Risk-Based Approach to Establishing Patient-Centric Dissolution Specifications

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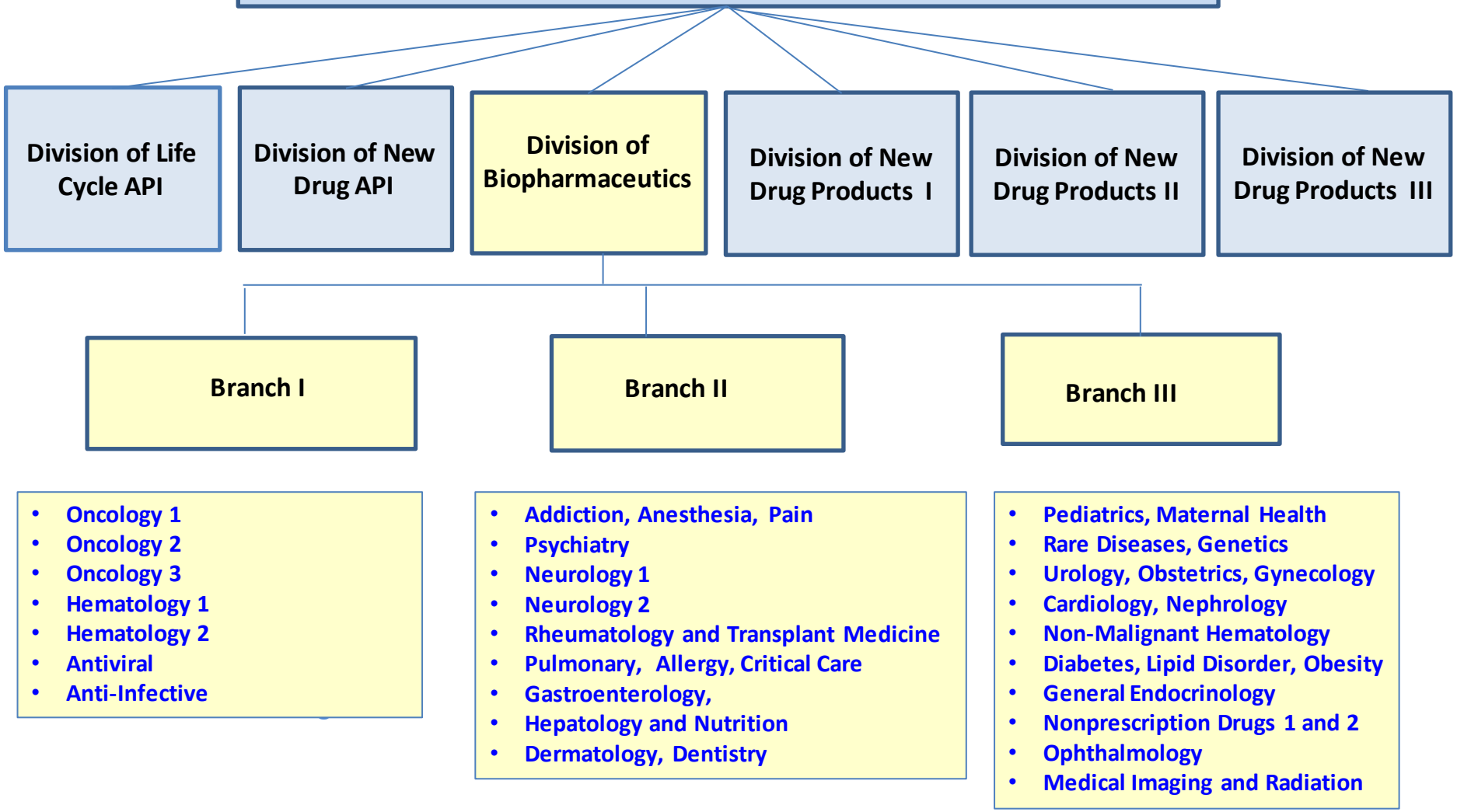
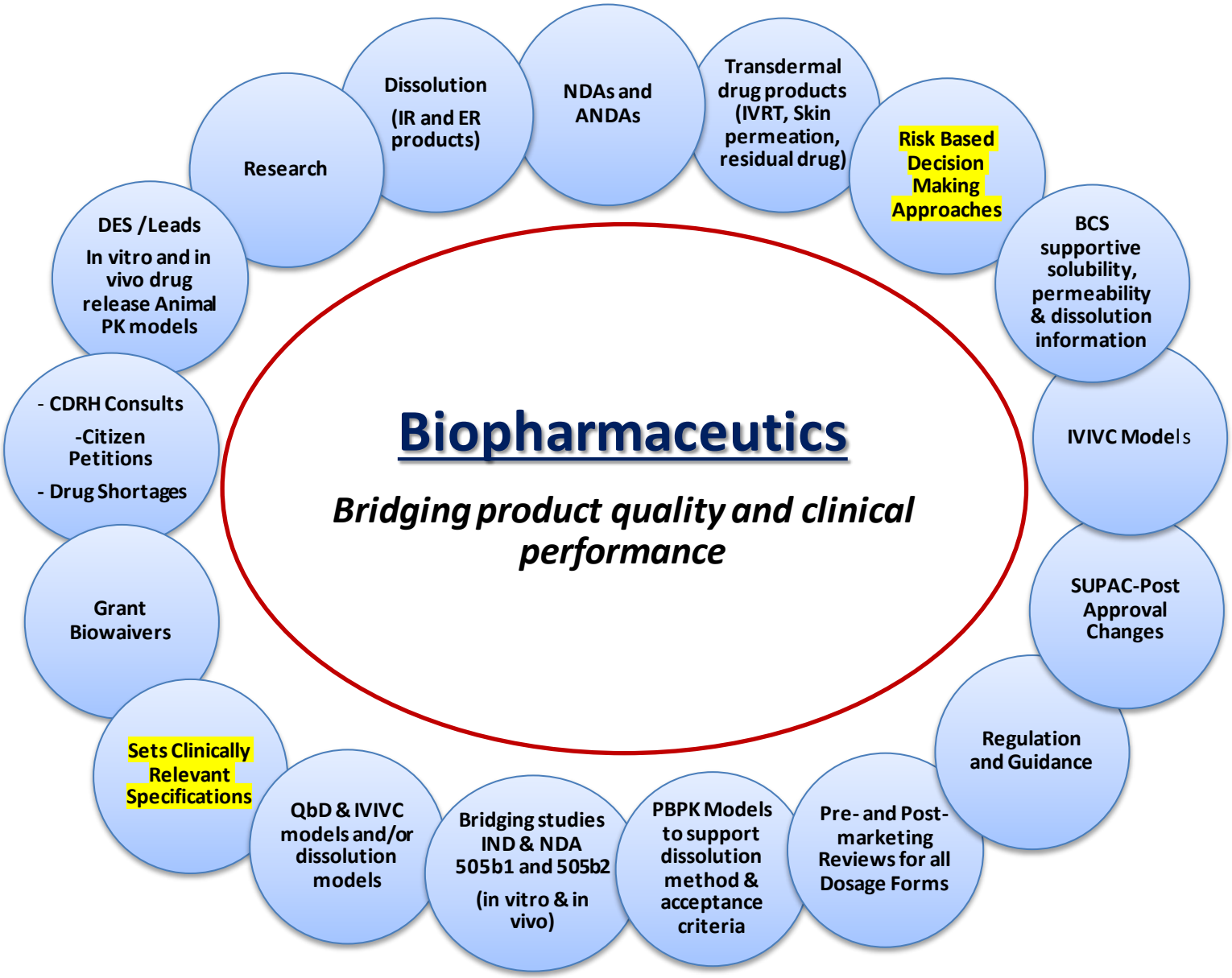
Outline

