Use of Knowledge-Aided Assessment and Structured Application (KASA) in Biopharmaceutics Assessment

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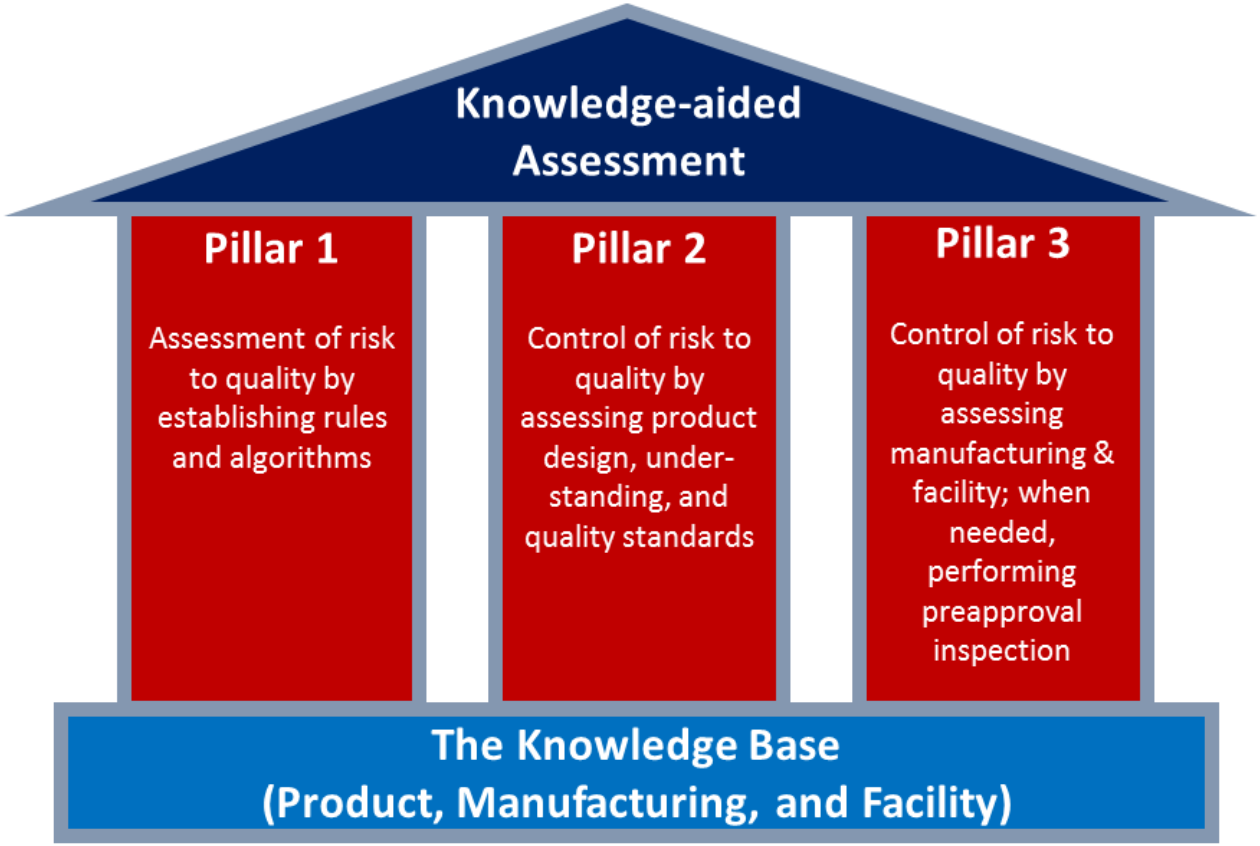
Presentation Objectives

- Describe how KASA is used in the assessment of biopharmaceutics information submitted in Abbreviated New Drug Applications (ANDAs)

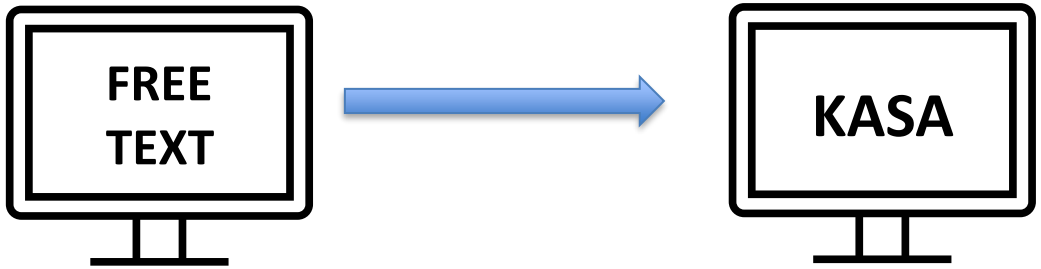
- Demonstrate the Biopharmaceutics risk assessment decision making process within KASA

