Biopharmaceutics Risk Assessment to Guide Dissolution Method Development for Solid Oral Dosage Forms

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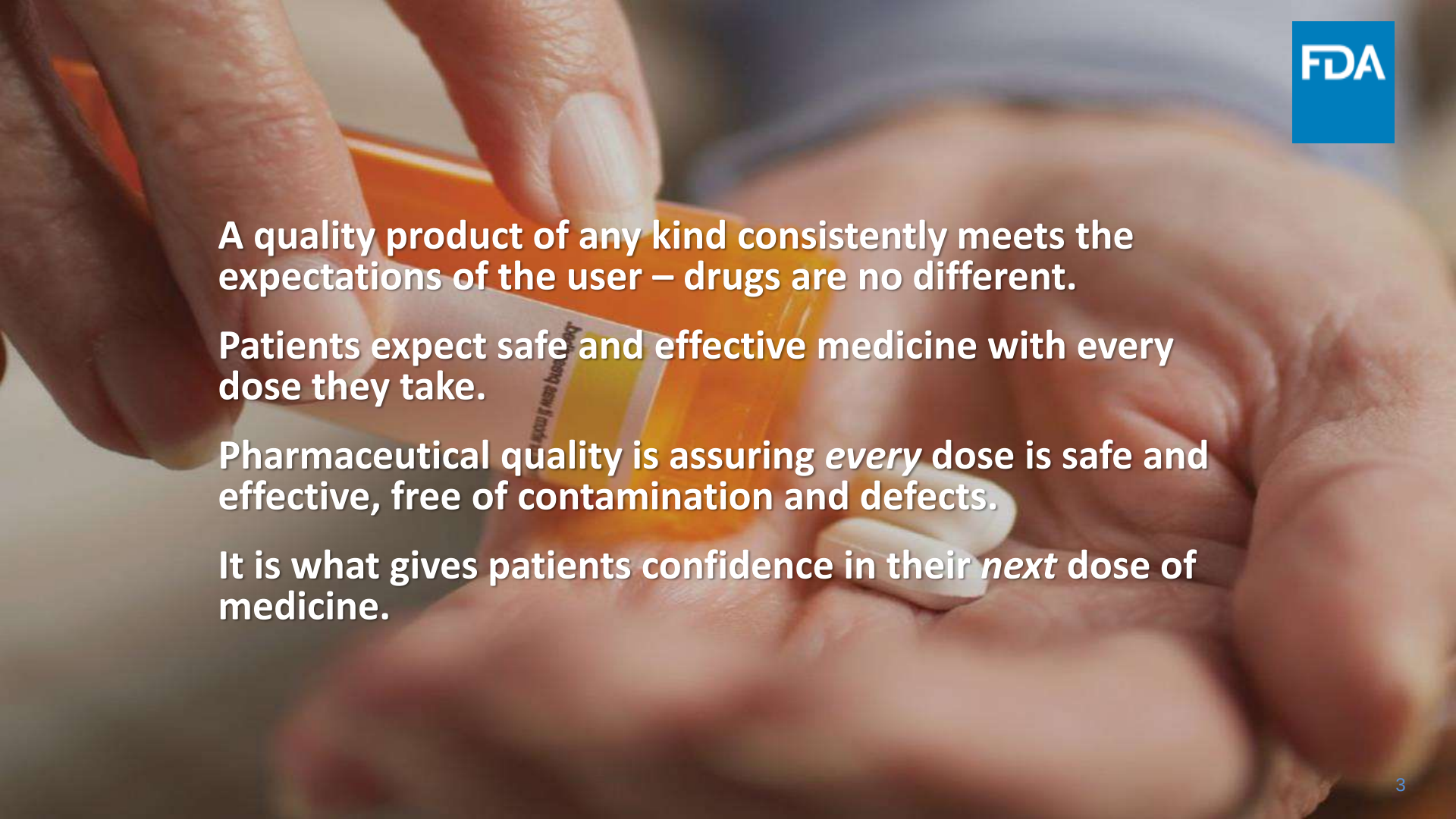


A quality product of any kind consistently meets the expectations of the user – drugs are no different.

