From Policy Direction to Evidence Path: Applying Biopharmaceutics Risk Assessment in Regulatory Review

Integrating product performance risk and evidence expectations for solid oral dosage forms

Rebecca Moody, PhD| Pharmaceutical Scientist, OPQAII, OPQ, CDER, FDA

Disclaimer

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

Important Limitations and Scientific Boundaries

1. This is a conceptual regulatory science proposal, not an official policy statement.
2. The framework guides judgement; it does not replace product-specific expert evaluation. Not all products fit neatly into discrete tiers.
3. It is recommended that model informed approaches (e.g., PBBM) be fit-for-purpose, with justified assumptions and robust sensitivity analyses.
4. It is designed to complement existing guidances (ICH M9/M13/M15, PBBM, ICH Q6/8/9/10, ICH Q12, etc.) but also be flexible for future advancements.

From Policy to Evidentiary Practice

How dissolution evidence supports regulatory decisions

Policy direction

Dissolution should be **fit for the regulatory decision** it supports.

Evidence question

What evidence shows that a method **appropriately reflects *in vivo* behavior?**

Focus of this talk

- Biopharmaceutics risk assessment
- Totality of evidence for clinically relevant dissolution
- Practical considerations for submission packages

Day 1 Recap:
Predictive Dissolution is Risk-Based

- Product risk is driven by
  - API properties
  - GI physiology
  - Formulation / release complexity
- Risk spans **very low** → **very high**
- Evidentiary need rises with risk
- **Goal:** dissolution should help distinguish clinically acceptable vs. clinically unacceptable performance
- Today's focus: **how a reviewer applies that framework**

Biopharmaceutics Risk-to-Evidence Review Pathway

Applying risk assessment tools to guide proportionate regulatory evidence decisions

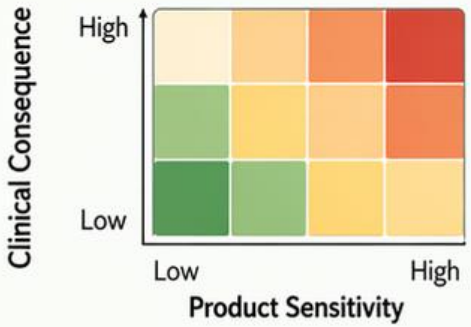
1 Identify Risk

Logic (Tree)

Determines whether a meaningful risk exists and directs the review pathway.

2 Diagnose Severity

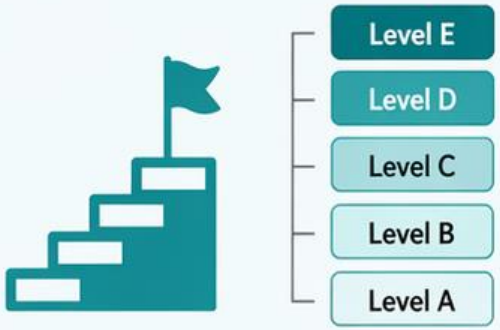
Placement (Matrix)



Assesses severity based on clinical consequence and product sensitivity.

3 Assign Evidence Tier

Requirement (Ladder)



Defines the proportionate level of evidence needed to answer the regulatory question.

Outcome

Predictable Review Logic

Consistent, transparent, science-based decisions.

Cross-Disciplinary Unity

Better alignment across CMC, biopharmaceutics, and clinical pharmacology.

Risk drives the depth of evidence.

Right evidence. Right amount. Right decision.

Reviewer Workflow for Applying the Framework

1

Define the regulatory context

The First Reviewer Question: What Decision Is This Test Supporting?

- Release specification?
- Initial approval / formulation justification?
- Additional-strength bridging?
- Postapproval change?
- Investigation / root cause?
- Potential waiver or reduction of in vivo work?

