Challenges in the Development and Validation of PBBM and Safe Space from Regulatory Perspective

Panel Discussion with Regulatory Agencies

February 17, 2022

Please note: this presentation, including questions from the audience, is being recorded and may be made available.

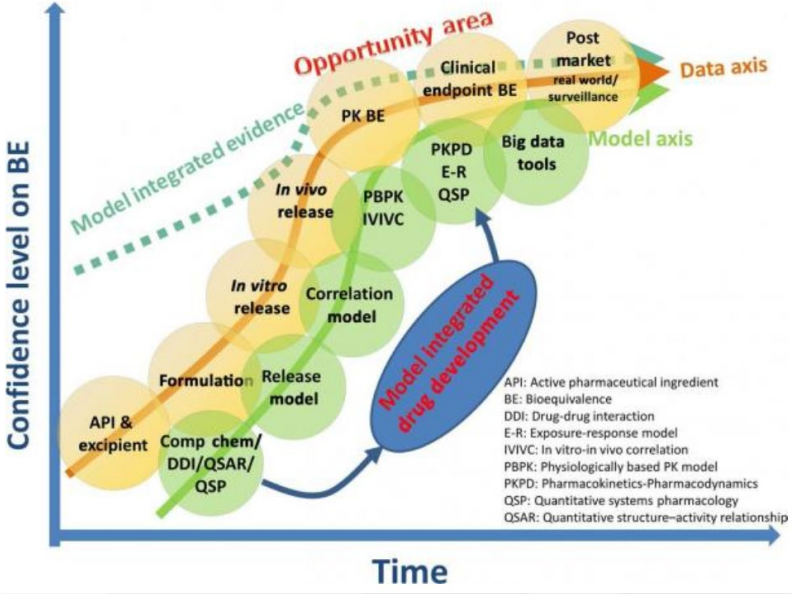
MIDD+22
Model Informed Drug Development +

Access to More Affordable Medicines, How is it Possible? The Impact of Modeling and Simulation

- "We are on an unsustainable path, where the cost of drug development is growing enormously, as well as the costs of new drugs. We need to do something now, to make the whole process less expensive and more efficient. Otherwise, we will not continue to reap the practical benefits of advances in science, in the form of new and better medicines. "..... We are also taking new steps to modernize how sponsors can evaluate clinical information and how FDA reviews this data as part of our regulatory process.
  - ..... **This includes more widespread use of modeling and simulation, and high-performance computing clusters within the FDA.**

Dr. Gottlieb (former FDA Commissioner), the Society of Regulatory Affairs Professionals (RAPS, 2017)

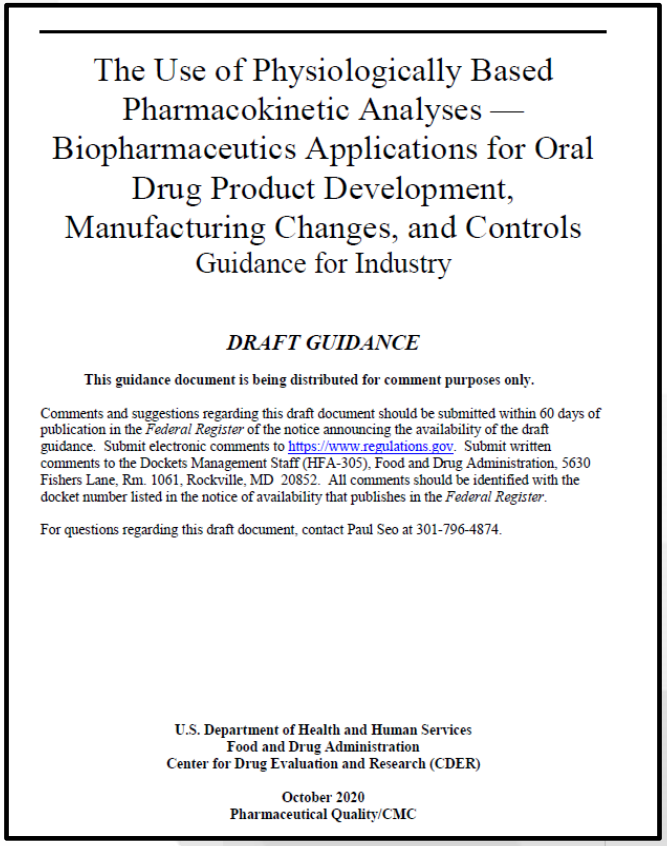
Model-integrated drug development for generic drugs



https://www.fda.gov/drugs/regulatory-science-action/impact-story-modeling-tools-could-modernize-generic-drug-development

