Clinically Relevant Dissolution Specifications: a Biopharmaceutics' Risk Based Approach: an FDA perspective

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The Academy of Pharmaceutical Sciences

Webinar Series

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

A quality product of any kind consistently meets the expectations of the user – drugs are no different.

Patients expect safe and effective medicine with every dose they take.

Pharmaceutical quality is assuring *every* dose is *safe and effective*, free of contamination and defects.

It is what gives patients confidence in their *next* dose of medicine.

Overview

- ***Historical perspective, dissolution testing***
- ***Biopharmaceutics Considerations for Selection of Dissolution specifications***
- ***Clinically Relevant Dissolution Specifications***
- ***Case studies***

Historical perspective, dissolution testing.

- 1951, J Edwards postulated about a correlation between in vivo dissolution and analgesic effect of aspirin.
- In 1950s, Shenoy et al, demonstrated a relationship between in vitro dissolution and the bioavailability of amphetamines.
- Eino Nelson attempted to demonstrate that "*solution rate determines maximum blood level*" of a drug.
- In late 1960s and early 1970s, in vitro dissolution testing became mandatory for several drug products.
- However, the work on in vivo relevance of dissolution continued…….

Historically perspective, dissolution testing….

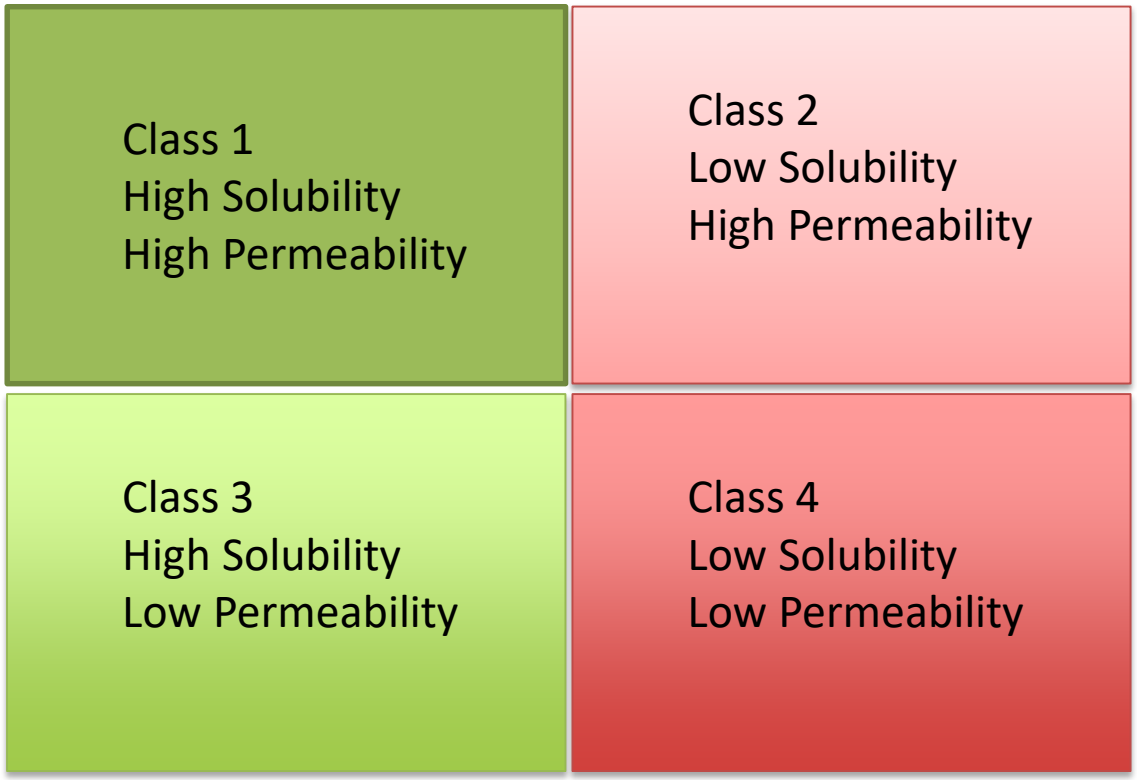
- FDA's Guidance: Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations: 1997
- FDA's Guidance: Dissolution testing of Immediate Release Solid Oral Dosage Forms: 1997
- FDA's Guidance: Waiver of in vivo bioavailability and bioequivalence studies for immediate release solid oral dosage forms based on a *Biopharmaceutics Classification system*: 2000
- FDA's Guidance: Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances: 2018
- FDA's Draft Guidance: The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls: 2020

Course Correction

- In the past few years, shift in paradigm of utility of in vitro testing to reflect or predict in vivo outcomes.

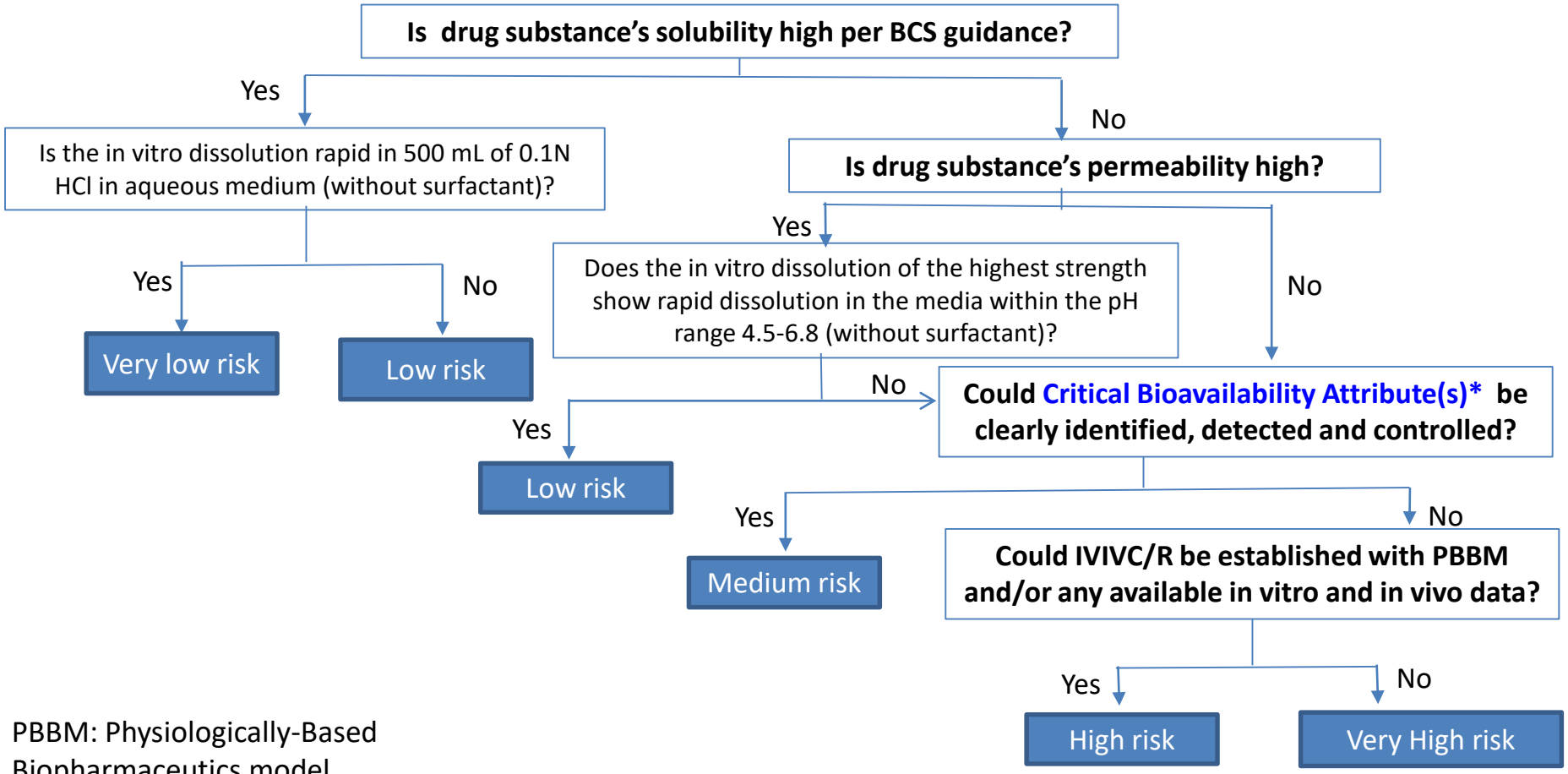
Biopharmaceutics Considerations for Selection of Dissolution Method and Acceptance Criterion for
Solid Oral Dosage Form Drug Products: A risk-based approach

