Regulatory Education for Industry (REdI) and CERSI Workshop

Current State and Future Expectations of Translational Modeling Strategies to Support Drug Product Development, Manufacturing Changes and Controls

September 23-25, 2019

College Park, MD

BREAKOUT SESSION B DAY 3:

Risk-based approach in the development and implementation of PBBM modeling to support drug product quality (e.g., clinically relevant specifications setting)

Moderators and scribes: Om Anand (FDA); Shefali Kakar (Novartis); Min Li (FDA); Xavier Pepin (AstraZeneca);

Session Background

The facts:

- Gastrointestinal fluid volume kinetics and gastrointestinal motility are highly relevant for the *in vivo* performance of oral IR and MR drug products.
- Both parameters contribute significantly to the variability of PK profiles.
- The role of mucus in oral drug delivery remains unclear.
- All three aspects are poorly considered in biopredictive *in vitro* and *in silico* tools.

How can we overcome this?

Session Outline

	Question	Moderator	Scribes
1	How is PBBM being used in support of product quality (e.g., product development, CRS, pre-/post-approval changes)? a. To provide an overview of survey results focusing on: 1) the risk with the use of a PBBM for supporting CRS and other applications (see the list of applications in the survey) 2) the health authorities acceptance of PBPM; 3) reasons for unsuccessful cases of PBBM	Min, Shefali	Xavier, Om
2	How do the Applicants/Sponsors approach implementation of the PBBM in support of drug product quality ? a. Is the implementation different depending on the level of risk or the purpose of the PBBM ? b. What would be an ideal decision strategy to determine plausible use of PBBM to support CMC changes through product lifecycle?	Xavier	Min, Shefali, Om
3	What has been the industry experience with Regulatory Agencies on acceptance of PBBM in support of drug product quality (e.g. CRS)? a. Is the acceptance rate based on the risk associated? Data available in support of model development and validation? b. What corrective measures must be implemented to increase acceptance rate?	Shefali	Xavier, Om, Min
4	What has been the Regulatory Agencies feedback on PBBM submissions?	Om	Xavier, Shefali, Min

Key Points from BO Session B, Day 3, Question 1

Review the survey results (slides to be inserted during D3 lunch break)

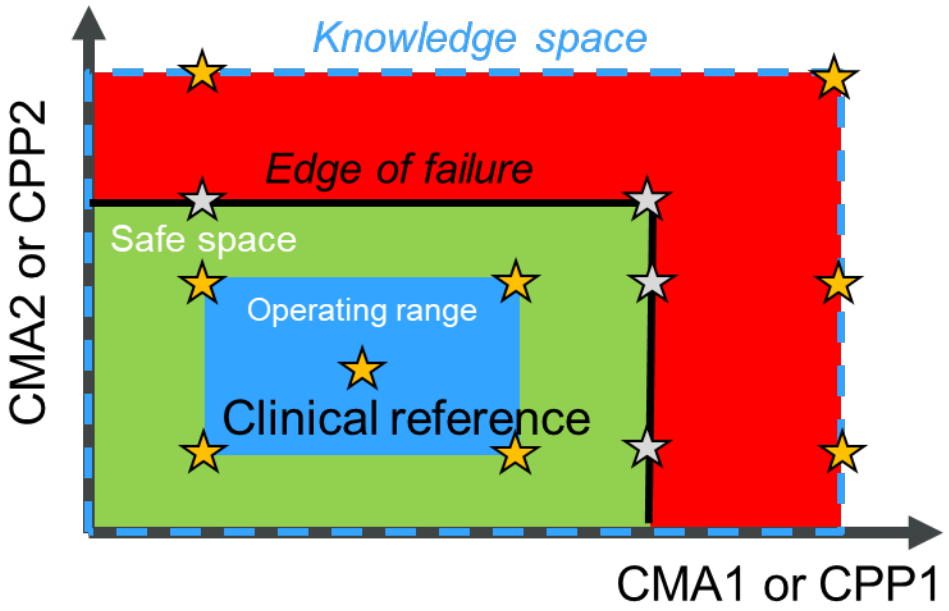
Does the audience feels represented in the survey ?

Do you have concrete examples you could share during the BO ?

Key Points from BO Session B, Day 3, Question 2

1.How do the Applicants/Sponsors approach implementation of the PBBM in support of drug product quality ?

- Is the implementation different depending on the level of risk or the purpose of the PBBM ?
- What would be an ideal decision strategy to determine plausible use of PBBM to support CMC changes through product lifecycle?