MIDD+22 Model Informed Drug Development +

FDA Guidance: The Use of PBBM in Support of Drug Product Quality



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DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

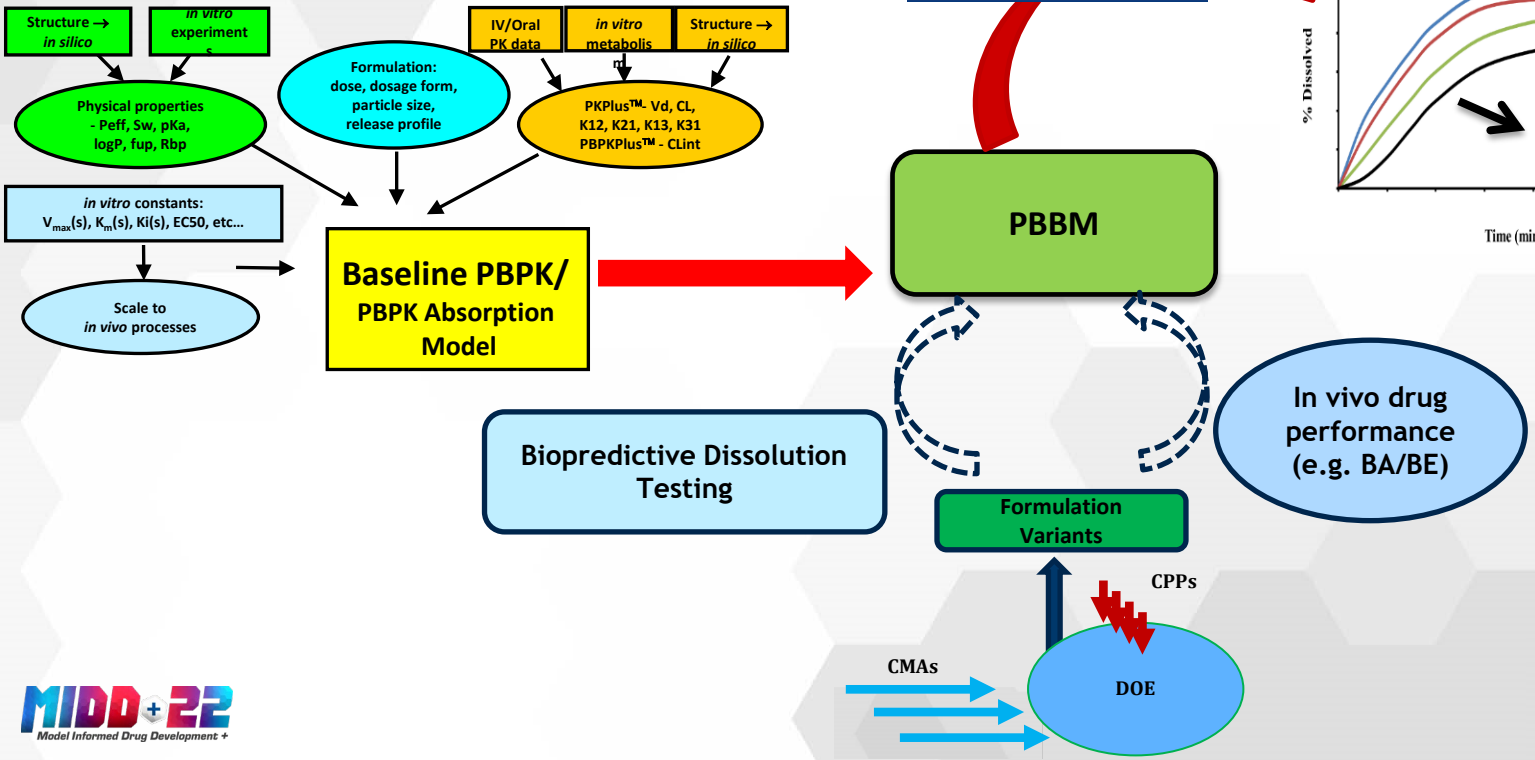
For questions regarding this draft document, contact Paul Seo at 301-796-4874.

