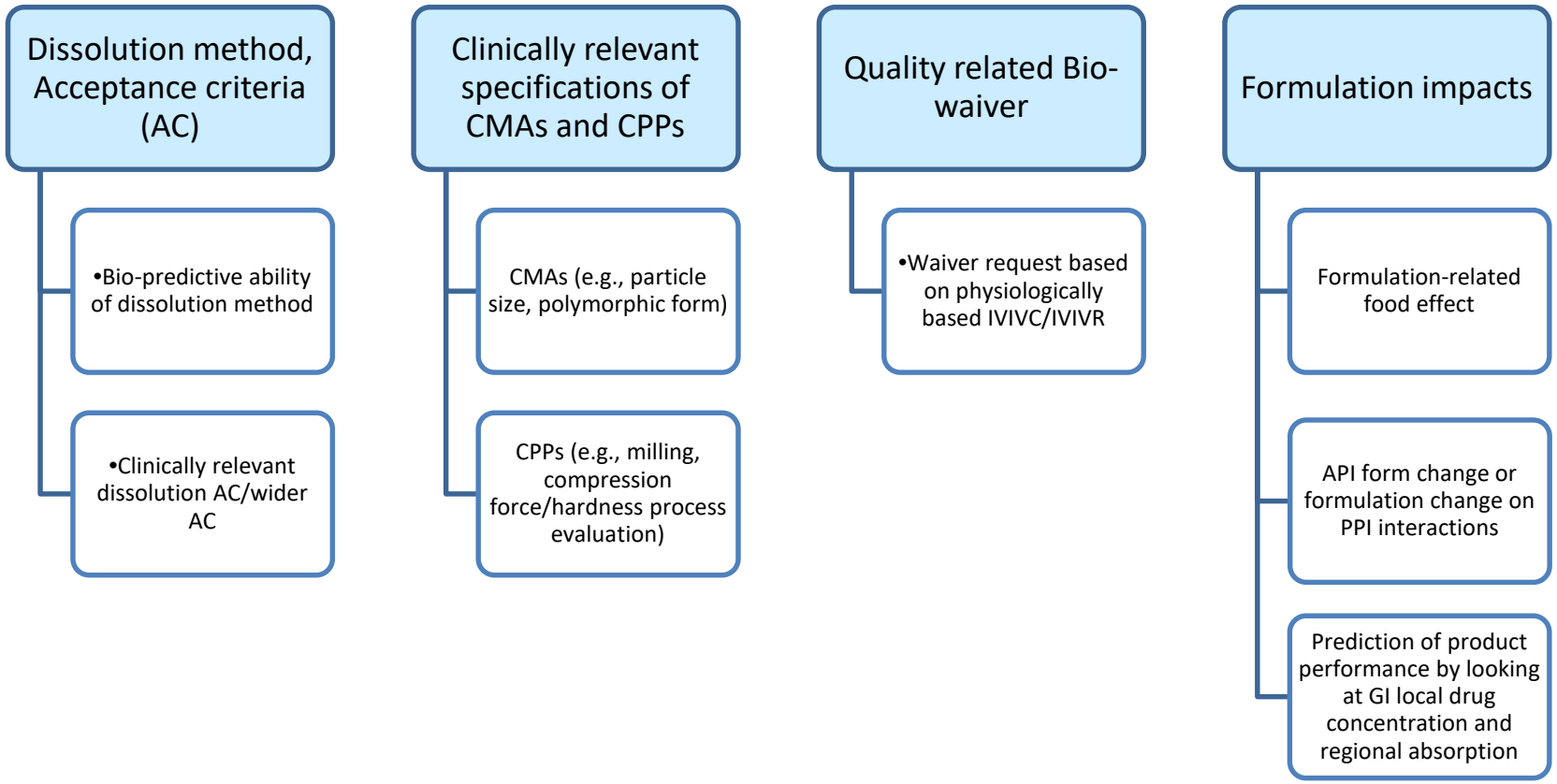
Outline

- Overview of review tasks at Division of Biopharmaceutics in FDA
- Physiologically-Based Biopharmaceutics Modeling (PBBM) in support of drug product quality
  - Common applications
  - Common deficiencies
  - Model workflow - general strategy
  - Case study
- Summary/Take Home Message