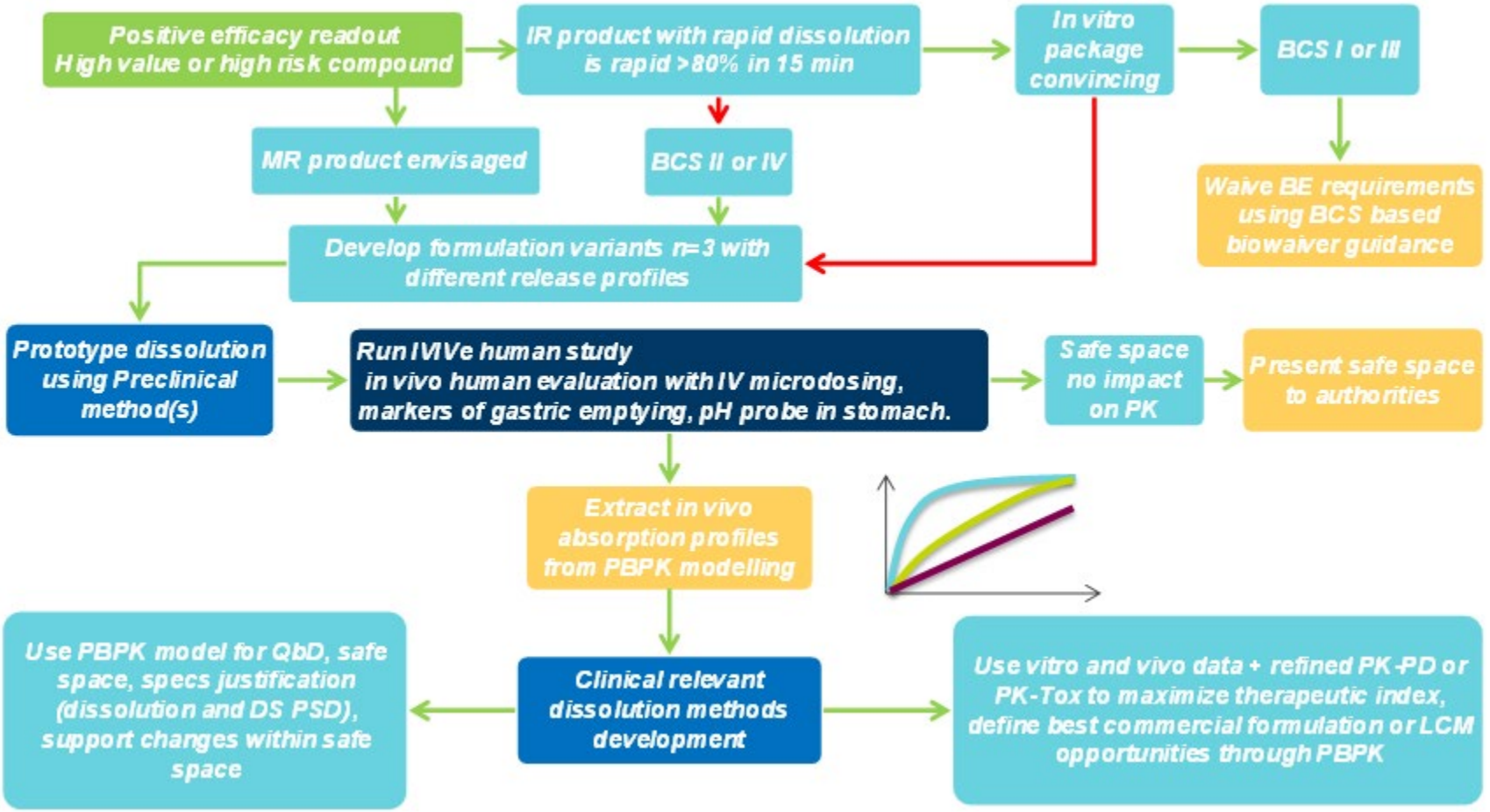
Size of the safe space

Justified specifications

Regulatory flexibility

Key Points from BO Session B, Day 3, Question 2

1. Strategy (AZ)



Key Points from BO Session B, Day 3, Question 2

Strategy

Are there other decision trees out there ?

How to reach harmonization across industry and regulators ?

Does the strategy depend on the PBBM application ?

Does the strategy depend on the level of risk associated with the modeling ?

Key Points from BO Session B, Day 3, Question 3

What has been the industry experience with Regulatory Agencies on acceptance of PBBM in support of drug product quality (e.g. CRS)?

a. Is the acceptance rate based on the risk associated? Data available in support of model development and validation?

b. What corrective measures must be implemented to increase acceptance rate?

Key Points from BO Session B, Day 3, Question 4

What has been the Regulatory Agencies feedback on Physiologically Based Biopharmaceutics Modeling (PBBM) submissions?

Agencies' feedback on:

- The proposed models
- Verification/validation data
- Simulation results/outcomes
- Other issues

Differences in feedback from various Regulatory Agencies

Overall Conclusions