- Division of Biopharmaceutics
- Clinically Relevant (Patient-Centric) Dissolution Specifications
- Biopharmaceutics Considerations for Selection of Dissolution Specifications-Risk-Based Approach
- FDA Relevant Guidance
- Case Studies
- Conclusions

OPQ's Office of New Drug Products

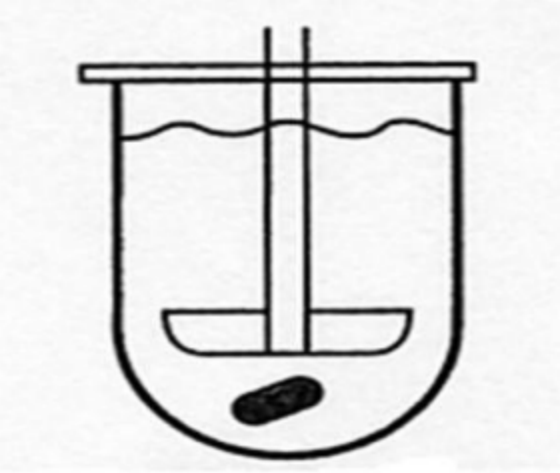


What do we do?

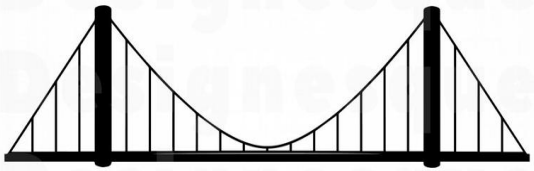

Biopharmaceutics
Bridging product quality and clinical performance
Research
Dissolution (IR and ER products)
NDAs and ANDAs
Transdermal drug products (IVRT, Skin permeation, residual drug)
Risk Based Decision Making Approaches
BCS supportive solubility, permeability & dissolution information
IVIVC Models
SUPAC-Post Approval Changes
Regulation and Guidance
Pre- and Post-marketing Reviews for all Dosage Forms
PBPK Models to support dissolution method & acceptance criteria
Bridging studies IND & NDA 505b1 and 505b2 (in vitro & in vivo)
QbD & IVIVC models and/or dissolution models
Sets Clinically Relevant Specifications
Grant Biowaivers
- CDRH Consults
-Citizen Petitions
- Drug Shortages
DES /Leads
In vitro and in vivo drug release Animal PK models

