Session 3: Medium Risk Drug Products

Using Biopharmaceutics Tools to Understand, Manage, and Mitigate Risk

A shift from descriptive laboratory testing to mechanistically informed control strategies.

James Mann
Predictive Dissolution

The Tool: Discriminating and predictive in vitro dissolution methods.

The Value: Links laboratory testing directly to in vivo performance to support robust risk mitigation and challenge failure modes.

Dorota Danielak
Physiological Variability

The Tool: Mechanistic in vitro testing combined with advanced modeling.

The Value: Captures dynamic GI factors (gastric emptying, motility, pH shifts) to actively de-risk development.

Emilija Fredro-Kumbaradzi
Generic Industry Integration

The Tool: Totality-of-evidence approach (API controls, dissolution, and modeling).

The Value: Synthesizes material attributes and formulation data into a cohesive package to assess medium-risk concerns.

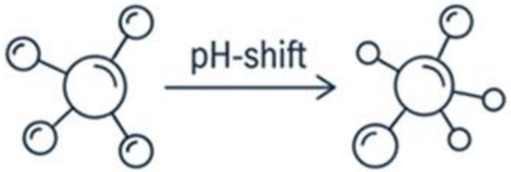
Hailing Zhang
Regulatory Framework

The Tool: Bio-discriminatory dissolution and PBBM/IVIVR models.

The Value: Establishes a structured pathway to define, manage, and regulate medium-risk products through predictive science.

Medium Risk is a Dynamic Interaction, Not a Single Archetype

Classical Mechanisms



- pH-dependent solubility
- Precipitation risk
- Bile-mediated solubilization

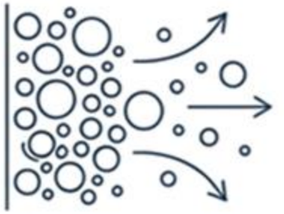
Medium Risk (Tier 3)

Risk is defined by how drug properties meaningfully interact with GI physiology—not merely by product type.

Dynamic GI Factors

- Gastric emptying variability
- Motility patterns
- Transient physiological pH conditions