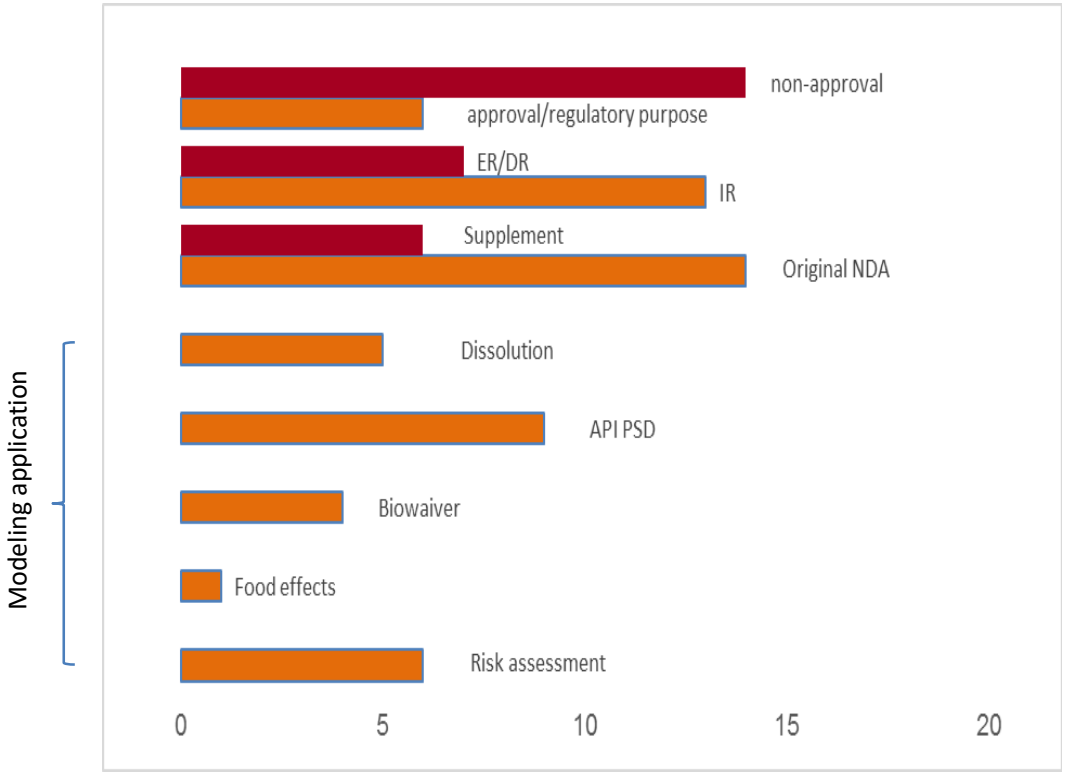
Overview of review tasks at FDA's Division of Biopharmaceutics



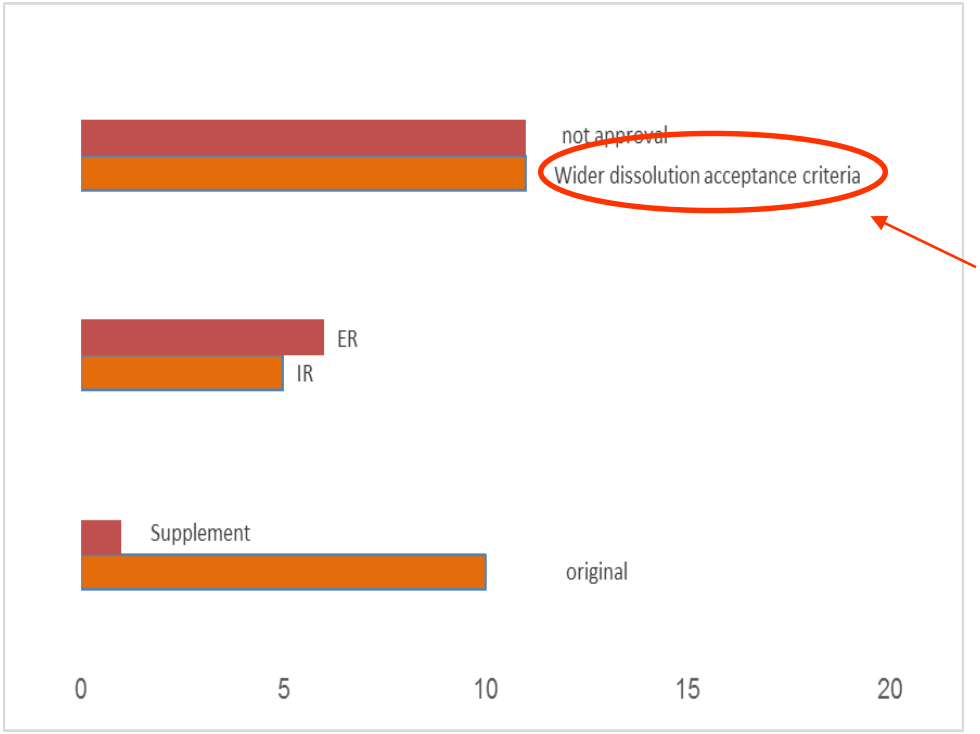
Common regulatory applications of PBBM in support of drug product quality