Role of Biopharmaceutics

Patient-Centric
Drug Product Quality



In vitro dissolution

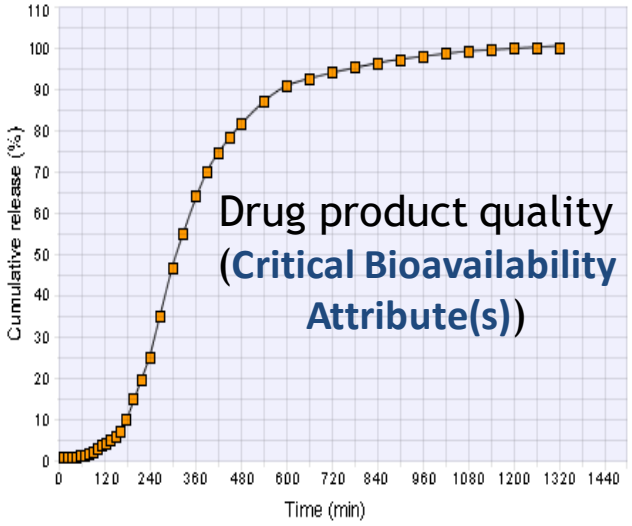


Biopharmaceutics

In vivo drug performance

Role of Biopharmaceutics

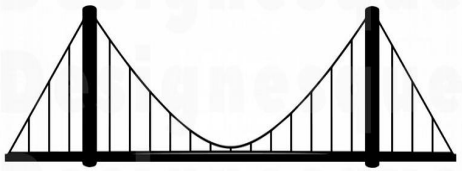
Patient-Centric
Drug Product Quality



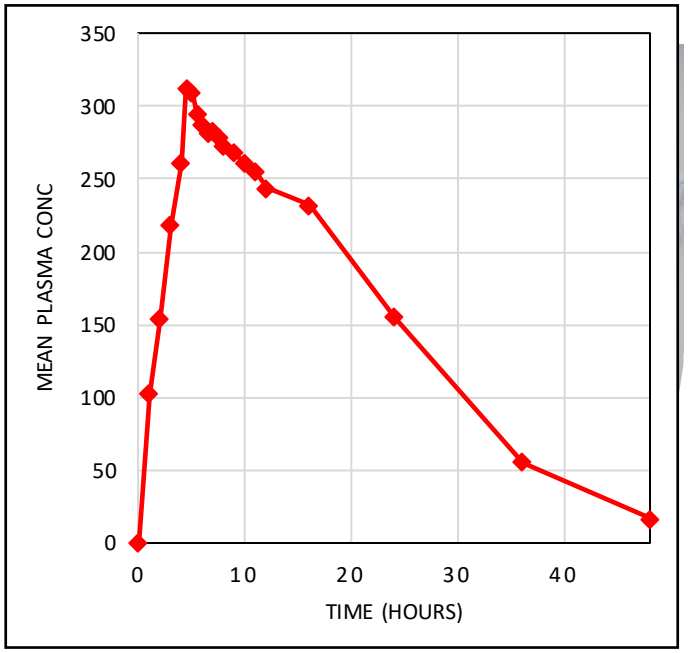
Drug product quality (**Critical Bioavailability Attribute(s)**)

In vitro dissolution

Clinically relevant drug product specifications



Biopharmaceutics



In vivo drug performance

Patient-Centric Quality Standards (PCQS)

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

- 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.

(Patient-Centric) Clinically Relevant Dissolution Specifications (CRDS)- Risk-Based Approach

