U.S. FOOD & DRUG ADMINISTRATION

Defining and Managing Medium-Risk Drug Products
Within the Risk-Based Biopharmaceutics Framework

An FDA Perspective

Hailing Zhang, Ph.D.
Division Director, DPQA XII, OPQA II | US FDA
April 30, 2026

M-CERSI Workshop: The Evolution of Biopharmaceutics: Risk Assessment and Clinical Relevance
April 30 – May 1, 2026
Rockville, MD

Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Overview

Context and Framework

The evolution toward predictive dissolution and the five-tier Biopharmaceutics Risk Assessment Framework.

Defining Medium Risk

The scientific drivers isolating medium-risk products: pH dependency, bile salts, and food effects.

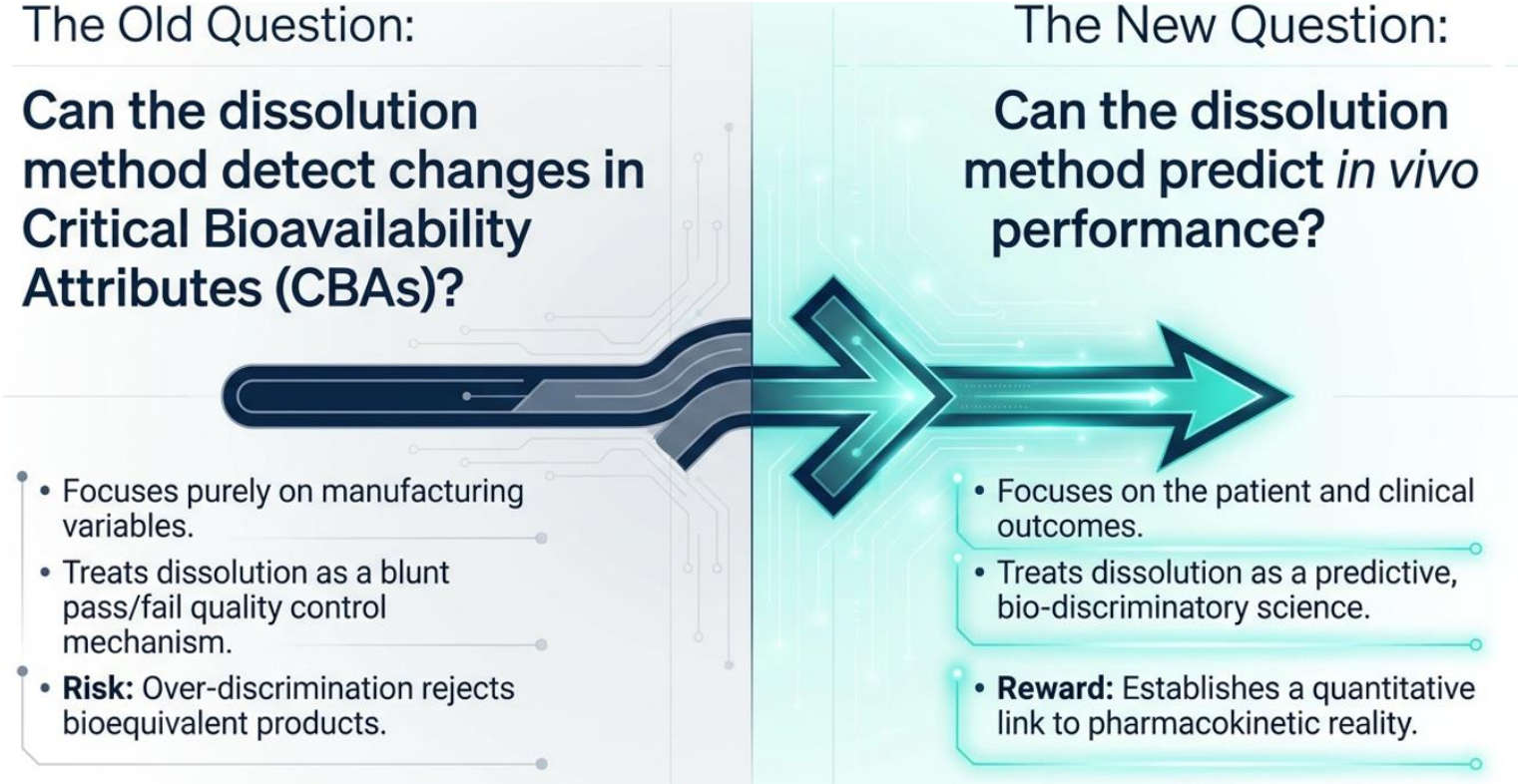
Managing Medium Risk

The regulatory toolkit: Biorelevant dissolution, PBBM validation, and defining the Bioequivalence Safe Space.