Number of NDA submissions containing PBBM in support of drug product quality (2008-2018)



Number of ANDA submissions containing PBBM in support of drug product quality (since 2016)



Modeling application seen so far

Common PBBM deficiencies observed in FDA submissions

- Model is not mechanistically sound,
  - Lack of parameter plausibility
  - API driven or formulation driven dissolution/absorption misinterpreted
  - In vitro dissolution not bio-predictive or not reflecting the in vivo dissolution
  - Assumption of 100% bioavailability, while incomplete absorption was indicated by in vivo study
- Verification data is insufficient,
  - Not objective oriented model verification
  - Inappropriate data selection for model verification
  - Additional verification needed for the intended purpose
- Model structure information is insufficient,
  - No formulation information
  - No mechanistic framework accounting for impact of quality attributes on absorption
  - No justification for input parameter values selected in drug, PK, formulation, physiology
  - Insufficient data/program files
- Reliability of simulation results is questionable,
  - Uncertainty of subject variability

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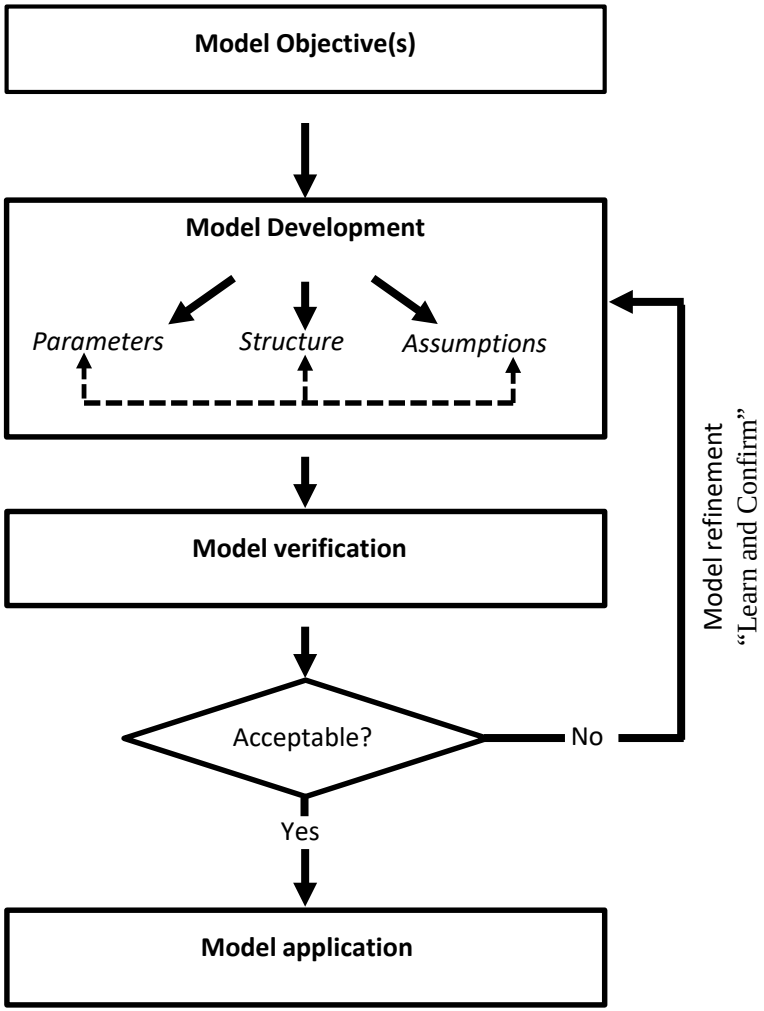
How to develop PBBM?

