U.S. FOOD & DRUG ADMINISTRATION

Predictive Biopharmaceutics: A Deep Dive into the Risk Assessment Framework

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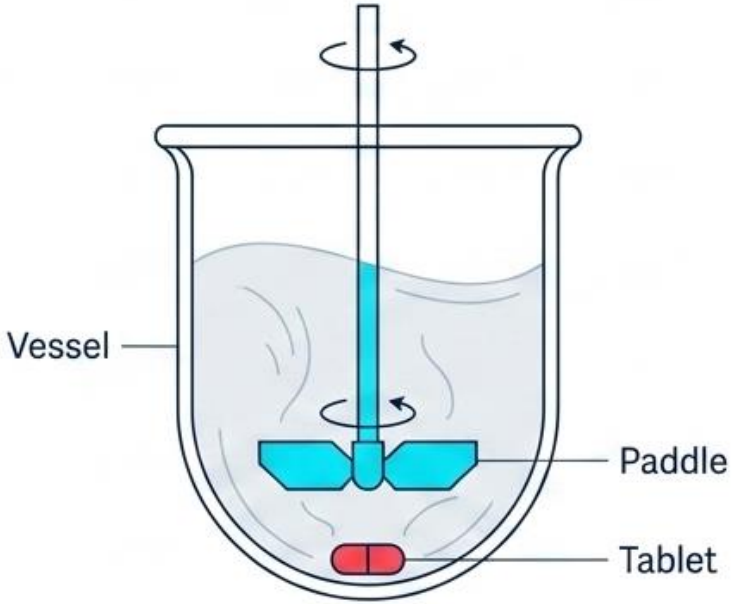
Disclaimer

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

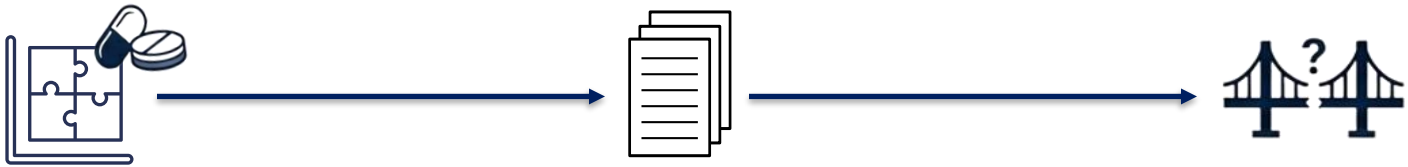
Dissolution Test: Background & Historical Role

- Only dissolved drug gets absorbed
- Measures how much and how fast the drug is released from the dosage form and dissolves in vitro
- Primarily for “quality control” but specifications (method and acceptance criteria) are generally proposed to decrease or eliminate the risk of batch failure