- Provide the advantages of enhanced Risk-Based communication toward PCQS in the KASA interface



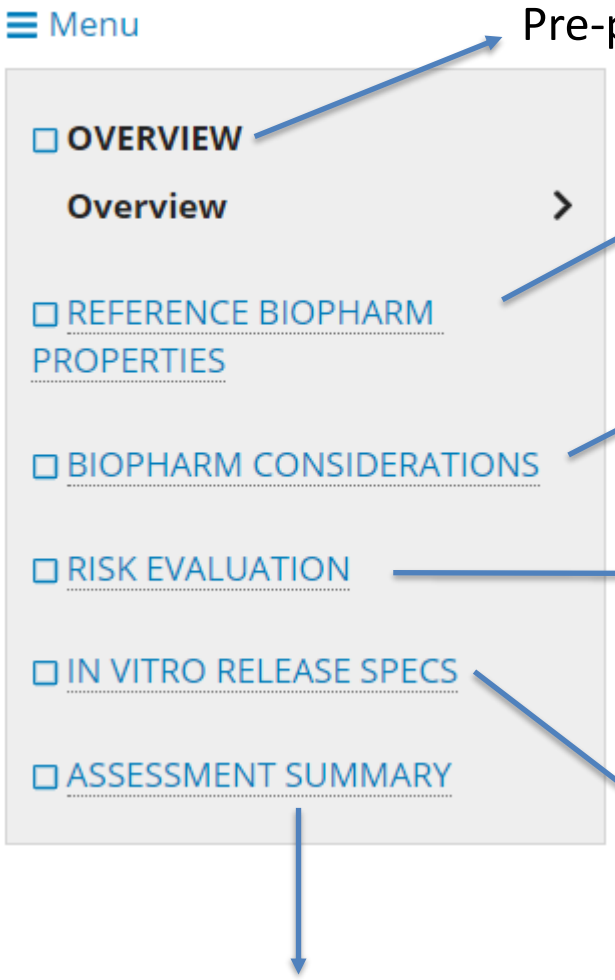
KASA for ANDA solid oral dosage forms (SODFs) provides transparency and consistency across applications for in vitro dissolution specification setting based on product understanding and biopharmaceutics risk to the drug product.

ANDA KASA Snapshot (Biopharm)



- Structured **six** Assessment Module Design
- Incorporation of comparative in vitro release profiles and PBPK/IVIVC Modeling Reports
- Question-Based Biopharmaceutics Risk Ranking
- Databased Lifecycle Management

ANDA KASA (Biopharm) Structure



Pre-populated application information

Relevant label information (e.g., clinical pharmacology properties)

Biopharmaceutic properties (e.g., solubility, BCS Classification)