Physiologically-Based Biopharmaceutics Modeling workflow

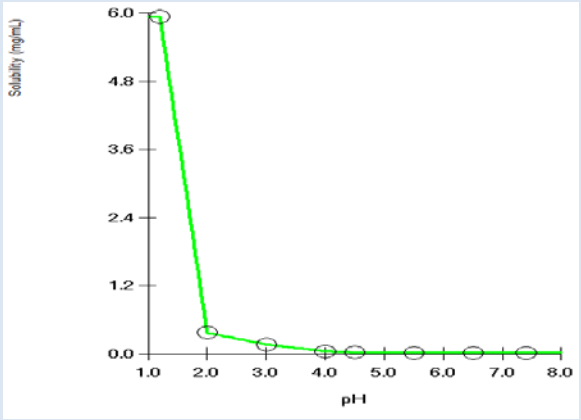


Case study:

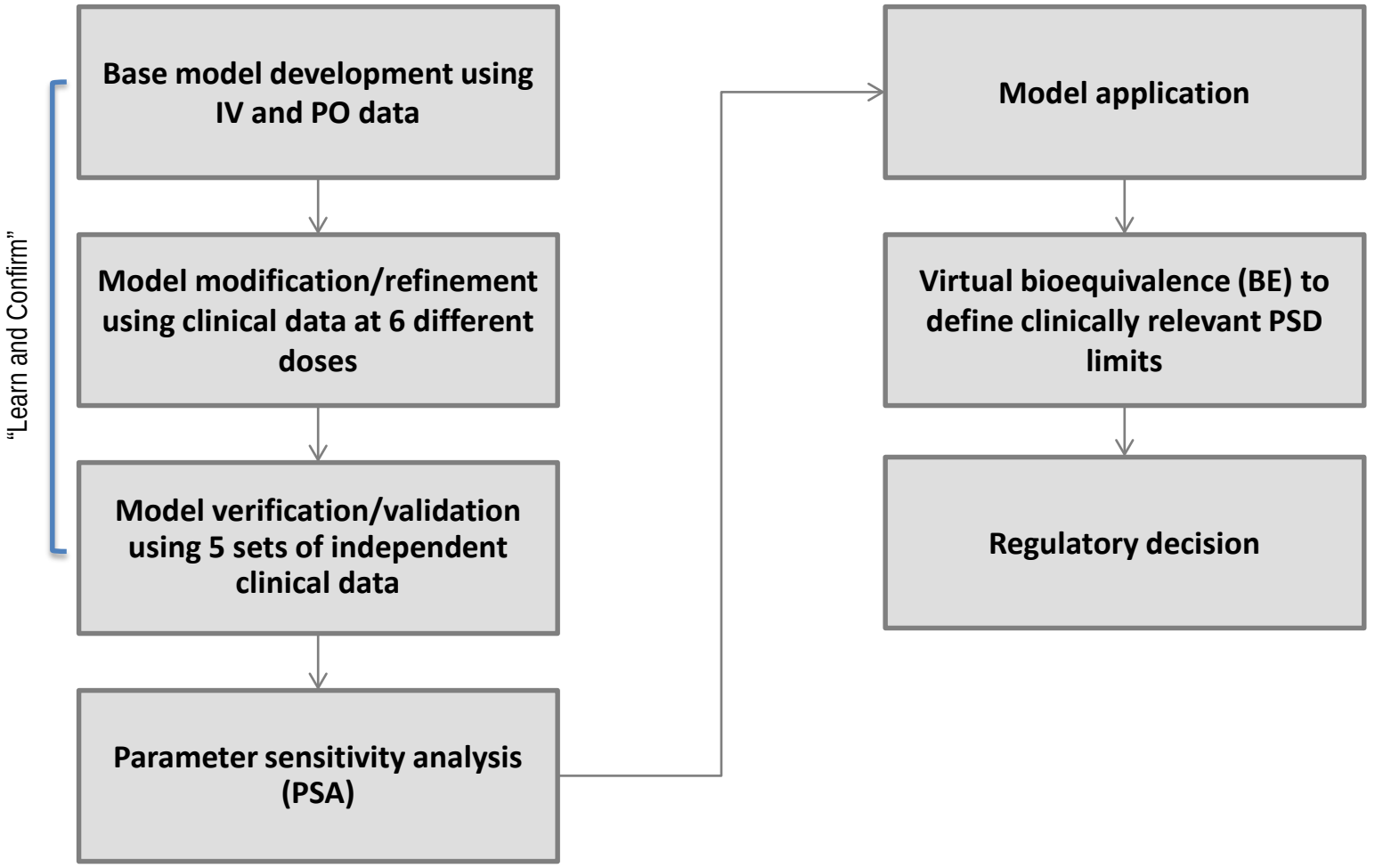
- **Objective: To establish clinically relevant API particle size specification/formulation design space for a BCS class IV immediate release oral dosage formulation**