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

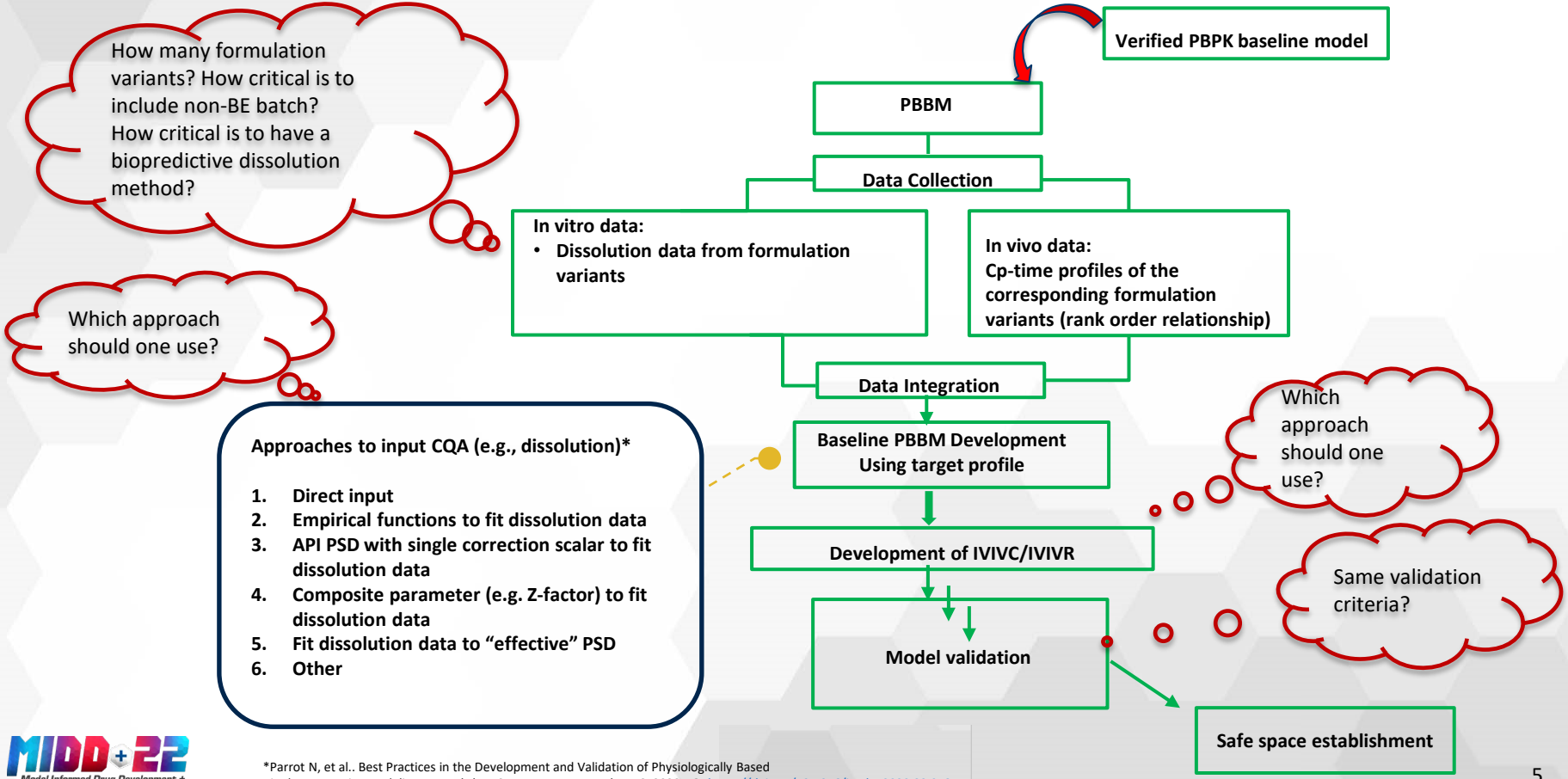
October 2020
Pharmaceutical Quality/CMC

What is PBBM?

NOT confined to building an IVIVC, offering a simpler path to biowaivers specially for IR drug products for which the rate of success of IVIVCs is rather low