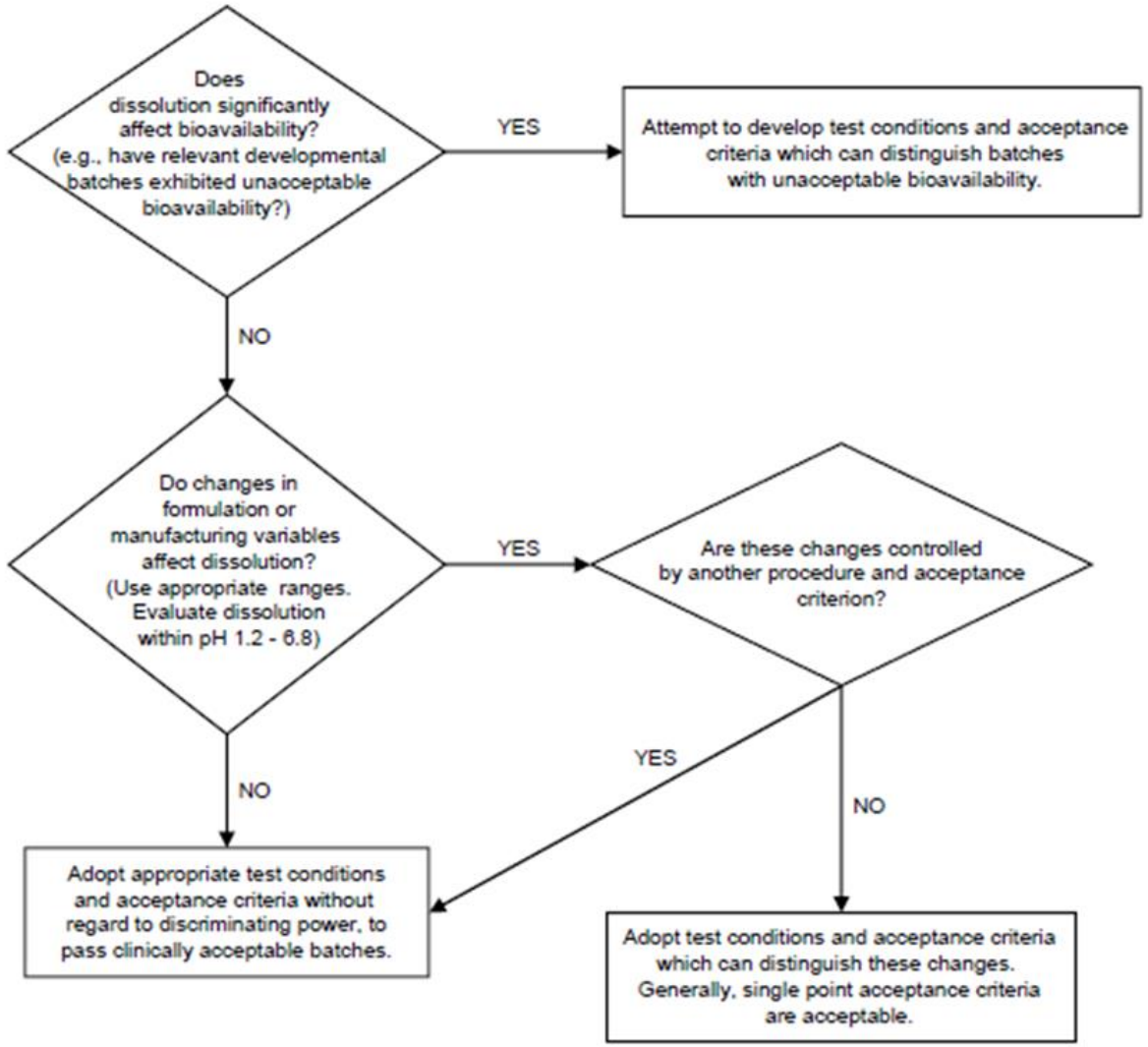
Biopharmaceutics risk assessment focusing on the evaluation of potential in vivo performance impact (e.g., BA/BE, efficacy and safety) due to quality design and controls of the drug product.

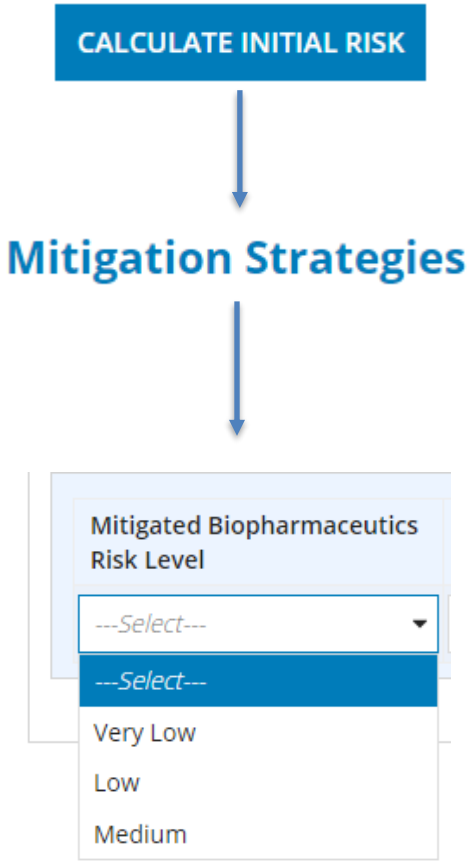
Dissolution method and acceptance criteria captured in a structural format

