Perspectives on the Future State of Dissolution Testing

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Future State of Dissolution Testing

“An in vitro dissolution test that provides predictive insight to in vivo performance. This ensures high quality drug products that maintain safety and efficacy throughout the product lifecycle. With a predictive dissolution, the impact of critical material attributes and critical process parameters on in vivo performance can be quantitatively assessed by in vitro dissolution. This provides scientific and risk-based knowledge to support patient-centric quality standards.”

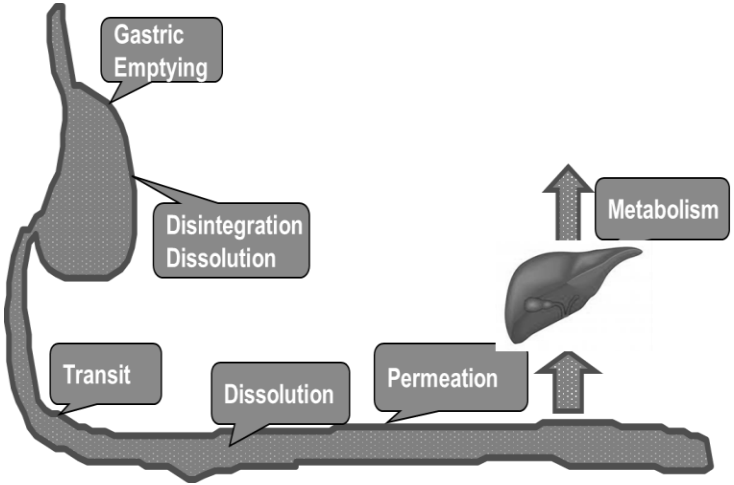
Biopharmaceutics Risk Assessment

- Biopharmaceutics risk assessment focuses on the evaluation of BA/BE impact attributed to physicochemical and biopharmaceutics properties of drug substance and the control strategy for the drug product.

- From industry perspective: to determine how much BA/BE risk associated with a drug product so that needed studies can be performed for product development and appropriate control strategy can be implemented.

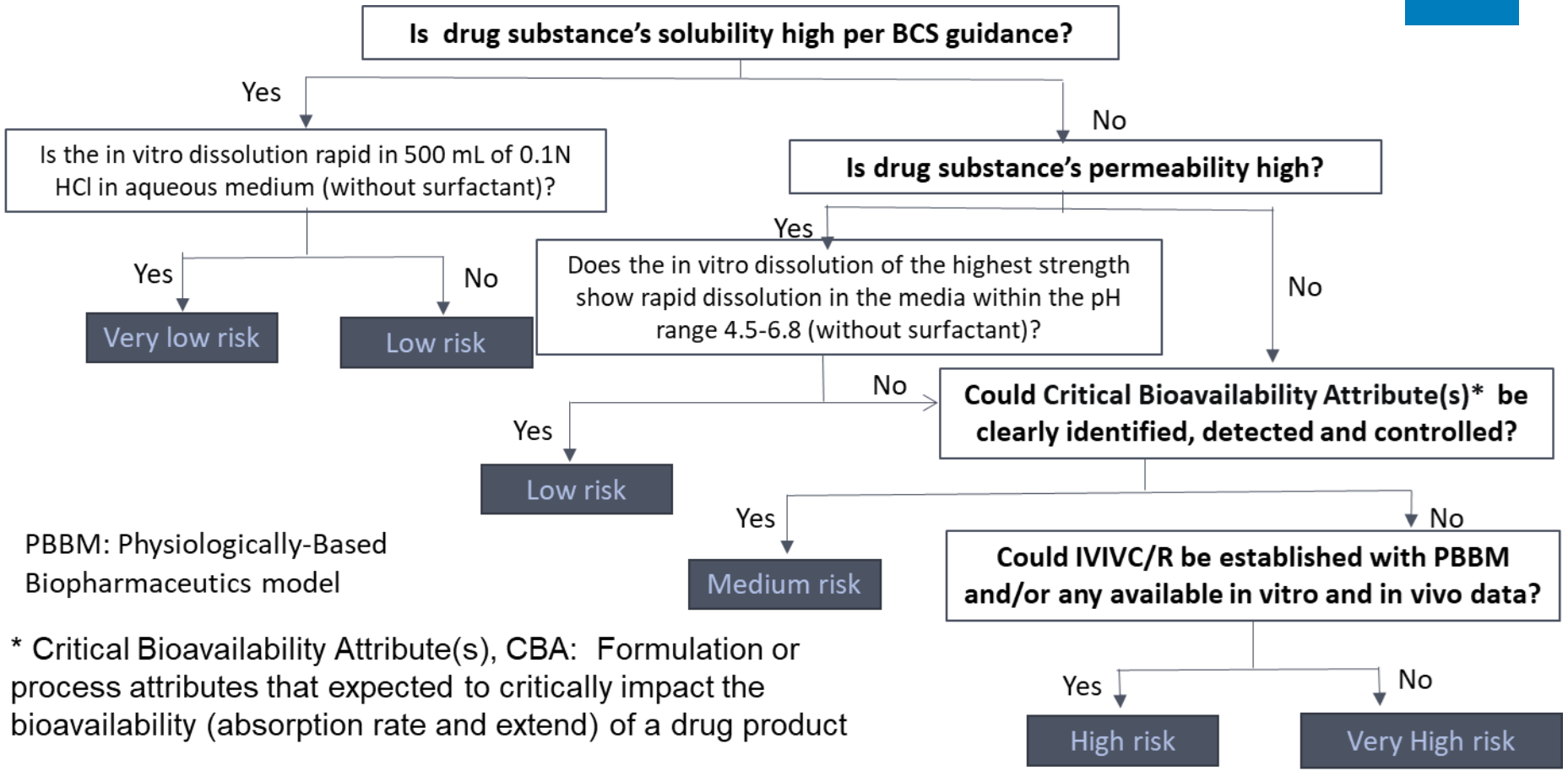
- From regulator perspective: to determine how much BA/BE risk associated and decide how much effort should be made for patient-centric dissolution specification to mitigate the risk.

