U.S. FOOD & DRUG ADMINISTRATION

Biopharmaceutics Risk Assessment Framework: Advancing Dissolution Testing Toward Clinically Relevant, Patient-Centric Quality Standards

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Session: Biopharmaceutics Risk Assessment Frameworks for Oral Solid Dosage Forms

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Presentation Outline

1. The Biopharmaceutics Risk Assessment Framework: Origin and Overview
2. Risk Classification — How It Can Work for Generic Products
3. Developing Patient-Centric QC Dissolution Methods
4. Scientific Strategies: Potential Opportunities for the Generic Sector
5. Case Study: Illustrating the Framework in Practice
6. Lifecycle Management and Future Directions
7. Open Questions and Invitation for Input

Where the Framework Comes From

Framework Development Timeline

2026 M-CERSI Workshop
- ↳ 200+ global participants
- ↳ Industry, academia, regulators

White Paper Publication
- ↳ Totality-of-evidence approach
- ↳ Five progressive risk tiers
- ↳ Three dissolution method types

GRx+Biosims™ 2026
- ↳ Engagement with generic sector
- ↳ Seeking industry's collaborative input

Why Does This Matter for Generic Drugs?

- Generic drugs account for ~90% of all U.S. prescriptions — improving dissolution science broadly benefits patients.
- Current methods often serve as manufacturing consistency checks rather than patient-centric quality indicators.
- Inconsistent review outcomes and one-size-fits-all approaches create development inefficiencies.

A Potential Opportunity Worth Exploring Together

- A risk-proportionate, patient-centric framework may align dissolution testing with clinical relevance.
- The totality-of-evidence approach may be compatible with the generic development context.

The Biopharmaceutics Risk Assessment Framework: Overview

Core Principle: Shift from "Can the method detect manufacturing differences?" → "Can the method serve as a clinically anchored quality indicator?"

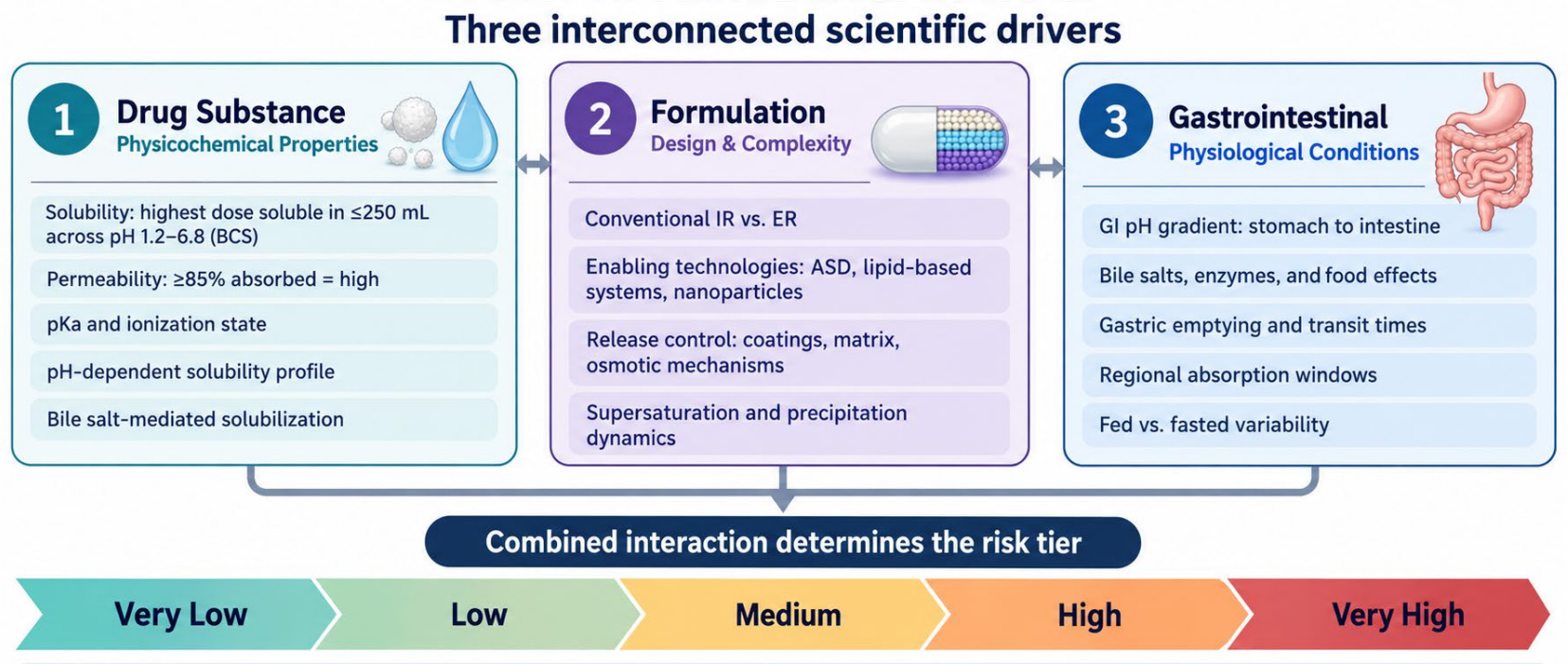
Three dissolution method types:

