Applications of Physiological Based Biopharmaceutics Modeling (PBBM) in Regulatory Submissions: FDA Perspective

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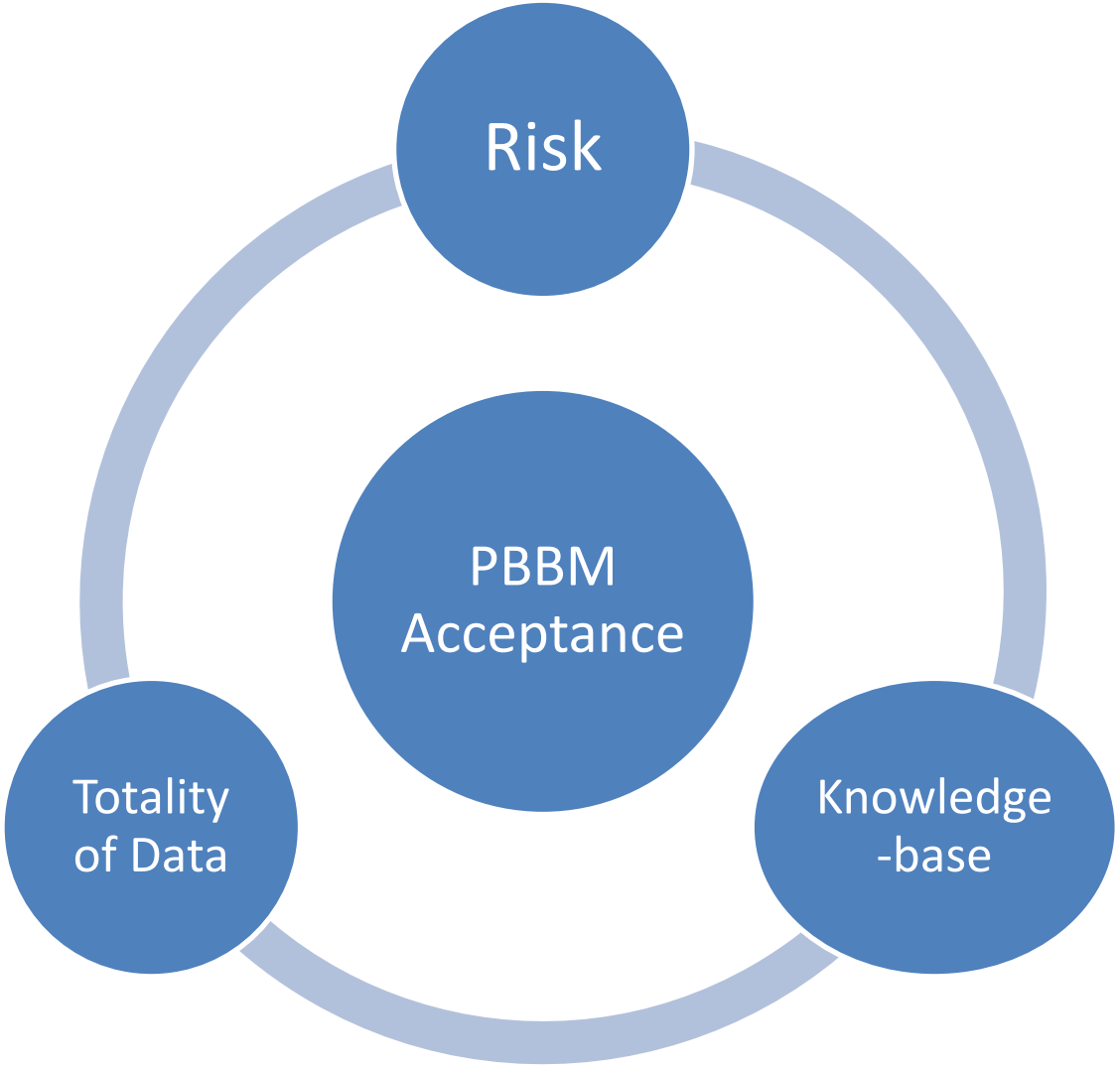
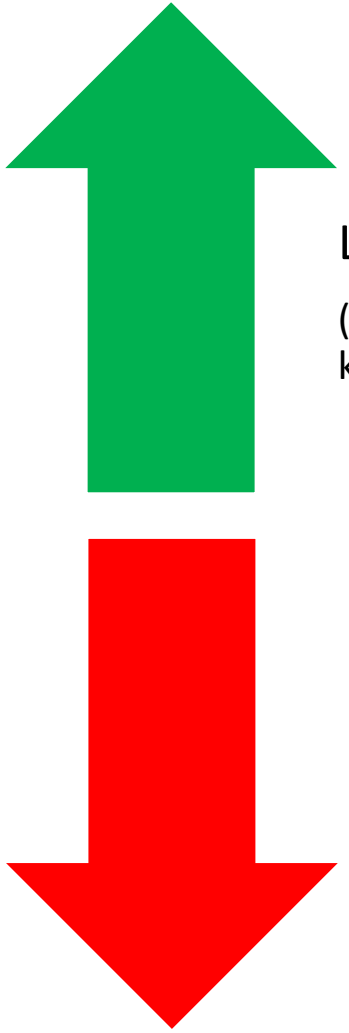
Guidance for Industry
Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations
1997
Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances
Guidance for Industry
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
August 2018
Biopharmaceutics
2018
ICH
harmonisation for better health
INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE
ICH HARMONISED GUIDELINE
BIOPHARMACEUTICS CLASSIFICATION SYSTEM-BASED BIOWAIVERS
M9
Final version
Adopted on 20 November 2019
2019
The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls
Guidance for Industry
DRAFT GUIDANCE
This guidance document is being distributed for comment purposes only.
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
October 2020
Pharmaceutical Quality/CMC
2020
Stay tuned
20??