Material & Process Attributes

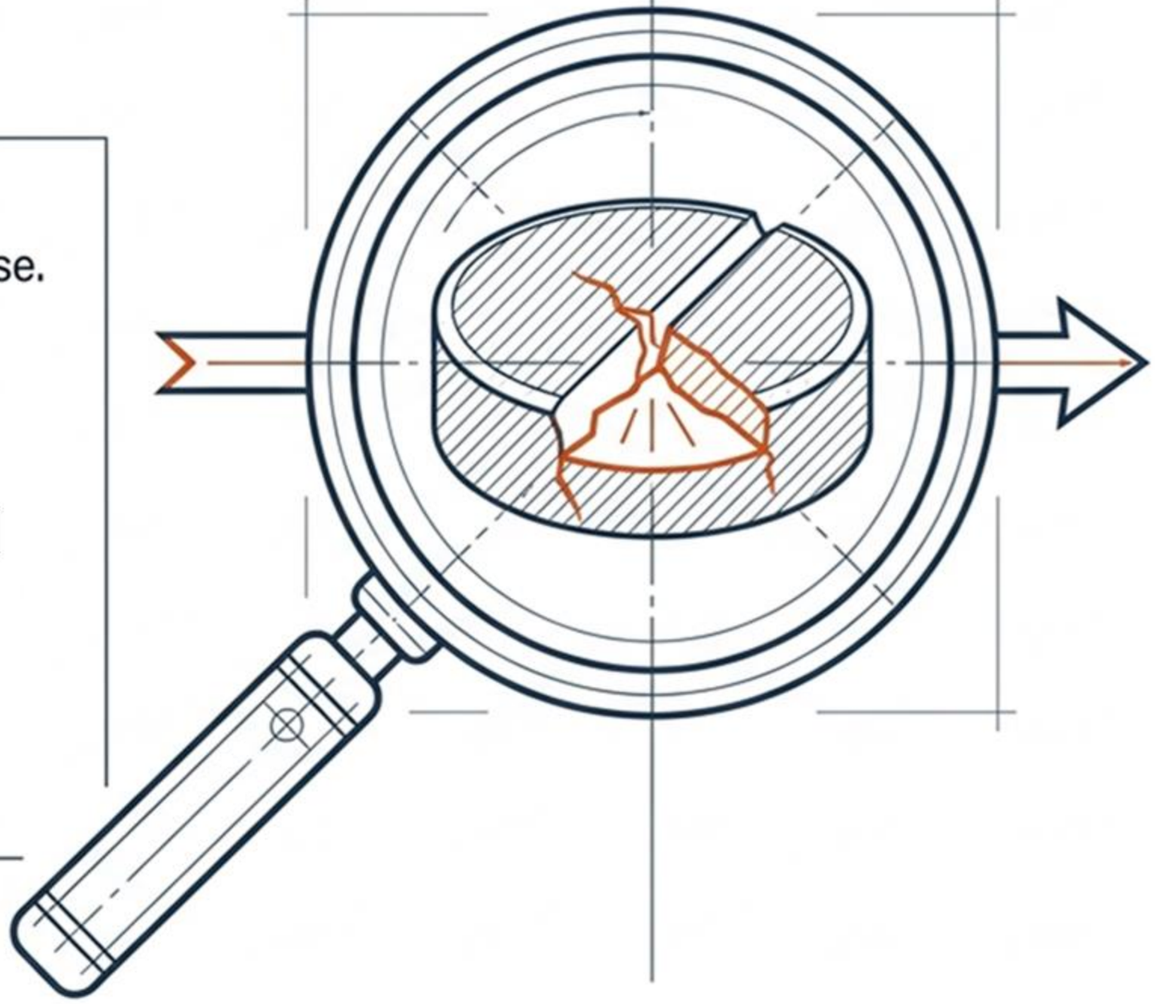


- API particle size distributions
- Formulation-process interactions

Dissolution Evolves into a Mechanistic Decision Tool

From: Descriptive Laboratory Tool

- Conventional quality control and batch release.
- Passive comparison of baseline formulations.
- Focus on standard compliance metrics.



To: Mechanistic Decision Tool

- Identifying critical physiological factors and formulation interactions.
- Actively probing product robustness and challenging failure modes.
- Supporting the establishment of Clinically Relevant Dissolution Specifications (CRDS).

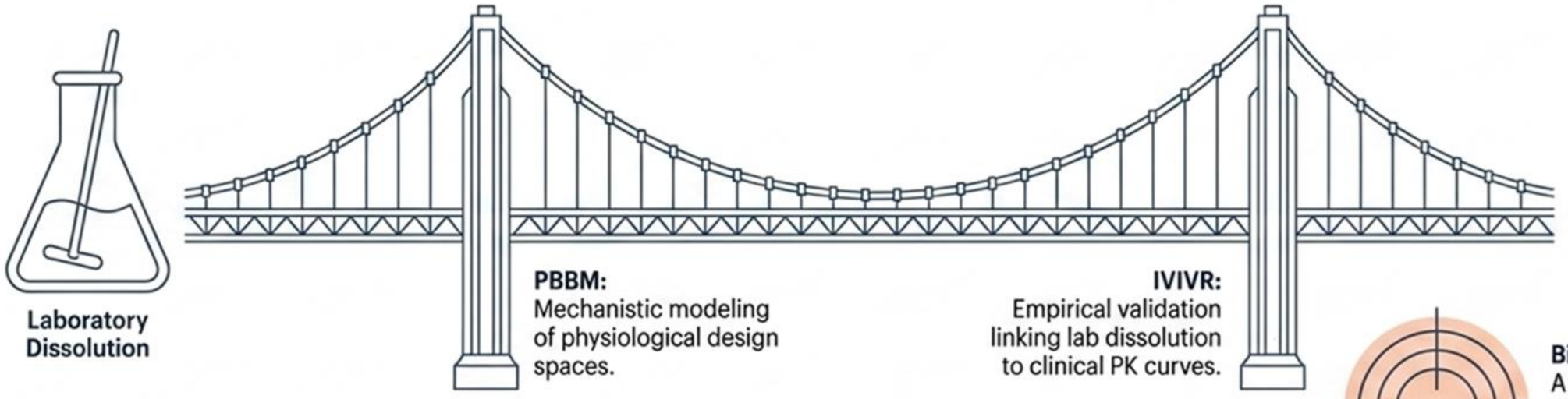
PBBM and IVIVR Construct the Biopredictive Bridge

Biorelevance

Mimicking physiological conditions (pH, bile salts). Necessary, but insufficient alone.

Biopredictivity

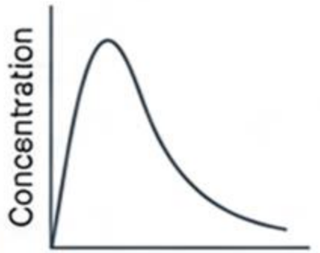
Validating in vitro methods against in vivo performance through mechanistic or empirical links.



Laboratory Dissolution

PBBM: Mechanistic modeling of physiological design spaces.

IVIVR: Empirical validation linking lab dissolution to clinical PK curves.