Discriminating	Biodiscriminating	Predictive
Detects in vitro differences Useful for manufacturing QC	Distinguishes BE from non-BE batches Anchored by IVIVR Practical target for most products	Quantitatively forecasts in vivo PK Supported by Level A IVIVC or PBBM

Five Risk Tiers (Drug Substance Properties × Formulation Complexity × GI Physiology)

- ❖ Very Low → Low → Medium → High → Very High
- ❖ Evidence recommendations are proportionate to the potential clinical impact of dissolution variability.
- ❖ Classification is dynamic — products may be reclassified as understanding grows.

How Is Risk Determined?



Five Risk Tiers: Mapping to Generic Product Types

Risk Tier	Typical Generic Product Types	QC Dissolution Strategy
Very Low	BCS Class 1 IR tablets/capsules	Standardized dissolution or disintegration testing
Low	BCS Class 3; BCS Class 2a weak acids (NSAIDs)	Standardized dissolution; BCS/IVIVR scientific basis sufficient
Medium	BCS Class 2 (weakly basic, non-ionized drugs)	Biorelevant media; qualitative/semi-quantitative IVIVR
High	ER formulations; ASD-based IR; lipid-based products	IVIVR/PBBM to validate biodiscriminating capability
Very High	NTI drugs in complex ER formulations	Dissolution + broader analytical/process controls

Risk Assessment— How It Can Work for Generic Products

- **Publicly available information that may support risk assessment:**
  - Drug substance properties: solubility, permeability, pKa, ionization state (BCS classification, ICH M9)
  - RLD formulation type: IR vs. ER, conventional vs. enabling technology (drug label, FDA approval packages)
  - Published clinical data: food effect studies, PK variability, known bioavailability issues
  - Regulatory precedents: existing biowaiver decisions, published IVIVR/PBBM literature

- **A possible four-step assessment workflow:**
  - Step 1: Characterize drug substance risk — assign BCS class; assess pH-solubility profile; identify rate-limiting step
  - Step 2: Assess formulation complexity — conventional IR (lower risk); ER or enabling technology (elevated risk)
  - Step 3: Integrate GI physiology sensitivity — food effect magnitude; fed/fasted PK ratio; absorption window data
  - Step 4: Assign tier; document uncertainty — sensitivity analysis for boundary cases; totality of evidence

Open question for the generic industry: What additional challenges or barriers exist for risk classfication in the ANDA development context that the framework does not currently address?

Risk Assessment in Practice: Tier-by-Tier

Key question: What is the dominant driver of in vivo dissolution variability?

Very Low / Low

- Drug substance properties dominate; GI physiology has minimal impact
- BCS Class 1: dissolution not rate-limiting under any GI condition
- BCS Class 3: permeation is rate-limiting; dissolution not a concern
- BCS Class 2a weak acids (NSAIDs): rapid intestinal dissolution; gastric emptying governs PK
- Evidence: published solubility/permeability data, biowaiver precedents, ICH M9

Medium

- GI physiology is the dominant driver; permeability is generally favorable
- Non-ionized and weakly basic BCS Class 2: pH-dependent dissolution and bile salt effects
- Food effect typically moderate-to-large (fed/fasted AUC ratio often >1.5)
- Evidence: pH-solubility profile, food effect data, mechanistic data from literature

High

- Drug product design and technology are the dominant drivers
- All ER: small changes in release-controlling parameters → meaningful PK changes
- ASD-based IR: supersaturation and precipitation kinetics tied to product attributes
- Evidence: formulation technology type, published PK variability, manufacturing sensitivity data

