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Extrapolation Outside Safe Space-Based PBBM: When is This Feasible?

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M-CERSI Workshop on PBBM

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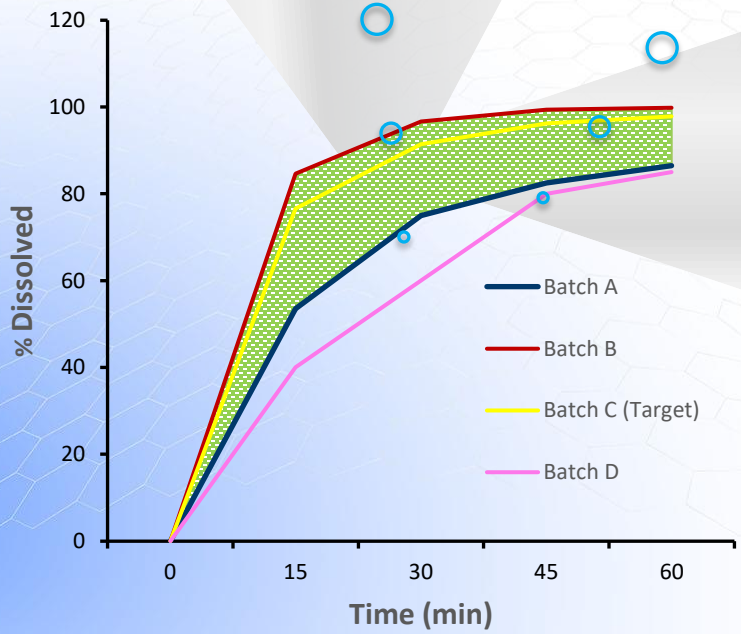
Outline

- **The Concept of Safe Space**
  - Approaches to Establish Safe Space
  - Data Needed
  - Definitions of Key Safe Space Elements
  - Key Questions/ Gaps in Knowledge in Data Needed and Approaches to Establish (and Expand) Safe Space
    - Feasible Path for Demonstrating the Applicability of the Safe Space to CMAs/CPPs not Evaluated in PK Studies
    - The Relevance of Formulation Variants around the Target
    - The Relevance of Rank Order Relationship
    - Extrapolation Outside the Safe Space, When May This be Feasible?
  - Case Studies on Extrapolation Outside the Safe Space
- **Take Home Message**

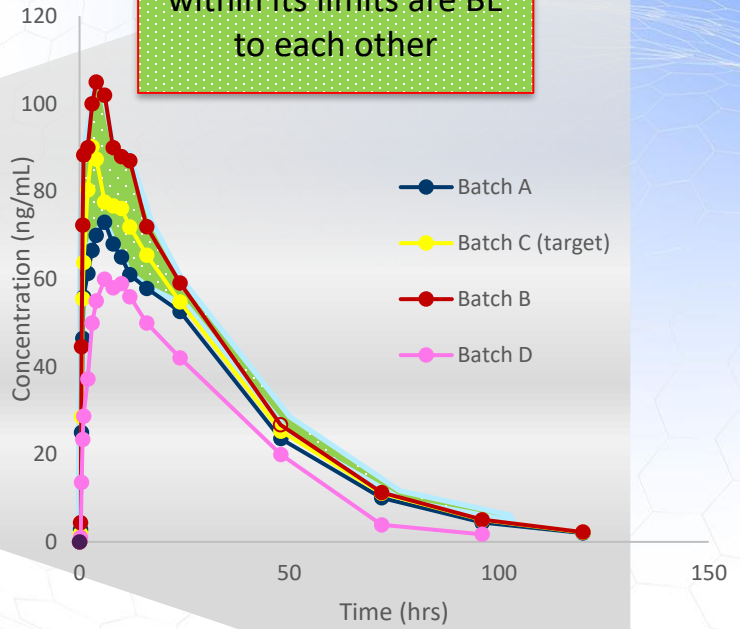
What is Safe Space?

Under which circumstances could one expand beyond these limits?

Is the presence of a non-BE batch critical for a PBBM-safe space?

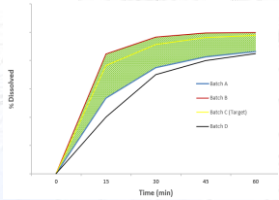


Safe space = all batches within its limits are BE to each other

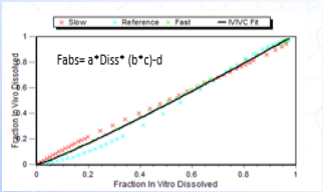


Approaches to Build Safe Space

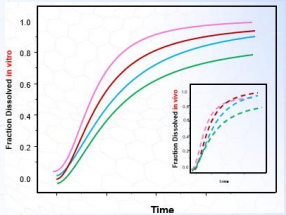
Bracketing Approach (conventional IVIVR)