BCS Provides a Framework for Risk Evaluation of IR Drug Products



2017 GUIDANCE: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System

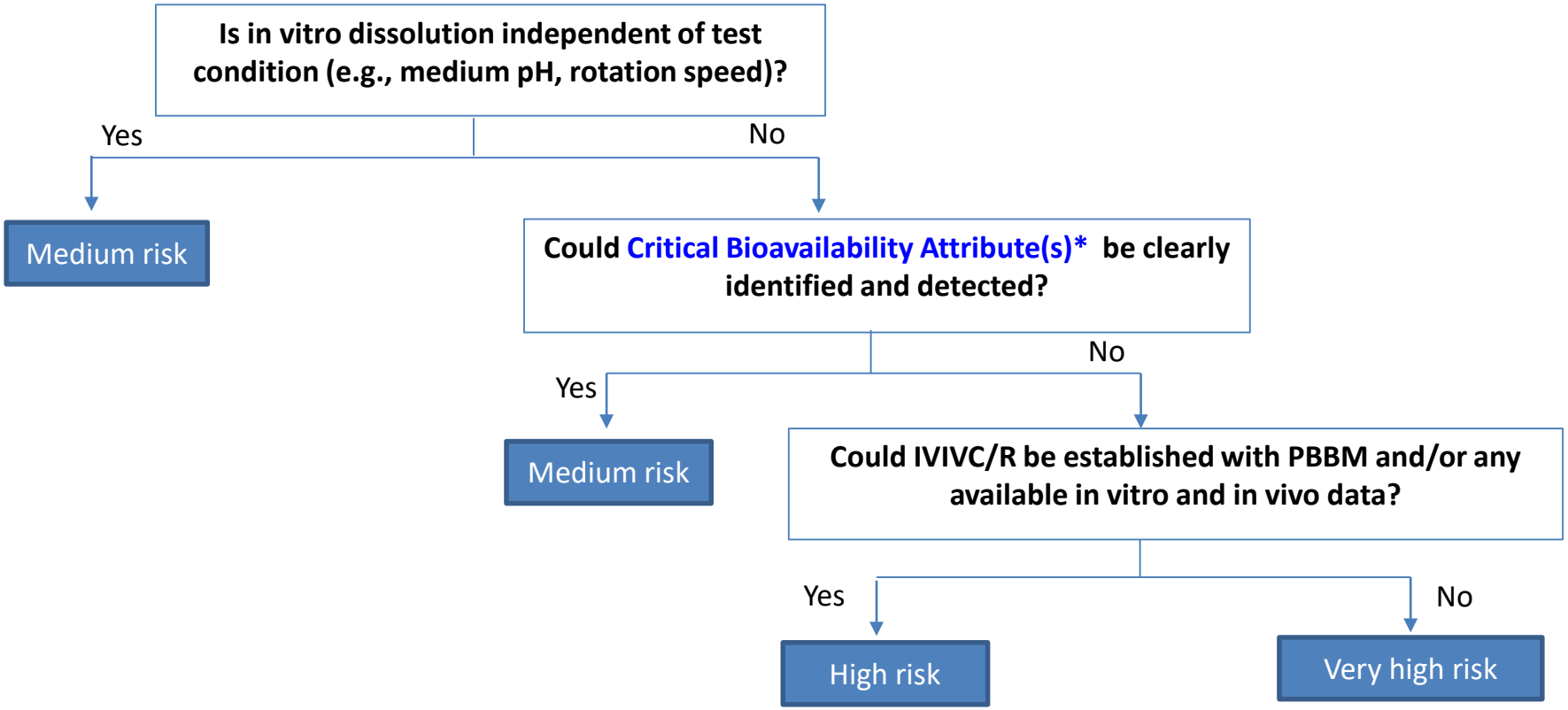
Biopharmaceutics risk assessment decision tree for IR solid oral dosage forms (Non-NTI or Non-rapid onset)



PBBM: Physiologically-Based Biopharmaceutics model

* **Critical Bioavailability Attribute(s), CBAs**: Formulation or process attributes those are expected to critically impact the bioavailability (absorption rate and extend) of a drug product

Biopharmaceutics risk assessment decision tree for ER solid oral dosage forms (Non-NTI)



PBBM: Physiologically-Based Biopharmaceutics Model

Biopharmaceutics Approaches to Mitigate BA/BE Risks

Level	Biopharmaceutics Approaches
Very Low	Standard dissolution test as per August 2018 FDA dissolution guidance (High solubility drug substances)
Low	Dissolution test with a scientifically sound condition. Limited method development is needed to justify method and/or acceptance criterion
Medium	In vitro approach to mitigate the risk. Dissolution test should target to detect meaningful changes in identified CBA(s) to provide insight into in vivo performance
High	IVIVR to support patient-centric dissolution test (Based on available in vitro/in vivo data and/or PBBM)
Very High	In vivo studies are used to develop IVIVC/R to support patient-centric dissolution test

Patient-centric quality standards (PCQS).

- PCQS are set of criteria and acceptance ranges to which a drug product should conform in order to deliver the therapeutic benefit indicated in the label.

- PCQS can increase flexibility within the pharmaceutical manufacturing sector, while maintaining quality by establishing acceptance criteria based on clinical performance instead of process capability or manufacturing process control.

- PCQS avoid under- or over-discriminating specifications.

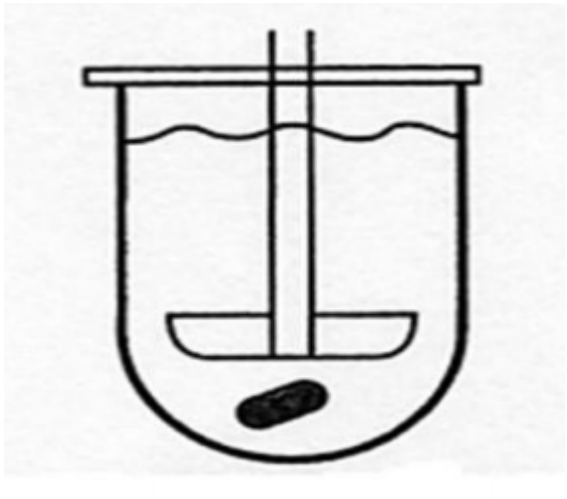
Clinically Relevant Dissolution Specifications (CRDS)

A specification that takes into consideration the clinical effect of variations in dissolution ensuring a consistent ***safety and efficacy*** *profile*

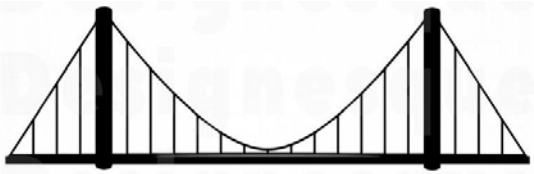
Establishing Clinically Relevant Dissolution Specifications: Biopharmaceutics Role