The Verazoline Fumarate Case Study

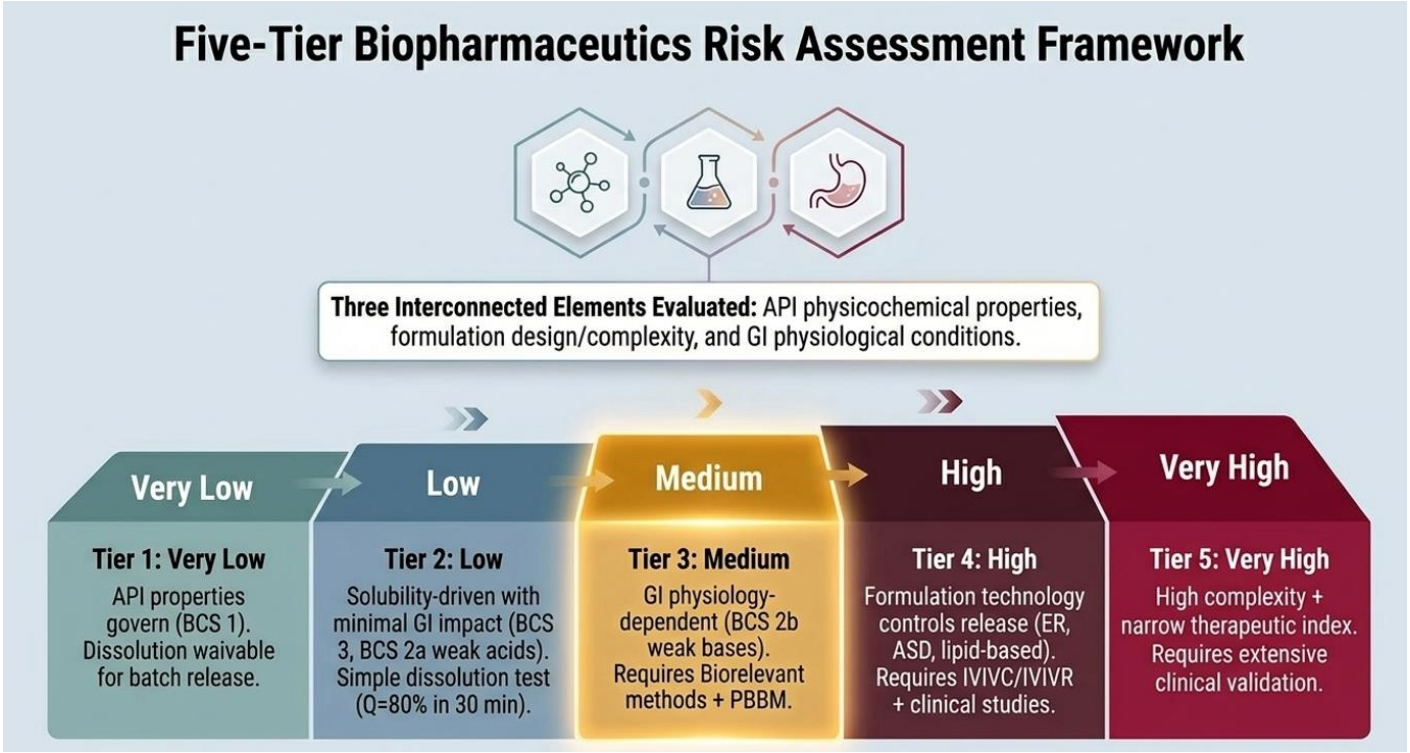
A start-to-finish hypothetical application proving the regulatory and lifecycle value of the framework.

Dissolution Test – From QC to Biodiscriminating



The Biopharmaceutics Risk Assessment Framework

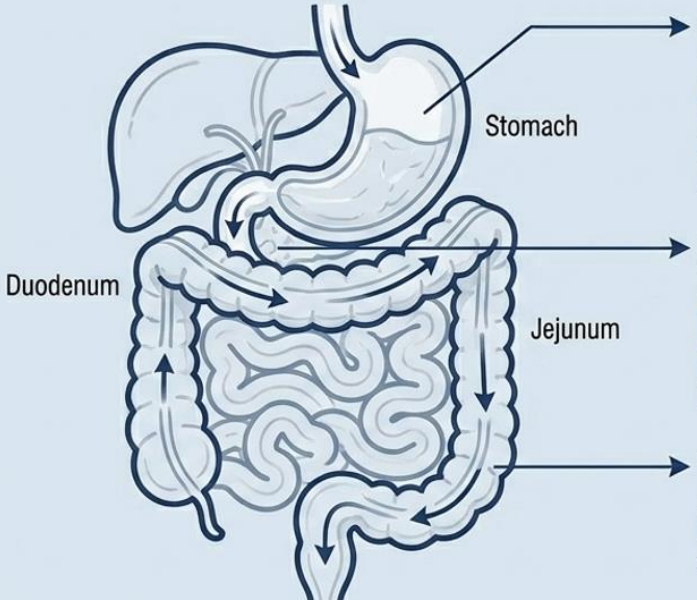
- A Structured Framework for Linking Dissolution to Clinical Performance



Defining Medium Risk Products

The Scientific Basis

In vivo dissolution is significantly impacted by GI variability. Permeability is high/moderate—if dissolution is controlled, absorption will follow.



Gastric pH
Fasted: 1.2–2.5
Fed: 3.0–5.0
Delays dissolution of weak bases in the stomach.

Intestinal Bile Salts
Fasted: 3–5 mM
Fed: 10–15 mM
Primary solubilization mechanism for lipophilic drugs.

Transit/Emptying
Slower gastric emptying and intestinal transit in the fed state alters the absorption window.

Primary Product Categories

- Weakly basic BCS Class 2b drugs (pKa 6–10)
- Lipophilic drugs dependent on bile salts
- Drugs with clinically meaningful food effects

Where Does Medium Risk Begin and End?

	Low Risk	Medium Risk	High Risk
BCS class	BCS3 or 2a (weak Acid)	BCS 2b or lipophilic BCS 2	BCS 4 with enabling tech or ER
Solubility	High at intestinal pH	pH –dependent (Low at intestinal pH)	Low (formulation –dependent)
Permeability	Low (rate-limiting)	High/Moderate	High/Moderate
GI pH Impact	Minimal GI impact	Significant GI impact	Variable GI impact
Formulation Role	Minimal formulation role	Moderate formulation role	Dominant formulation role
Dissolution Method	Simple dissolution	Biorelevant Dissolution (+PBBM or IVIVR)	IVIVC/IVIVR
Clinical Data Needed	Minimal clinical data	1-2 studies (Food effect, BA etc.)	Clinical studies with 3-4 formulation variants

Decision Boundary: Dose GI Physiology meaningfully impact absorption?