Concise summary and communication for life-cycle management

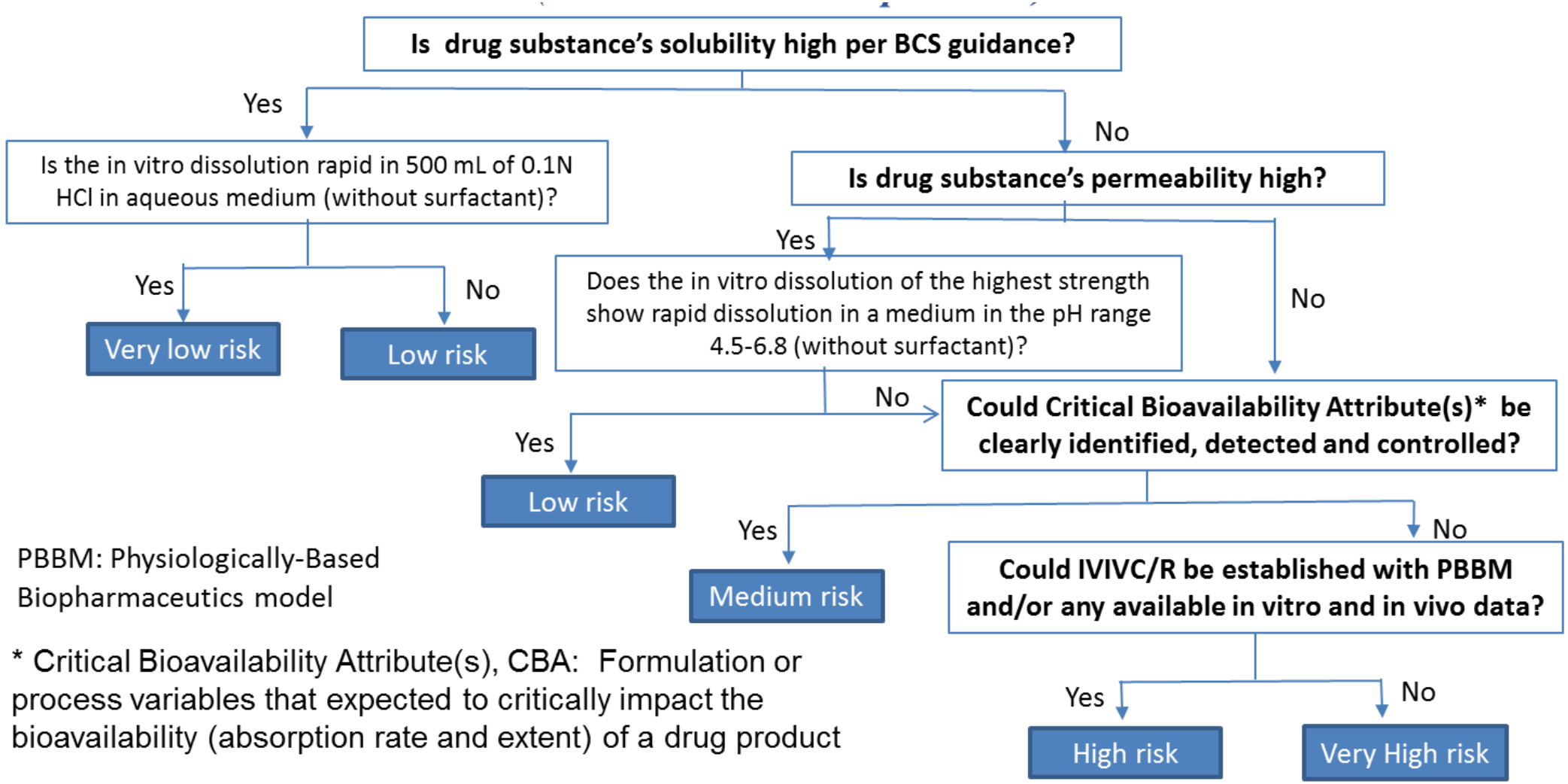
Risk Evaluation

ICH Q6A Specifications





Initial Risk Assessment



PBBM: Physiologically-Based Biopharmaceutics model

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

Initial Biopharmaceutics Risk Categories

Biopharmaceutics Risk Level	Examples of Biopharmaceutics Risk Mitigation Approaches
Very Low	Standardized dissolution test
Low	Adequate method development to justify dissolution method and acceptance criterion
Medium	In vitro approach is used to mitigate the biopharmaceutics risk. Dissolution test should target to detect meaningful changes in identified critical bioavailability attributes to provide insight into the in vivo performance
High	IVIVR is used 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

Regulatory flexibility Based on Risk rather than Manufacturing Capability

DEFICIENCY CASE EXAMPLES

Comment: Provide justification to support a wider dissolution specification (than Q=80% in minutes) for IR drug product containing highly soluble drug substance.