Role of Biopharmaceutics

Patient-Centric
Drug Product Quality



In vitro dissolution

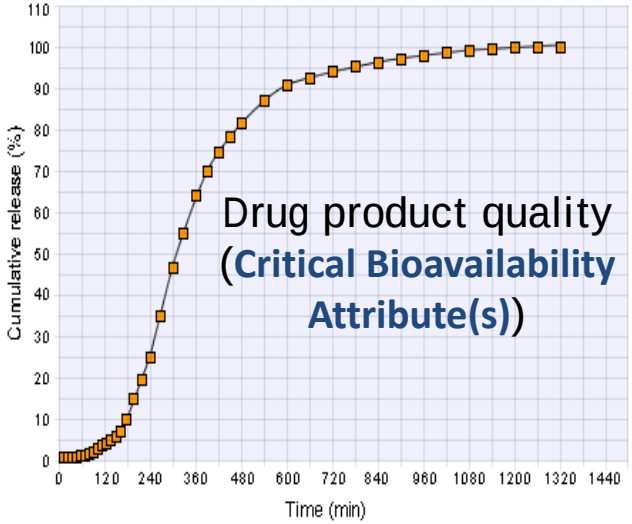


Biopharmaceutics

In vivo drug performance

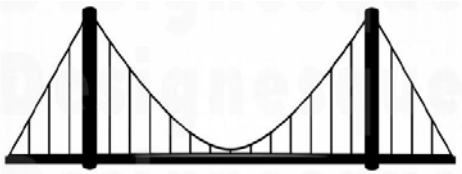
Role of Biopharmaceutics

Patient-Centric Drug Product Quality

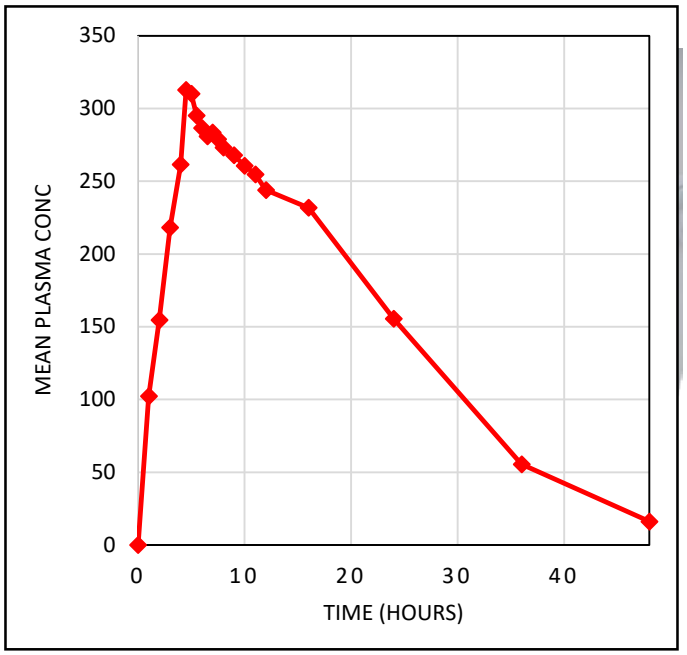


In vitro dissolution

Clinically relevant drug product specifications



Biopharmaceutics

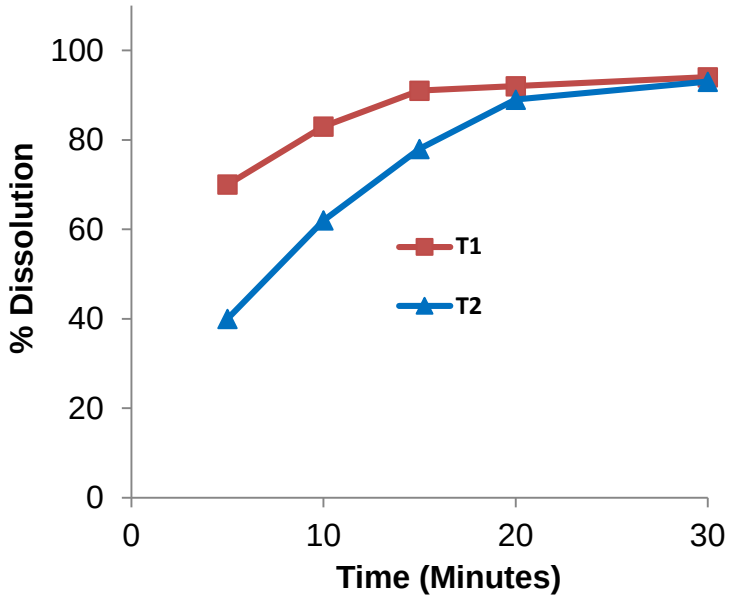


In vivo drug performance

Low risk products

BCS Class 1
High Solubility
High Permeability
Rapid Dissolution

BCS Class 3
High Solubility
Low Permeability
Very Rapid Dissolution

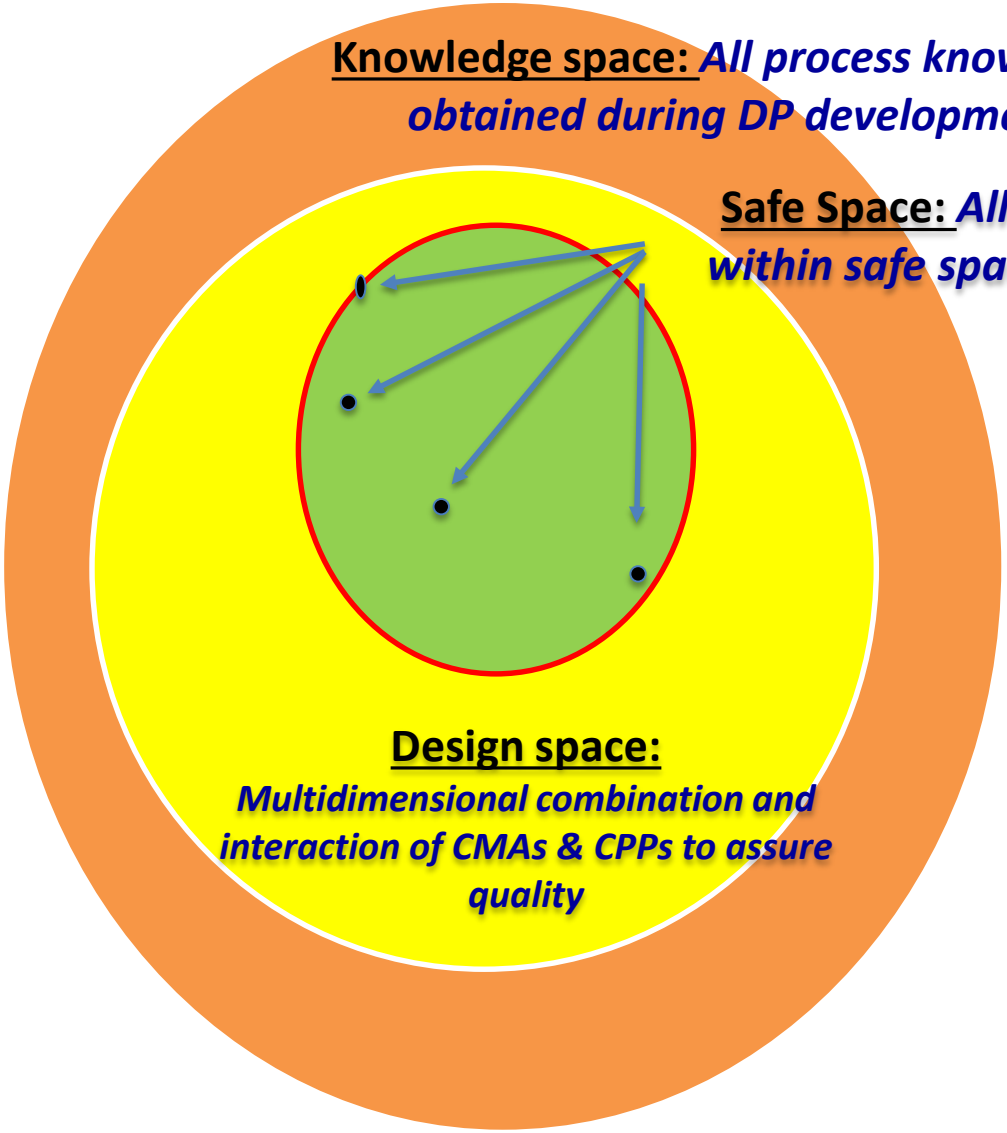


Rapid dissolution under mild invitro conditions [500 mL/0.1N HCl/USP 1 (100 rpm)or USP 2 (50rpm)] can assure bio performance, and the dissolution specifications [80%(Q)/30 minutes] may be considered clinically relevant.

