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

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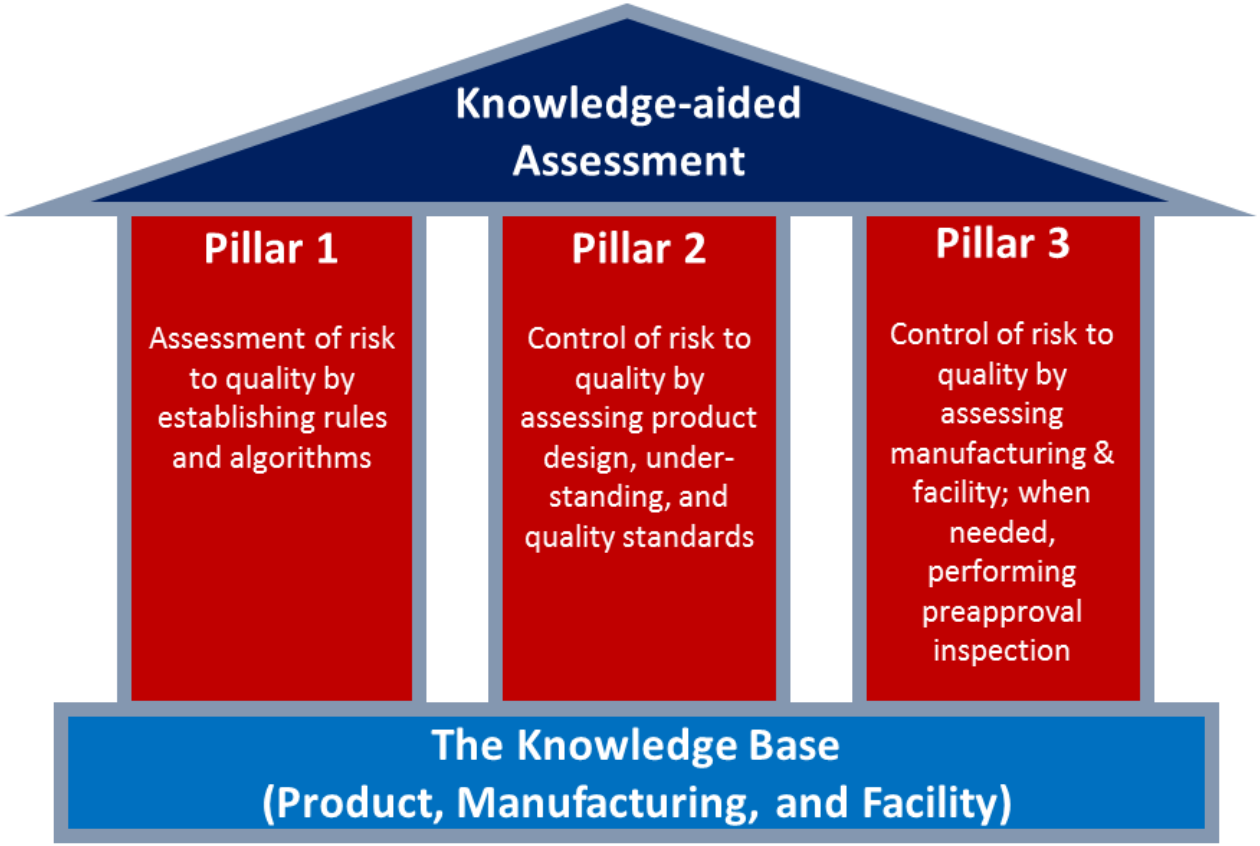
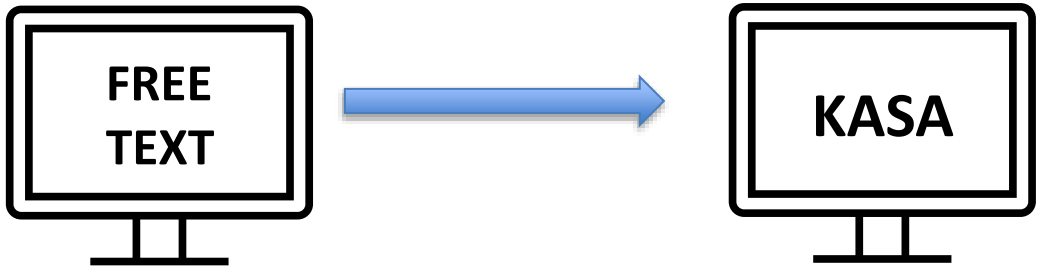
# Presentation Objectives