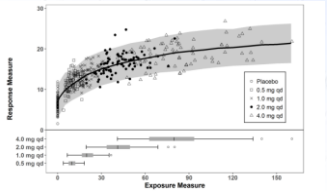
Conventional IVIVC



Safe Space

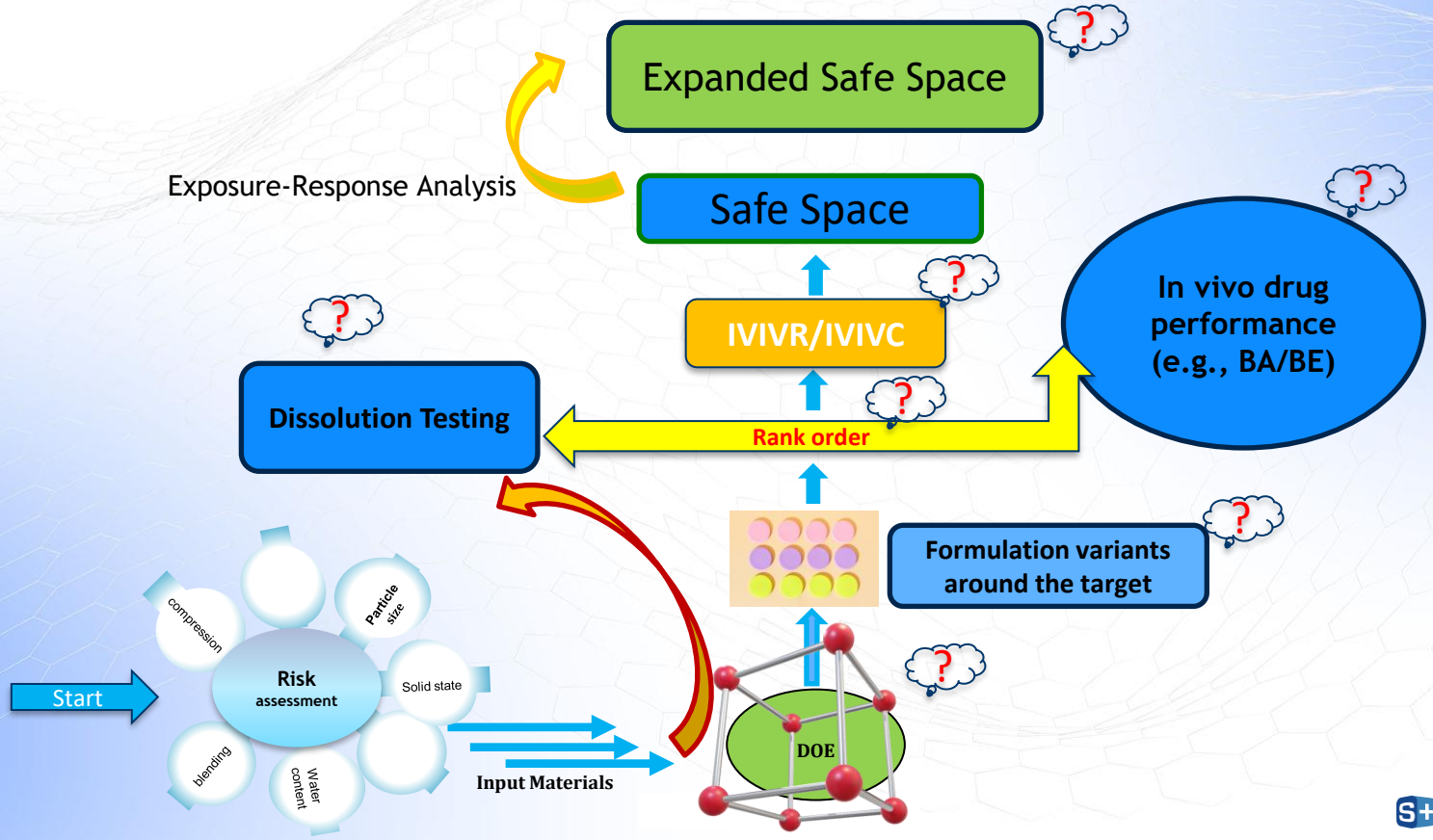


PBBM-based IVIVR/C



Exposure-Response Analysis

What Data are Needed to Establish a Dissolution Safe Space?



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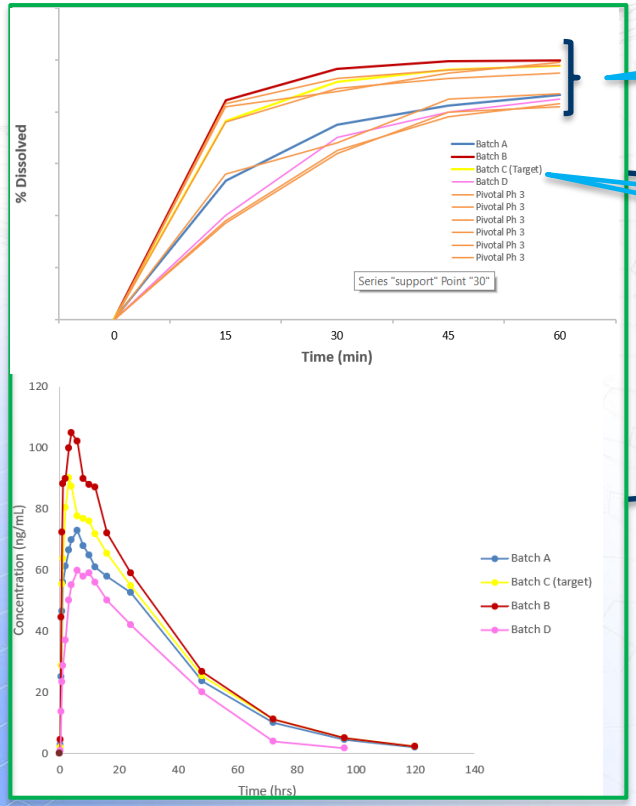
Definitions of Key Safe Space Elements