PBBM in Pharmaceutical Quality





Lower Risk

(e.g., larger dataset, established knowledge-base, setting AC)

Higher Risk

(e.g., more unknowns, large impact, full biowaivers)

PBBM Snapshot

- An estimated **50** A/NDA and IND submissions involved PBPK modeling/simulations to support Biopharmaceutics

- **48%** of the PBPK modeling/simulations to support Biopharmaceutics were found acceptable

- Currently **all** PBPK modeling/simulations to support Biopharmaceutics are assessed as part of the regulatory submission

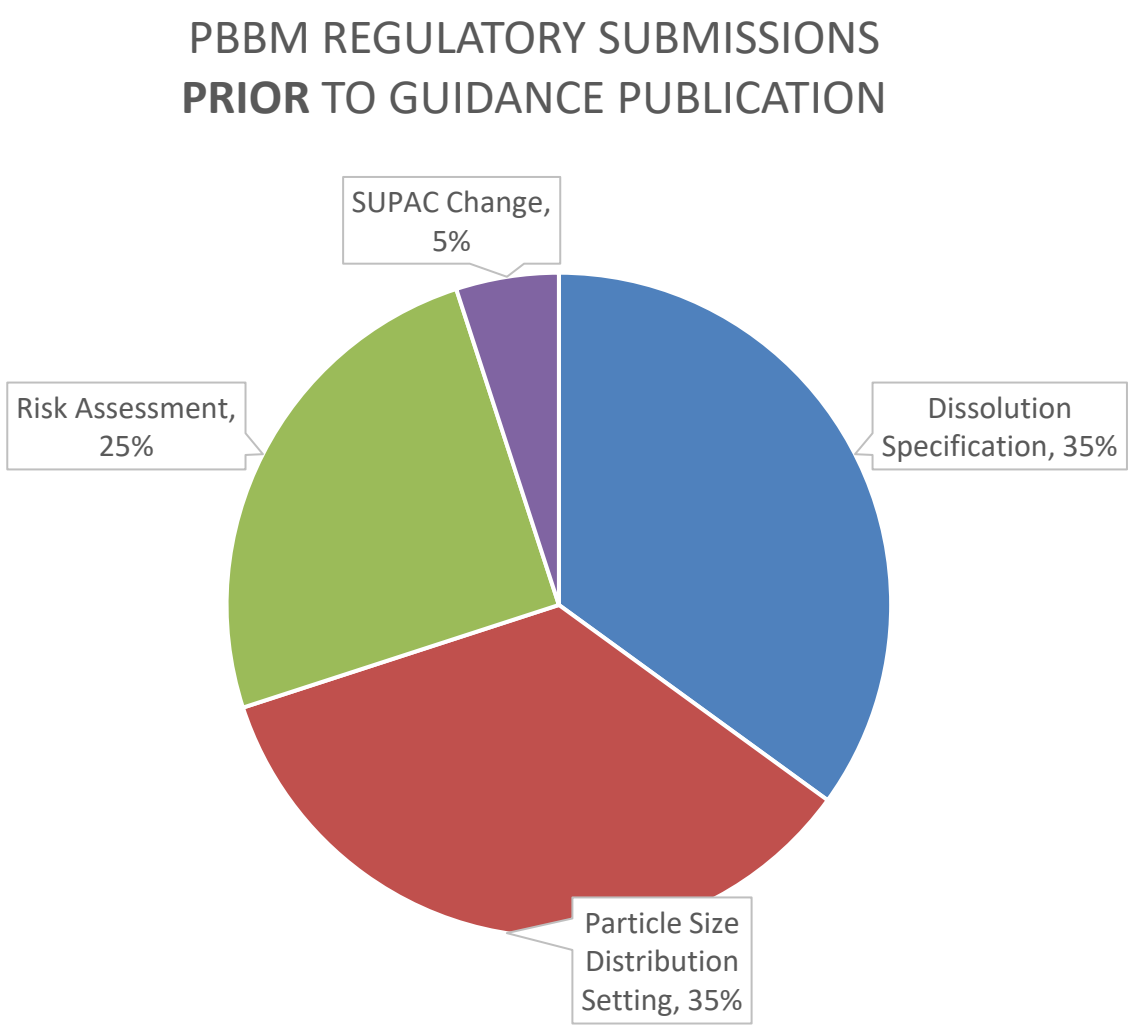
PBBM Case Examples

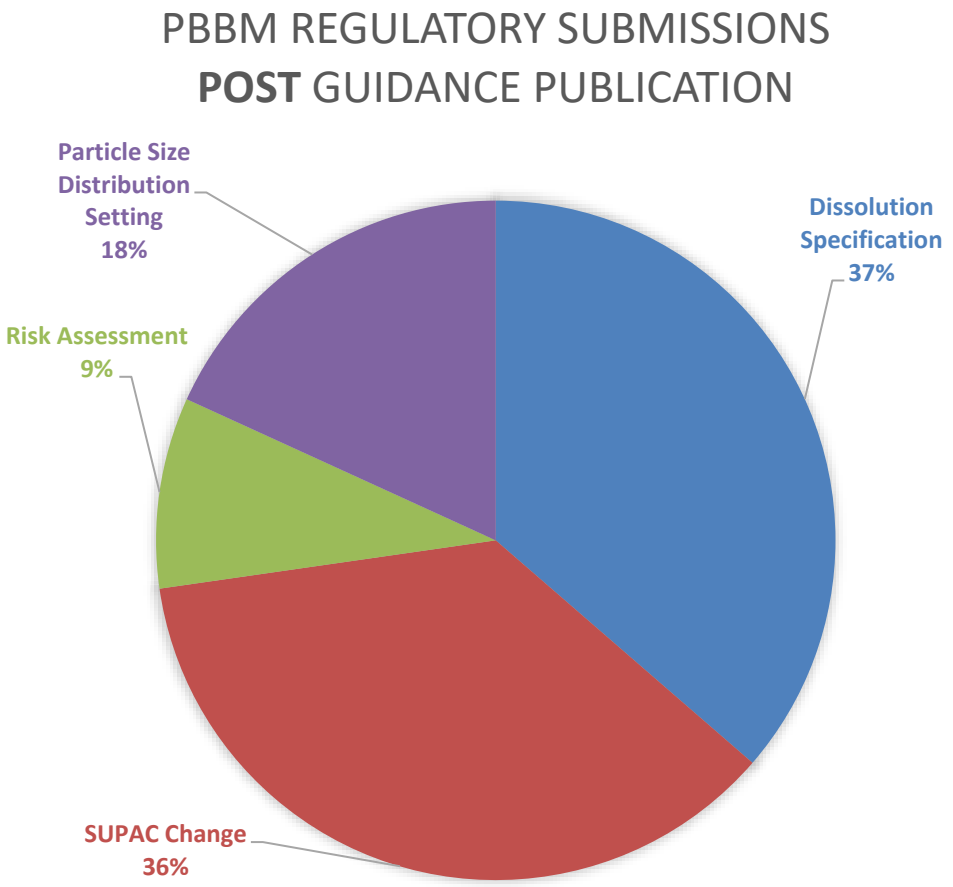
- Dissolution Method Acceptance Criteria
  - Justify a biopredictive method/AC and discriminatory capability
  - Allowed widening of specifications but allowed for ability of dissolution method to reject non-BE batch