Building safe space [Bioequivalence Space]:

Boundaries defined by in vitro specifications, such as dissolution or other relevant drug product quality attributes, within which drug product variants are anticipated to be bioequivalent to one another

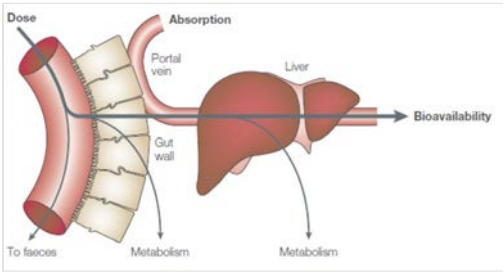
Safe Space [Bioequivalence Space]



Different approaches to build safe space

Safe space (BE space)

- IVIVR (Bracketing approach) (dissolution guidance, 1997)
- PBBM based IVIVR/IVIVC
- Conventional IVIVC
- Exposure –Response analysis



IVIVR: in vitro in vivo relationship; IVIVC: in vitro in vivo correlation; BE: bioequivalence

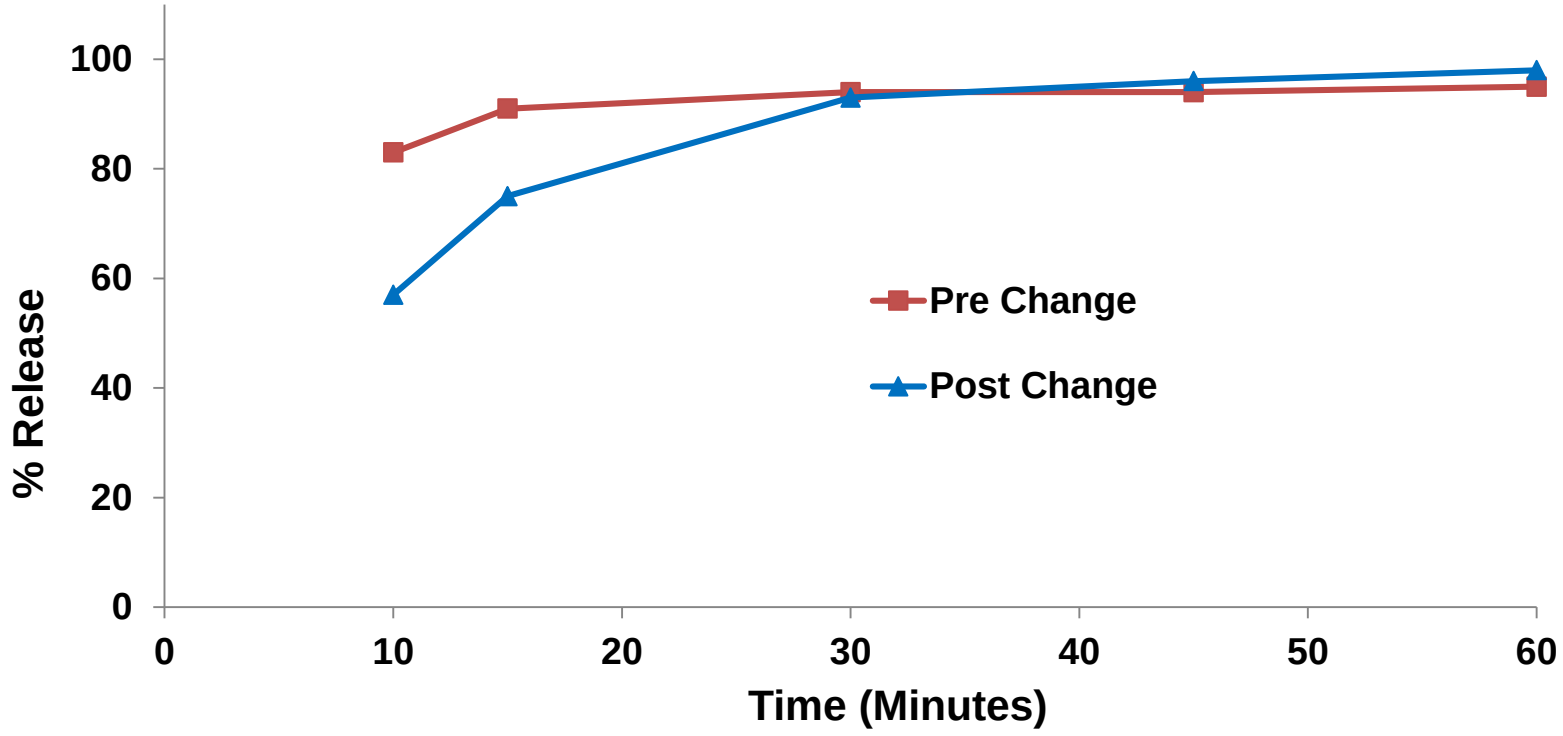
Case studies of Building safe space: FDA's experience

- ***Case study 1:***
  - ***Building safe space using Bracketing approach (IVIVR)***
- ***Case study 2:***
  - ***Building safe space using IVIVC***
- ***Case study 3:***
  - ***Building safe space using PBBM-based IVIVR***
  - ***Virtual BE***

