U.S. FOOD & DRUG ADMINISTRATION

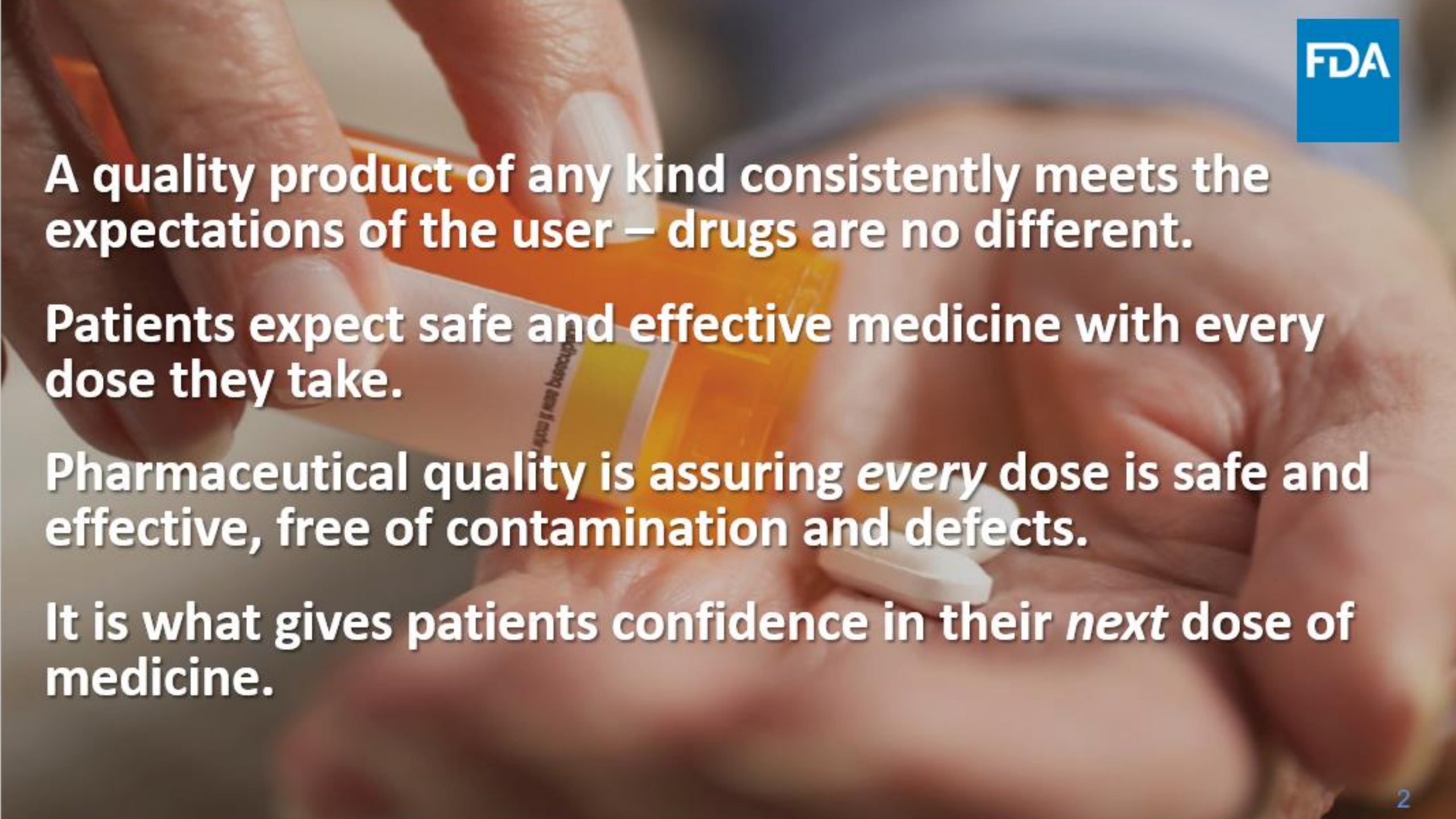
Risk-Based Release Testing for Low-Risk Products: Disintegration Substitution and Clinically Justified Use of Standard Dissolution Method

Hardikkumar Patel, Ph.D.

Senior Assessor, DPQA XII, OPQA II, OPQ, CDER, FDA

Public Workshop: The Evolution of Biopharmaceutics: Risk Assessment and Clinical Relevance

May 1, 2026



A quality product of any kind consistently meets the expectations of the user – drugs are no different.