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

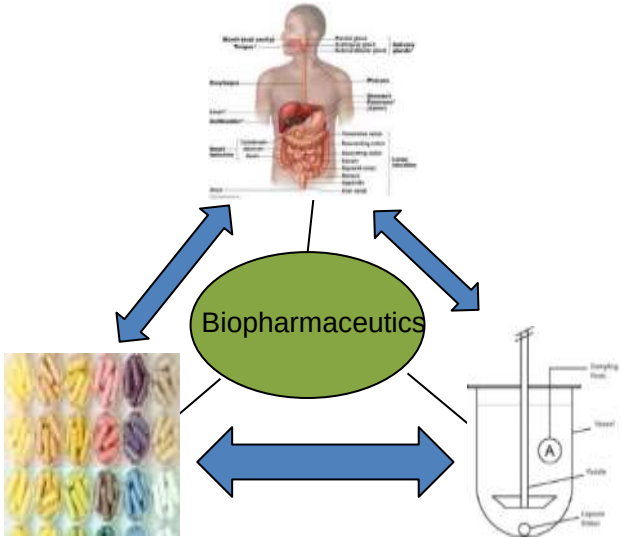
Pharmaceutical quality is assuring *every* dose is safe and effective, free of contamination and defects.

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

Learning Objectives

- To understand the purpose of biopharmaceutics risk assessment
- To learn how to conduct biopharmaceutics risk assessment
- To understand the role of in vitro dissolution test for BA/BE risk mitigation

Product Quality link to In Vivo Performance through Biopharmaceutics

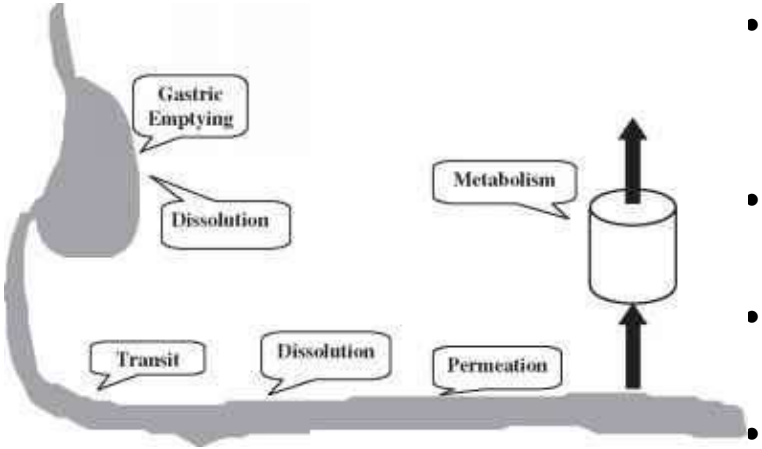


- Biopharmaceutics is the study of the physical and chemical properties of a drug, and its dosage form, as related to the onset, duration, and intensity of drug action.
- Clinical relevance (impact on BA/BE) is emphasized in structured assessment for biopharmaceutics risk assessment and mitigation.
- Tools: BA/BE, disintegration, in vitro dissolution, IVIVC/R, in silico, etc.
- Goal: to assure quality product to provide consistent efficacy and safety for patients.

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 Associated with Solid Oral Dosage Forms



Based on a comprehensive product understanding including:

- The formulation design for the intended clinical use: IR/MR
- Drug substance solubility and permeability
- Drug release mechanism
- Drug absorption and disposition characteristics
- Safety and efficacy profile