Biopharmaceutics Risk Associated with Oral Solid Dosage Forms



- Based on a comprehensive product understanding including:
  - The formulation design for the intended clinical use
  - Drug substance solubility and permeability
  - Drug release mechanism
  - Drug absorption and disposition characteristics
  - Safety and efficacy profile

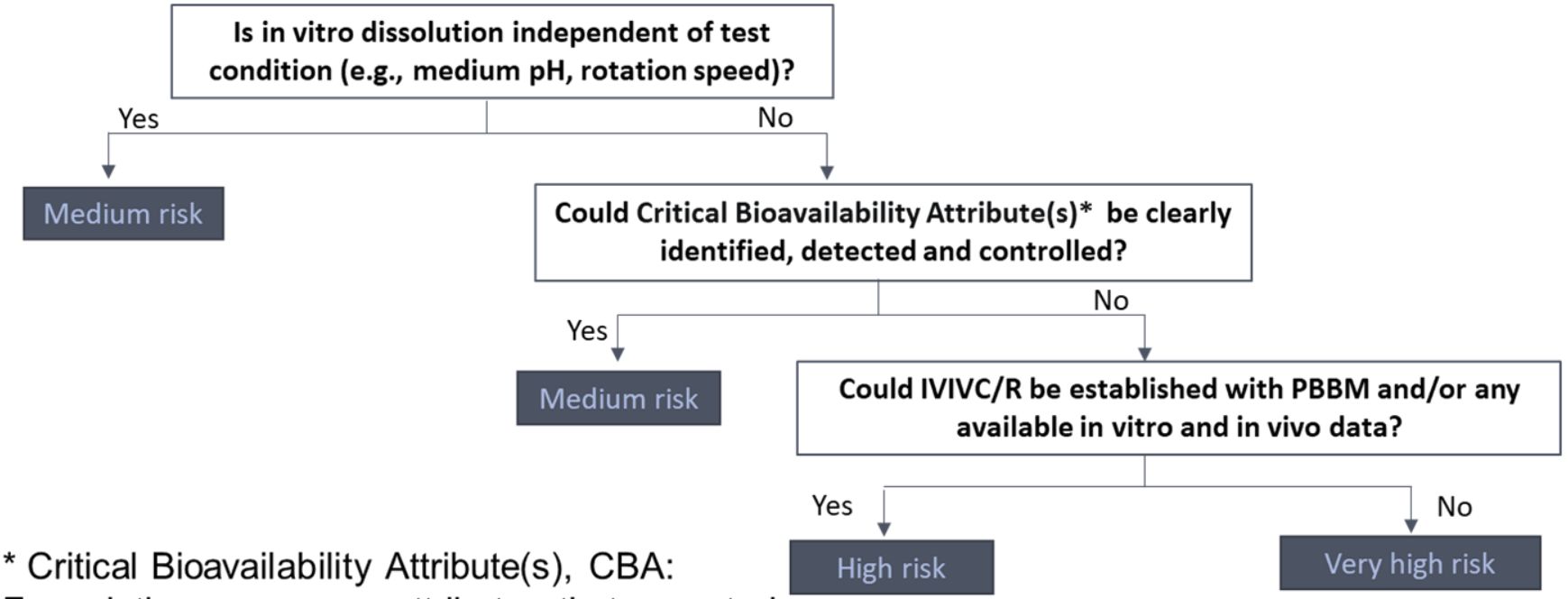
Biopharmaceutics risk assessment decision tree for IR solid oral dosage forms (Non-NTI or Non-rapid onset)