Formulation Variants: batches of drug product under investigation with variations (target formulation) in its CMAs/CPPs/CFVs

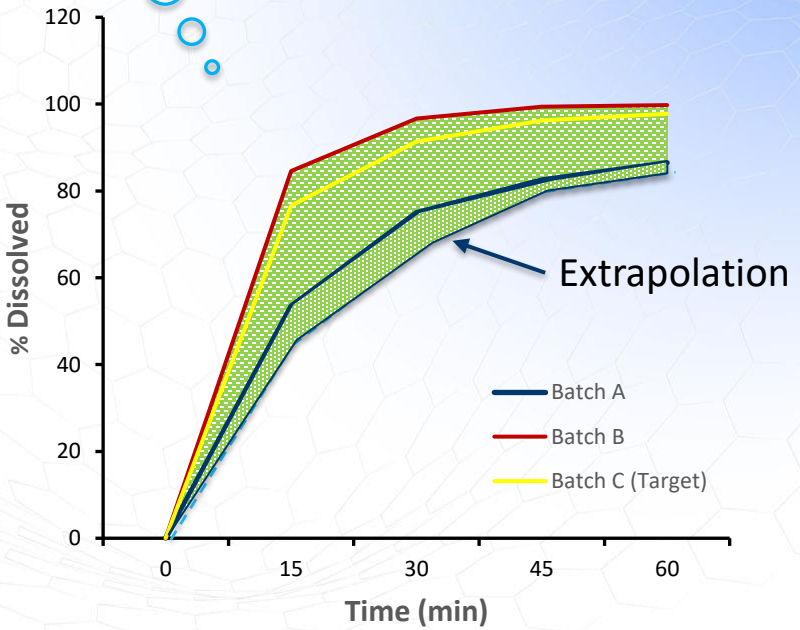
Target profile: formulation evaluated in pivotal BA/BE and/or efficacy and safety trials

Knowledge space: group of drug product batches evaluated in BA/BE studies and pivotal efficacy / safety trials, with their corresponding dissolution profiles

Extrapolation outside the safe space: When in the absence of a non-BE batch, M&S (e.g., PBBM) is used to determine the edge of failure or to predict whether a dissolution profile will be within BE limits

When extrapolation is justifiable, which batch should be used as the reference? The upper bound? The target profile?

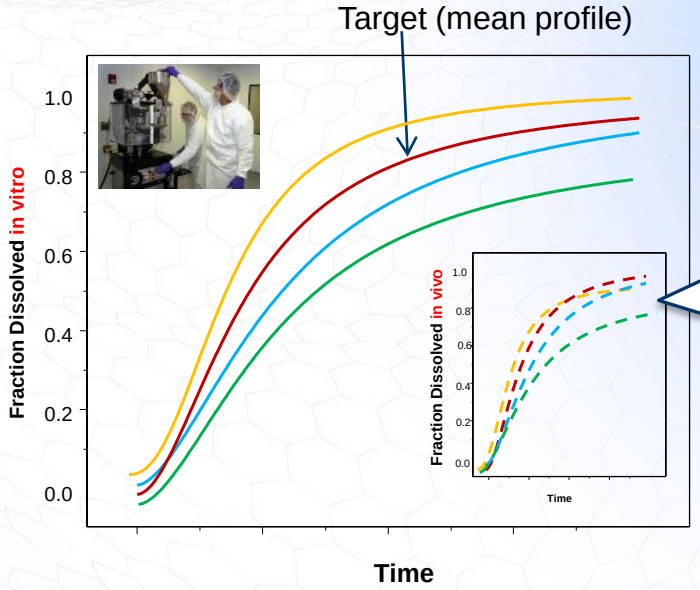
When can this be considered justified?



Safe space = all batches within its limits are BE to each other

Mechanistic IVIVR: Process for determining the link between CMAs/CPPs/CFVs and a response derived from an in vitro dissolution profile and its in vivo impact (e.g., ***in vivo dissolution/release profile***) using PBBM

- To have regulatory application, this should be a rank-order response derived from evaluating formulation variants around the target profile



As part of drug product development, relying on this initial in vitro-in vivo link is warranted given the relatively smaller amount data available at early phases of development

Critical to determine the sensitivity / ***predictive*** ability of the dissolution method ***within this range***

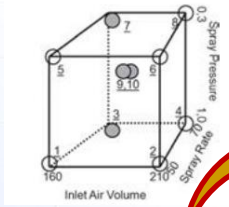
Key Questions/Gaps in Knowledge on Data Needed/Establishment of Safe Space

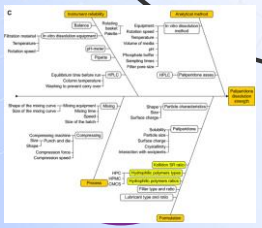
The Relevance of QbD Data to Ensure Robust Safe Space

Is a safe space built on dissolution/PK formulation variants which evaluated only one failure mode (e.g., API PSD) applicable to other CMAs/CPPs?