Decision Boundary: Does the formulation technology itself dictate bioavailability?

The Mechanistic Drivers of Medium Risk - pH and Bile Salts

pH-Dependent Solubility

Weak Bases: Highly soluble in acidic gastric conditions, but solubility drops significantly as drug transits to intestinal pH.

- High risk of precipitation in the intestine.
- Solubility varies 100–1,000-fold across GI.

Bile Salt Solubilization

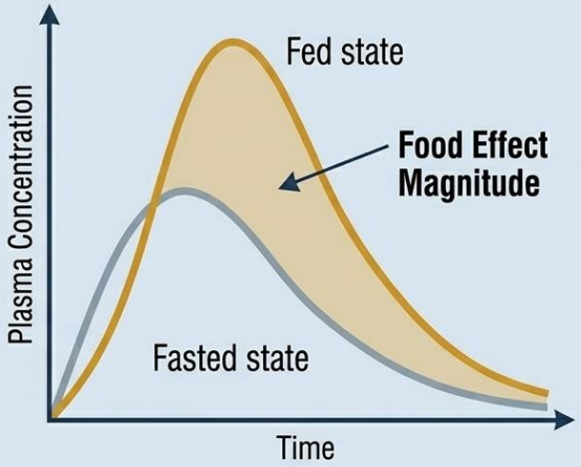
Lipophilic Drugs: Mixed micelles solubilize drugs in the lumen. Bile salts vary 3–10x between fasted and fed states.

- Primary mechanism for intestinal dissolution.
- Captured by FaSSIF/FeSSIF.

Food Effects

- A Clinical Signal of Medium-Risk Behavior

Why Food Effects Signal Medium Risk

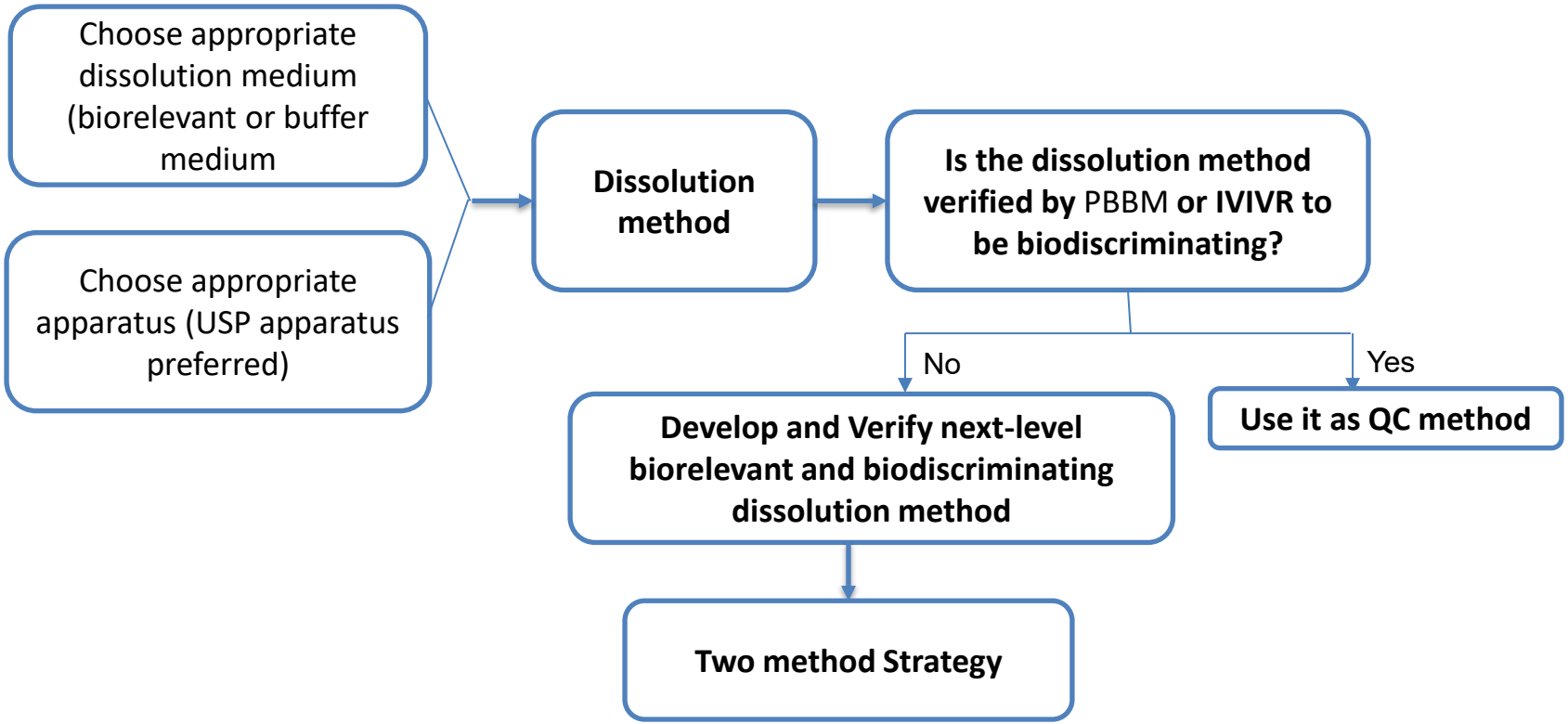


- The fed state alters multiple parameters at once (pH increases, bile salts surge 3-10x, emptying slows).