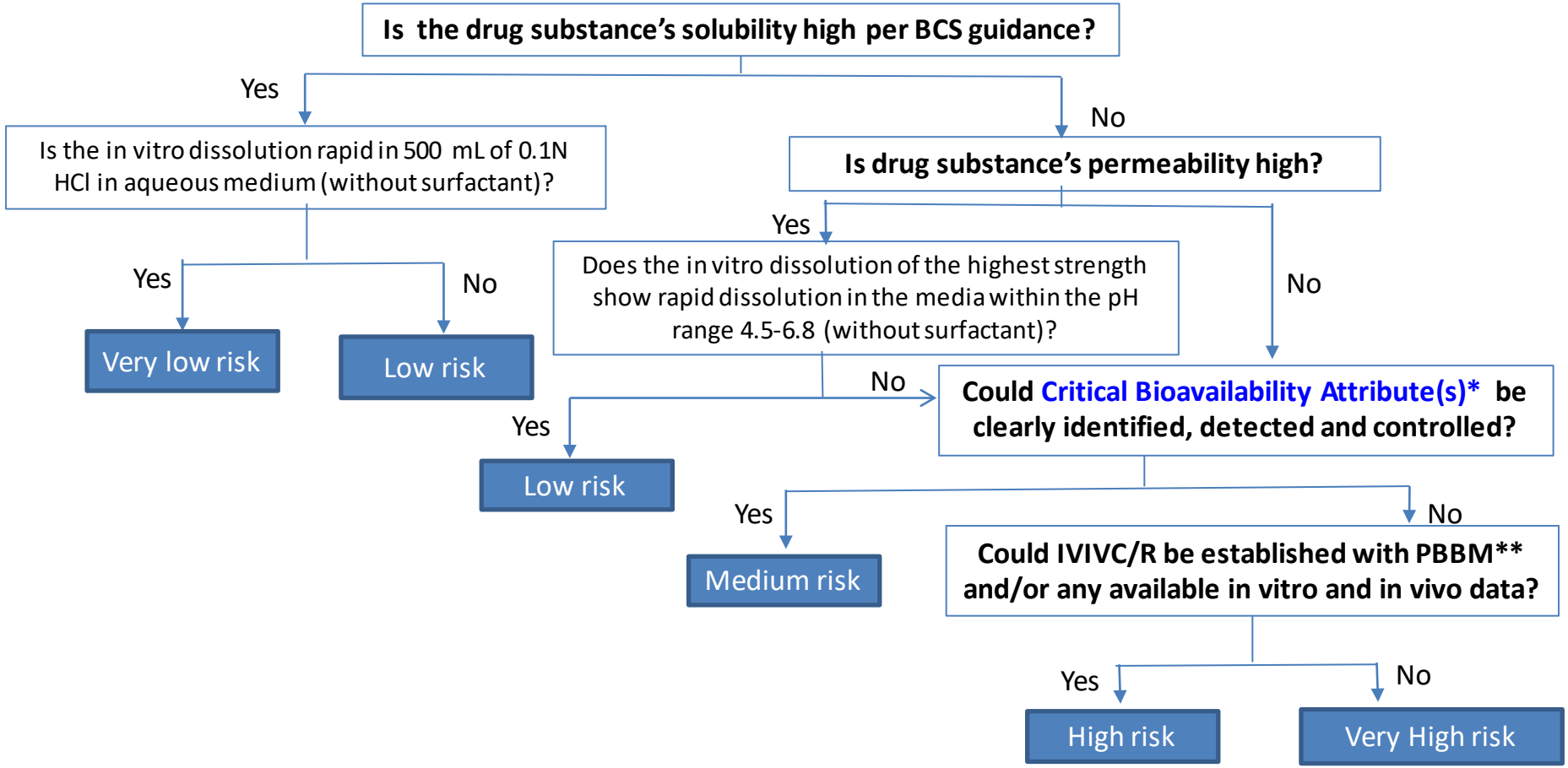
CRDS = A specification (method and acceptance criteria(ion)) that takes into consideration the clinical effect of variations in dissolution ensuring a consistent **safety and efficacy** profile.

Risk that needs to be avoided =

- Risk that the drug product does not perform as expected; risk that the commercial drug product does not have the same **safety and efficacy** profile as the drug product that was tested in the clinical trials.
- Risk that a safe and effective drug product batch has out of specification (OOS) results

Initial Risk Assessment for Solid Oral Dosage Forms using BCS

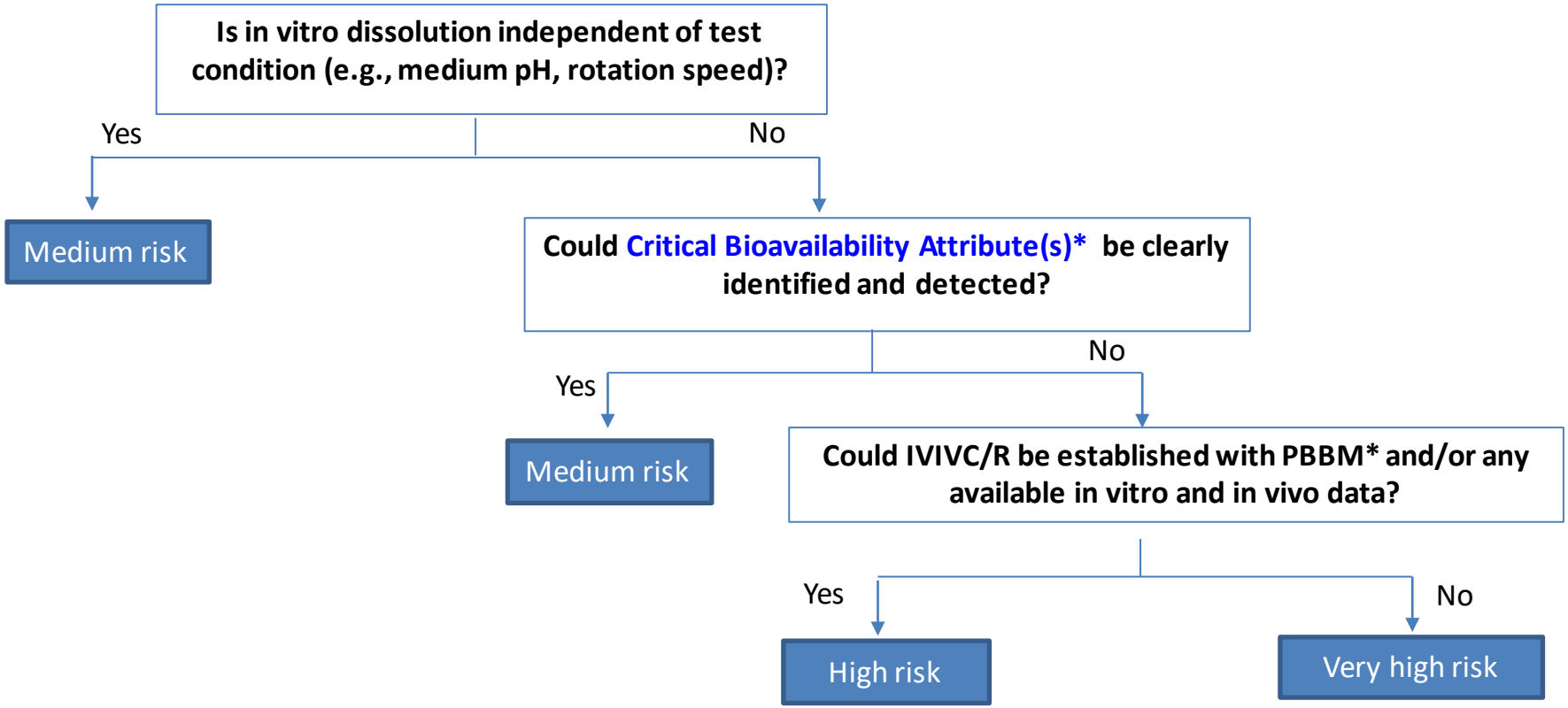
Initial Biopharmaceutics Risk Assessment Decision Tree For IR Solid Oral Dosage Forms (non-NTI And non-rapid Onset)