PBBM: Physiologically-Based Biopharmaceutics model

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

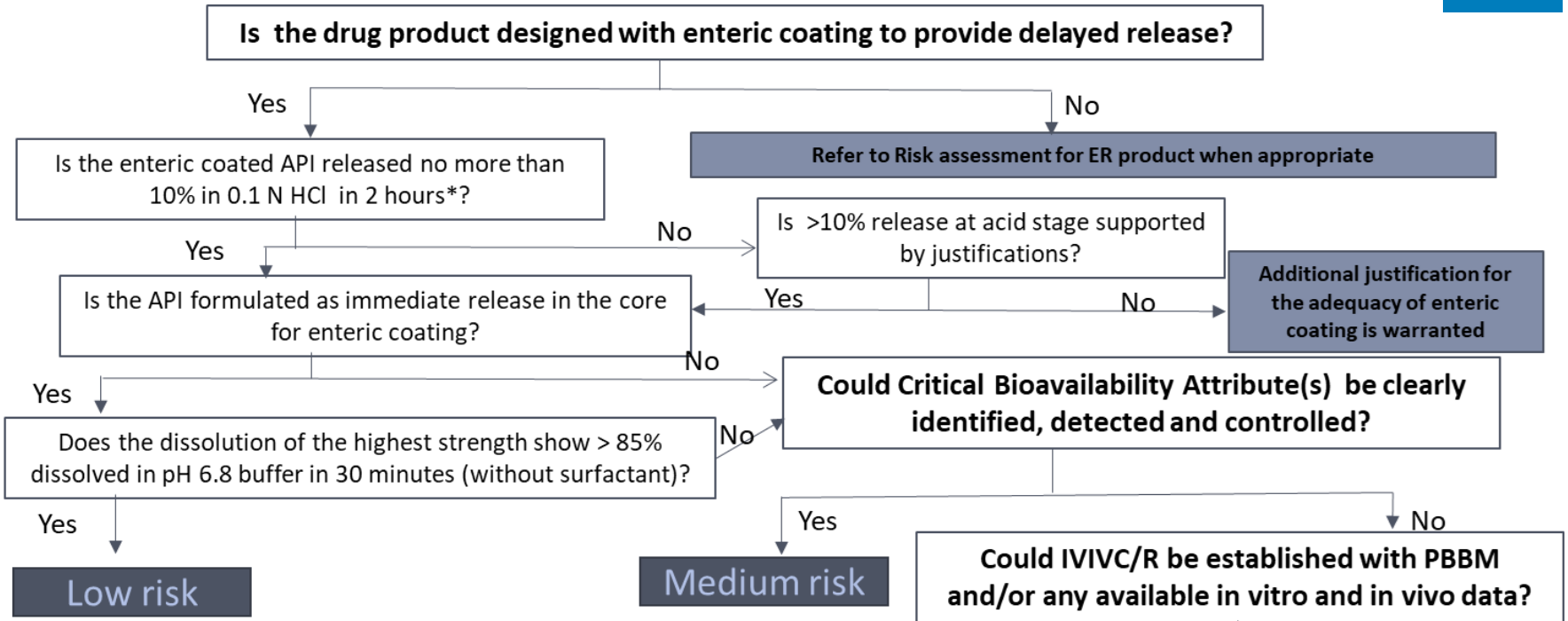
Biopharmaceutics Risk Assessment Decision Tree for ER Solid Oral Dosage Forms (Non-NTI)



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

PBBM: Physiologically-Based Biopharmaceutics Model

Biopharmaceutics Risk Assessment Decision Tree for DR Solid Oral Dosage Forms (Non-Locally acting drug products)



* This test can be conducted using the conditions in USP for DR product. The volume for acid stage should be at least 250 mL. The medium pH can be slightly different (e.g., pH 2 or 3) based on the design of the product and justifications.