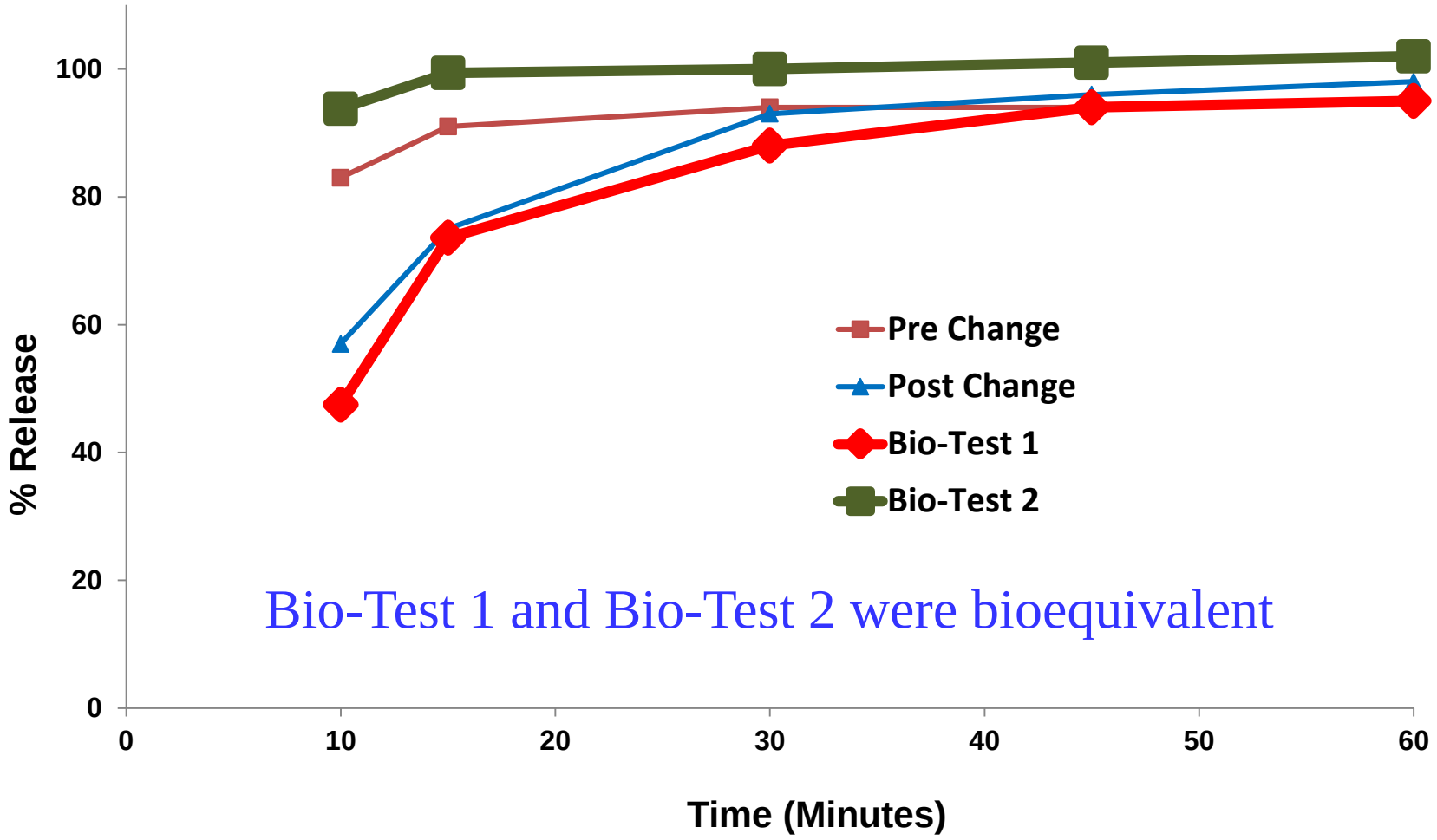
Case Study 1: Building safe space using Bracketing approach (IVIVR)

Manufacturing site change and minor changes to the manufacturing procedure. No change in the IR formulation. Drug substance has very low aqueous solubility

$f_2 = 38$



Case Study 1: Building safe space using Bracketing approach (IVIVR) Cont'd…



"Safe space" supersedes f_2 similarity testing.

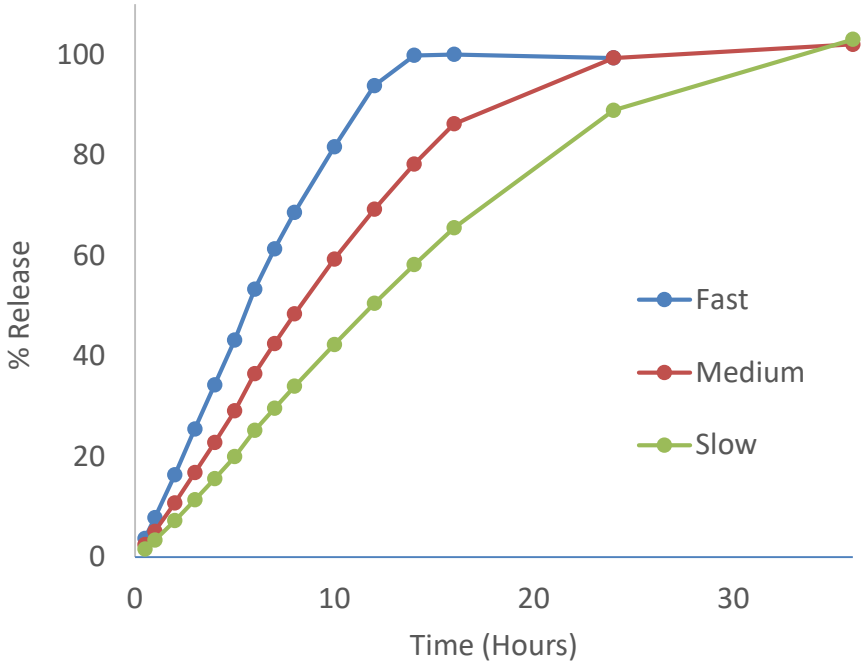
Case Study 2

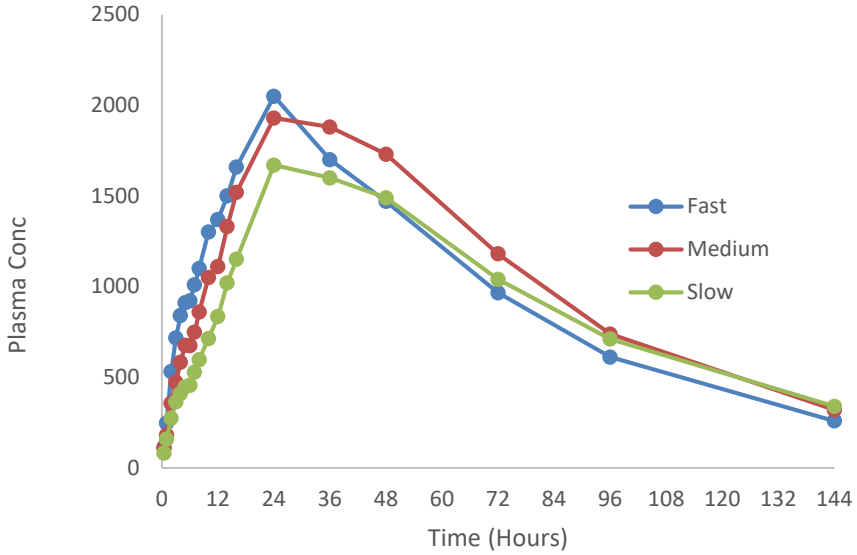
- ***Objective:*** *To develop IVIVC and build safe space for an Extended-Release Tablet formulation.*

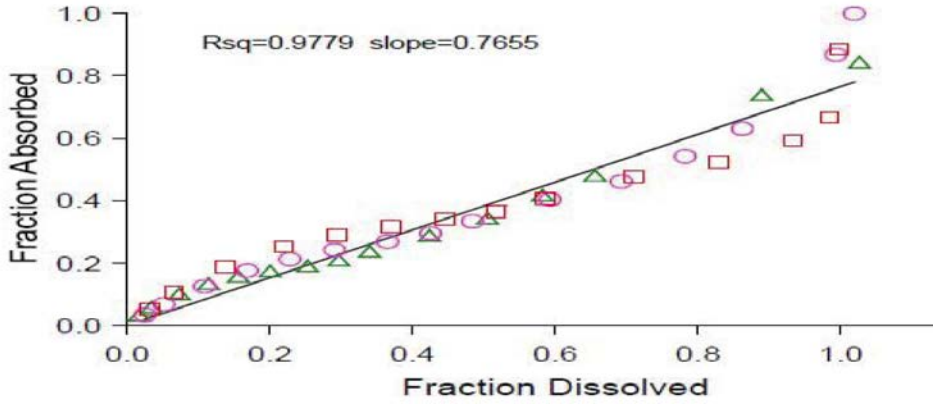
- *Data from the clinical studies were used to Develop and validate Level A IVIVC.*

- *During the development and validation of the IVIVC, the invitro dissolution conditions were altered to provide an optimal dissolution method (lower basket rotational speed and lower surfactant levels), a mathematical model was developed and validated.*