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

**PBBM: Physiologically-Based Biopharmaceutics Model (Physiologically based Pharmacokinetic [PBPK] Analysis for Biopharmaceutics Applications)

Initial Biopharmaceutics Risk Assessment Decision Tree for ER Solid Oral Dosage Forms (non-NTI)



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

**PBBM: Physiologically-Based Biopharmaceutics model

Biopharmaceutics Approaches to Mitigate the Risks

Risk Level	Biopharmaceutics Approaches
Very Low	Standard dissolution test and acceptance criterion as per the August 2018 FDA dissolution guidance (drug products containing high solubility drug substances)
Low	Dissolution test with scientifically sound conditions. Limited method development is needed to justify method and/or acceptance criterion
Medium	Dissolution test and acceptance criteria(ion) should target to detect meaningful changes in identified CBA(s)
High	IVIVC/R and/or PBBM could be used to support patient-centric dissolution test and acceptance criteria(ion)
Very High	Additional in vivo studies could be used to try to develop IVIVC/R and/or PBBM to support patient-centric dissolution test and acceptance criteria(ion)

FDA Relevant Guidance

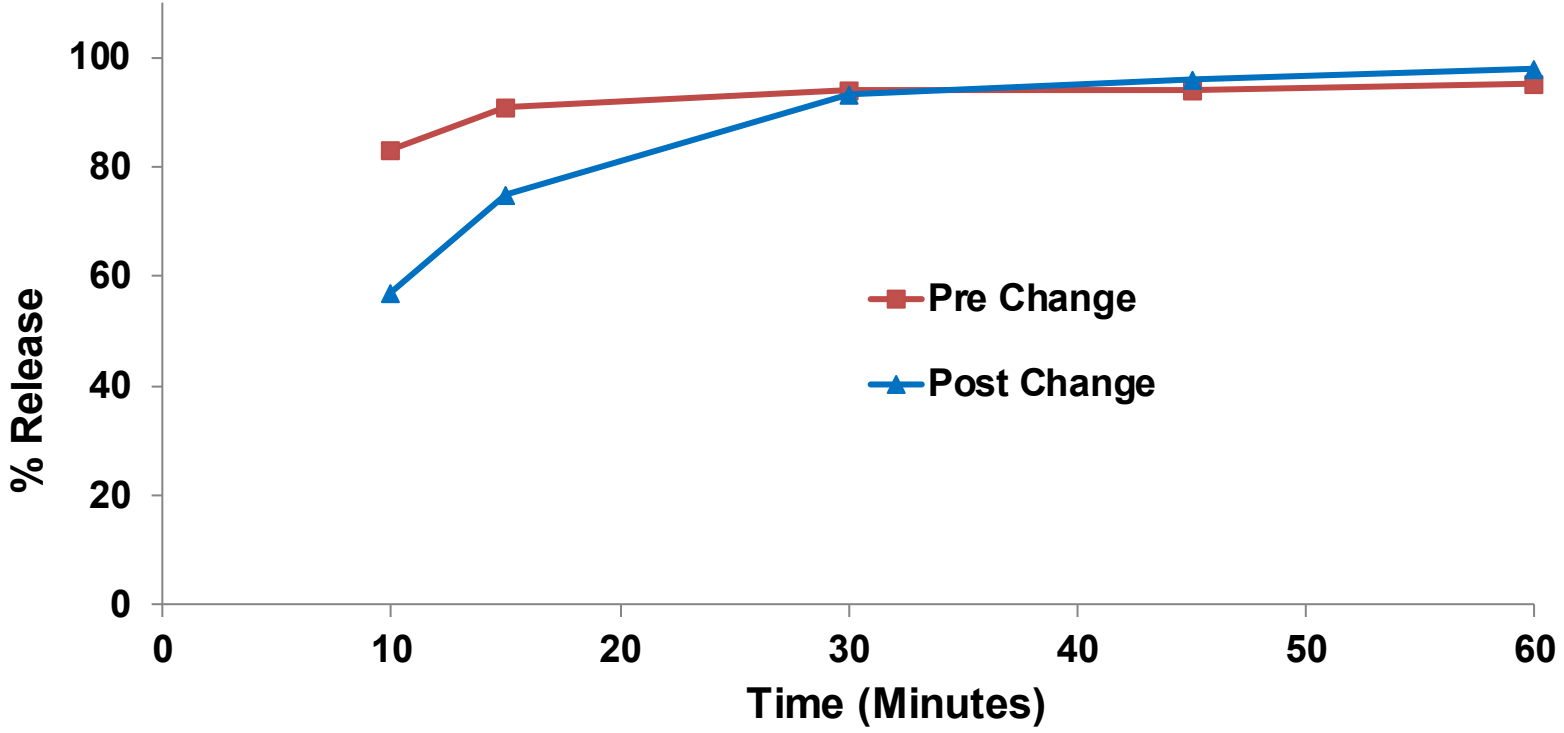
- M9 Biopharmaceutics Classification System-Based Biowaivers: 2021
- FDA's Draft Guidance: The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls: 2020
- FDA's Guidance: Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances: 2018
- FDA's 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