Biopharmaceutics Risk Level Classification

Level	Detectability and Predictability
Very Low	High using the standard test in the FDA guidance
Low	High as long as an appropriate method is selected to provide in vivo insight
Medium	High as long as CBA(s) can be clearly identified, detected, and controlled by product and manufacturing controls
High	Low as the BA/BE impact cannot be clearly identified, detected and controlled by product and manufacturing controls. However, in vivo impact can be potentially predicted based on the available data
Very High	Very Low as the BA/BE impact could not be clearly identified, detected, and controlled by product and manufacturing controls and in vivo impact cannot be predicted based on the available data

Dissolution Test to Mitigate BA/BE Risks (Non-NTI or Non-Rapid Onset)

Level	Biopharmaceutics Risk Mitigation Approaches
Very Low	Standard dissolution test as per August 2018 FDA guidance
Low	Limited method development is needed to justify dissolution method and/or acceptance criterion
Medium	In vitro approach is used 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

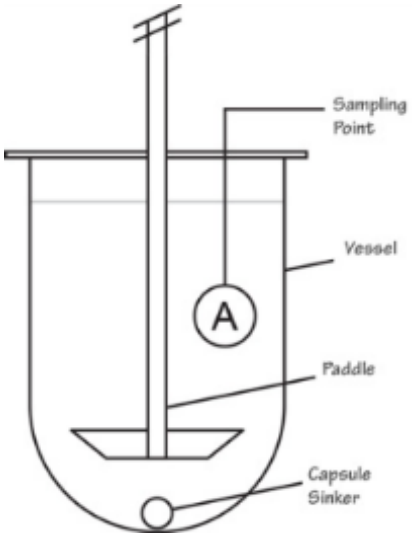
Dissolution Test to Mitigate BA/BE Risks for IR Solid Oral Drug Products Containing High Solubility Drug Substances

Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances

Guidance for Industry

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

August 2018
Biopharmaceutics



"For immediate-release solid oral drug products containing a high solubility drug substance (as defined herein), the dissolution criterion is Q=80% in 30 minutes"

Challenge 1: Standard Dissolution Tests for Low Risk Level Product?

- Especially for BCS Class 2a (acid drugs) and some BCS Class 2b (basic drugs)

- Does the in vitro dissolution of the highest strength show rapid dissolution in the media within the pH range 4.5-6.8 (without surfactant)?

- Opportunity: Developing in vitro tests targeting to provide in vivo insight for risk assessment and mitigation; biowaiver extension potential

Min Li et al. Understanding In Vivo Dissolution of Immediate Release (IR) Solid Oral Drug Products Containing Weak Acid BCS Class 2 (BCS Class 2a) Drugs. AAPS Journal 2021

- The comparisons of in vivo drug dissolution rate, which was characterized by in vivo dissolution half-life (T_{half}), indicate that solubility has a minimal impact on in vivo drug dissolution rate for NSAIDs.

- Gastric emptying…most likely governs drug dissolution and absorption of NSAIDs. For BCS Class 2a IR solid oral drug products, large variability of gastric emptying and MMC as well as the strong driving force of intestinal absorption probably outweigh the impact of solubility on drug in vivo dissolution.

- With appropriate biorelevant conditions, the *in vitro* dissolution rate can provide insight for *in vivo* dissolution. Future work on biorelevant dissolution testing for BCS class 2a IR solid oral drug products will be investigated with the ultimate goal to define conditions capable to predict the *in vivo* dissolution.

Challenge 2: How to Assess the BA/BE Discriminating Ability of a Dissolution Method for Medium Risk Level?

- Critical Bioavailability Attribute(s), CBA: Formulation or process attributes that expected to critically impact the bioavailability (absorption rate and extend) of a drug product
  - CBAs is previously called In vitro surrogates that control in vivo BA/BE.
- Could CBAs be clearly identified, detected and controlled?
- Reviewers' questions: what should be considered CBA? To which extent the discrimination ability is acceptable?
- Opportunity: Can we have biorelevant dissolution testing for medium risk level products to be used for risk mitigation, e.g., as a golden standard for discriminating ability?