Case Study 2: Developing/validating IVIVC







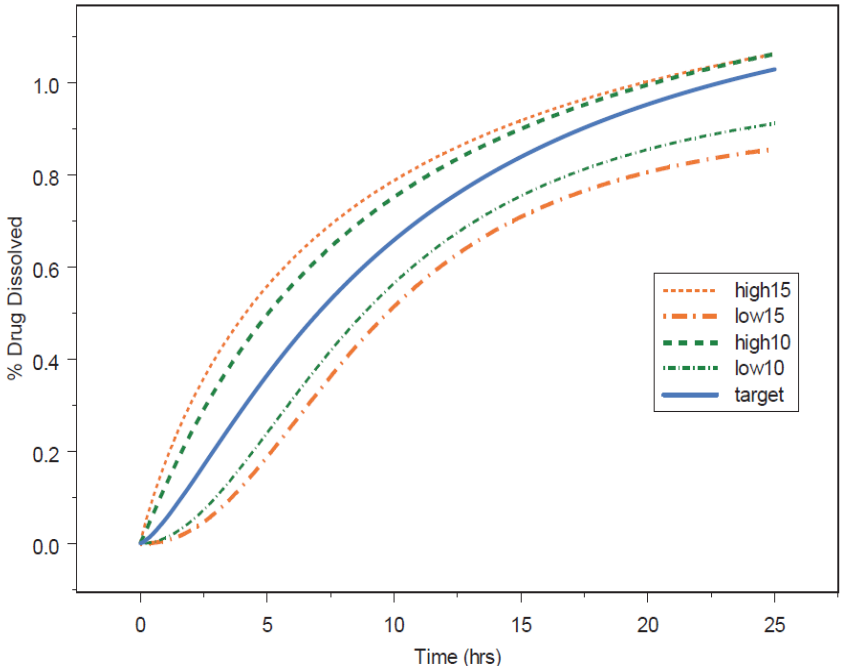
Case Study 2: Using IVIVC

- *Level A IVIVC was used to establish clinically relevant dissolution specifications (method and acceptance criteria).*

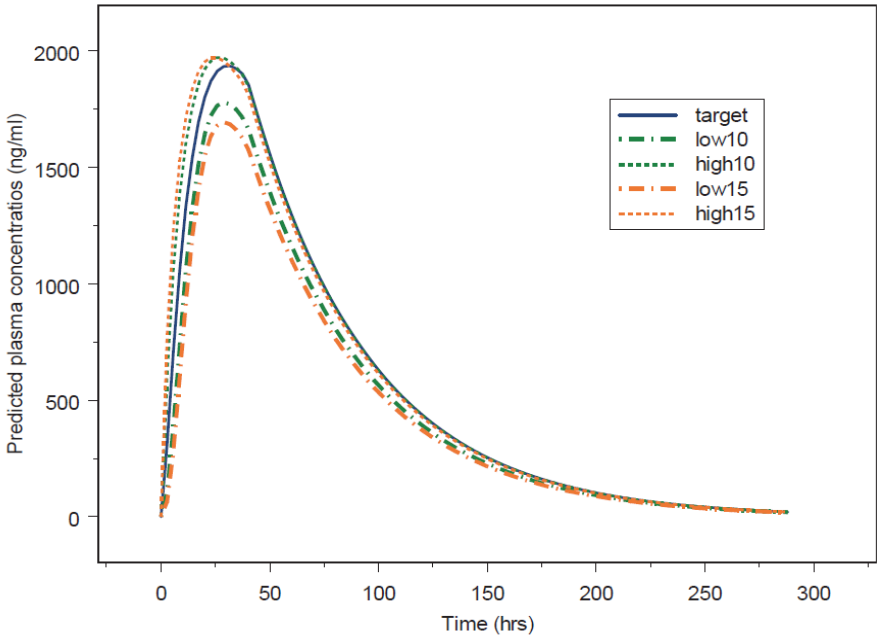
- *Validated IVIVC was used for biowaiver purposes.*

- *Validated IVIVC was used to demonstrate safe space and widening of dissolution acceptance criteria.*

Case Study 2: Safe Space identified



Predicted mean dissolution profiles using the Weibull model



Predicted mean concentration-time profiles

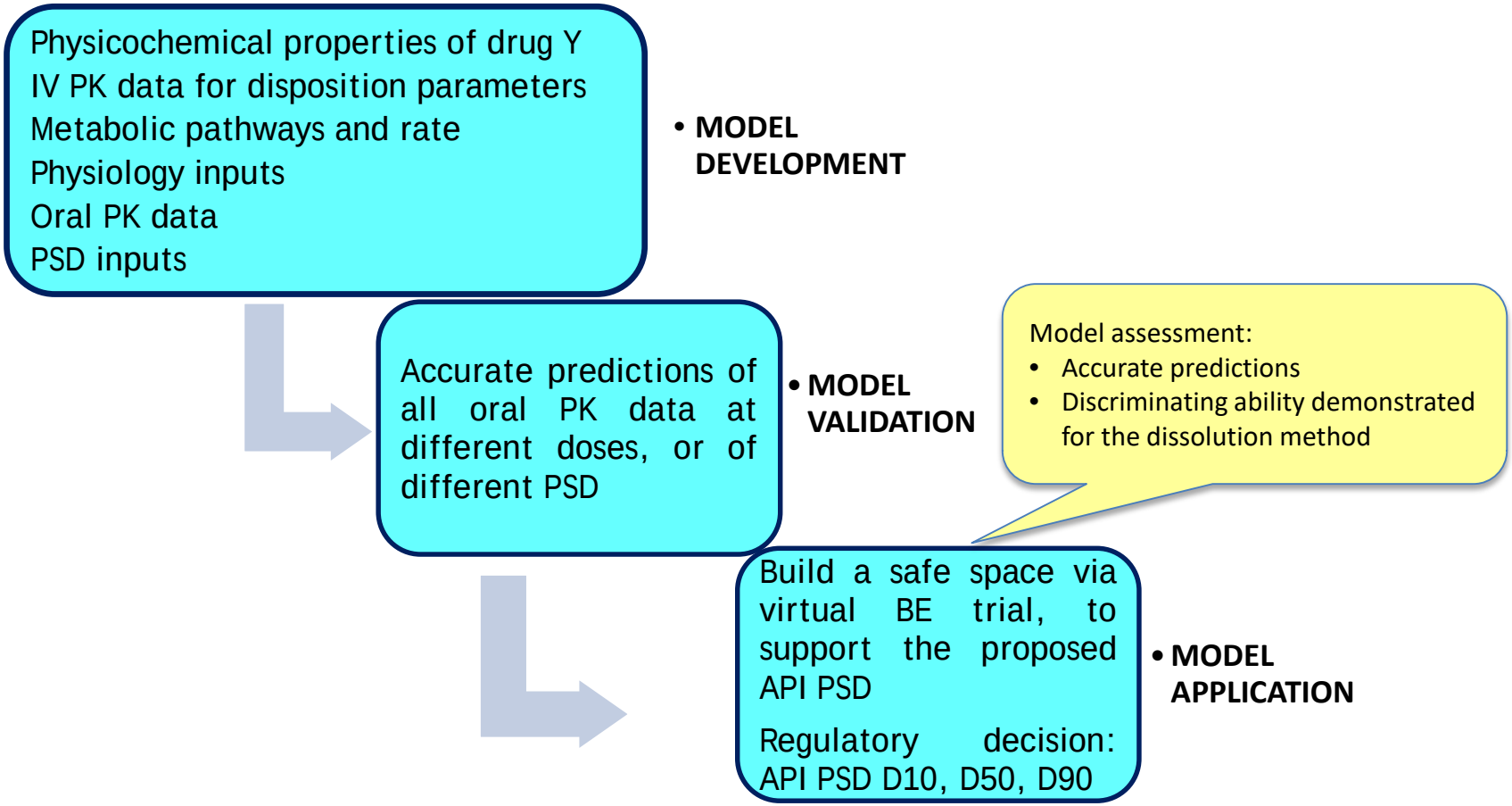
Based on the predicted results, wider dissolution acceptance (±15%) criteria were accepted.