Case studies of building a safe space:

- Case study 1:
  - Building a safe space using a bracketing approach
- Case study 2:
  - Building a safe space using an IVIVC

Case Study 1: Building a safe space using a bracketing approach

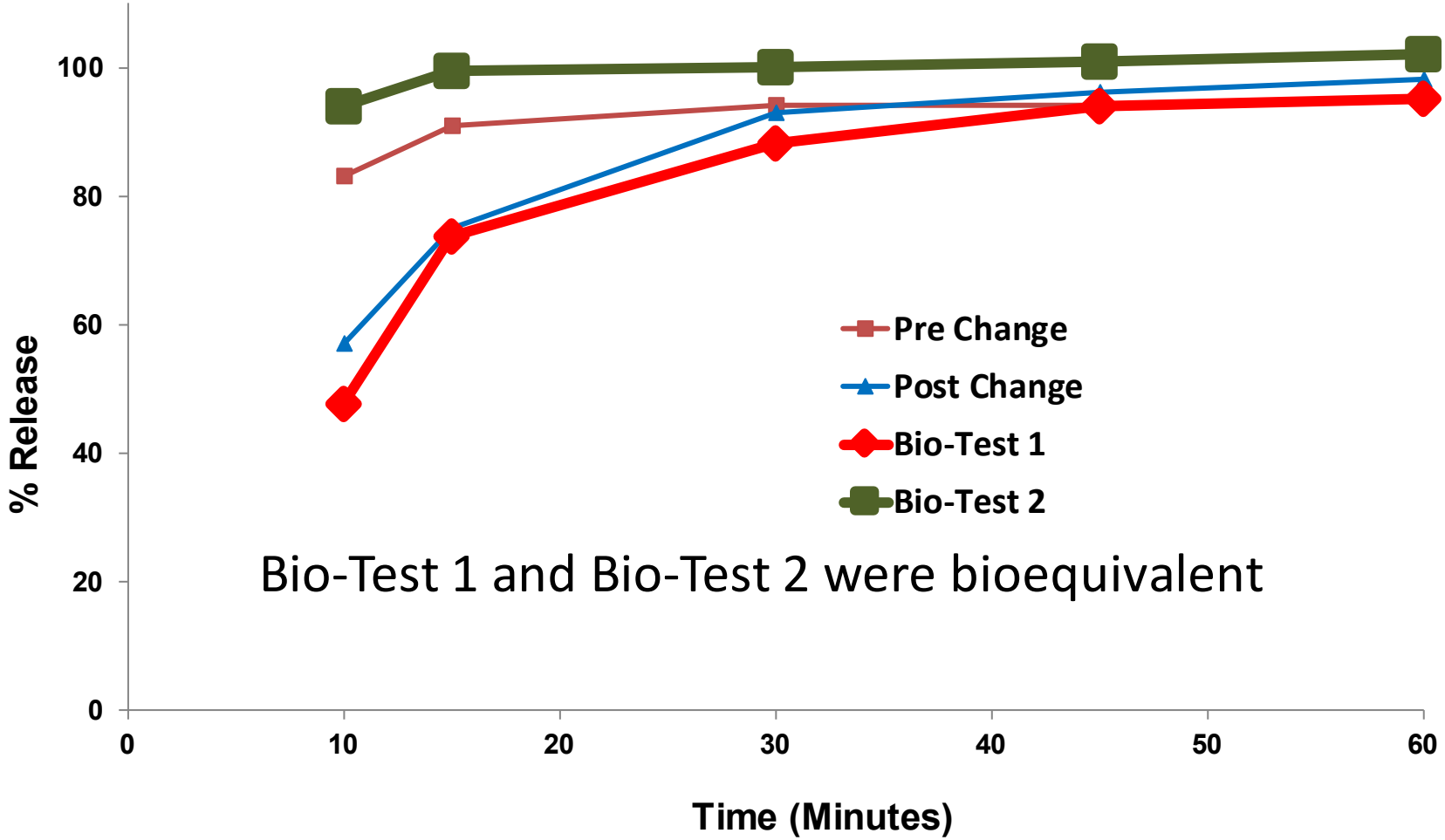
Dissolution comparison to support manufacturing site change and minor changes to the manufacturing procedure. No change in the IR formulation.