Think about risk factors, focus on higher risks

Conduct DOEs (multivariate level) to confirm high/low risk





Design experiments to understand high risk

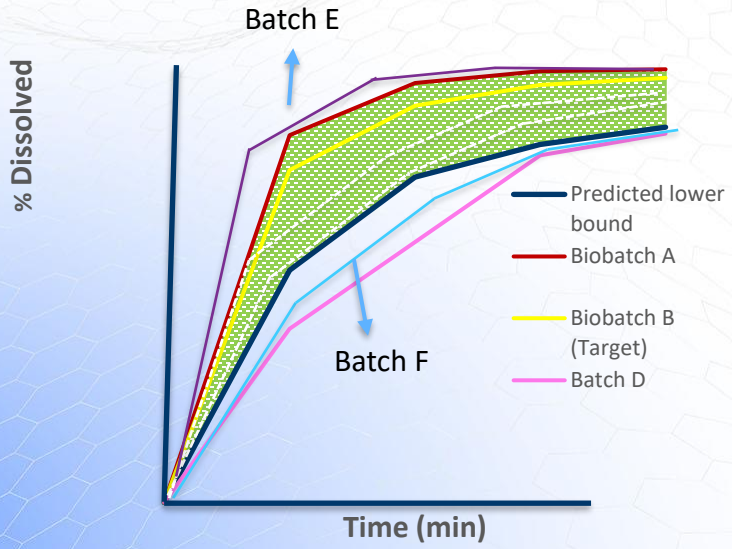
Dissolution as endpoint

Integrate knowledge e.g., selection of formulation variants to represent the limits of the dissolution safe space

Identify critical control points and inform the ranges of the design spaces that are clinically relevant

Achieve drug product / process understanding

Understanding the Risk of Applying Safe Space to CMAs/CPPs not Evaluated in PK Studies



Batch	API PSD (D50 microns)	Hardness (kP)
A	24	10
B	56	11
D	75	11
Ranges proposed	20-60	8-14
E	20	8
F	60	14

→ Risk to Patients

→ Risk to Company

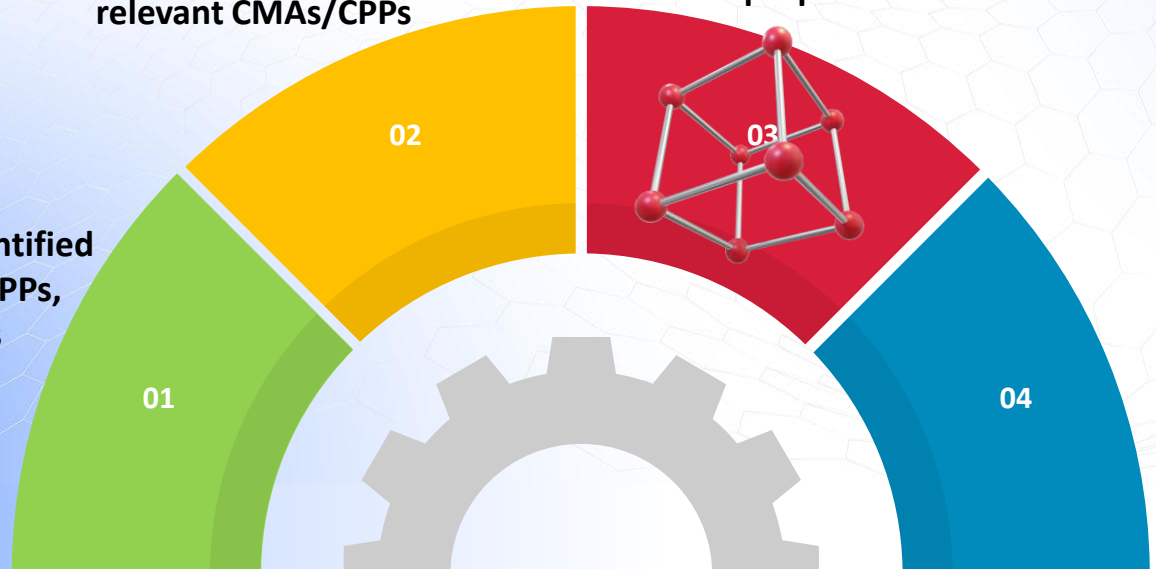
Approach for Demonstrating the Applicability of the Safe Space to CMAs/CPPs not Evaluated in PK Studies