Case study 3

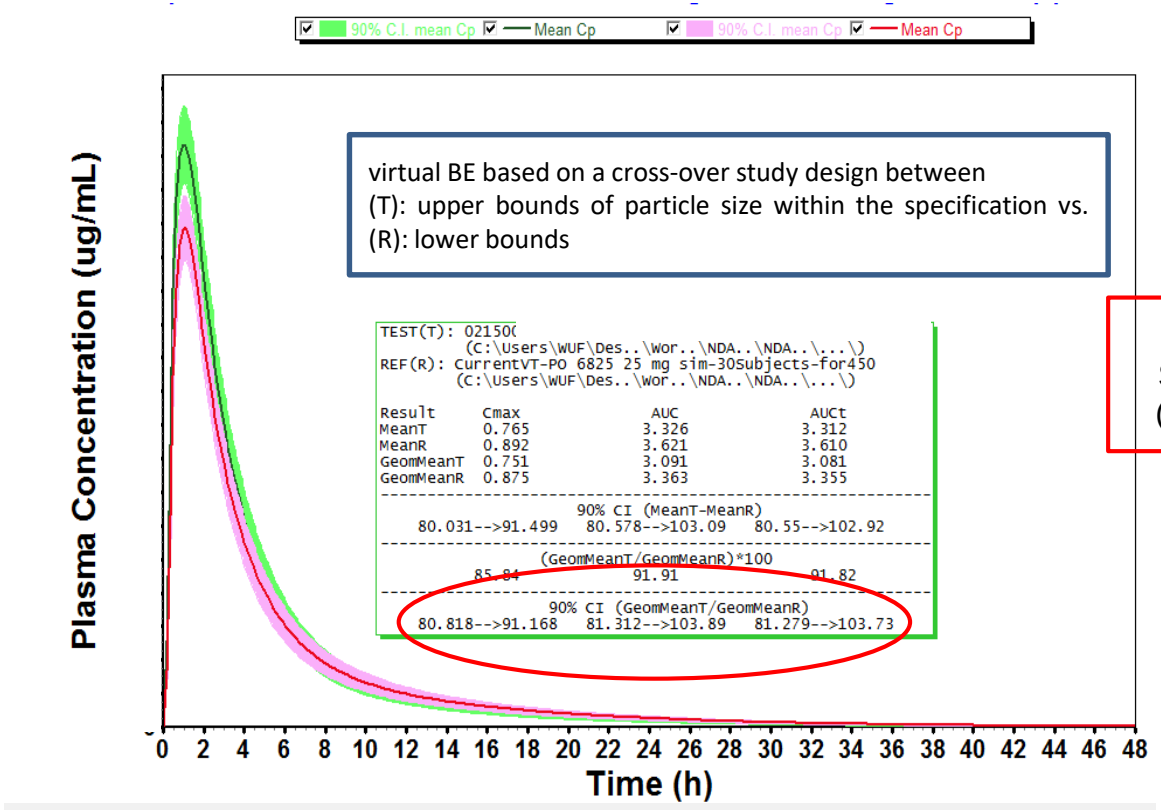
- ***Objective: To build safe space for an Immediate release capsule formulation containing a poorly soluble and poorly permeable drug***