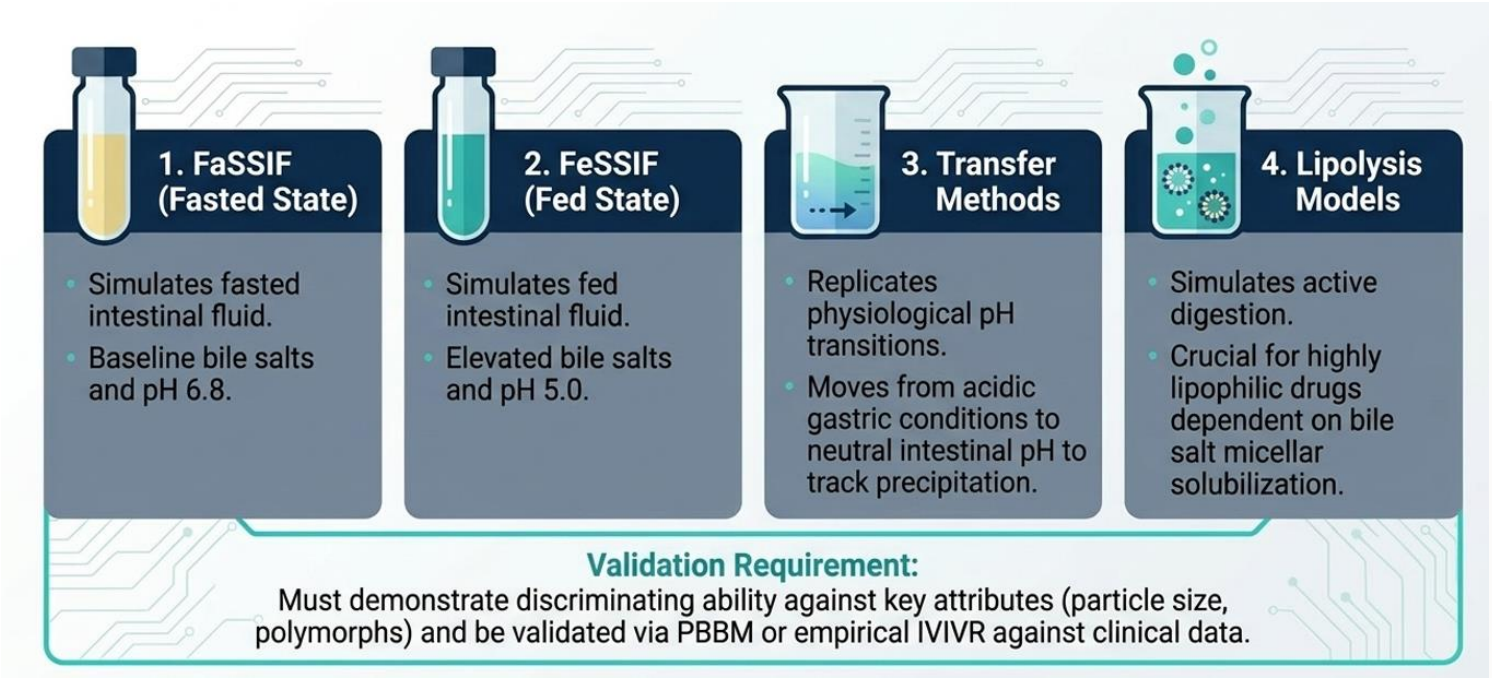
Magnitude as a Risk Indicator
<20% AUC change: Minimal (leans Low Risk)
20–50% AUC change: Moderate (Consistent with Medium Risk)
>50% AUC change: Large (Strong Medium-Risk indicator; PBBM essential)
>100% AUC change: Very large (Consider High Risk; complex interactions)

Regulatory Implication
A clinically meaningful food effect triggers the need for biorelevant dissolution (FeSSIF) and PBBM to capture in vivo variability.