Very High

- Biopharmaceutics risk + clinical risk: PK variability → serious consequences
- Elevation from High when: NTI designation, black box warning, or rapid onset requirement
- PBBM and IVIVC/R inform but may not replace in vivo confirmation for significant changes
- Evidence: NTI designation, published PK variability, clinical consequence data

Developing Patient-Centric QC Dissolution Methods

- **Proposed goal: biodiscriminating dissolution may be the practical, achievable standard for most products**
  - Clinically anchored via IVIVR; full Level A IVIVC may not be required for most products

- **Risk-tier-specific approaches we propose for discussion:**
  - Very Low / Low: Standardized methods; disintegration as surrogate where justified; minimal additional characterization
  - Medium: Biorelevant media (FaSSIF/FeSSIF, pH transfer, biphasic); qualitative or semi-quantitative IVIVR as supporting evidence
  - High: Method design reflecting release-controlling mechanism; IVIVR + PBBM to validate biodiscriminating capability
  - Very High: Dissolution as one element of a broader analytical and process control strategy

- **Validation principle:**
  - Rank-order preservation — not absolute value reproducibility — is the key robustness criterion for biorelevant QC methods

- **Important consideration for generics:**
  - Generic products may use different formulation technologies than the RLD, potentially shifting the risk tier
  - **Dissolution methods should be scientifically justified for the generic product's own formulation**

Scientific Strategies: Potential Opportunities for the Generic Sector

The following approaches may be applicable to generic development — we welcome the industry's perspective on practicality, feasibility, and gaps.

Strategy 1 | Reconstruct biopharmaceutics understanding from public sources

- Published literature: solubility, permeability, food effect, mechanistic PK
- FDA review documents, Drugs@FDA, drug labels
- Reverse-engineering using commercially available RLD batches

Strategy 2 | Leverage existing formulation development data

- Multiple formulation variants generate dissolution profiles spanning a range of designs
- In vitro data + PBBM may predict in vivo performance without full validation
- Pilot BE outcomes across variants: ready-made IVIVR foundation

Strategy 3 | Leverage scientific tools and collaborative platforms

- BCS/ICH M9; FaSSIF/FeSSIF, pH transfer, biphasic, lipolysis tools
- Published IVIVR/PBBM models; commercial PBBM platforms
- Shared datasets and validated methods - reduced investment

Strategy 4 | Combine all three strategies above

- Integrated approach maximizes the use of existing assets
- Most robust path to establishing a biodiscriminating QC method for ANDAs

The IVIVR: What Generic Manufacturers Need to Know

An IVIVR is the scientific bridge that makes a dissolution method biodiscriminating

What Is an IVIVR?

Demonstrates that in vitro dissolution differences correspond to meaningful in vivo BE outcomes.

Does NOT require a full Level A IVIVC for most products:

→ Qualitative: directional correspondence (lower dissolution → lower Cmax/AUC)

→ Semi-quantitative: rank-order of in vitro profiles matches rank-order of in vivo PK

→ Quantitative (Level A IVIVC): full point-to-point PK prediction; preferred for certain ER

Building an IVIVR in a Generic Context

- In vitro dissolution profiles of formulation variants spanning a range of release rates (already generated during development)
- Pilot BE outcomes (pass/fail) from those same variants — links in vitro to in vivo empirically
- PBBM-predicted PK for each variant — mechanistic IVIVR even without a full clinical dataset
- Published PK data for the drug substance as supportive evidence

***Hypothesis**: Existing development data — in vitro profiles + PBBM + pilot BE outcomes — may establish an IVIVR without new dedicated clinical studies.*

We invite the industry to test this hypothesis.

Case Study: The Framework in Practice

- **Product: BCS Class II weakly basic IR capsule (low-solubility, pH-dependent)**
  - Solubility decreases ~20-fold across physiological pH range (acidic → neutral)
  - Dissolution and solubility are rate-limiting for absorption
  - **Framework classification: Medium Risk**

- **Scientific questions addressed:**
  - Is API particle size distribution (PSD) a Critical Material Attribute (CMA) impacting in vitro dissolution and in vivo bioavailability?
  - Can the QC dissolution method be shown to be biodiscriminating with respect to API-PSD?
  - Can a bioequivalence safe space be established to support the API-PSD specification?