- 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



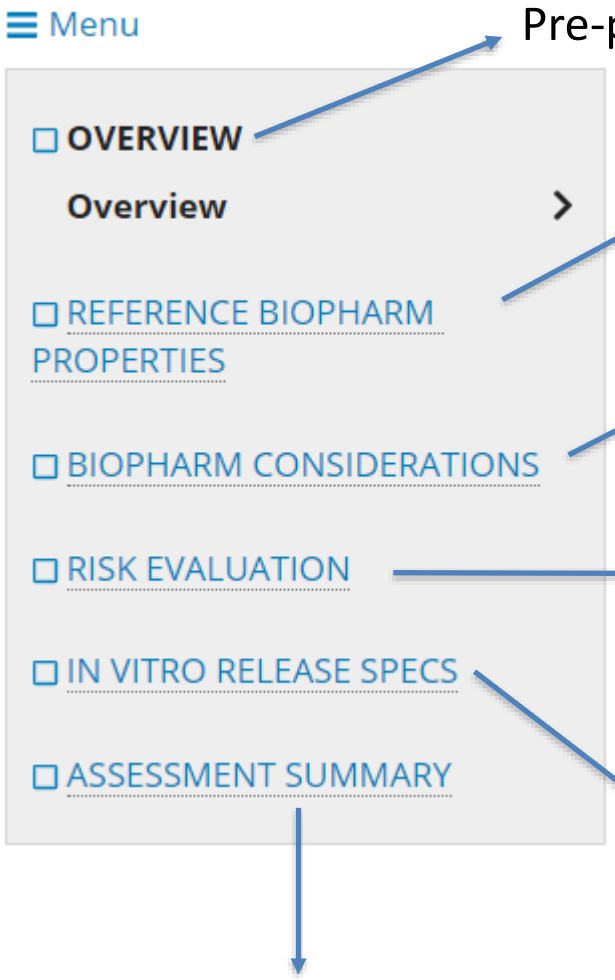

KASA for ANDA solid oral dosage forms (SODFs) provides transparency and consistency across applications for in vitro dissolution specification setting based on product understanding and biopharmaceutics risk to the drug product.

# 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)

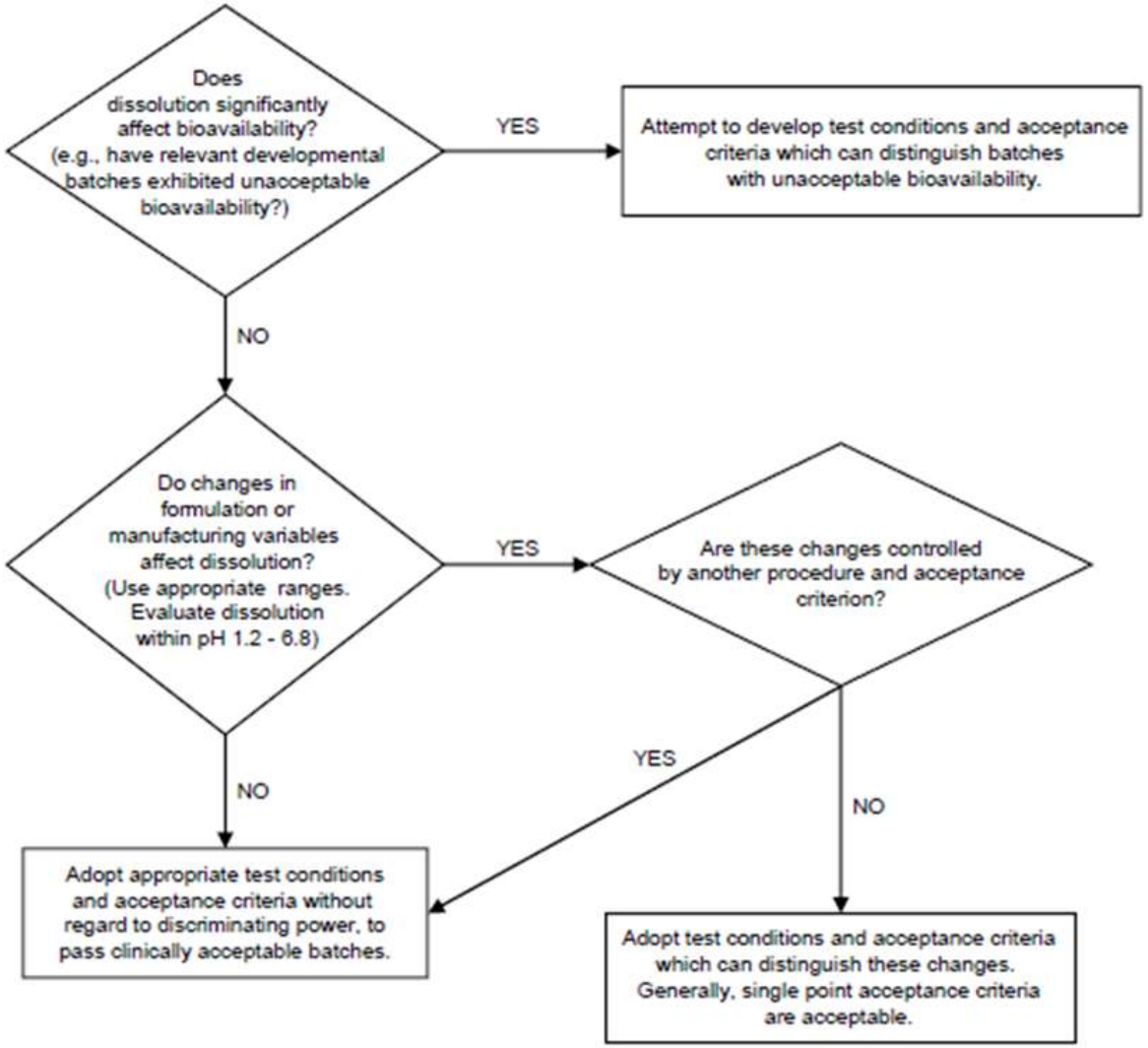
Biopharmaceutics risk assessment focusing on the evaluation of potential in vivo performance impact (e.g., BA/BE, efficacy and safety) due to quality design and controls of the drug product.