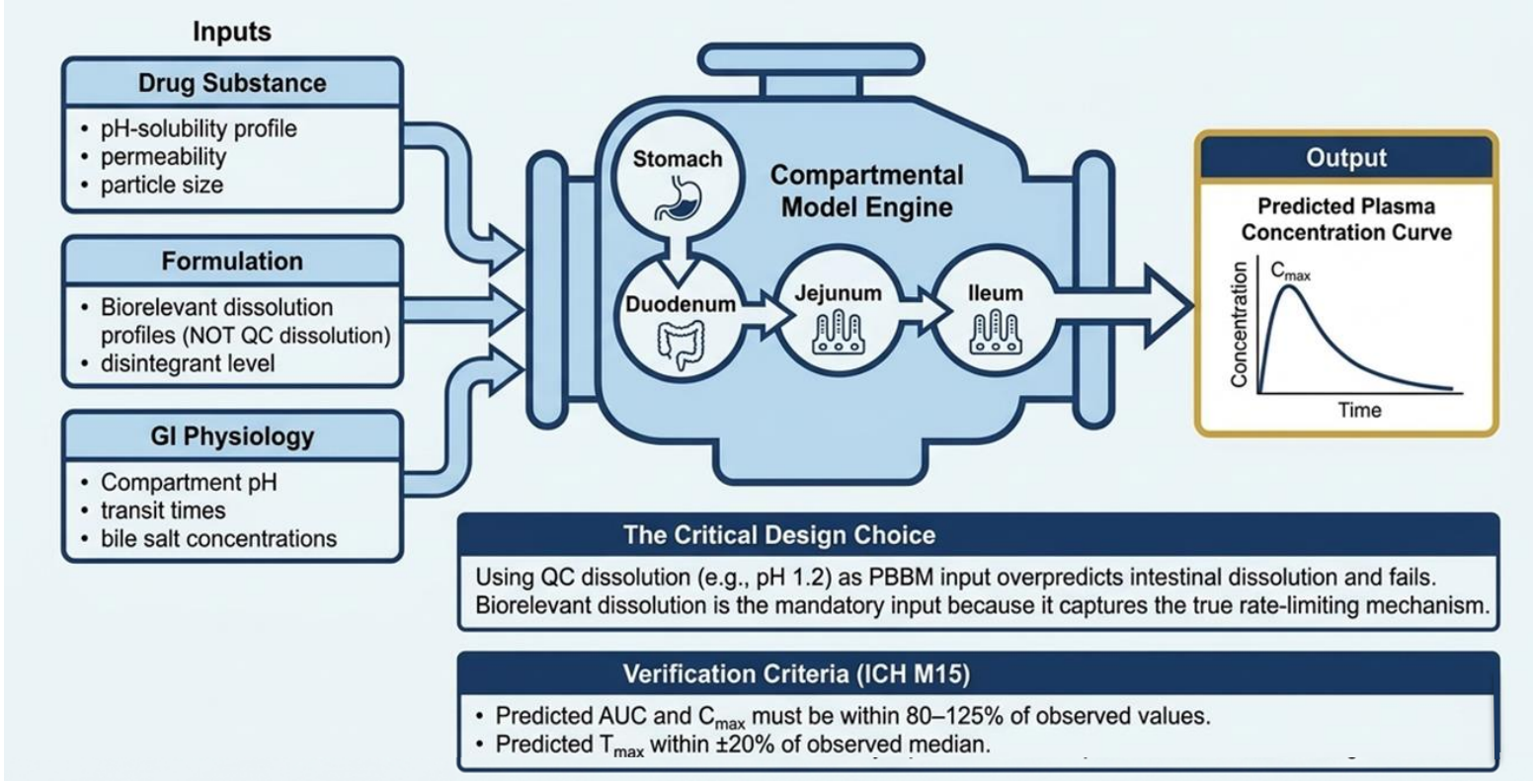
Managing Medium Risk



Managing Medium Risk: Biorelevant Dissolution- Capturing GI Physiology In Vitro



Managing Medium Risk: PBBM to Validate in Vitro-in Vivo Link



Managing Medium Risk: Define the Safe Space

From Validation to Specification

- **External Validation:** Ensures the model predicts outcomes accurately beyond the training set.
- **Virtual BE Trials:** Simulating profiles across manufacturing variability ranges.
- **Safe Space Definition:** Identifying the dissolution range guaranteeing BE.
- **Clinically Relevant Specs:** Set with a clear margin above the "failure edge".

Managing Medium Risk: IVIVR to Validate in Vitro-in Vivo Link

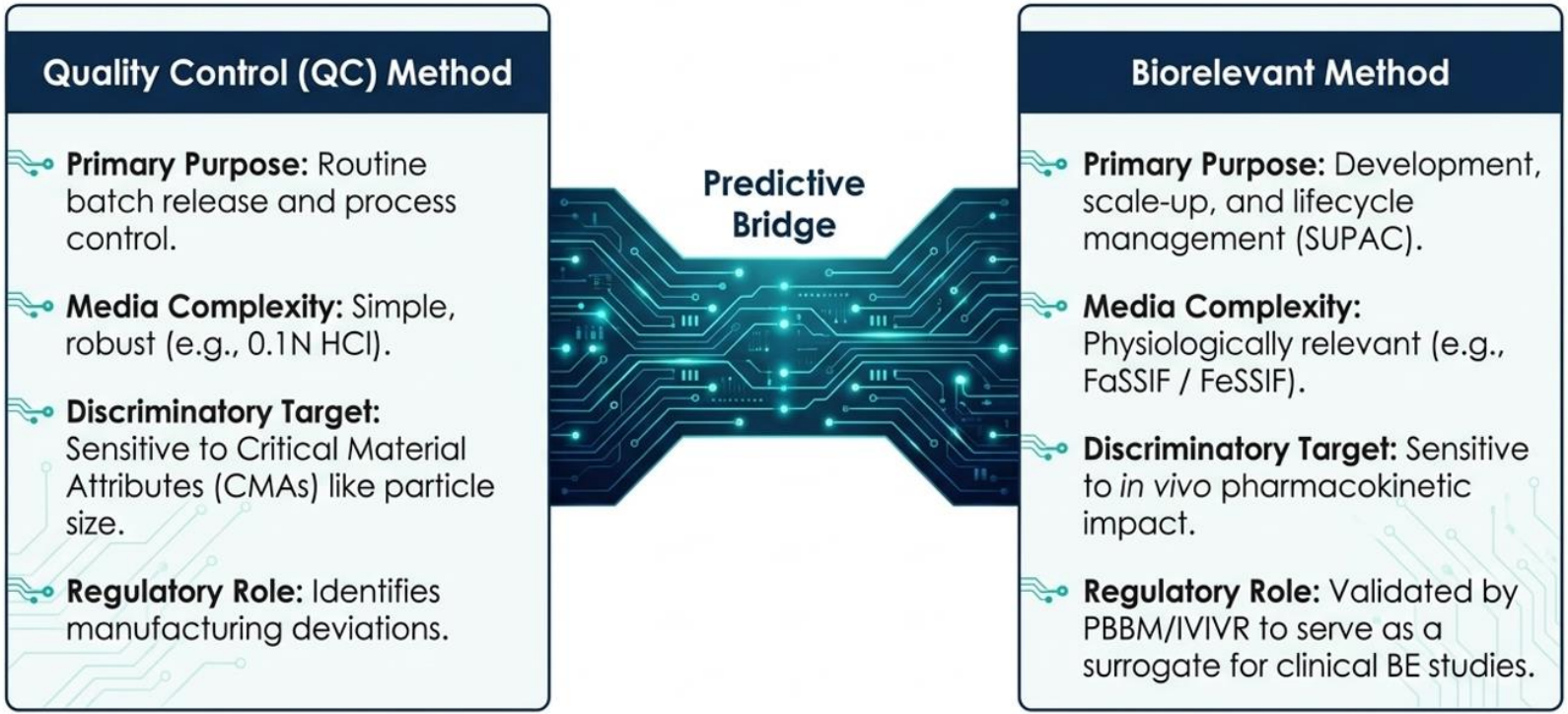
- *Clinical BE studies with formulation variants*
- *Demonstrates rank-order or quantitative relationship*
- *Consistent correlation between dissolution and BE outcomes*
- *Defines safe space*