Response: Scientifically-sound explanation for root cause of slower dissolution e.g.,

- Borderline BCS solubility/sink conditions
- Tablet surface properties/wetting issues
- Cone formation due to excipients, or granules
- Drug-excipient interactions

Comment: Provide evidence/information to demonstrate no impact on in vivo BA/BE and/or safety/efficacy.

Response:

- In vivo BA/BE study
- IVIVR
- PBPK modeling and simulation/sensitivity analysis
- Exposure-response relationship (e.g., Cmax is not critical for efficacy)
- No change of Cmax/Cmin for chronic use

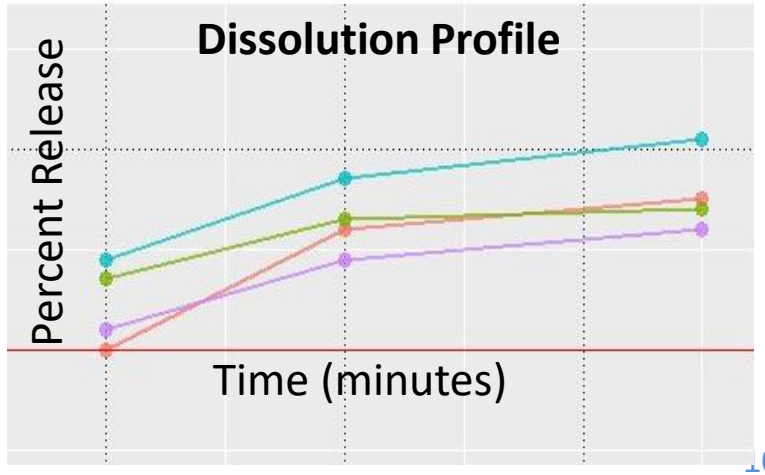
In Vitro Release Specifications

Iteration 1 - Original Review

No	Strength	Apparatus	Rotation Speed	Unit	Temp (C)	Medium/Volume (mL)	Acceptance Criteria
1	All Strengths	2-Paddle w/sinker	75	rpm	37	Phosphate buffer pH 6.8 with 3% Tween 20 - Volume: 900 ml	45 min, Q - 80%

Iteration 2 - IR Response

No	Strength	Apparatus	Rotation Speed	Unit	Temp (C)	Medium/Volume (mL)	Acceptance Criteria
1	All Strengths	2-Paddle w/sinker	100	rpm	37	Phosphate Buffer - Volume: 500 ml	30 min, Q - 80%