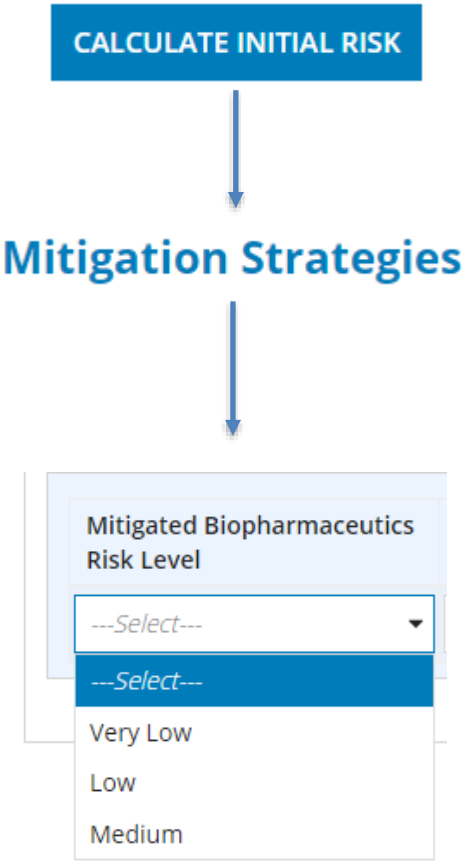
Dissolution method and acceptance criteria captured in a structural format