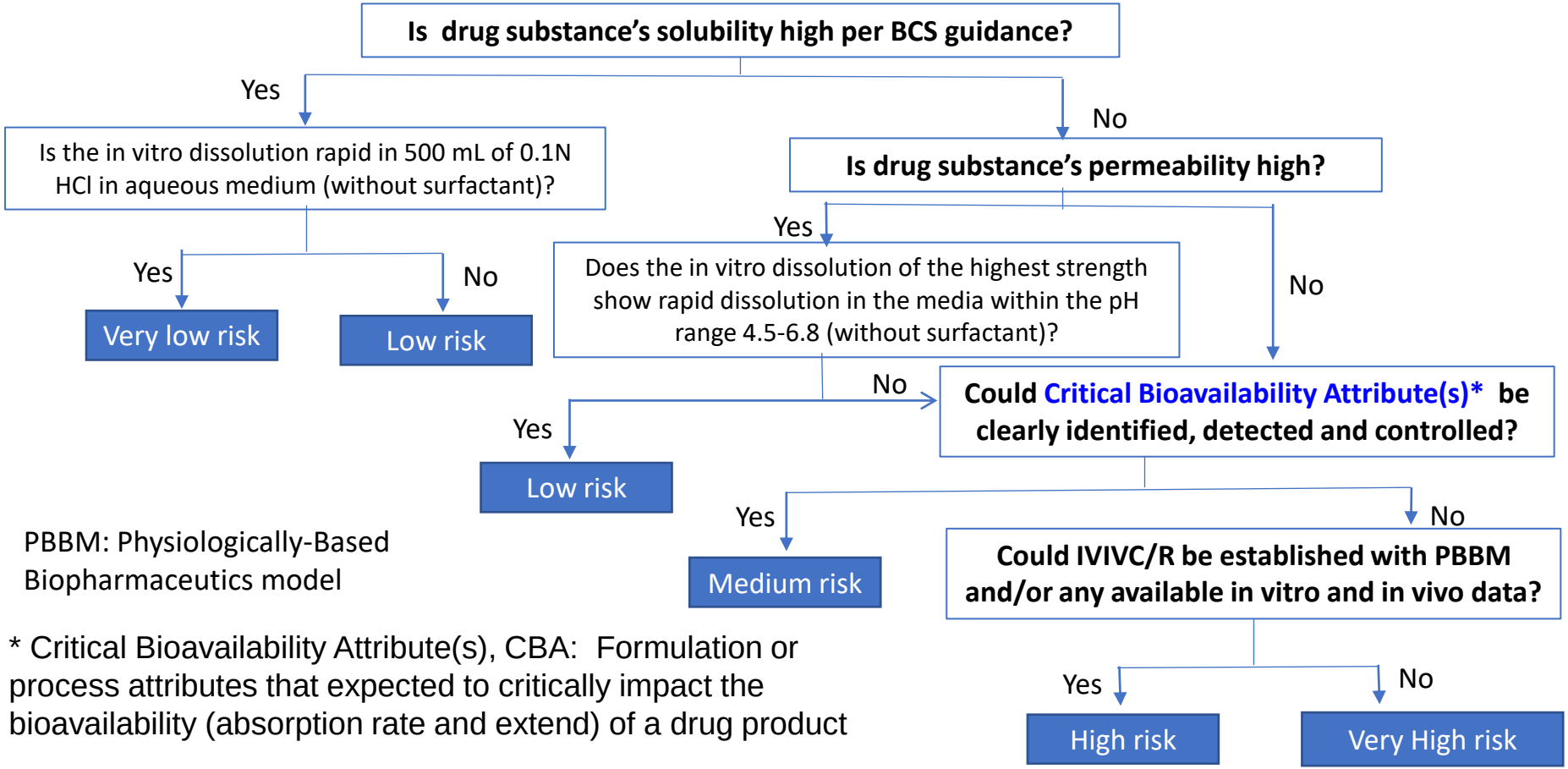
Biopharmaceutics Risk Assessment

- Biopharmaceutics risk assessment focuses on the **evaluation of BA/BE impact** attributed to **physico-chemical 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 specifications to mitigate the risk.

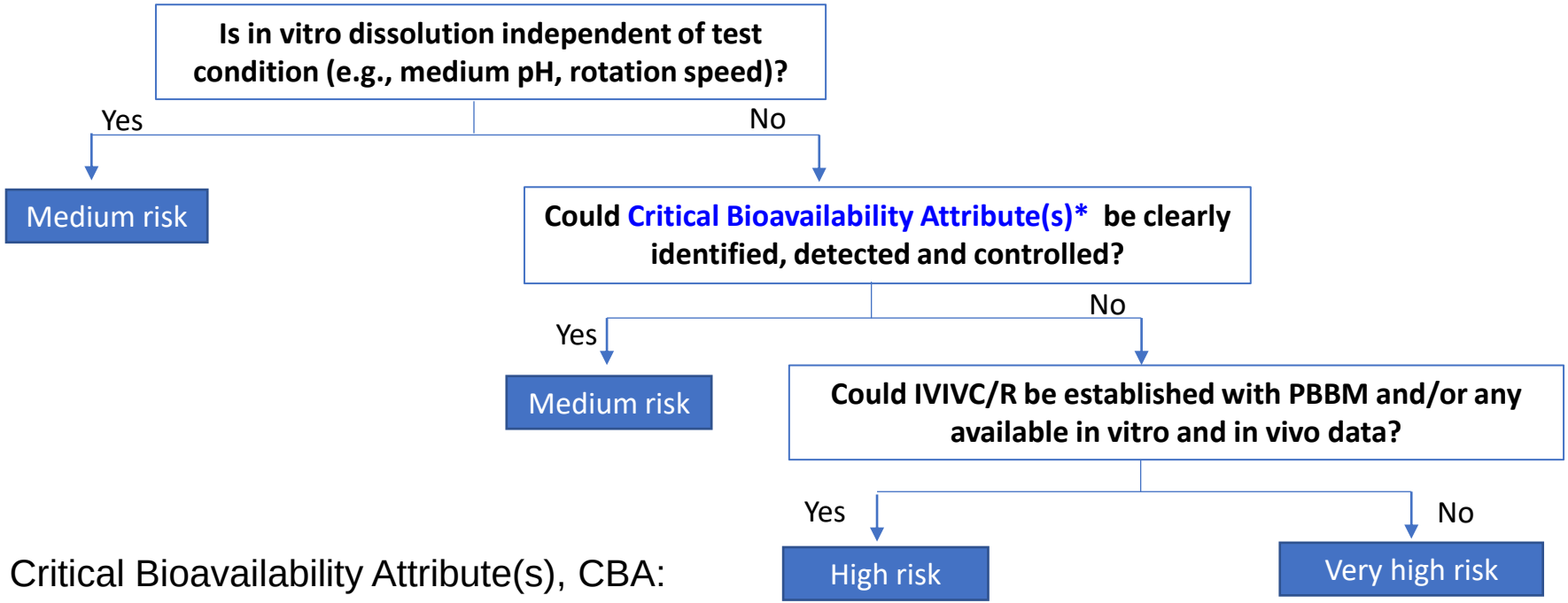
Initial Biopharmaceutics Risk Assessment Decision Tree for IR Solid Oral Dosage Forms (Non-NTI or Non-rapid onset)