- ***Justify the drug substance particle size specifications***

Data/information provided in this case study

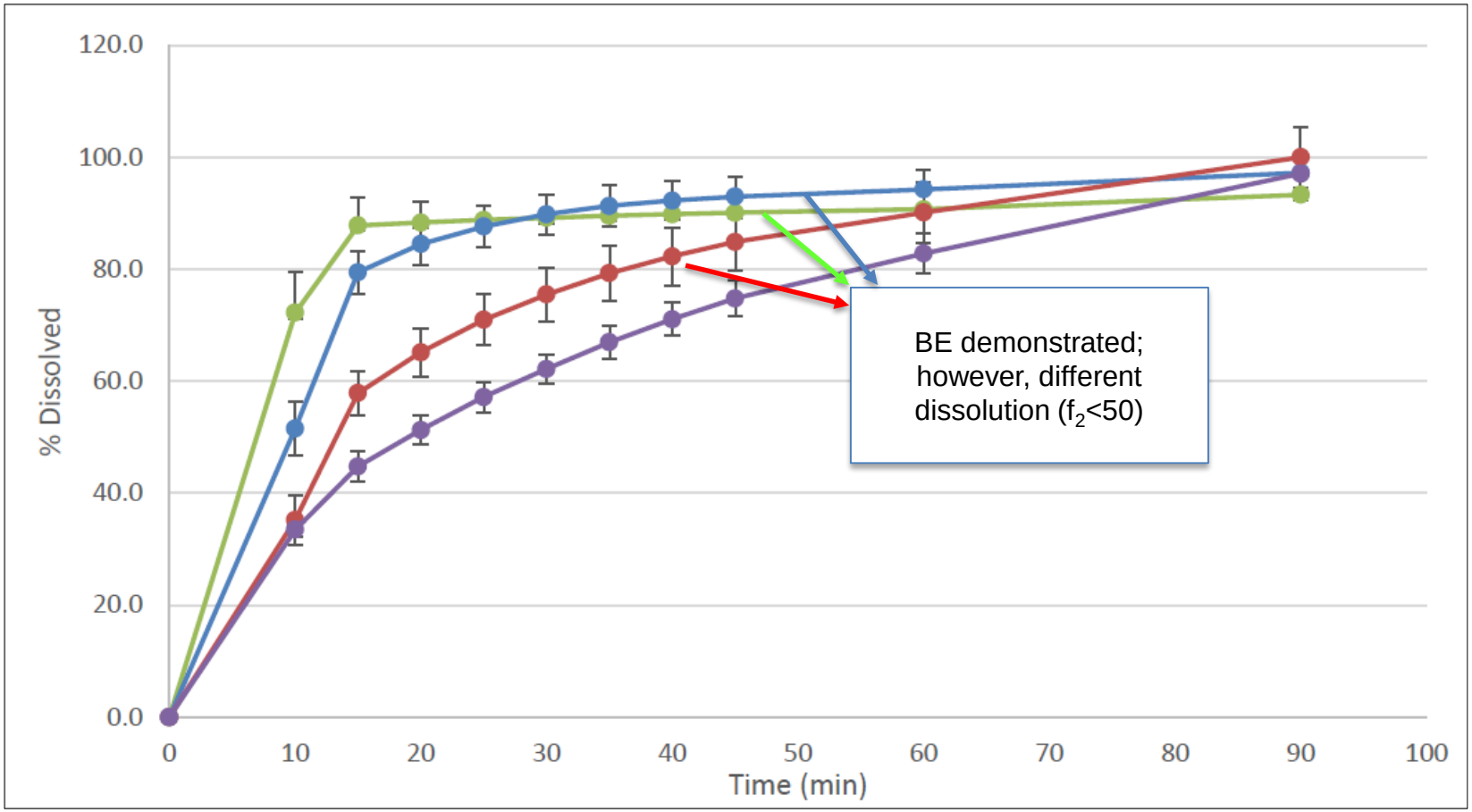


Safe space identified by virtual BE

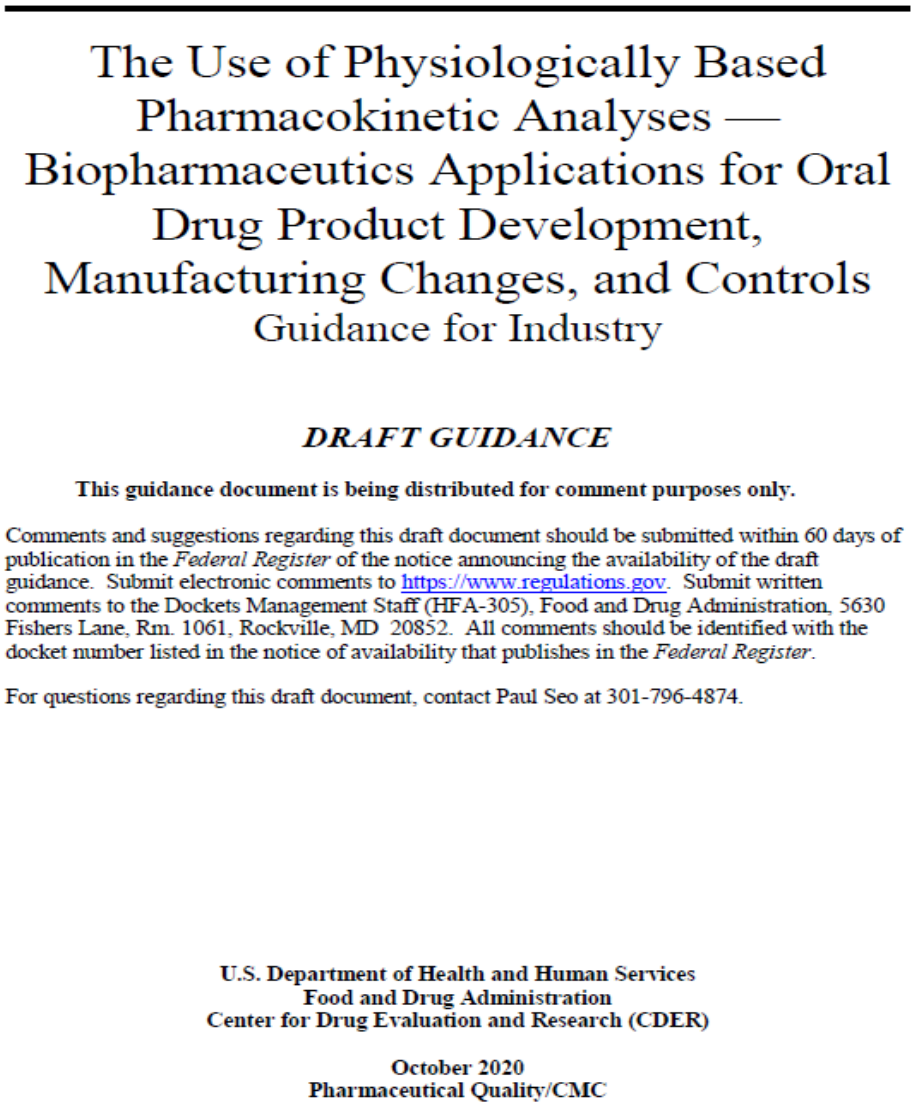


Regulatory flexibility:
Setting wide DP specification
(drug substance particle size)

Presence of safe space overrides the value of dissolution similarity



Moving Forward ….



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*.

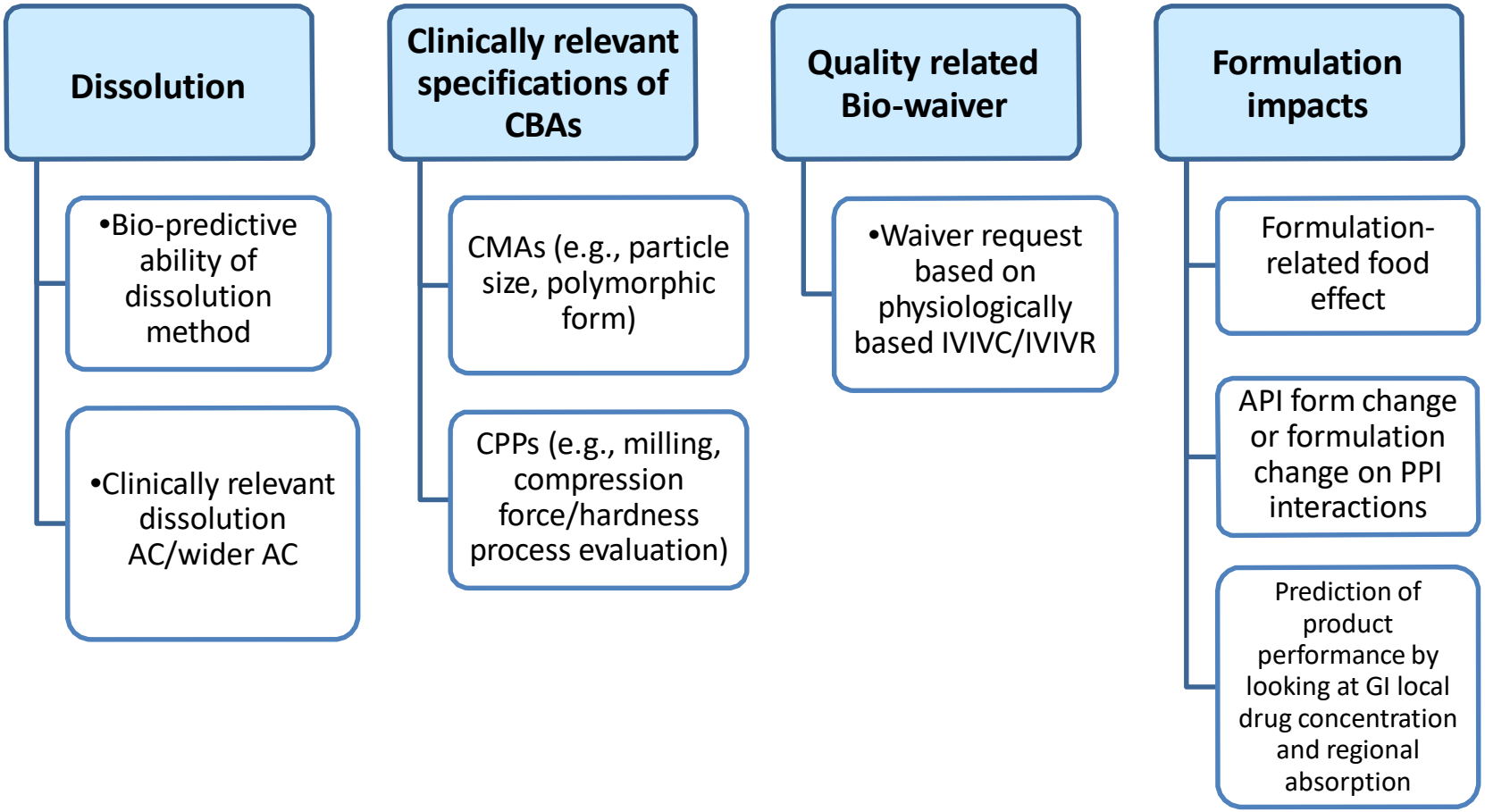
For questions regarding this draft document, contact Paul Seo at 301-796-4874.

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

October 2020
Pharmaceutical Quality/CMC

- General recommendations regarding the development, evaluation, and use of physiologically based pharmacokinetic (PBPK) analyses for biopharmaceutics applications for oral drug product development, manufacturing changes, and controls.

Common regulatory applications of PBBM in support of drug product quality



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Thank you!

References

- **Draft Guidance for Industry: The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls Guidance for Industry. October 2020, CDER/FDA.**
- **Guidance for Industry: Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances. August 2018, CDER/FDA.**
- **Guidance for Industry: Extended-Release Oral Dosage Forms: Development, Evaluation, and Application of in vitro/in vivo Correlations. September 1997, CDER/FDA.**
- **Guidance for industry, Dissolution Testing of Immediate Release Solid Oral Dosage Forms. August 1997, CDER/FDA.**
- **Guidance for industry, Waiver of in vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. August 2000, CDER/FDA.**
- **Current State and Future Expectations of Translational Modeling Strategies to Support Drug Product Development, Manufacturing Changes and Controls: A Workshop Summary Report: *Journal of Pharmaceutical Sciences Volume 110, Issue 2, February 2021, Pages 555-566***
- ***Abdou et al: Dissolution Chapter 35: Remington: The Science and Practice of Pharmacy: 20th Edition: Lippincott Williams***


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