Concise summary and communication for life-cycle management

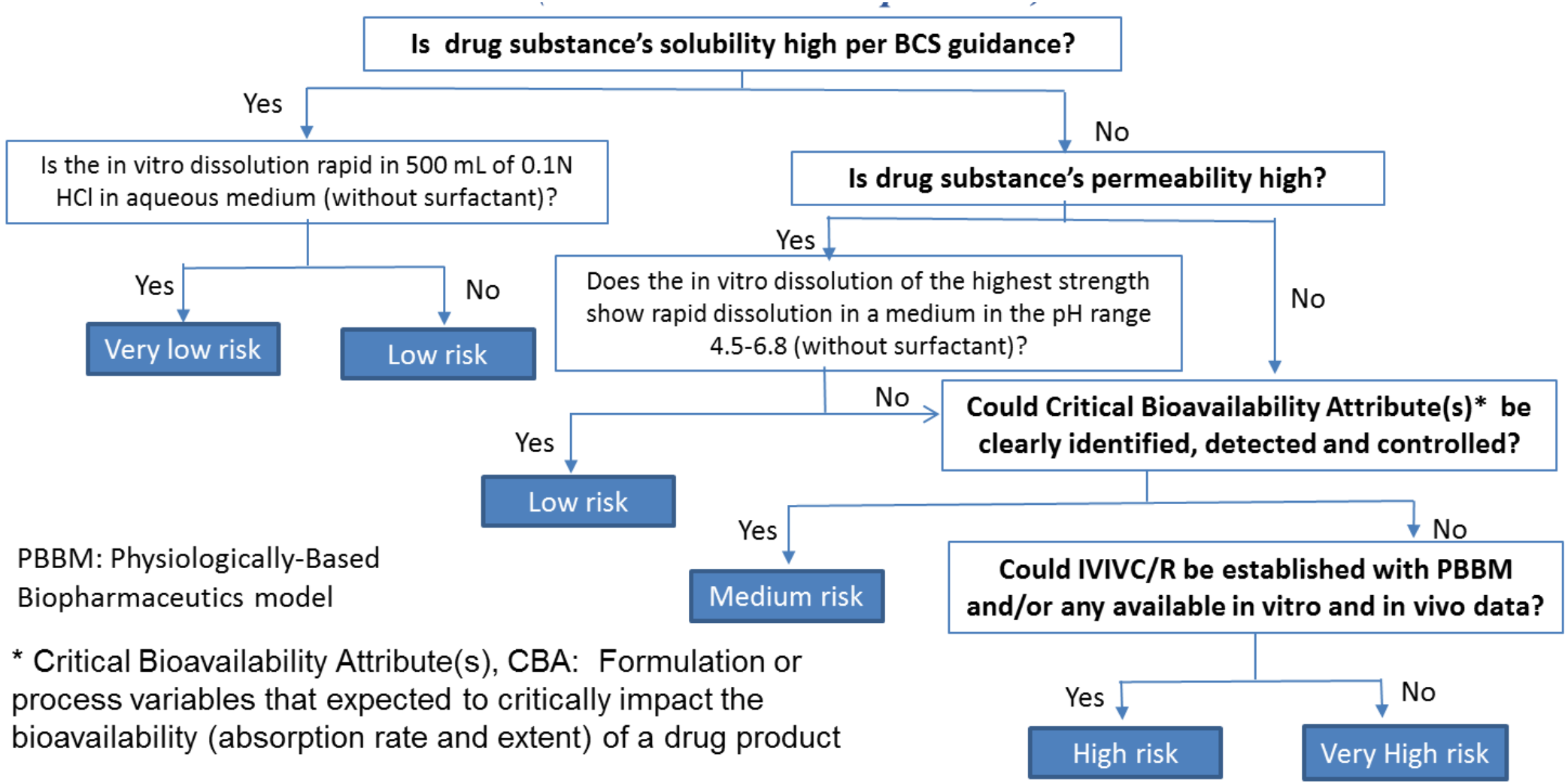
# Risk Evaluation

## 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

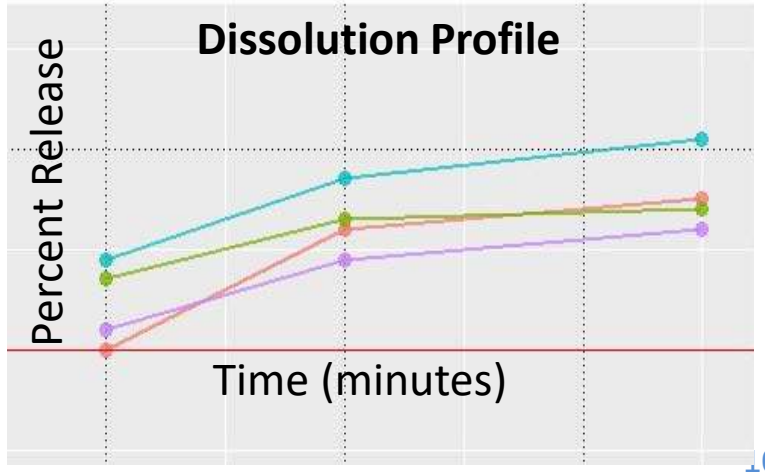