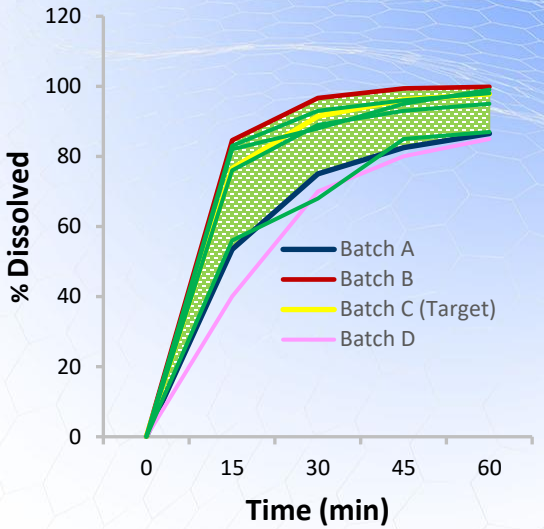
List all identified CMAs, CPPs, CFVs

Identify the ranges of proposed design spaces (DSs) for relevant CMAs/CPPs

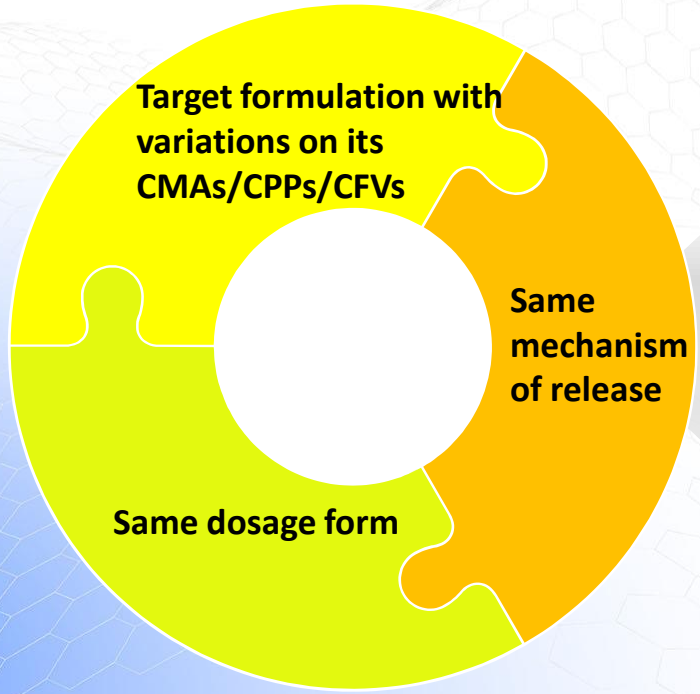
Run dissolution testing in a multivariate manner e.g., on the extremes of the proposed DSs

Input dissolution profiles in PBBM to evaluate applicability





Relevance of Formulation Variants Around The Target



Different Release Mechanism (especially in vivo)

- Capsules
- Tablets
- Suspensions
- Gels
- MR formulations
- others

Will likely result in a different shape in the rank order relationship being sought

Note that PK data from these formulations are key for defining the baseline PBPK absorption model

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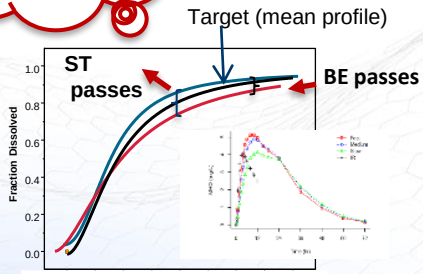
Relevance of Rank Order for a Robust Safe Space

PBBM likely to define a very narrow safe space and unlikely to expand the ranges of safe space



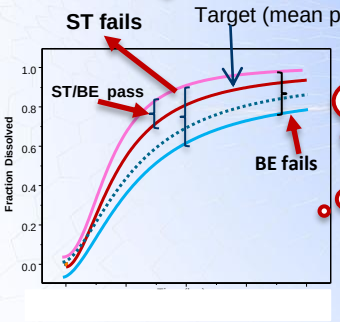
ST passes / BE passes

Dissolution method not sensitive to changes in CMAs/CPPs within tested ranges

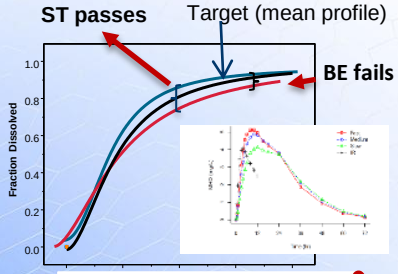
ST passes / BE passes and ST fails / BE fails

(rank order relationship)

Target and two formulation variants tested in a BA/BE study



PBBM is likely to define/expand the ranges of safe space

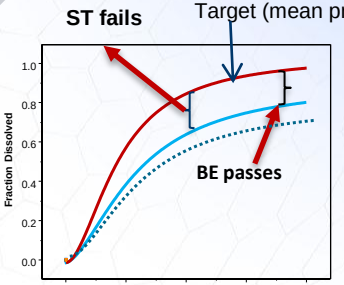


ST passes / BE fails

Dissolution method is under discriminating

ST fails / BE passes

Dissolution method is over discriminating



PBBM likely to define but may not expand the ranges of safe space (extrapolation may not be acceptable by regulatory agencies)

Target and two formulation variants tested in a BA/BE study

Target and formulation variant tested in a BA/BE study

It is not possible to build a safe space ***with in vitro dissolution as an input***

Divergence from in vitro dissolution does not necessarily imply absence of BE within specified limits

ST= Dissolution similarity testing

Extrapolation Outside the Safe Space: When May This be Feasible?