If the drug substance has high aqueous solubility, in general, meeting Q=80% at 30 minutes for pre- and post- change batches is sufficient to support the change.

Cont'd Case Study 1: Building a safe space using a bracketing approach

If the drug substance has very low aqueous solubility, and if dissolution data for two BE batches are available, a safe space can be created.



Bio-Test 1 and Bio-Test 2 were bioequivalent

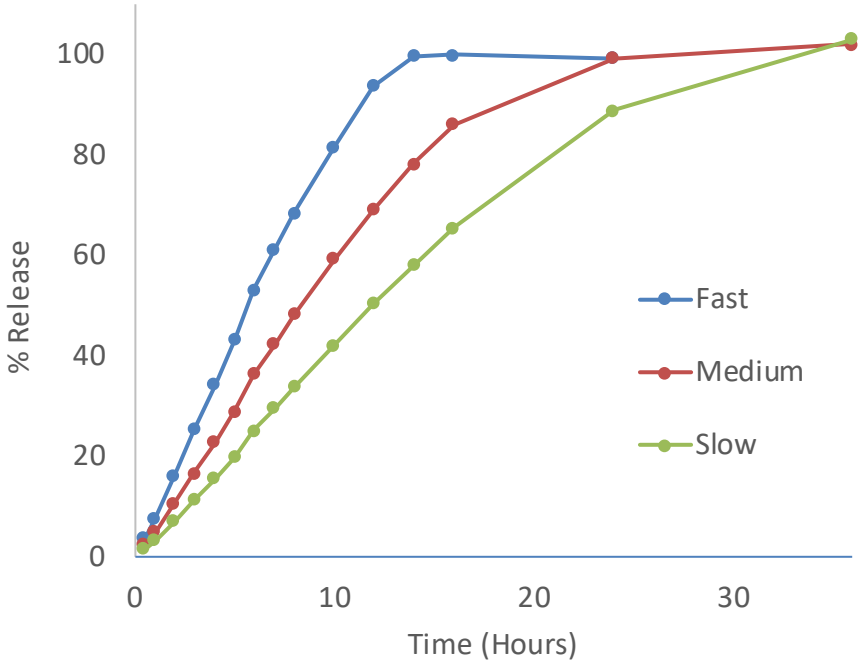
Case Study 2: Building a safe space using an IVIVC

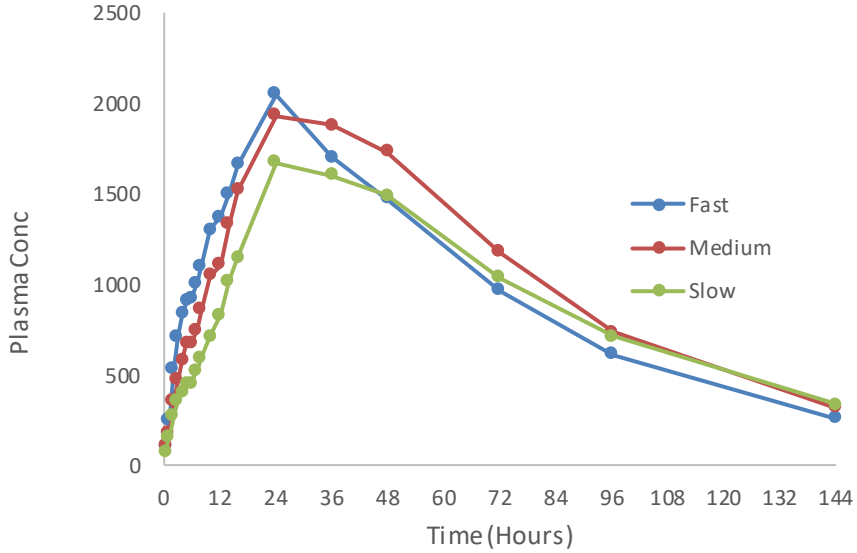
- The Applicant developed an IVIVC and build a safe space for an Extended-Release Tablet formulation.

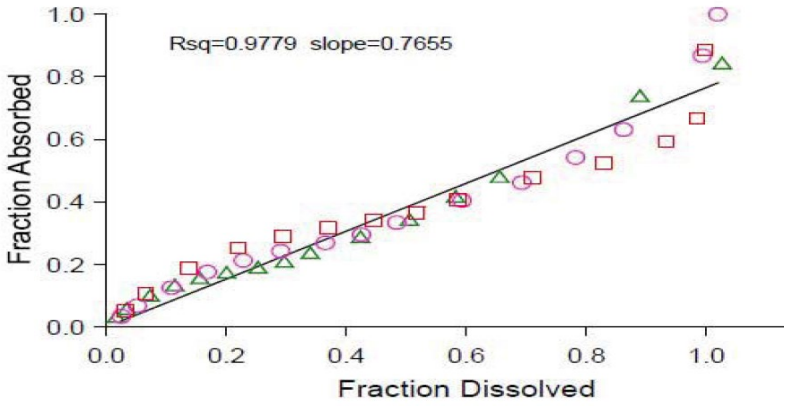
- Data from the clinical studies were used to develop and validate a Level A IVIVC.