Patients expect safe and effective medicine with every dose they take.

Pharmaceutical quality is assuring *every* dose is safe and effective, free of contamination and defects.

It is what gives patients confidence in their *next* dose of medicine.

Disclaimer

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

Outline

01	**Concept framing**	Why product-level biopharmaceutics risk may differ from API-level classification
02	**Case Study 1**	Justifying a standard, clinically relevant dissolution method
03	**Case Studies 2–3**	Justifying disintegration as a surrogate test
04	**Cross-case discussion**	Comparison, role of clinical data, and key takeaways

Concept: Risk-Based Release Testing

BCS as a foundation

BCS is a foundational framework for classifying drug substances by solubility and permeability and is often used as an initial screen for biopharmaceutics risk.

Product-level biopharmaceutics risk

BCS criteria alone should not dictate the appropriate release-testing strategy for the finished drug product. A product with borderline high-solubility or low-solubility API may still present a low biopharmaceutical risk profile from a product-level perspective, based on the totality of available evidence.

Fit-for-purpose release testing

The release test should be fit for purpose and aligned with the totality of evidence for the finished product.

Is In Vivo Dissolution the Rate-Limiting Step to Absorption?

Do the API's physicochemical properties and clinical PK data collectively support the conclusion that in vivo dissolution is unlikely to be the rate-limiting step to absorption?

API-driven performance

When regional solubility and rapid Tmax appear to govern absorption, the formulation's primary role shifts toward ensuring consistent disintegration and release rather than determining bioavailability.

Risk assessment

Release-test decisions should be based on clinical/PK data, physicochemical properties, and in vitro performance.

Fit-for-purpose test

For products with a demonstrated low biopharmaceutical risk profile, a standard dissolution method or disintegration test may be sufficient to confirm routine manufacturing consistency. Highly discriminating methods may add limited value when the totality of evidence supports consistent in vivo performance.

Decisions addressed in this presentation

Decision 1

Standard dissolution method

Question

When is a simple, non-discriminating dissolution method sufficient to ensure in vivo performance?

Goal: Confirm routine manufacturing consistency when in vivo performance is robust.

Decision 2

Disintegration substitution

Question

When can disintegration serve as a scientifically justified and regulatorily acceptable alternative to dissolution testing?

Goal: Establish when disintegration is an appropriate surrogate for routine release performance.

Guiding principle: Focus on product-level risk and the totality of evidence.

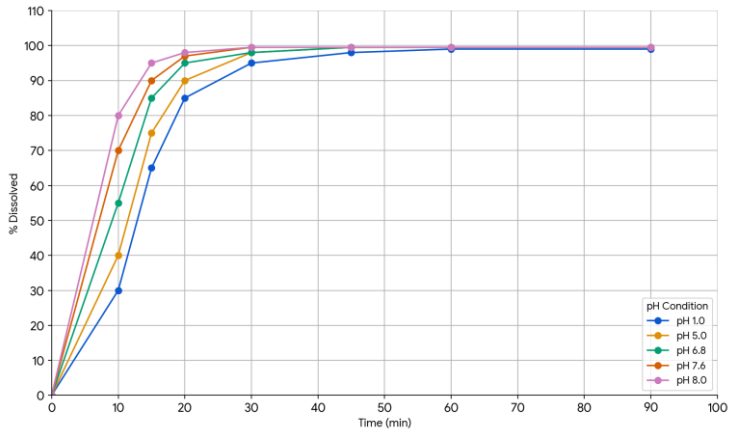
Case Study 1: Product Background and Biopharmaceutics Context

Attribute	Observation
Product	High-strength immediate-release HPMC capsule
API	Salt form; strongly pH-dependent solubility; high permeability
BCS status	Sponsor classified the API as BCS Class II because solubility at pH 6.8 marginally failed for the proposed dose in 250 mL.
Formulation / process	>85% API with MCC, SSG, and Mg stearate; dry granulation by roller compaction
Additional factor	Form X to Form Y polymorphic transition could occur on stability

Question *Can a simple, physiologically relevant dissolution method be justified even though classical high-solubility criteria are not fully met?*

Case Study 1: Why a Standard Dissolution Method Was Justified

Observed product behavior



Rapid dissolution was observed across the physiologic pH range; no surfactant was required.