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

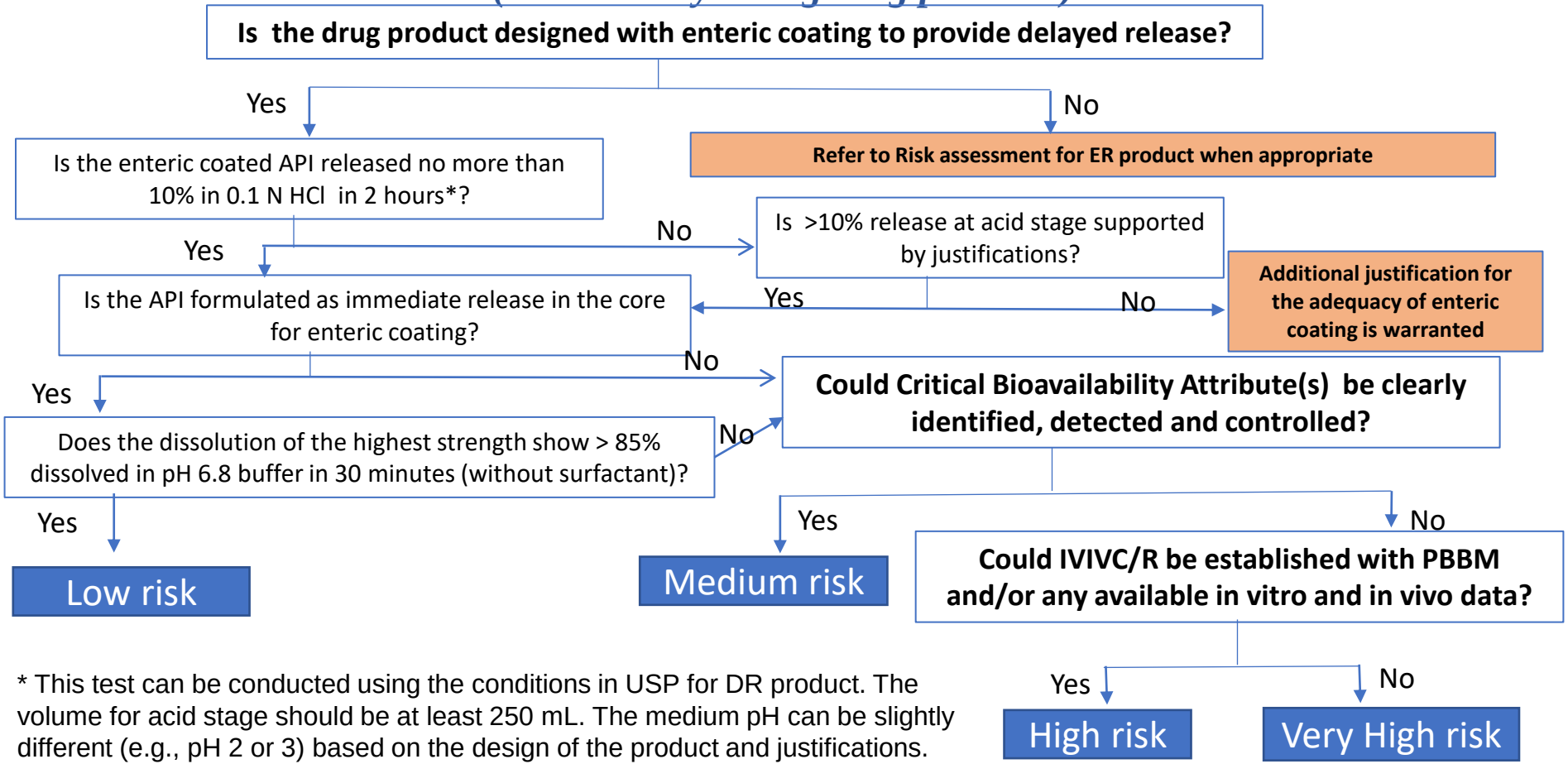
Initial Biopharmaceutics Risk Assessment Decision Tree for ER Solid Oral Dosage Forms (Non-NTI)