Post-Approval Changes Supported by Biorelevant Method + PBBM

	Traditional Requirement	New PBBM-Enabled Pathway
API Particle Size Widening	Clinical BE study	Biowaiver if within safe space ✅
Manufacturing Site Transfer	Clinical BE study	Biowaiver if dissolution comparable ✅
Formulation/Composition Changes	Clinical BE study	Biowaiver if within safe space ✅
OOS Dissolution Investigation	Batch rejection/clinical study	PBBM virtual BE assessment ✅

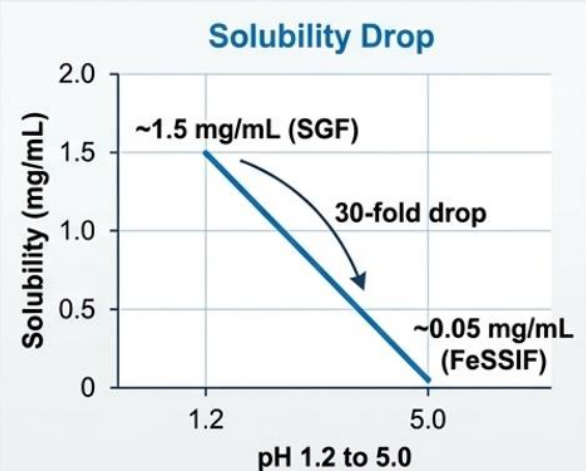
Risk Reclassification
If the PBBM-defined safe space is exceptionally wide, totality of evidence may support a formal downgrade from Medium to Low risk, further simplifying future lifecycle requirements.

Managing Medium Risk: the Two-Method Control Strategy



Case Study

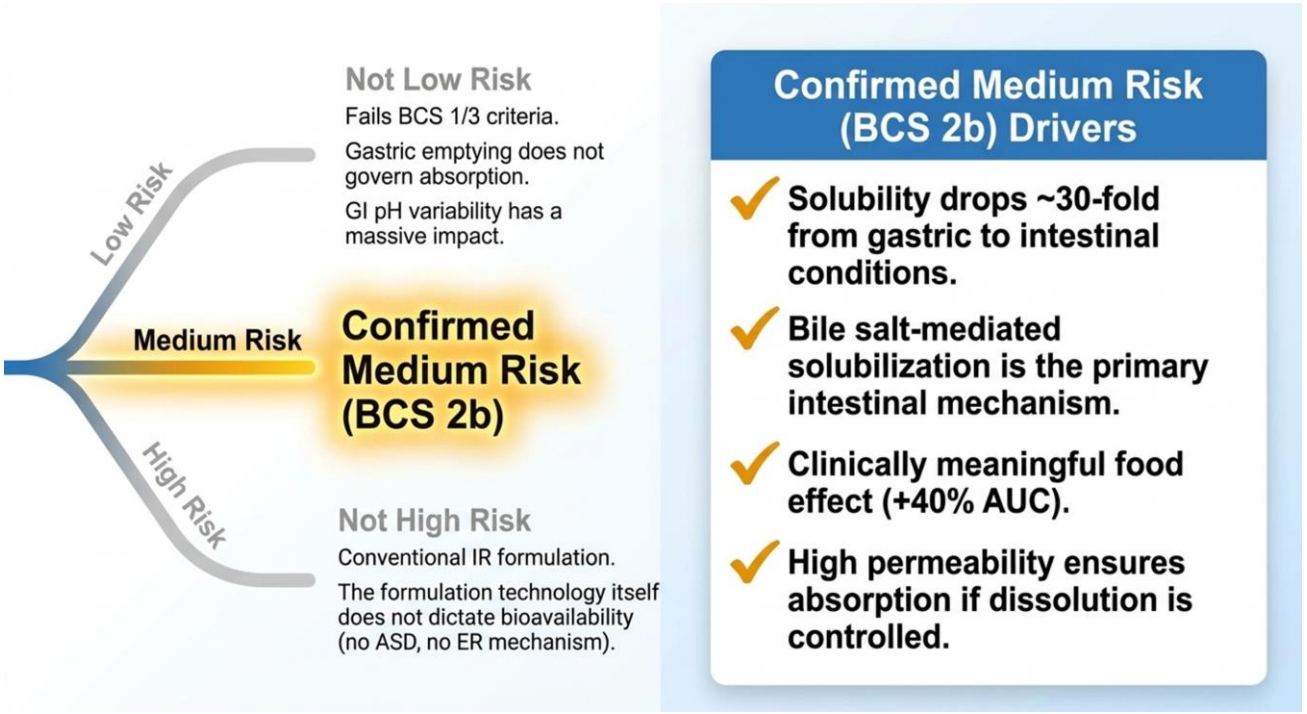
Verazoline Fumarate (VZF) – a **hypothetical** antimicrobial drug