- Oncology drug for treatment of leukemia
- Immediate release capsule
- 2 strengths: low and high compositionally proportional
- BCS class 4
- High strength used in model development
- Wide particle size range used in pivotal clinical trials

Drug parameters:

MW	417
pKa	3.9
logP	2.6
Solubility	
Peff Density	0.14 x 10-4 cm/sec (human) 1.37 g/mL
Dissolution	Rapid dissolution in acidic medium

Modeling workflow



Modeling input and output

API and product formulation input:
Solubility vs. pH profiles
logP, pKa
Dose and dose volume
Diffusion coefficient
Permeability
Metabolic/transport kinetics
Dissolution:
IR: particle size and density; MR: dissolution profiles

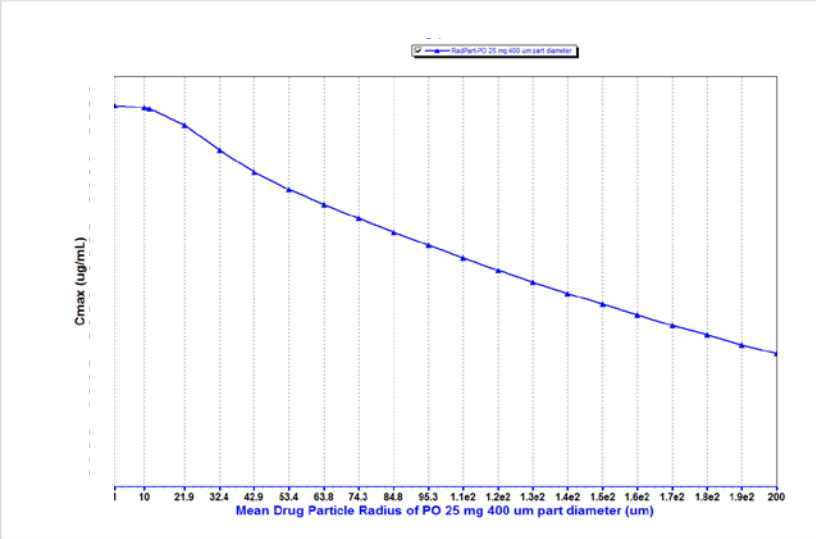
Physiology input:
pH in GI
GI transit time
GI fluid volume
Bile salt
Enzymes/transporters distribution
Blood flow

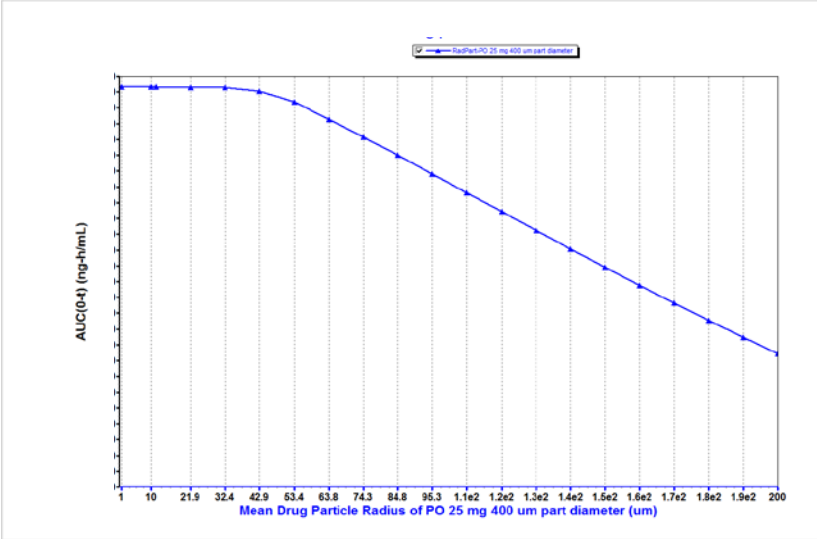
PK input:
Clearance
Vd
Inter-compartment rate constant
Protein binding
Tissue/organ parameters for drug distribution and elimination

Model output:
PK profiles
Cmax
AUC
Tmax
In vivo dissolution
Fa, Fg
F
Drug in regional GI

Input determines your output!