Same science, different evidentiary threshold

Reviewer Workflow for Applying the Framework

2

Assign preliminary product risk

Drug Substance
- Solubility limits
- Permeability
- Dissolution-rate limitation
- Precipitation risk
- Absorption window

Drug Product
- Formulation complexity
- Release-controlling excipients
- Particle size dependence
- Matrix/coating sensitivity

Clinical Consequence
- Narrow Therapeutic Index (NTI)
- Steep exposure-response
- Early exposure sensitivity
- Dose dumping

Bridging/Change
- Magnitude of formulation/process change
- Clinical-to-commercial drift
- Scale/site impact

Reviewer Workflow for Applying the Framework

3

Determine Evidence Required

- **Product risk** sets the scientific starting point
- **Decision consequence** sets tolerance for uncertainty
- **Residual uncertainty** determines whether more evidence is needed
- Escalate only as far as necessary:
  - standard in vitro
  - biorelevant / physiologic in vitro
  - deliberate variants
  - targeted PK / BE
  - IVIVR / IVIVC
  - PBPK / PBBM / virtual BE, where fit for purpose

Evidence Burden = Biopharmaceutic Risk × Decision Consequence × Residual Uncertainty

Reviewer Workflow for Applying the Framework

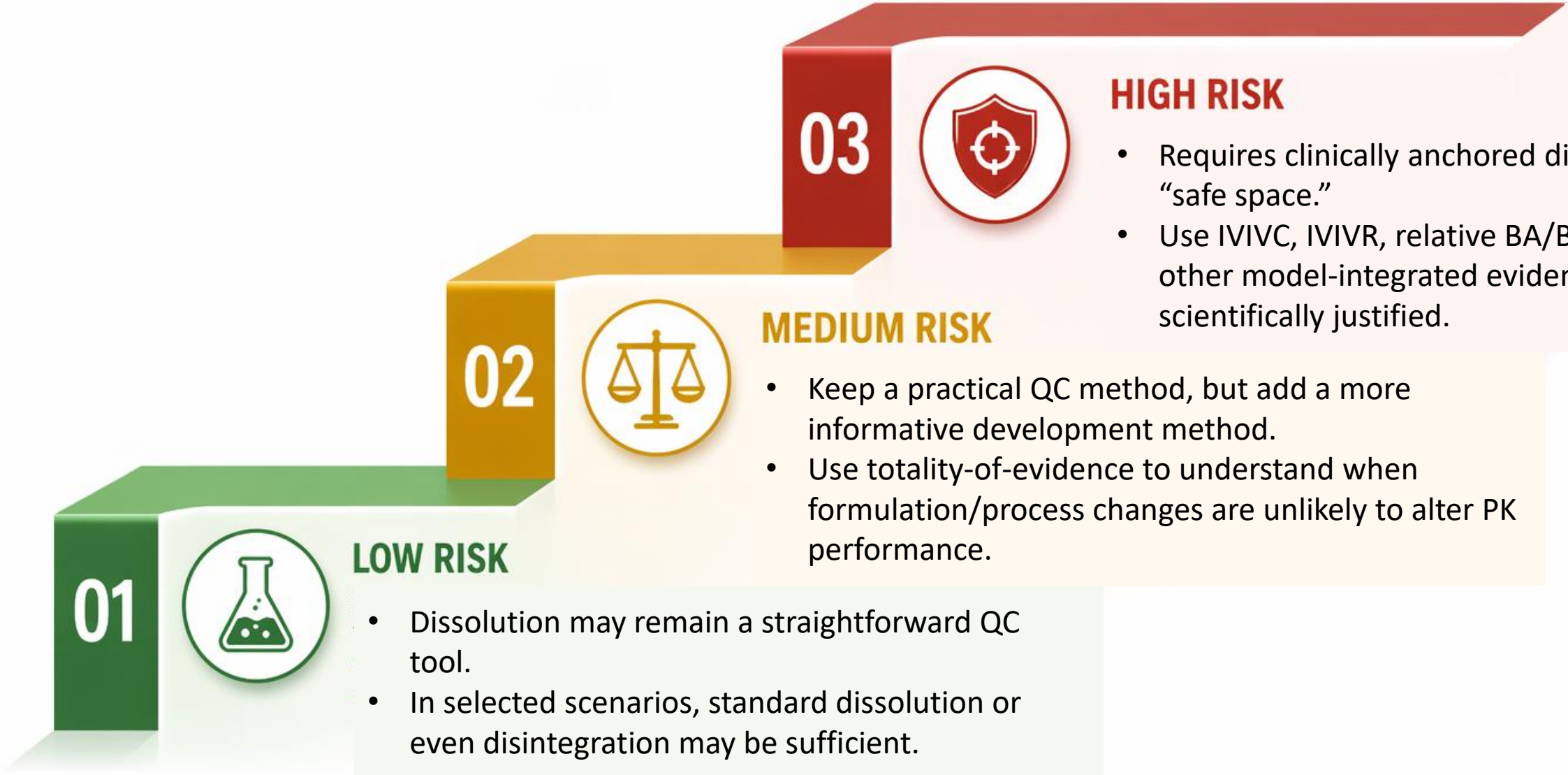
4

Assess the Dissolution Method

- Is the **medium / apparatus / hydrodynamic condition** scientifically justified?
- Does the method capture the mechanism expected to drive in vivo performance?
- Does it discriminate the **right changes**, not just any change?
- Were deliberate, interpretable variants studied?
- Is there a credible clinical or mechanistic bridge?
- Can the method support a clinically meaningful acceptance range?
- Avoid both:
  - **Overdiscriminating** methods
  - **Underdiscriminating** methods

Does the Dissolution Method Appropriately Reflect In Vivo Behavior?

Reviewer Expectations by Risk Tier



HIGH RISK

- Requires clinically anchored dissolution "safe space."
- Use IVIVC, IVIVR, relative BA/BE, PBBM, or other model-integrated evidence where scientifically justified.

MEDIUM RISK

- Keep a practical QC method, but add a more informative development method.
- Use totality-of-evidence to understand when formulation/process changes are unlikely to alter PK performance.

LOW RISK

- Dissolution may remain a straightforward QC tool.
- In selected scenarios, standard dissolution or even disintegration may be sufficient.

Totality of Evidence Supporting Clinically Relevant Dissolution

FDA

1 Empirical clinical anchors