Case Study Introduction	
Dosage:	Immediate-release film-coated tablets (100 mg & 200 mg), oral, with food.
Manufacturing:	Conventional wet granulation.
Key Drug Properties	
BCS Class:	Class 2 (low solubility, high permeability).
Chemical Nature:	Weakly basic (pKa ~7.5) with LogP ~5.5.
Solubility Drop:	~1.5 mg/mL in SGF (pH 1.2) vs. ~0.05 mg/mL in FeSSIF (pH 5.0) — a ~30-fold drop.
Food Effect:	AUC increases ~40% under fed conditions.

Case Study

Verazoline Fumarate (VZF) – a **hypothetical** antimicrobial drug



Case Study

Verazoline Fumarate (VZF) – a hypothetical antimicrobial drug

The Standard QC Method: USP Apparatus II, 0.1N HCl (pH 1.2), 75 rpm.

- **Result:** Discriminates API particle size, but fails to reflect intestinal dissolution conditions.

Batch	QC Rank	In Vivo PK Rank
Batch A (Reference, 12 µm)	2nd	1st
Batch B (Test 1, 15 µm)	1st	2nd
Batch C (Test 2, 48 µm)	3rd	3rd

The Crisis: Stage 3 OOS Stability Lots

Lots VZF-Lot-S1 and VZF-Lot-S2 passed initial release but failed QC dissolution at Stage 3.

The Regulatory Question: Do these OOS results translate to a clinically meaningful loss of exposure?

Case Study

Verazoline Fumarate (VZF) – a **hypothetical** antimicrobial drug

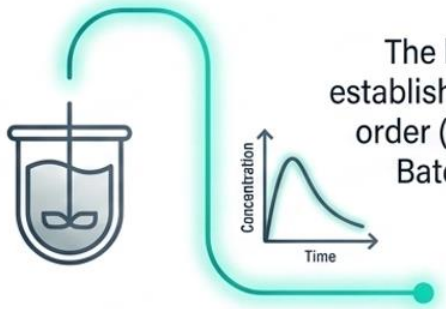
Developing the Biorelevant Solution

Screening the Media:

- ✗ **SGF (pH 1.2):** Gastric only. Does not match in vivo rank order. (Rejected)
- ✗ **FaSSIF (pH 6.8):** Fasted intestinal. Partial match. (Rejected)
- ✓ **FeSSIF (pH 5.0):** Fed intestinal. Captures bile-salt solubilization. Matches in vivo rank order perfectly. (Selected)

The Selected Biorelevant Method:

- USP Apparatus II, 900 mL FeSSIF (pH 5.0), 75 rpm.



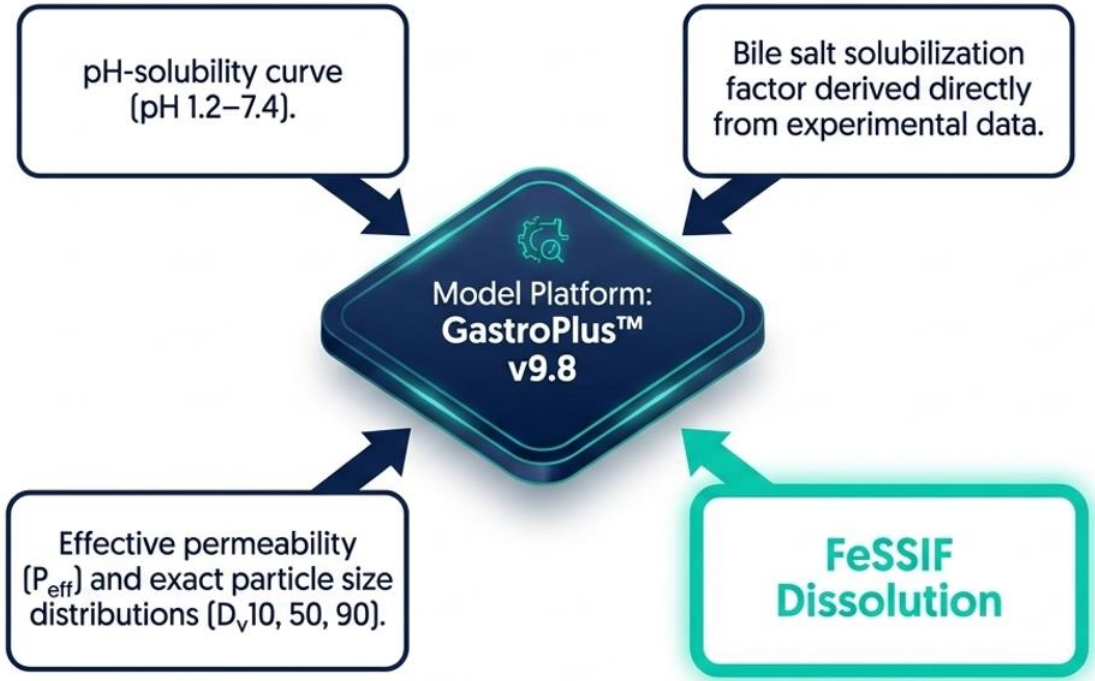
The Result:

The biorelevant method establishes the correct rank order (Batch A > Batch B > Batch C), proving it is a bio-predictive tool.