# In Vitro Release Specifications

### 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% |



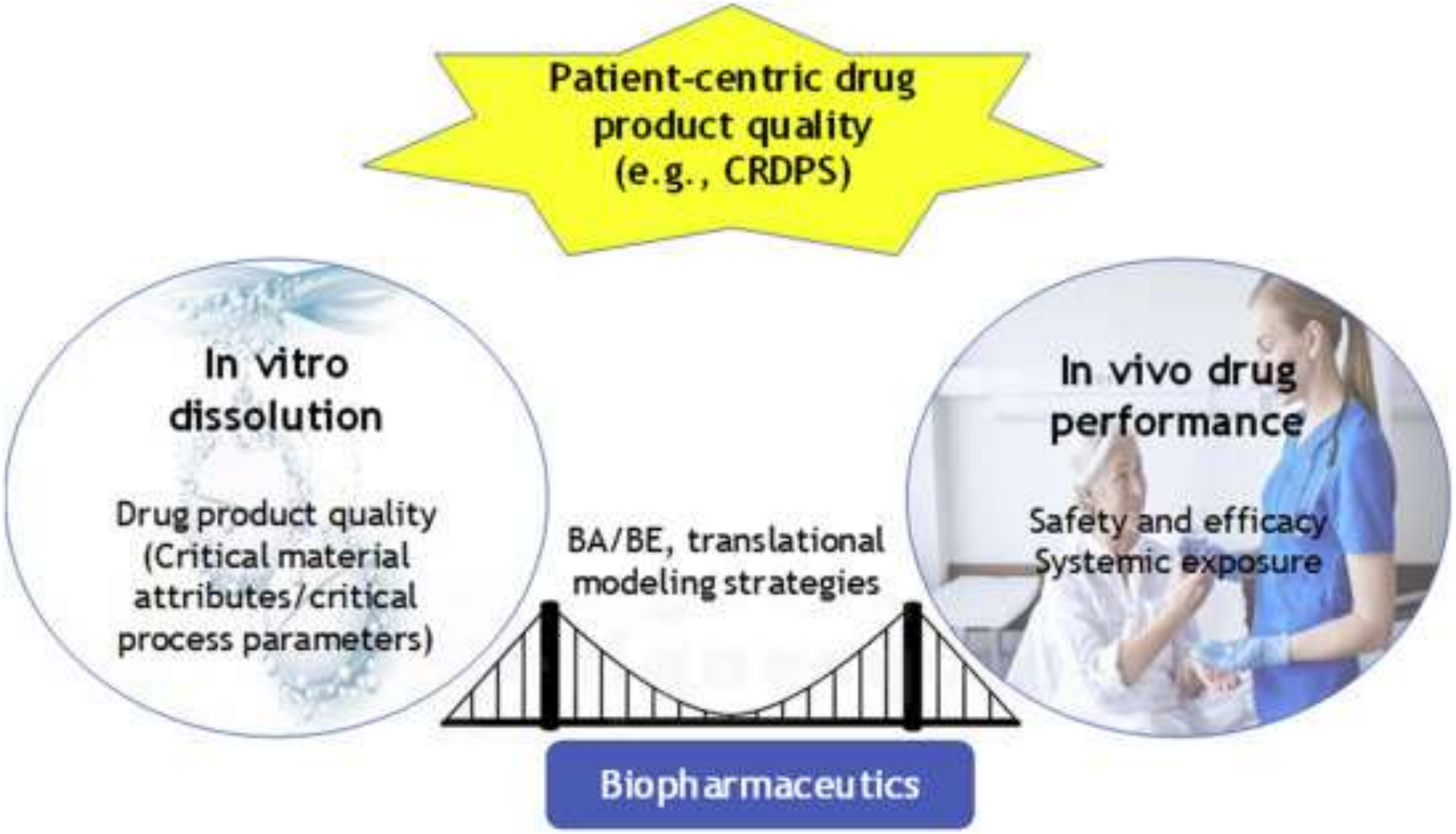
# Key Considerations for Selecting an Appropriate Dissolution Specification