- PK
- Relative BA/BE
- Food-effect studies
- Formulation-variant studies

2 In vitro / mechanistic anchors

- Biorelevant media
- pH-shift testing
- Physiologic conditions
- Informative variants

3 Model-informed anchors

- IVIVR / IVIVC
- PBPK / PBBM
- Virtual BE, where justified

4 Credibility elements

- Assumptions
- Sensitivity analyses
- Verification / validation
- Consequence of being wrong

Principle: No single evidence type is automatically sufficient.

Practical Considerations for Regulatory Submission Packages

Core framing

- Question of interest
- Risk tier and rationale
- Method purpose
- Mechanistic rationale
- Informative variants studied

Evidence and decision support

- Clinical or model anchor
- Uncertainty assessment
- Proposed acceptance range
- Lifecycle use case / claim supported

Organize the package so the review logic is easy to follow

Make the argument transparent and reviewable

A Fit-for-Purpose Dissolution Strategy Across the Lifecycle

Consider a 3-bucket framework:

- **QC / release control**
  - Main question: “Is the batch consistently manufactured?”
- **Development / mechanistic understanding**
  - Main question: “Which material, formulation, and process factors matter for in vivo performance?”
- **Regulatory bridging / surrogate use**
  - Main question: “Can dissolution plus supporting evidence reduce or replace additional in vivo work?”

The future is not necessarily QC versus clinically relevant dissolution; it is a fit-for-purpose toolkit.

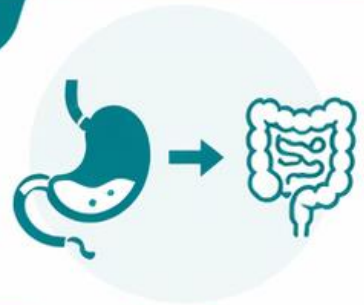
Regulatory submissions should tell the story of how dissolution was used to better understand the product and design clinically relevant control strategies, and how dissolution will be used to assure in vivo performance across product lifecycle.

Select the Dissolution Method Based on the Question and Intended Use

The goal is *not* to build the most complex dissolution method. The goal is to develop the right method for the right purpose and use PBBM to confirm clinical relevance.

Match tool complexity to decision need

1



Transfer-focused

Best for studying GI transfer behavior

Examples:
BioGIT, GIS,
USP 3/4 transfer methods

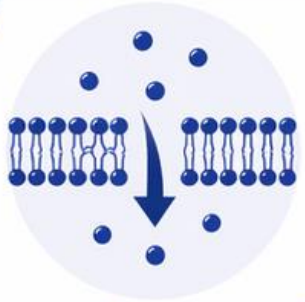
2

Mechanics-focused

Best for stress and mechanical effects

Examples:
StressTest, DOFTA,
GastroDuo, PhysioCell

3



Absorption-coupled

Best when dissolution and permeation interact

Examples:
Dissolution–permeation systems, AMI barriers, Diamod, Tiny-TIM applications