Sponsor proposed a non-physiologic high-pH method to slow release and demonstrate discriminatory ability.

Key evidence supporting low product risk

- Rapid dissolution was demonstrated across pH 1.2, 4.5, and 6.8 without surfactant
- Under physiologic conditions, media-volume changes did not materially alter the release profile
- Form X and Form Y showed comparable solubility and dissolution; supportive in vivo Form X/Form Y comparison was available
- Clinical PK was consistent with rapid dissolution and absorption

Interpretation and Outcome

- A non-physiologic high-pH method selected only to slow release was not considered appropriate
- FDA accepted USP Apparatus I (basket) in 0.1N HCl at a physiologically relevant volume

Case Study 2: Product Background and Q6A Context

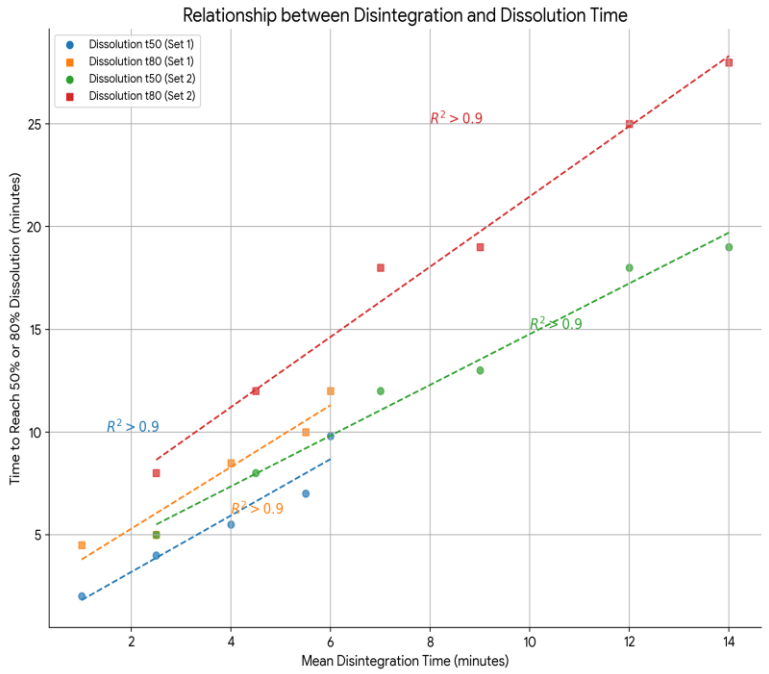
Attribute	Observation
Product	Two strengths of an immediate-release tablet
API	Non-ionizable, pH-independent solubility; high permeability supported by near-complete absolute bioavailability
BCS status	BCS Class I; dose/solubility volume was well below 250 mL across the physiological pH range

Question

Can disintegration replace dissolution when Q6A is effectively met in substance and the surrogate relationship is strong?

Case Study 2: Rationale for Disintegration as Surrogate

Observed product behavior



Disintegration and dissolution showed a strong linear relationship across manufacturing conditions.

Key evidence supporting low product risk

- Dissolution exceeded 85% in 15 minutes for both strengths across the tested physiologic conditions
- Disintegration time and dissolution time showed strong linear relationships ($R^2 > 0.9$) across a range of manufacturing conditions
- Disintegration discriminated relevant manufacturing changes

Interpretation and Outcome

- Surrogate relationship and process understanding were demonstrated
- FDA accepted USP disintegration as the release and stability test

Case Study 3: Product Background and Q6A Context

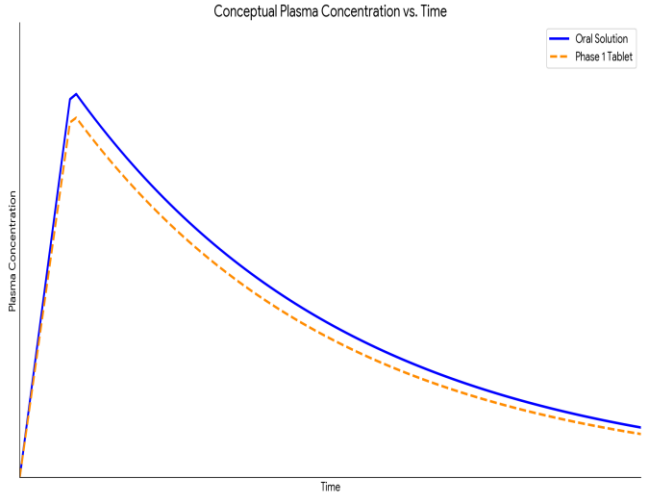
Attribute	Observation
Product	Immediate-release film-coated tablet
API	High solubility across pH 1.2 to 6.8
Dissolution development	Rapid dissolution at pH 1.2 and 4.5; coning at pH 6.8 was addressed using Apex vessels
DoE finding	Across formulation and process variables, neither dissolution nor disintegration meaningfully discriminated variability
Clinical bridge	PK study compared the tablet directly with an oral solution at the same dose