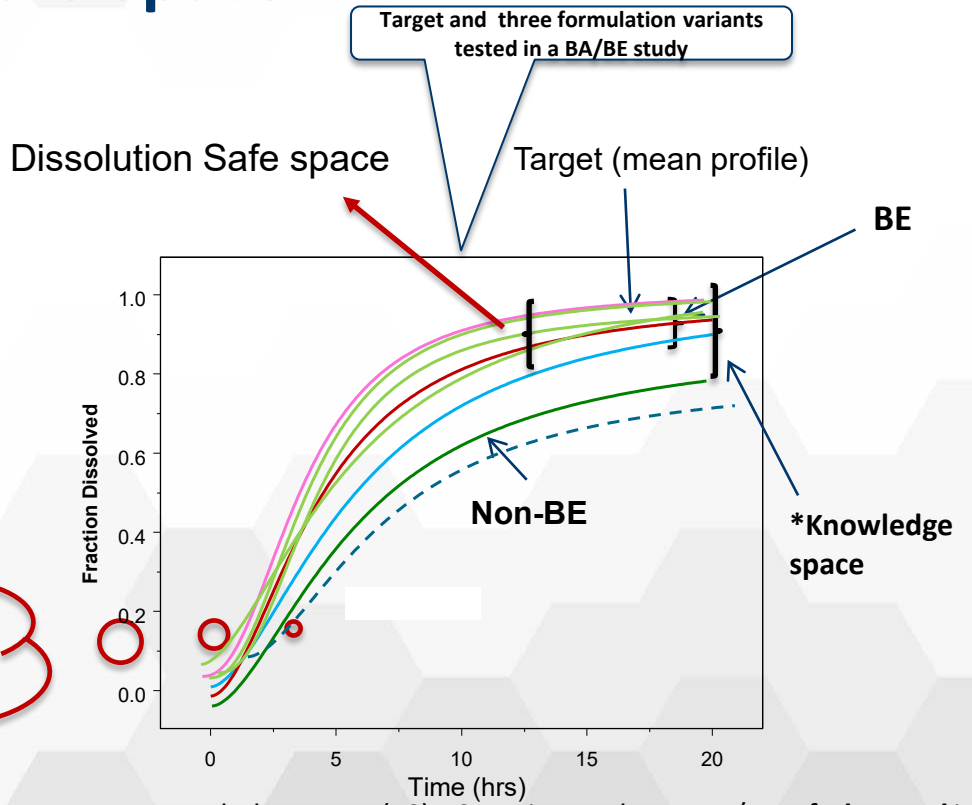
Proposed Workflow for Building a PBBM



*Parrot N, et al.. Best Practices in the Development and Validation of Physiologically Based Biopharmaceutics Modeling. A Workshop Summary Report. JPharmS, 2020 DOI:https://doi.org/10.1016/j.xphs.2020.09.058

What is Safe Space?

- Boundaries defined by **dissolution profiles** within which drug product variants **(around the target)** are anticipated to be bioequivalent to one another[1]



In the absence of non-BE data, in which circumstances is it possible to extrapolate beyond the knowledge space?

*Knowledge space (KS)= Constitutes the range/set of ***observed*** in vitro and corresponding in vivo data used in building the space

1. PBBM guidance

Questions for Panel Discussion

Panelists

- Susan Cole, MHRA
- Gustavo Mendes Lima Santos, ANVISA
- Shereeni Veerasingham, Health Canada
- Liang Zhao, OGD/FDA

Question 1

What would be the largest, single change that would cause an upsurge in the use and acceptance of PBBM/PBPK modeling and simulation in support of drug product quality biowaivers?

Question 2

When building a PBBM model and a safe space for an immediate release (IR) drug product, what are the data requirements for dissolution and PK? How critical is the incorporation of a non-BE batch?

Question 3

What metrics and criteria should be used for judging the predictive performance of PBBM-IVIVR and/or PBBM-IVIVC? Would the same criteria apply for HVDs?

Question 4

Under which scenarios could one consider extrapolating outside the knowledge space in order to expand the limits of drug product specifications? What data would be required to increase confidence in or support the extrapolation?

Question 5

When defining the boundaries of a safe space, should the upper and lower boundaries be compared to one another or should the upper boundary to target (e.g. biobatch/Phase 3 batch) and the lower boundary to target be compared?

Question 6

What metrics and criteria should one use for judging the appropriate approach for incorporation of dissolution data into platform/ model?

Question 7

Please comment on your experience for building a PBBM-IVIVR vs. PBBM-IVIVC model for extended release (ER) formulations. Do you think it is critical to build an IVIVC model rather than an IVIVR for ER formulations?

Question 8

Is the establishment of an in vitro /in vivo link essential for drug products containing low solubility APIs and if so, how critical is it to include in vitro dissolution as input into the platform/model?

Question 9

What are the primary opportunity areas to utilize PBBM/PBPK modeling for establishment of Bioequivalence?

Question 10

What are the primary opportunity areas to utilize PBBM/PBPK modeling for establishment of Bioequivalence?

Q&A

Questions & Answers