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

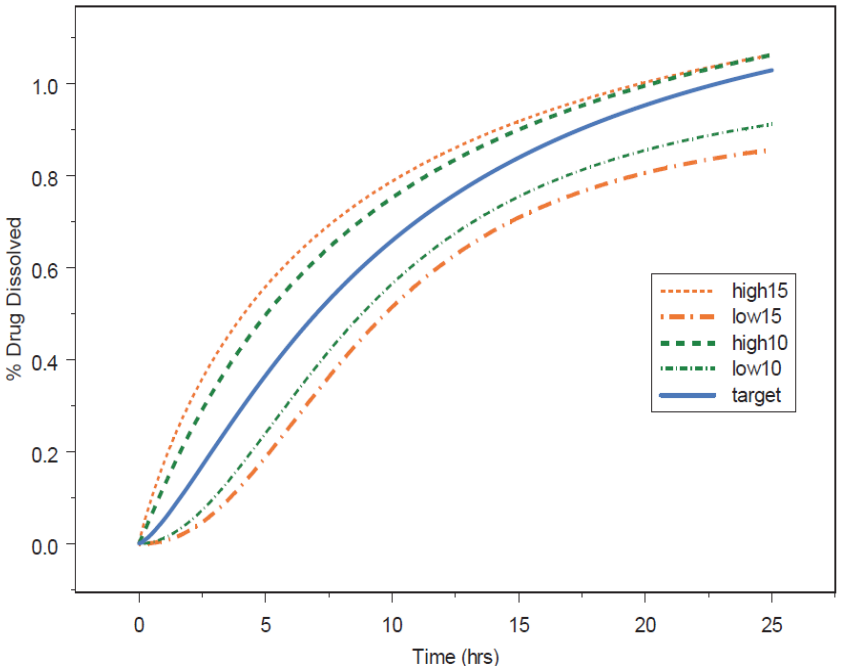
Case Study 2: Developing/Validating IVIVC



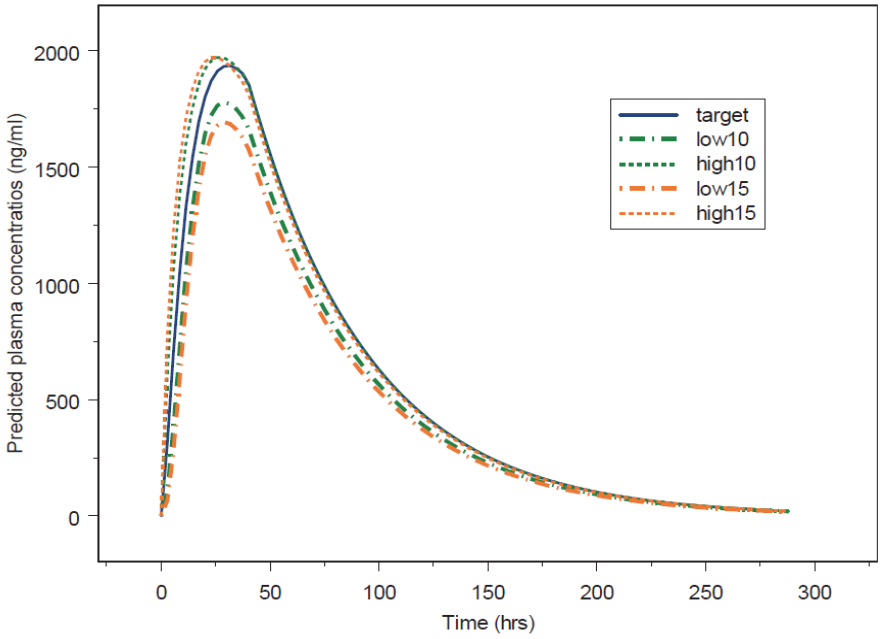




Case Study 2: Safe Space Identified



Simulated mean dissolution profiles using the Weibull model



Predicted mean concentration-time profiles

Based on the predicted results, wider dissolution acceptance criteria ranges were accepted (±15% instead of ±10% generally recommended).

Case Study 2: Using IVIVC

- Level A IVIVC was used to establish clinically relevant dissolution specifications (method and acceptance criteria).
- The validated IVIVC was used for biowaiver purposes.
- The validated IVIVC was used to build a safe space and to widen the dissolution acceptance criteria.

Conclusions

FDA encourages Risk-Based Approaches to Establish Patient-Centric Dissolution Specifications Based on Modeling:

- ✓ Understanding of the drug product's Critical Bioavailability Attribute(s) (CBAs)
- ✓ Establishment of clinically relevant drug product specifications, including dissolution
- ✓ Potential for developing IVIVC and/or PBBM models
- ✓ Stronger link between in vitro dissolution and in vivo performance
- ✓ Potential for wider dissolution acceptance criteria/ranges
- ✓ Avoiding unnecessary out of specification (OOS) results

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Thank you!