- Patient-Centric Quality Specifications of Critical Material Attributes and Critical Process Parameters
  - Justify CMA specifications for particle size and polymorphic form
  - Justify CPPs for milling method and pressure force/hardness, dwell time

- SUPAC and risk assessment
  - SUPAC level 3 change requiring a bioequivalence study
  - Comparison of pre- and post-change products using previously established PBPK model
  - Totality of data used to make the biopharmaceutics assessment of SUPAC change (e.g., quality, clinical, model predictions, dosage form, risk)

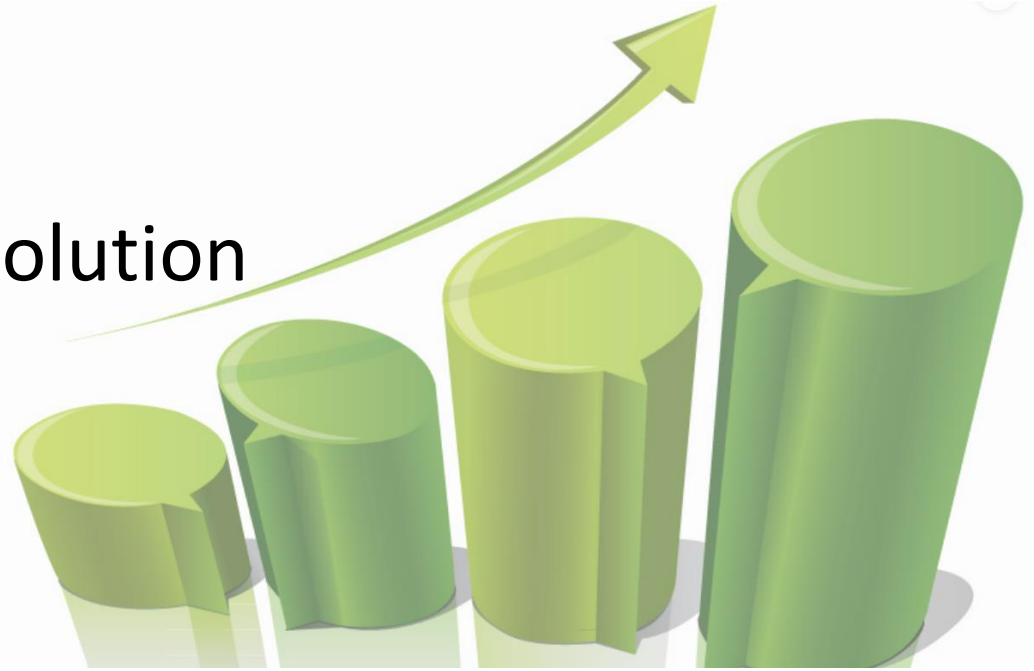
PBBM Regulatory Submissions





Submission Improvements
Post Guidance Publication

- ✓ Dedicated Modeling Report
- ✓ Clearly defined Model Purpose
- ✓ Scientifically justified selection of Dissolution Model
- ✓ Readable Model/Supporting Files