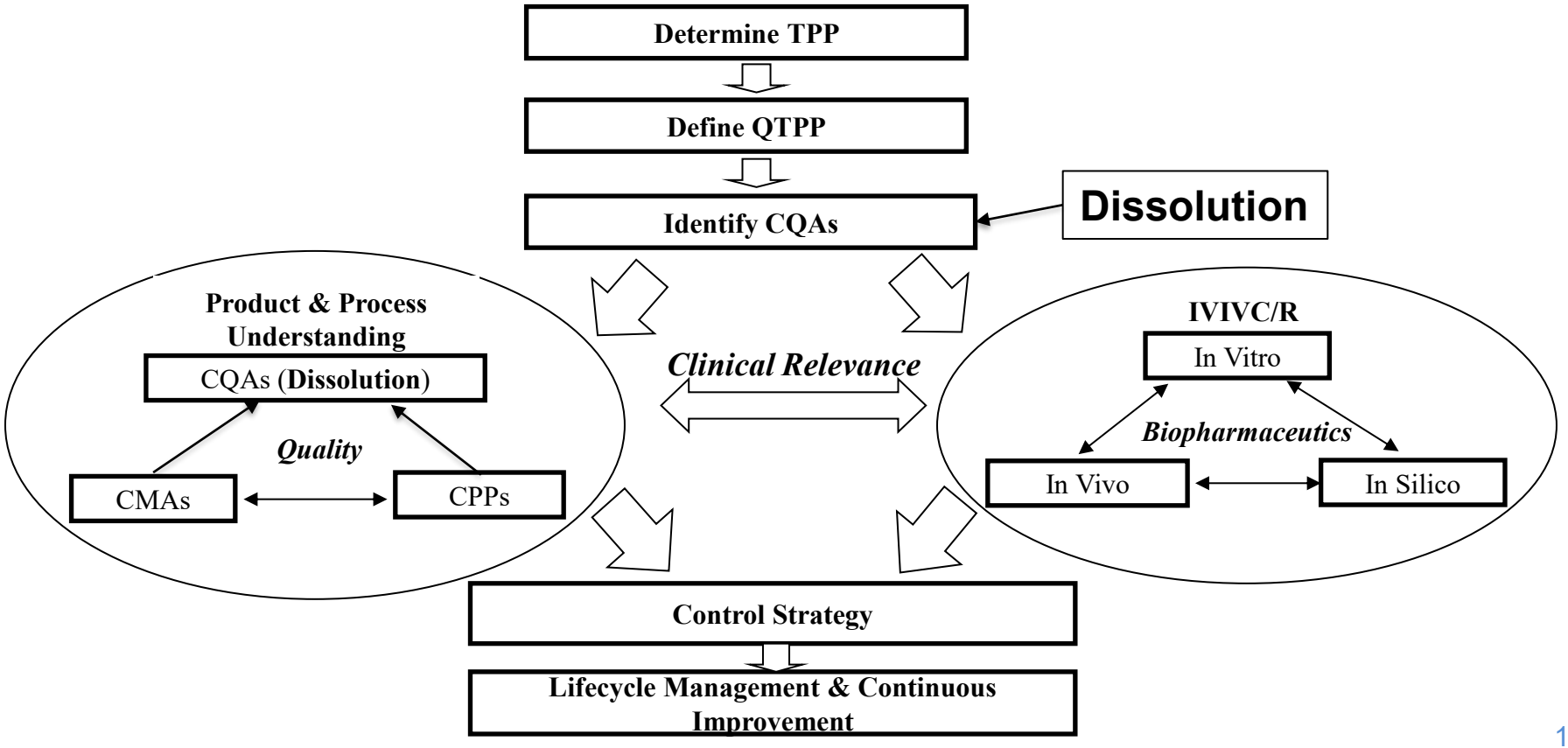
Challenge 3: IVIVC/R Development for High and Very High Risk Levels?

- The conventional methodology as well as PBPK methodology have limitations.
- Knowledge gap is the difference between in vitro and in vivo dissolution; especially for ER products.
- Opportunity: Mechanistic understanding and modeling of in vitro and in vivo dissolution for ER solid oral product to aid in PBBM to predict BA/BE

Challenge 4: Clarification of Quality Control vs. Predictive Roles

- **Quality Control Dissolution:** Focused on batch-to-batch consistency and detecting manufacturing deviations (traditional role).
- **Predictive Dissolution:** Specifically designed to provide in vivo insight and detect BE vs non-BE batches.
- Clearly delineate when each type is required and how they complement each other, rather than treating dissolution as a single test serving dual purposes.

Dissolution and QbD



FDA Quality Definition

- 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