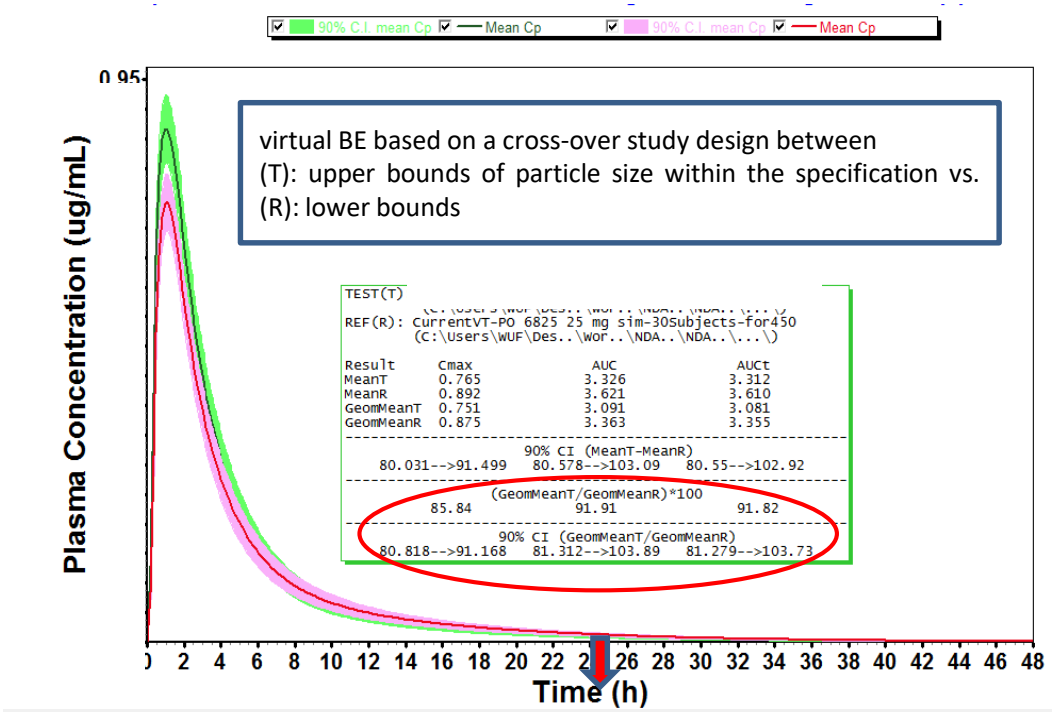
PSA showing the effect of particle size on systemic exposure





Conduct PSA for your parameters of uncertainty!

Virtual BE supporting regulatory decision



Setting clinically relevant particle size

Conduct virtual BE to take into consideration variability of individual parameters !

Summary

The use of Physiologically-Based Biopharmaceutics Modeling contributes to:

- Enhanced drug product understanding, in conjunction with quality by design (QbD) approach
- Patient-centric product quality
- Establishment of *in vitro and in vivo* link, a key element in setting clinically relevant drug product specifications
- Potential reduction in the number of in vivo BA/BE studies (e.g., due to formulation or manufacturing process changes) prior to approval process or post-approval changes.

Take home messages (1): A few questions to raise before developing a model

- What is the proposed model purpose or intended regulatory use?
- Are there sufficient data for model development and verification to justify the intended purpose?
- Are the data robust?
- What is the appropriate model strategy?
- Early communication with Division of Biopharmaceutics is encouraged!

Take home messages (2): Document checklist for FDA submission (not limited to)

- Model report (stating model objective and your “thought” process)
- Modeling workflow
- Drug product/formulation information and process understanding
- Solubility data
- Relevant dissolution information and dissolution profile data
- PK data and study design
- Sources of parameters
- Coding or mathematical equations
- Hypothesis
- Datasets (allowing executing independent analysis)

Acknowledgements

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  - Dr. Paul Seo
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Thank you!