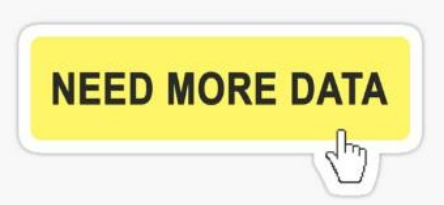


Observed Deficiency Categories

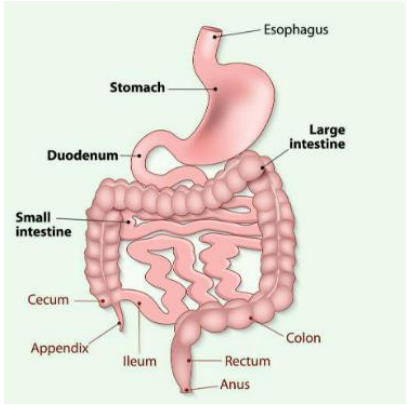
- Inadequate model development
- Inappropriate model validation
- Drug product specific anomalies

Challenges for PBBM in Regulatory Submissions

- Sparce in vivo data available for model verification



- Knowledge in GI physiology continues to expand

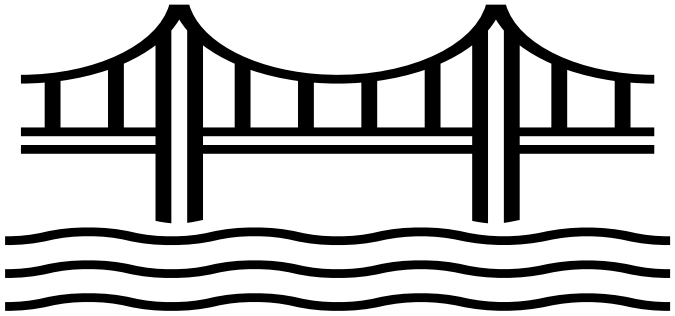


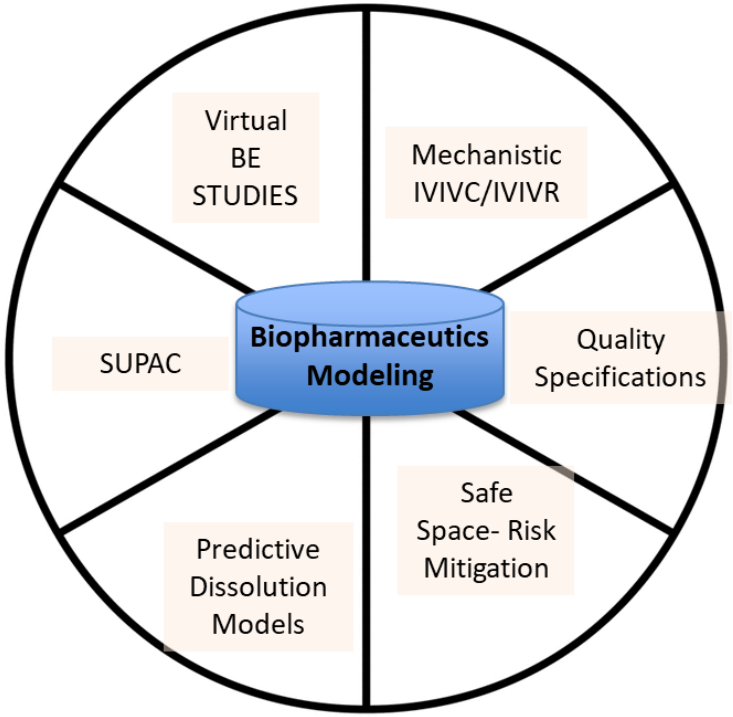
- Constraints of Model validation

- Regulatory Harmonization does not happen overnight

Future State

"In vitro tests and physiological based biopharmaceutics modeling (PBBM) that provides predictive insight to in vivo performance. This ensures high quality drug products that maintain safety and efficacy throughout the product lifecycle. With a predictive dissolution and modeling, the impact of critical bioavailability attributes* on in vivo performance can be quantitatively assessed. This provides scientific and risk-based knowledge to support patient-centric quality standards."





Adapted from: Anand, O., Pepin, X.J.H., Kolhatkar, V. *et al.* The Use of Physiologically Based Pharmacokinetic Analyses—in Biopharmaceutics Applications -Regulatory and Industry Perspectives. *Pharm Res* **39**, 1681–1700 (2022).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