* 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

Initial 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 biopredictive 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 biopredictive dissolution test

*Standard Dissolution Tests for Solid Oral IR-Drug Products with High Solubility API**

Guidance Recommended Dissolution Testing Conditions:

A: Basket Method (USP apparatus 1)

500 mL of 0.1N HCl in aqueous medium

37±0.5° C/100 RPM

No surfactant in medium

B: Paddle Method (USP apparatus 2)

500 mL of 0.1N HCl in aqueous medium

37±0.5° C/50 RPM

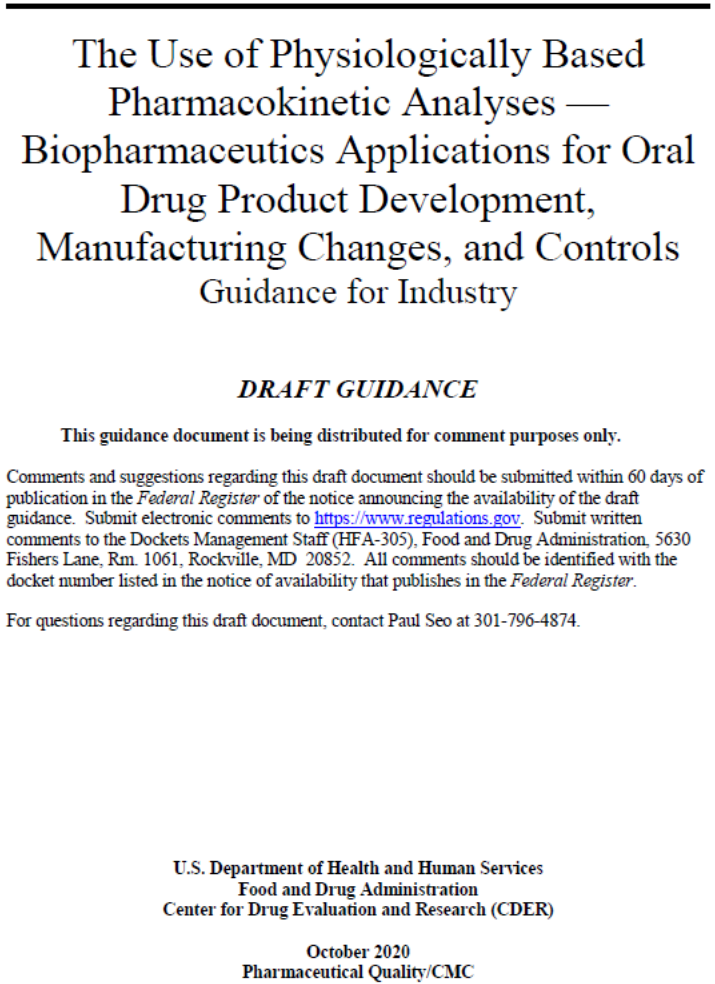
No surfactant in medium

Guidance Recommended Acceptance Criterion

Q=80% in 30 minutes.

***2018 GUIDANCE:** Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances

PBBM for high biopharm. risk products



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
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- 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.

- Biopharmaceutics applications include establishing clinically relevant dissolution specifications and quality risk assessment for post-approval manufacturing changes.

Summary

- The role of Biopharmaceutics
- Biopharmaceutics risk assessment
- Initial Biopharmaceutics risk decision trees
- Risk mitigations

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Challenge Question #1

What is the purpose of Biopharmaceutics risk assessment :

A. To make tighter quality standard

B. To force the industry to develop IVIVC/R

C. To provide scientific and risk-based framework to support patient-centric quality standards

Challenge Question #2

Which biopharm. risk mitigation strategy is most appropriate for a very low risk oral solid IR product ?

A. Implement the USP or FDA database method

B. Implement the standard test recommended in FDA guidance: Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances

C. Develop IVIVR/C to support a biopredictive dissolution method

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Thank you for your attention!


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