4

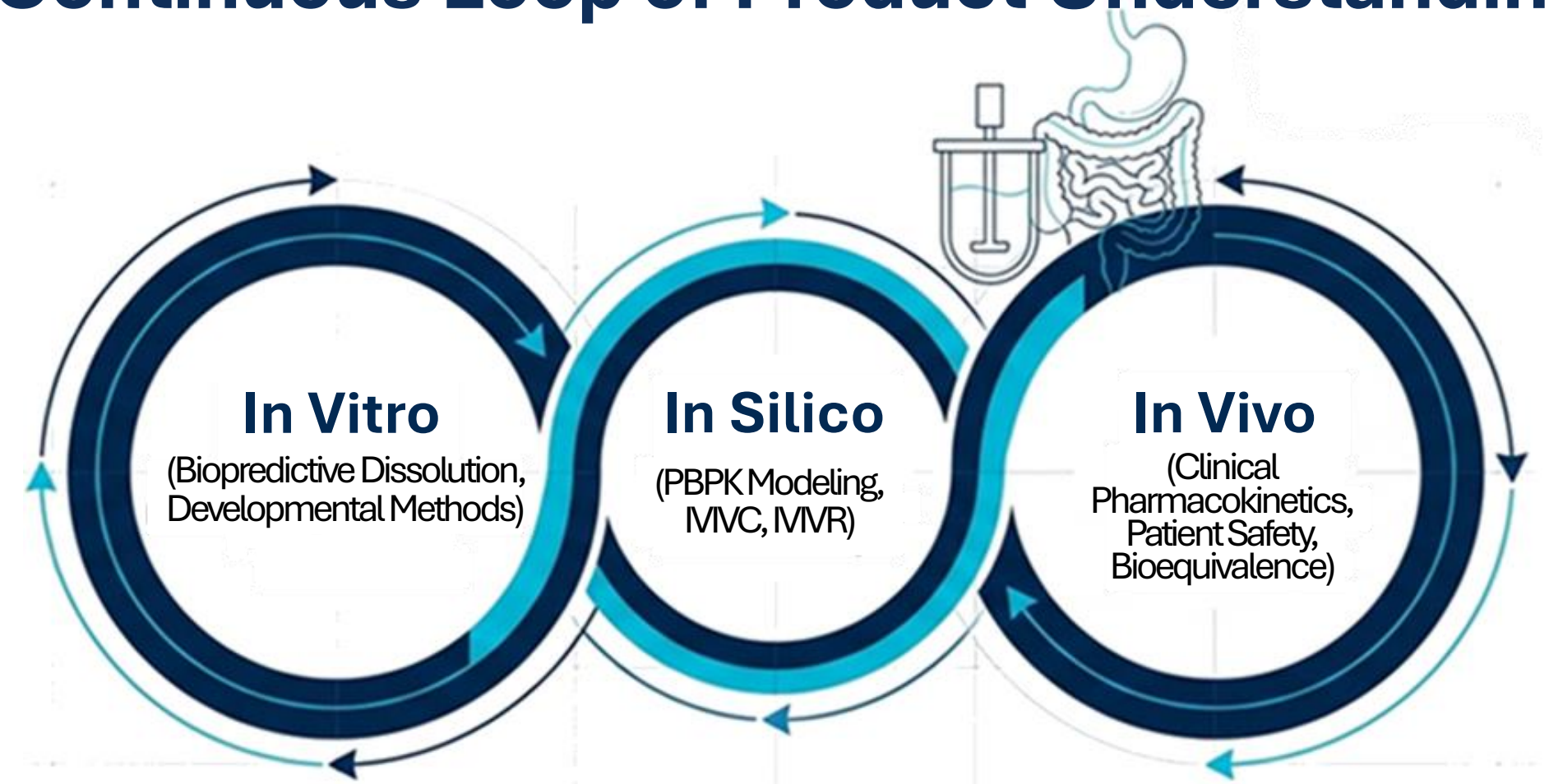
Region / event-specific

Best for localized GI or event-driven questions

Examples:
Biorelevant disintegration testers, oral cavity models, dynamic colon models