Initial question

If both tests show limited discrimination, can disintegration still be justified because the product is inherently low risk?

Case Study 3: Rationale for Disintegration as Surrogate

Observed product behavior



The oral-solution bridge provided the most direct clinical reassurance

Key evidence supporting low product risk

- High solubility and rapid dissolution were demonstrated across the physiologic pH range
- The clinical PK study showed tablet performance comparable to an oral solution
- The formulation proved robust; failing batches could not be generated even under intentionally stressed conditions
- The comparable and limited discriminatory power of both tests was interpreted, in this case, as consistent with inherently low biopharmaceutical risk rather than evidence of inadequate control

Interpretation and Outcome

- Alternative assurances supported disintegration even without a strong discriminatory advantage over dissolution
- In this case, the totality of evidence supported disintegration in an inherently low-risk product.

Cross-Case Comparison of Evidence and Regulatory Outcome

Case	Apparent concern	Most influential evidence	Accepted strategy
1	Borderline BCS II due to pH 6.8 solubility; polymorph transition on stability.	Rapid physiologic dissolution, supportive PK, low polymorph risk.	**Standard dissolution method accepted.**
2	Literal Q6A deviations and strength-dependent specification setting.	Disintegration–dissolution relationship, discrimination for manufacturing changes, strong process understanding.	**Disintegration accepted as a surrogate test.**
3	Neither dissolution nor disintegration strongly discriminated process variation.	High solubility, rapid dissolution, oral-solution PK bridge, and formulation/process robustness.	**Disintegration accepted based on totality of evidence.**

Roles of Clinical/PK data in Supporting Low-Risk Conclusions

As the residual uncertainty after physicochemical and in vitro assessment increased, direct clinical evidence became more influential.

Increasing role of clinical evidence in resolving residual uncertainty

Context-setting role

- Human PK supported high permeability / extensive absorption
- Strengthened the low-risk context; the primary surrogate basis remained the disintegration–dissolution relationship and process understanding

Case Study 2

Strong supportive role

- Clinical PK was consistent with rapid absorption
- Supportive in vivo Form X/Form Y comparison helped show that borderline solubility and polymorphic change did not translate into meaningful product-level risk

Case Study 1

Most direct clinical bridge

- Tablet-to-oral-solution PK bridge showed product release was unlikely to be clinically limiting in vivo
- Supported disintegration even though both in vitro tests had limited discriminatory power

Case Study 3

Takeaway: Clinical data were not interchangeable across the three cases; their importance increased as the in vitro case became less straightforward.

Key Takeaways

1. Finished-product biopharmaceutics risk can be lower than API-level BCS classification alone would suggest when supported by clinical data, formulation/process understanding, and in vitro performance.

2. A standard, non-discriminating dissolution method is appropriate when clinically relevant performance is established, and the test serves to confirm routine manufacturing consistency.

3. Disintegration is most straightforward when a convincing surrogate basis is shown; strong alternative assurances may also be sufficient for some low-risk products.

4. Fit-for-purpose release testing is not less rigorous; it aligns testing strategy with the actual biopharmaceutical risk profile of the finished product.

References

• ICH Q6A: Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (1999).

• ICH M9: Biopharmaceutics Classification System-Based Biowaivers (2019).

• FDA Guidance for Industry: Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances (2018).

Acknowledgements

- M-CERSI planning team
- Dr. Hailing Zhang
- Dr. Anitha Govada
- Dr. Rushikesh Sable
- Dr. Hansong Chen
- Dr. Haritha Mandula
- Dr. Rebeca Moody
- Biopharm review team (OPQA I and II)

Thank you!