- 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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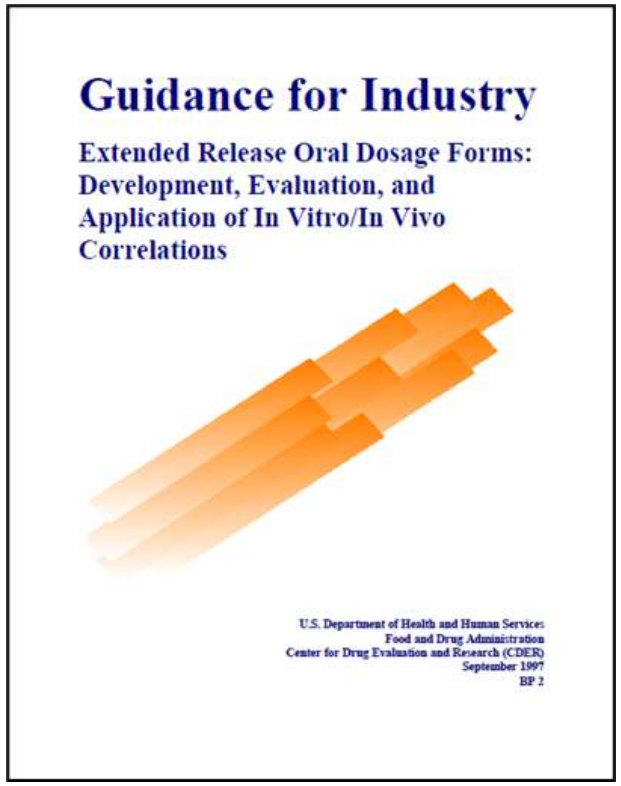
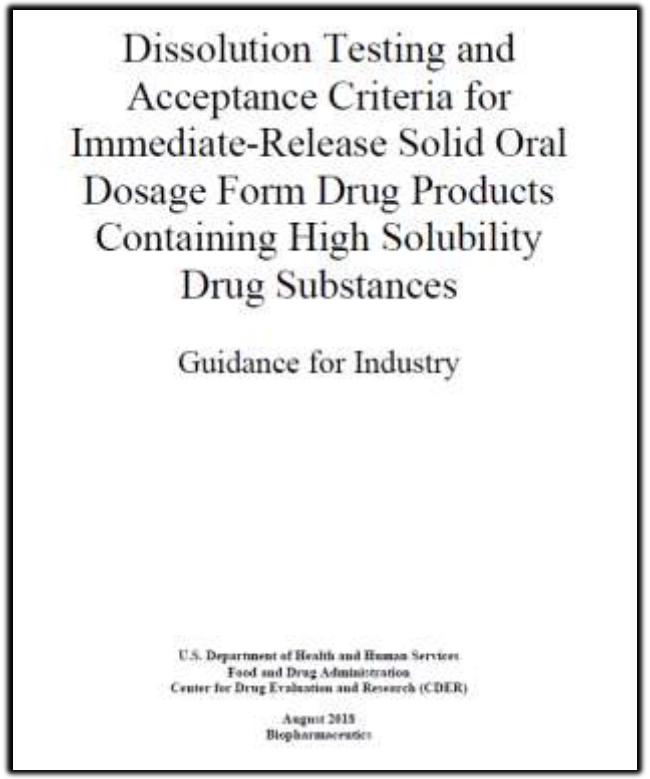
# Implementation of Current Guidance Toward PCQS


Guidance for Industry

Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations

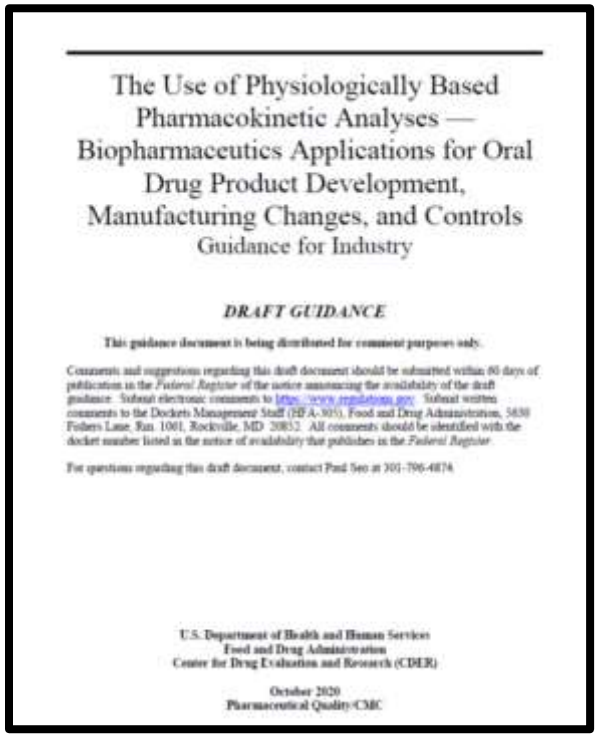
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
September 1997
BP 2


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


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

# 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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- ❑ Enhanced risk communication toward PCQS
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- ✓ ALL OF THE ABOVE

# 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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