Ref: OrBiTo Decision Tree

The Continuous Loop of Product Understanding



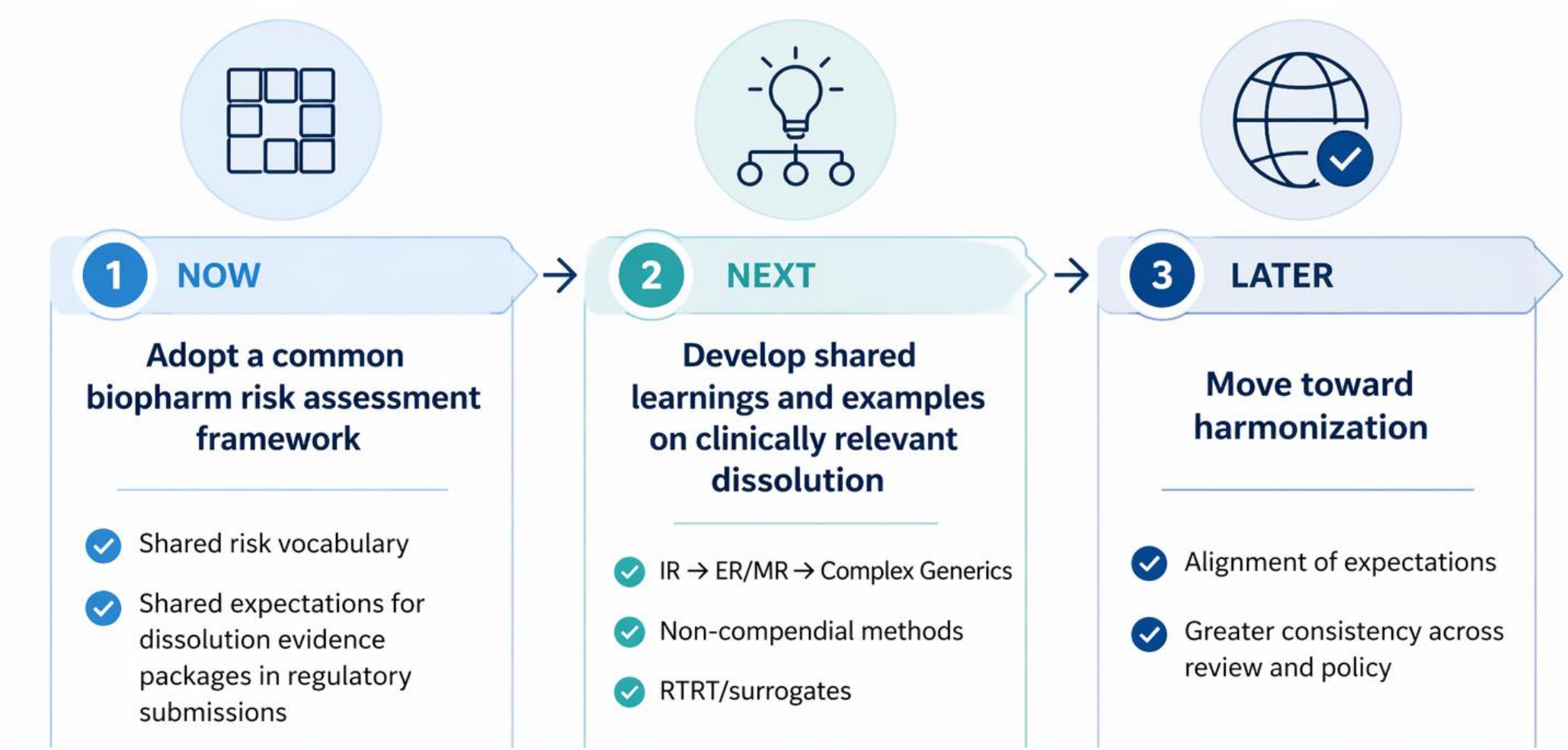
Dissolution is not merely an endpoint quality check. Choosing the right dissolution method as part of a Model-Informed Drug Development (MIDD) strategy, can make it a continuous feedback loop that bridges in vitro with clinical outcomes across the entire lifecycle of a drug.

Take-Home Messages

- Dissolution should be fit-for-purpose and may not be one-size-fits-all.
- *Defining question during assessment*: Does the method appropriately reflect in vivo behavior for the decision at hand?
  - The evidence path should be driven by:
    - Risk
    - Decision Consequence
    - Residual Uncertainty
- The end state is a globally convergent framework where stronger mechanistic understanding enables smarter specifications, fewer unnecessary in vivo studies, and more efficient lifecycle management.

Next Steps: How Do We Get There?

A phased approach to advance biopharm risk assessment and drive convergence

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