MR drug products, IR drug product containing BCS class 2/4 drug substance

No changes in excipients, or justification of lack of impact by added/deleted excipients

IR Drug Products containing BCS class 1/3 drug substance

Efficacy and safety Trials supporting product approval

Manufacturing /dissolution variability

Use of PBBM model to predict the concentration of batches with dissolution outside the safe space

Exposure-Response Analysis

Real World Data evidence

Manufacturing variability/dissolution commercial batches

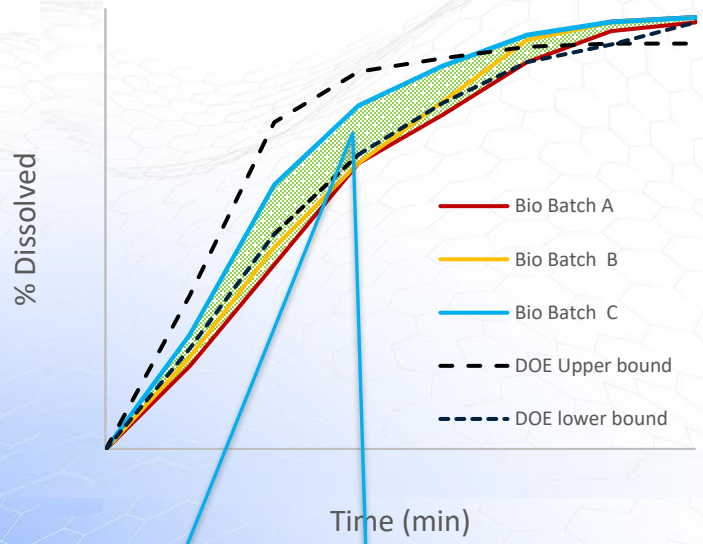
Case Studies on Extrapolation Outside the Safe Space

CASE STUDY 1:
Establishment of Safe Space to Support Post-Approval Changes (from in Lab-Dissolution Testing to RTRT Dissolution Model)

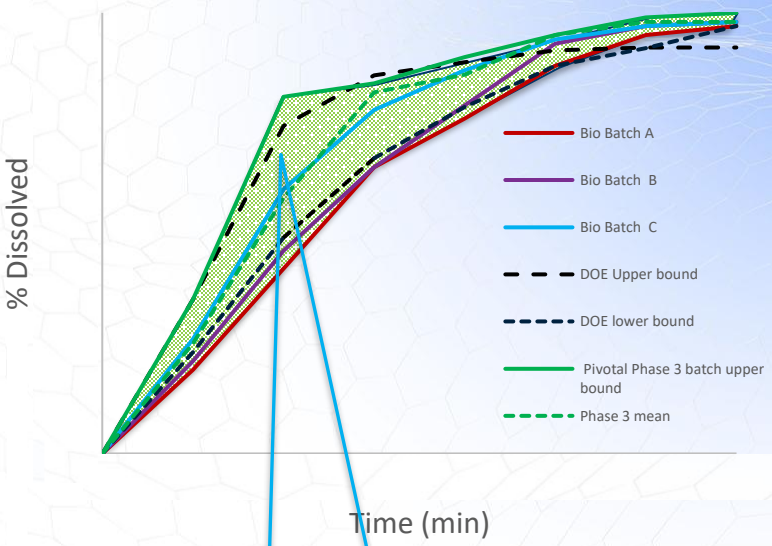
Drug Product Background

- Drug substance is BCS Class 2
- IR Tablet approved using a batch process
- NDA dissolution method shown to be discriminating to CMAs/CPPs
- QbD Approach with quality built into the manufacturing process as part of original NDA
  - Additional multiple dedicated DOEs to build and validate dissolution model submitted as part of sNDA
    - Multivariate level of all identified failure modes
- Limits of design space for CMAs/CPPs under sNDA were the same or tighter than those in original NDA
- PBBM developed and validated during original NDA stage using GastroPlus®
  - Effect of changes in API PSD (including out of proposed specs) were accurately predicted and confirmed based on the results of popPK

Safe Space Development and Extrapolation/Expansion



- Safe space established based on BA/BE and PBBM. The model predicted no impact on Cmax and AUC for faster profiles.
- Agency was concerned about applicability of the model outside the safe space



Safe space expanded base on manufacturing/dissolution variability of batches tested in pivotal Phase 3 trials