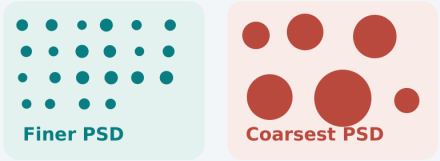
Approach: ***PBBM + virtual BE simulations across formulation variants spanning a range of API-PSD values***

Case Study: Linking PSD, Dissolution, and In Vivo Performance

1 Identify the material attribute → **2 Predict bioequivalence** → **3 Confirm QC discrimination**

API particle-size distribution (PSD)

Systematically varied across formulations



Smaller D50 / D90

D50 ≈ 84 µm
D90 ≈ 191 µm

Critical material attribute (CMA)

PSD differences produced distinct in vitro dissolution profiles in the QC method.

PBBM-based virtual BE simulations

PBPK model inputs

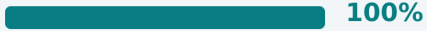
Physicochemical properties + PSD + available clinical PK data

Validated against single- and multiple-dose studies

10 trials per variant • 33 virtual subjects

Virtual BE pass rate

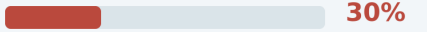
Finer PSD variants



100%

vs. reference and bio-batch

Coarsest PSD variant

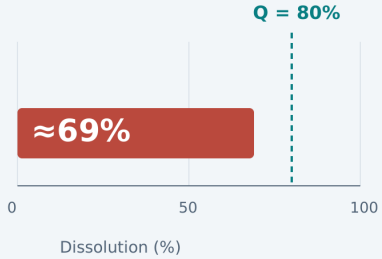


30%

vs. bio-batch

Coarsest variant rejected by QC

Mean dissolution at 15 minutes



Below the Q = 80% criterion

QC method correctly identified the variant with a low simulated BE pass rate as unacceptable.

PSD safe space supports specification setting

Safe space established between the bio-batch PSD and the last passing variant PSD.

The dissolution acceptance criterion protects against subtherapeutic exposure.

Case Study: Key Lessons Aligned with the Framework

1 Risk classification guided the strategy

Medium risk defined where evidence was needed

Medium risk designation → GI physiology + API PSD → Proportionate evidence strategy

Focus on key drivers kept the evidence proportionate to risk and avoided excessive evidence generation.

2 Validated PBBM gave mechanistic insight

PSD variation informed the safe space

PSD variation → Validated PBBM + VBE simulations → Predicted in vivo consequences

Simulations guided the safe space without additional clinical studies.

3 Variant data formed an IVIVR foundation

Existing development data linked in vitro to in vivo

In vitro dissolution across PSD variants + VBE outcomes → In vitro-in vivo relationship

Analogous to using pilot BE data generated during routine development.

4 QC dissolution was biodiscriminating

The method distinguished batches by BE outcome

QC dissolution method → BE-passing / BE-failing → Lifecycle management tool

Biodiscrimination supports durable lifecycle management.

Lifecycle Management: Sustaining Patient-Centric Quality

- **A validated biodiscriminating QC dissolution method may be a durable lifecycle asset:**
  - Science-based assessment of post-approval changes: scale-up, site transfer, excipient changes, process parameter changes
  - May reduce the need for new BE studies for many changes within the established safe space

- **The bioequivalence safe space:**
  - Defines formulation/process variability boundaries within which BE is assured by in vitro data alone
  - Established through IVIVR, PBBM, or both — proportionate to the product's risk tier

- **Risk reclassification as evidence accumulates:**
  - Post-approval dissolution, stability, and real-world data may support risk downgrading
  - Reclassification may expand the scope of changes supportable by in vitro data alone

Scientific Opportunities and Future Directions

Research Priorities

- Biorelevant dissolution method development for medium and high risk generic drug substances
- PBBM validation approaches for enabling technology formulations (ASDs, lipid-based, nanoparticles)

Open Scientific Questions — We Hope to Hear from the Generic Industry

① How to use publicly available data for risk assessment in the ANDA development context

② Can existing development data (in vitro profiles, PBBM, pilot BE outcomes) establish an IVIVR for generic products?

③ What challenges specific to the generic sector does the framework not yet adequately address?

④ How can industry, FDA, and academia collaborate to advance and validate the framework for generic applications?

We commit

❖ Seek and incorporate generic industry input into framework implementation

❖ Continue to engage the generic industry through workshops and bilateral scientific discussions

❖ Expand research to facilitate the implementation of the framework

❖ Advance global harmonization through ICH M9 and ICH M15

Thank You

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