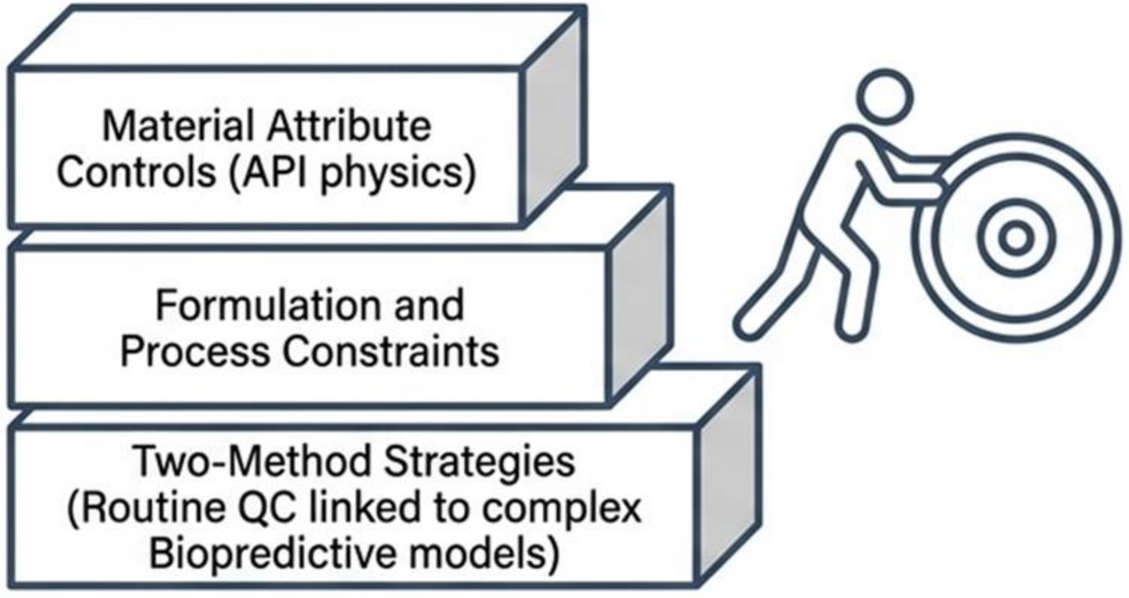
Clinical PK Curves

Bioequivalence Safe Space: A validated range of dissolution profiles within which clinical bioequivalence is mathematically assured.

Active Risk Mitigation Through Integrated Control Strategies

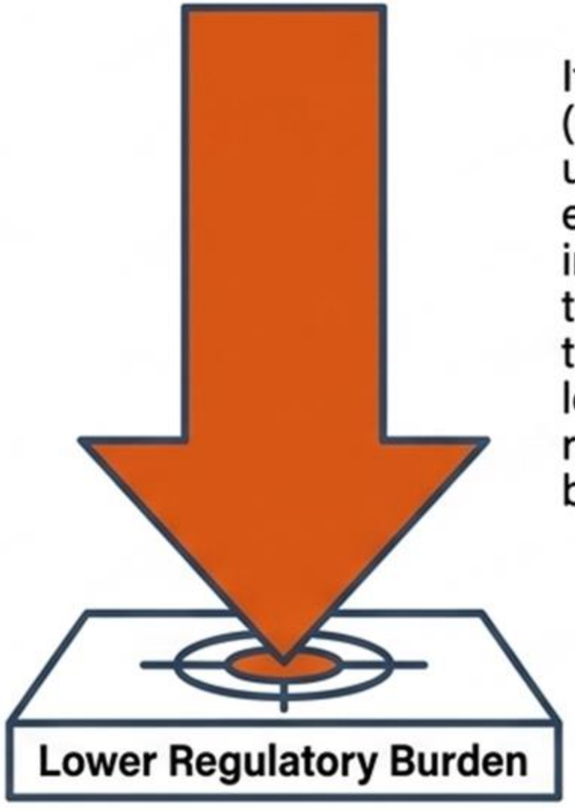
The Paradigm Shift: Moving from asking "What dissolution method?" to "What combination of tools provides assurance?"

Multi-Layered Control Framework



The "Serious Effort" Mandate:
Regulatory confidence requires generating genuine scientific insight that ensures bioperformance, rather than merely passing a standardized quality control test.

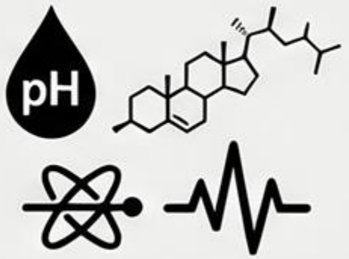
The Risk Downgrading Pathway



If a sponsor demonstrates (through deep mechanistic understanding and integrated evidence) that a product is insensitive to GI variability, the medium-risk status can transition to a lower, less-stringent regulatory tier, reducing post-approval burden.

FIVE KEY TAKE-HOME MESSAGES

Mechanistic Diversity



Medium risk represents multiple pathways (pH, bile, motility), not a single product class

Dissolution as a Decision Tool

Evolving from a descriptive laboratory tool to a mechanistically informed performance indicator

Predictive Bridges

Using PBBM and IVIVR to validate the clinical relevance of in vitro methods.

Integrated Control

Dissolution serves as one part of a broader strategy including material and process controls.

Proactive Risk Reduction

Stronger scientific understanding helps shift behavior from risk-aversion to active bioperformance management

THE CLOSING VISION

Value-Driven Framework

The framework's real value lies in managing, mitigating, and reducing bioperformance risk.

Foundation for Action

This summary provides the basis for breakout discussions on differentiation and control strategies.