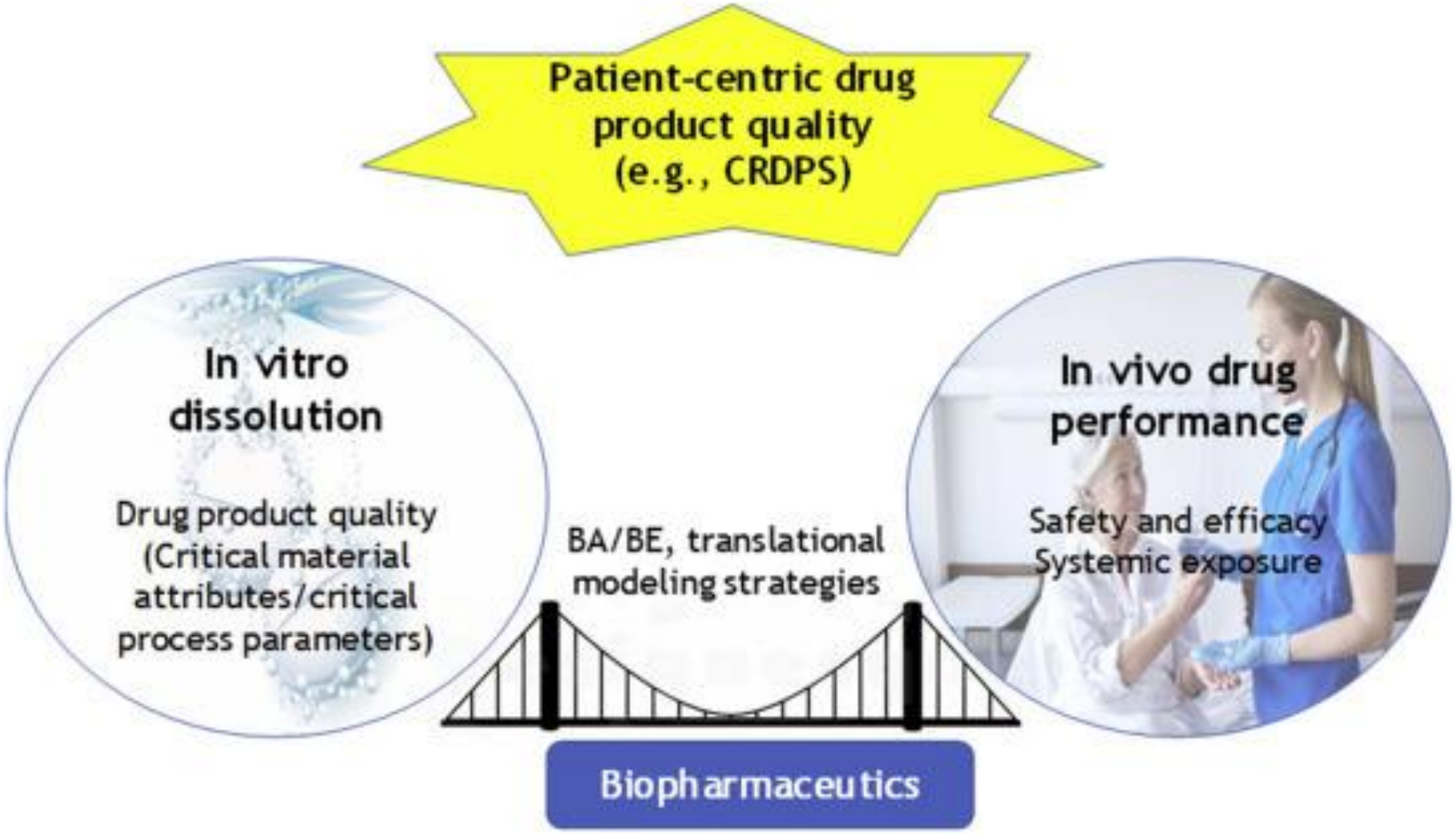
Key Considerations for Selecting an Appropriate Dissolution Specification

- Therapeutic use of the drug product
  - Narrow Therapeutic Index Drug Product/High Risk Drug Substance
  - Onset of action
  - Efficacy and safety profiles
- Drug release/absorption timeframe (IR/ER/DR)
- Rate limiting step for drug absorption
  - BCS classification
  - MR formulation design
- Predictive performance of the dissolution method
- The capability of dissolution specification to reject batches with unsatisfactory product quality

Dissolution Informed Quality and Lifecycle Management

Dosage Form Design Considerations: Advances in Pharmaceutical Product Development and Research 2018, Pages 287-336