Case Study

Verazoline Fumarate (VZF) – a hypothetical antimicrobial drug

Constructing the VZF Mechanistic Model



The Critical Input Decision:

- Why FeSSIF instead of QC dissolution?
- Using the QC (pH 1.2) input would overpredict dissolution and **completely miss the rate-limiting step.**
- FeSSIF data mechanistically captures the bile salt-mediated solubilization that actually drives intestinal absorption.

Case Study

Verazoline Fumarate (VZF) – a hypothetical antimicrobial drug

Validating the Biopredictive Performance

Internal Verification
(Study VZF-C101 - Fed State)

Batch (Role)	Predicted AUC Ratio	Predicted Cmax Ratio
Batch A (Reference):	0.97	0.96
Batch B (Test 1):	1.04	1.04
Batch C (Test 2):	1.04	1.06

Result: All predicted ratios for all batches fall comfortably within the 80–125% acceptance window.

External Validation
(Study VZF-C102 - Food Effect)

- The model successfully predicted the ~40% AUC increase under fed vs. fasted conditions.
- Accurately predicted the delayed T_{max} and reduced PK variability under fed conditions.
- **Crucial Detail**: The model was NOT re-fitted to this dataset. This constitutes true external validation.

Case Study

Verazoline Fumarate (VZF) – a hypothetical antimicrobial drug

The Virtual Trial Design:

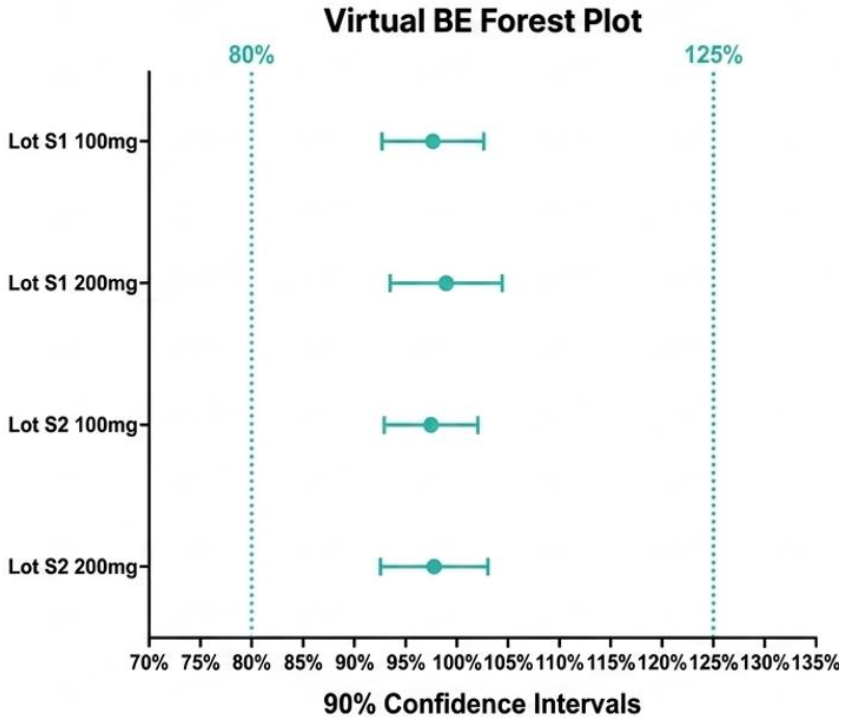
- 10 virtual crossover trials × 30 subjects each (Fed state conditions).
- Reference: VZF-Lot-Reference vs. Test: VZF-Lot-S1 & VZF-Lot-S2.

The Results:

- Despite failing the pH 1.2 QC test, the slower dissolution in the biorelevant method did not translate to an in vivo failure.
- Predicted AUC Ratios: 0.95 to 0.97.
- Predicted C_{max} Ratios: 0.93 to 0.95.

The Regulatory Conclusion:

The OOS batches are bioequivalent. There is no clinical risk, and no new clinical study is required.



Case Study

Verazoline Fumarate (VZF) – a hypothetical antimicrobial drug

Unlocking Regulatory Flexibility via Biowaivers

Post-Approval Changes Supported by the Safe Space:

API Particle Size Widening (e.g., Dv90 up to 60 µm)	✓ **Evidence:** Biorelevant dissolution remains within safe space + PBBM validation.
Manufacturing Site Transfer	✓ **Evidence:** Biorelevant dissolution comparison against the reference + PBBM.
Batch Scale-Up (10x)	✓ **Evidence:** Biorelevant dissolution profiles remain within the safe space.
Disintegrant Level Changes (±15%)	✓ **Evidence:** Biorelevant dissolution profiles remain within the safe space.
Stability OOS Investigations	✓ **Evidence:** PBBM Virtual BE trials proving lack of clinical impact.

Summary

- *Define medium risk products – demand understanding of GI physiology impact on in vivo dissolution;*
- *Dissolution method –verified by PBBM or IVIVR to be biodiscriminating*
- *Invest PBBM- mechanistic modeling transform biorelevant dissolution from a laboratory exercise into a powerful regulatory tool.*

Acknowledgement

Dr. Bhagwant Rege, Division Director, DPQA VI, OPQA I, OPQ, CDER, FDA

Dr Xiaoming Xu, Division Director, DPQR V, OPQR, OPQ, CDER, FDA

Dr. Ahmed Zidan, Senior Pharmacologist, DPQR V, OPQR, OPQ, CDER, FDA