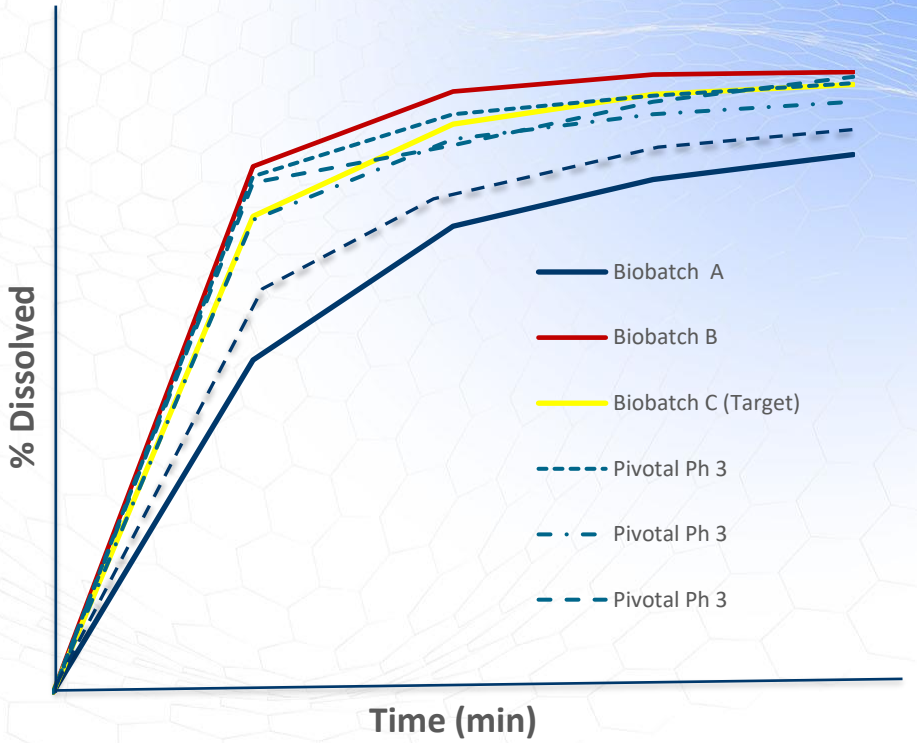
Extrapolated Safe Space Case 1 Study Summary

- PBBM model developed and successfully validated with fit-for-purpose data
- No non-BE batch data available
- Agency was concerned on the use of the model for extrapolation outside the safe space
- Dissolution data from Pivotal Phase 3 trials were used to extrapolate/expand the safe space to cover the variability observed on the dissolution data used in the development and validation of the RTRT dissolution model
  - Rendered the dissolution method and drug product specifications/design spaces clinically relevant
- Safe space (upper bound) was further supported with Real Word Data Evidence
  - MedWatch and analysis showed no side effects reported on commercial product with dissolution variability as high as that for pivotal Ph 3 clinical trials

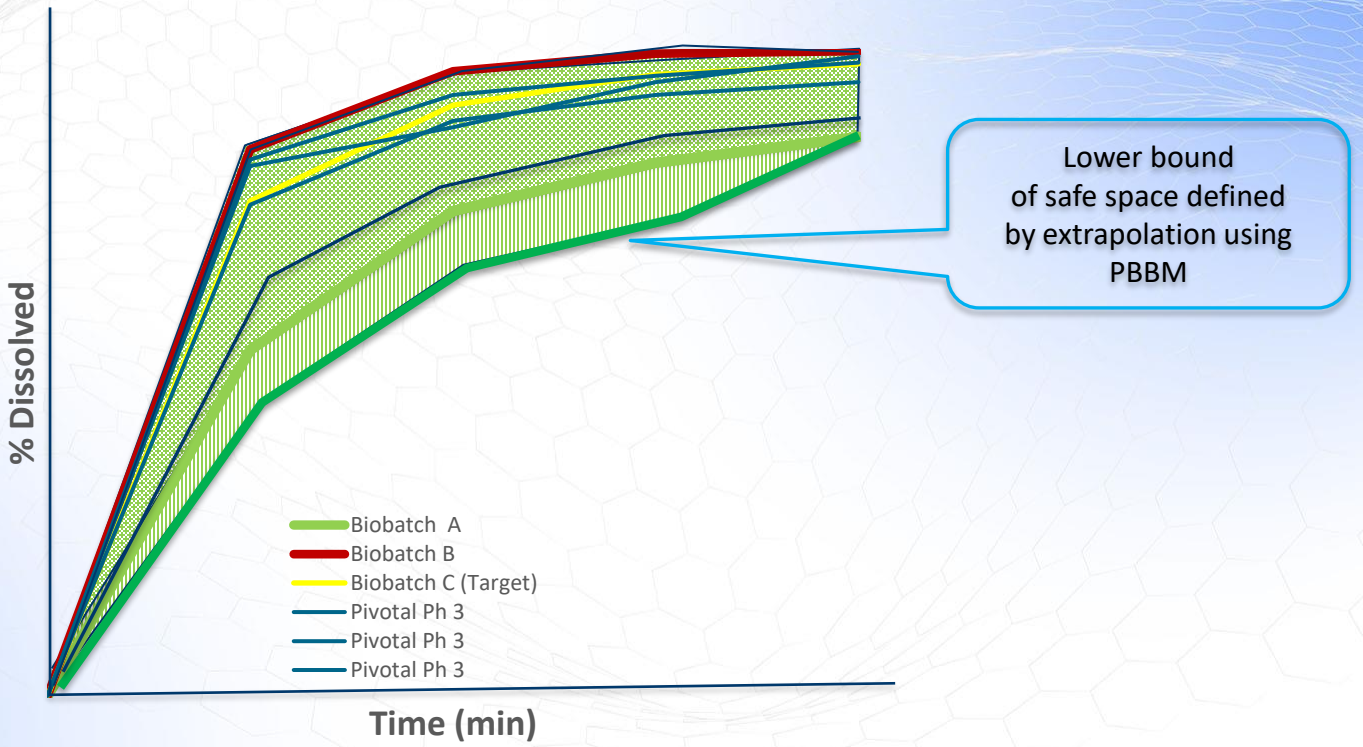
Establishment of Safe Space to Support Widening the Dissolution Acceptance Criterion for IR Tablet