Role of Biopharmaceutics in Patient-Centric Assessment of Quality



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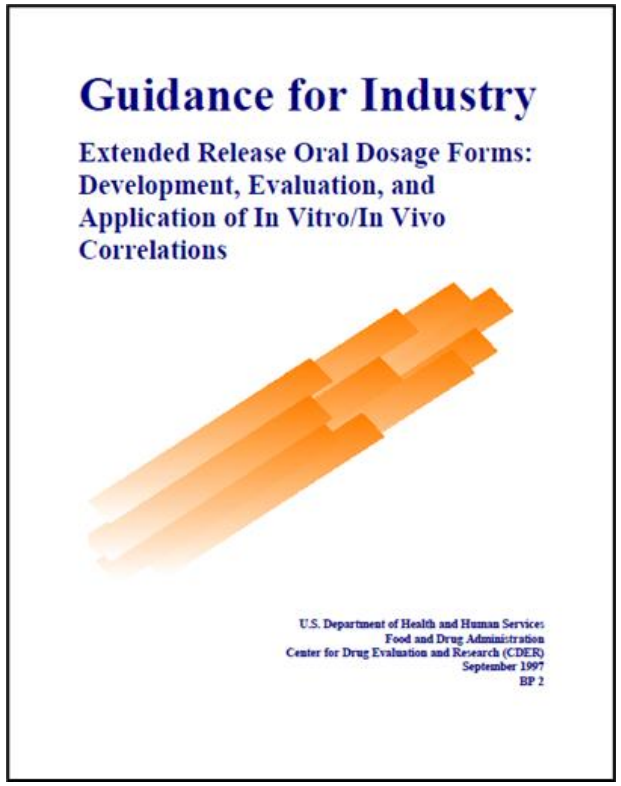
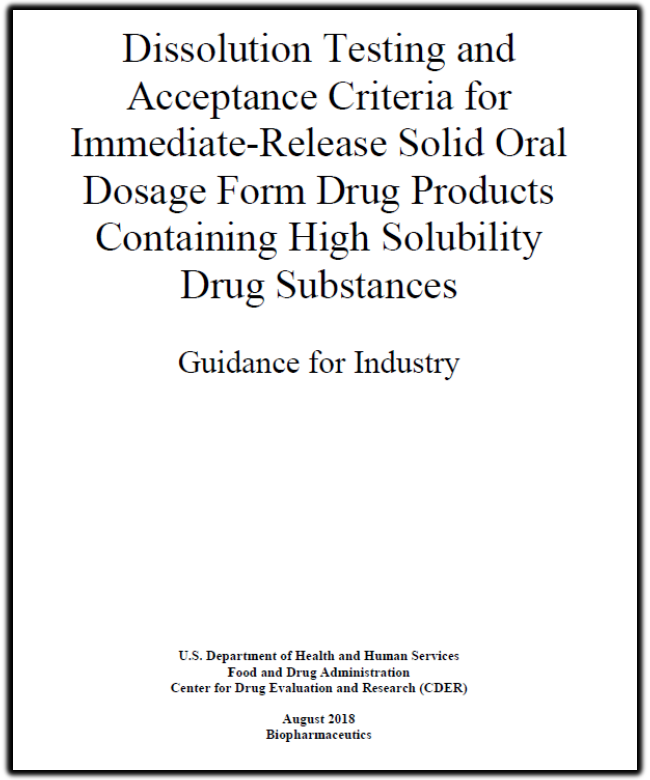
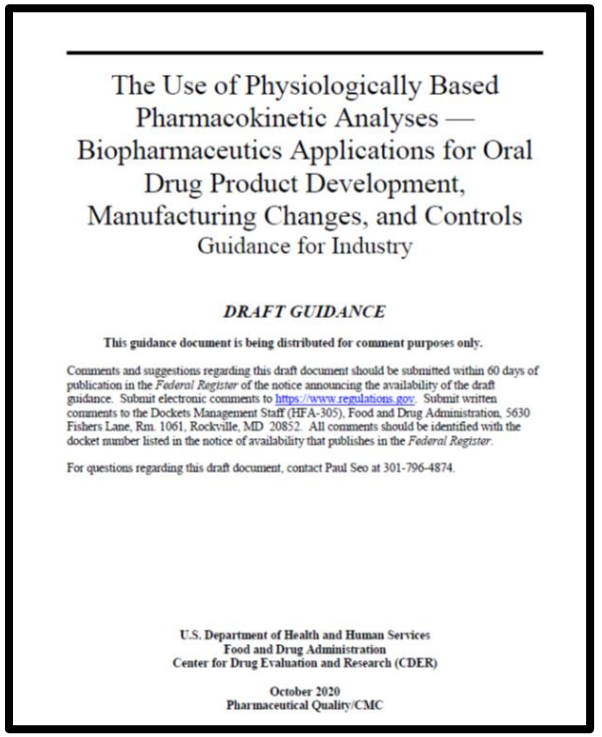
Implementation of Current Guidance Toward PCQS







CHALLENGE QUESTION
What Does KASA provide for the ANDA Biopharmaceutics Assessment?

- ❑ Structured knowledge to facilitate biopharmaceutics risk assessment
- ❑ Scientifically-sound biopharmaceutics risk assessment focusing on clinical performance
- ❑ Enhanced risk communication toward PCQS
- ❑ Improved assessment efficiency and consistency
- ❑ ALL OF THE ABOVE

CHALLENGE QUESTION
What Does KASA provide for the ANDA Biopharmaceutics Assessment?

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Acknowledgments

Development and Implementation of KASA is a GROUP effort. I would like to highlight the contributions provided by the following members:

- Colleagues and Staff in Office of New Drug Products
- Division of Biopharmaceutics KASA WG Members and User Acceptance Testers
- Office of Pharmaceutical Quality KASA Steering Committee

THANK YOU

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