Drug Product Background

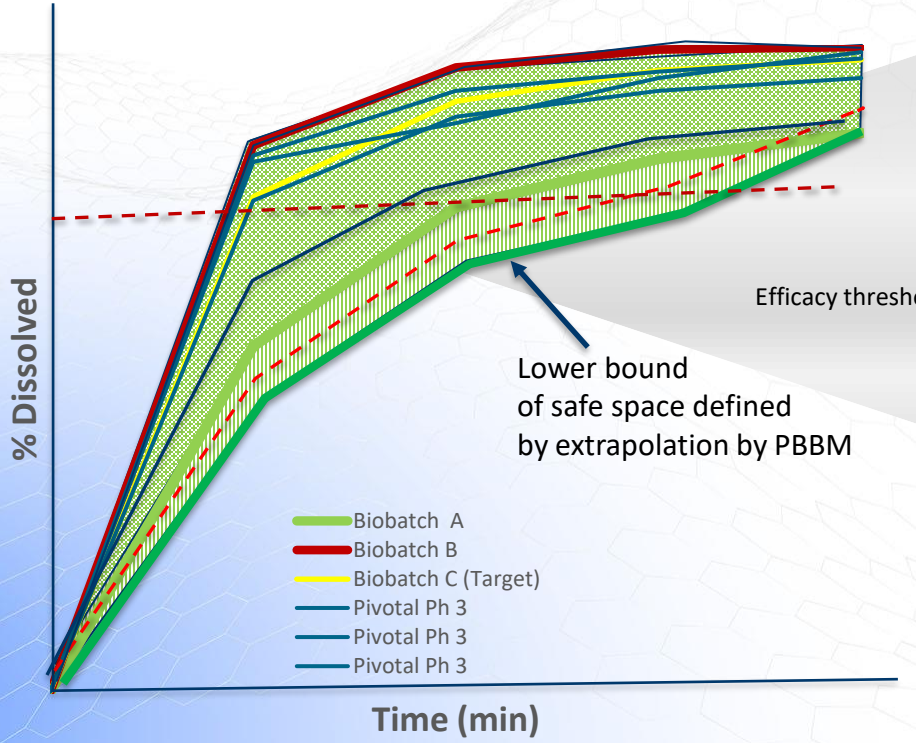
- Drug substance is BCS Class 2
- Proposed dissolution method is discriminating for several CMAs/CPPs
- PBBM developed and validated using GastroPlus®
  - Very rich set of data used to successfully develop and validate the model
    - more than 10 PK studies
    - more than 2 fit-for-purpose data (BE studies with formulation variants around the target)
  - No non-BE batch data available



Safe Space Extrapolation/Expansion

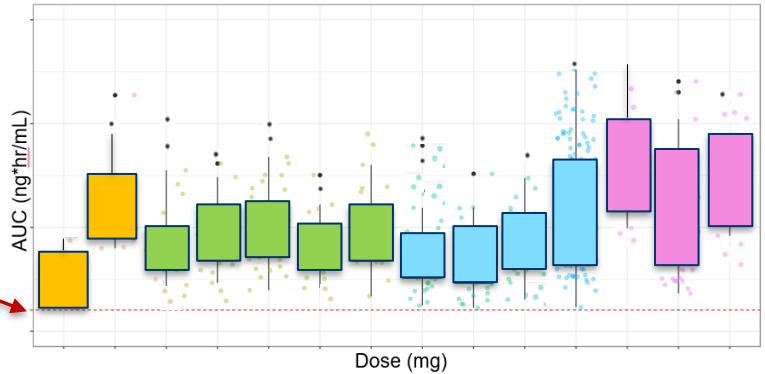


Safe Space Extrapolation/Expansion



Lower bound
of safe space defined
by extrapolation by PBBM

Efficacy threshold



Safe space lower bound supported by exposure/dose-response data available

Extrapolated Safe Space Case Study 2 Summary

- PBBM model developed and successfully validated with fit-for-purpose data
- No non-BE batch data available
- Safe space extrapolated beyond knowledge space (on lower bound) to support widening the dissolution acceptance criterion
  - Cmax and AUC predicted values were well above threshold defined for efficacy endpoint

Take Home Message

- The foundation of Safe Space lies in the principles of IVIVC and IVIVR and is then "governed' by IVIVC/IVIVR tenets
  - It necessitates at least two release rates with corresponding CP-time profiles (in rank order)
    - non-BE data is highly desirable but should not be a requirement
- The applicability of the safe space to CMAs/CPPs not evaluated in PK studies needs to be justified
- Safe space is dosage form-specific and should be built using formulation variants around the target
- Extrapolation outside the knowledge space/safe space for ER formulations/BCS class II/IV is regarded as high-risk, unless otherwise justified by additional data such as ER analysis
  - During drug product development, the use of extrapolation is warranted
- Establishment of a safe space serves as a foundational step towards ensuring drug product quality that is centered around the patient