Evolution of Dissolution Test

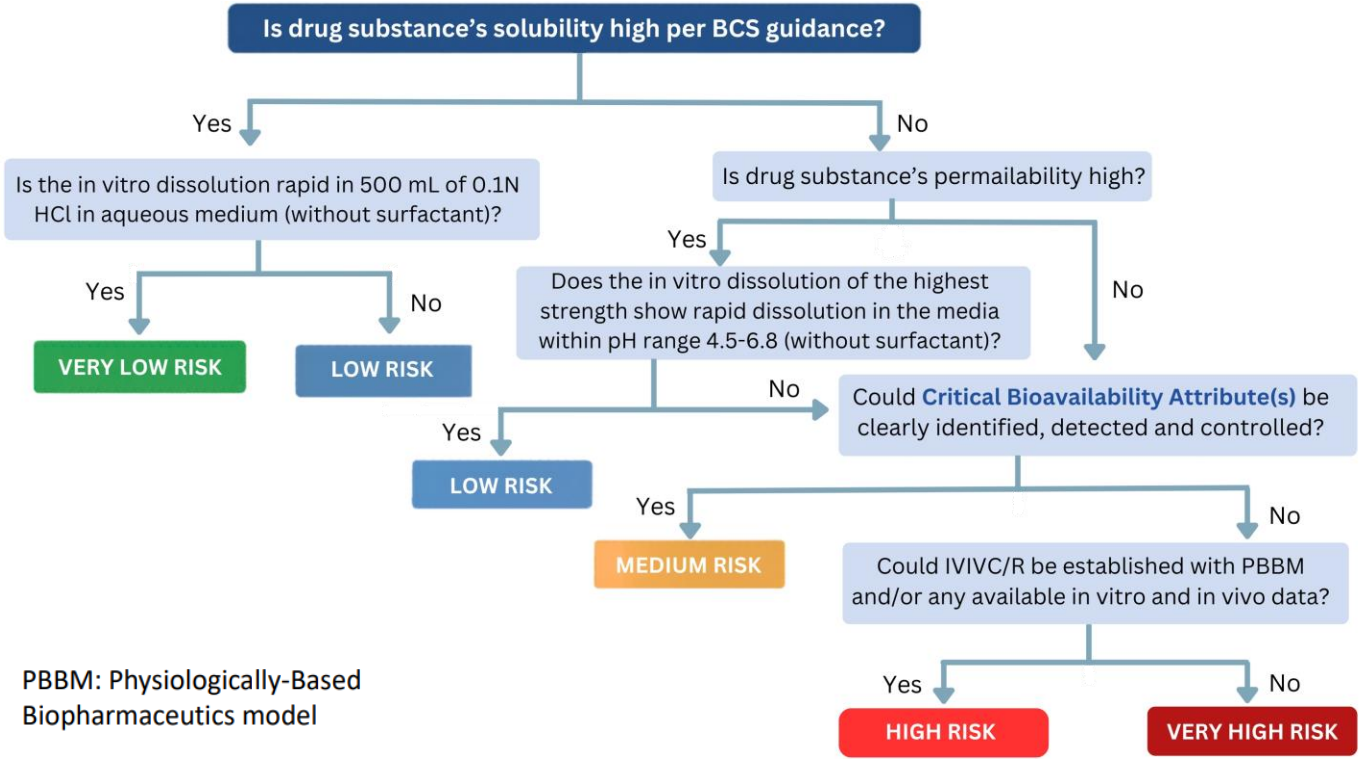
- The Biopharmaceutics Classification System (BCS) became the first framework in 1995 to systematically link drug properties (solubility, permeability) and dissolution to in vivo performance.
- FDA guidances published subsequently formalized the role of dissolution in distinguishing acceptable from unacceptable products based on in vivo performance.
  - FDA Guidance for Industry: Dissolution testing of Immediate Release Solid Oral Dosage Forms
  - SUPAC IR and MR guidances
  - FDA Guidance for Industry: In vitro-In vivo Correlations
- Challenge: In vitro dissolution continued to suffer from lack of correlation to in vivo dissolution and hence, clinical relevance.



Biopharmaceutics Risk Assessment: Current Practice

- FDA created Biopharmaceutics Risk Assessment framework for oral drug products to assess the risk of not achieving the desired in vivo performance resulting in risk levels from very low to very high
- Risk assessments for immediate release (IR) drug products are anchored by BCS framework
- Identification / control of “Critical Bioavailability Attributes (CBAs)” determines risk mitigation and control strategies for products with medium risk and above

Biopharmaceutics Risk Assessment: IR Products



*** Critical Bioavailability Attribute(s), CBAs:** Formulation or process attributes those are expected to critically impact the bioavailability (absorption rate and extend) of a drug product

Biopharmaceutics Risk Assessment: Limitations of Identification and Control of CBAs

- Dissolution methods developed solely to discriminate against CBAs often lack demonstrated correlation to in vivo performance and are likely to result in overdiscriminating methods (or underdiscrimination if focused on the wrong CBA)
- CBAs are theoretical and not universally applicable to all drug products
- CMAs, CPPs and CFVs interact with each other and collectively affect formulation performance
- CMAs, CPPs and CFVs are better controlled by direct testing rather than dissolution

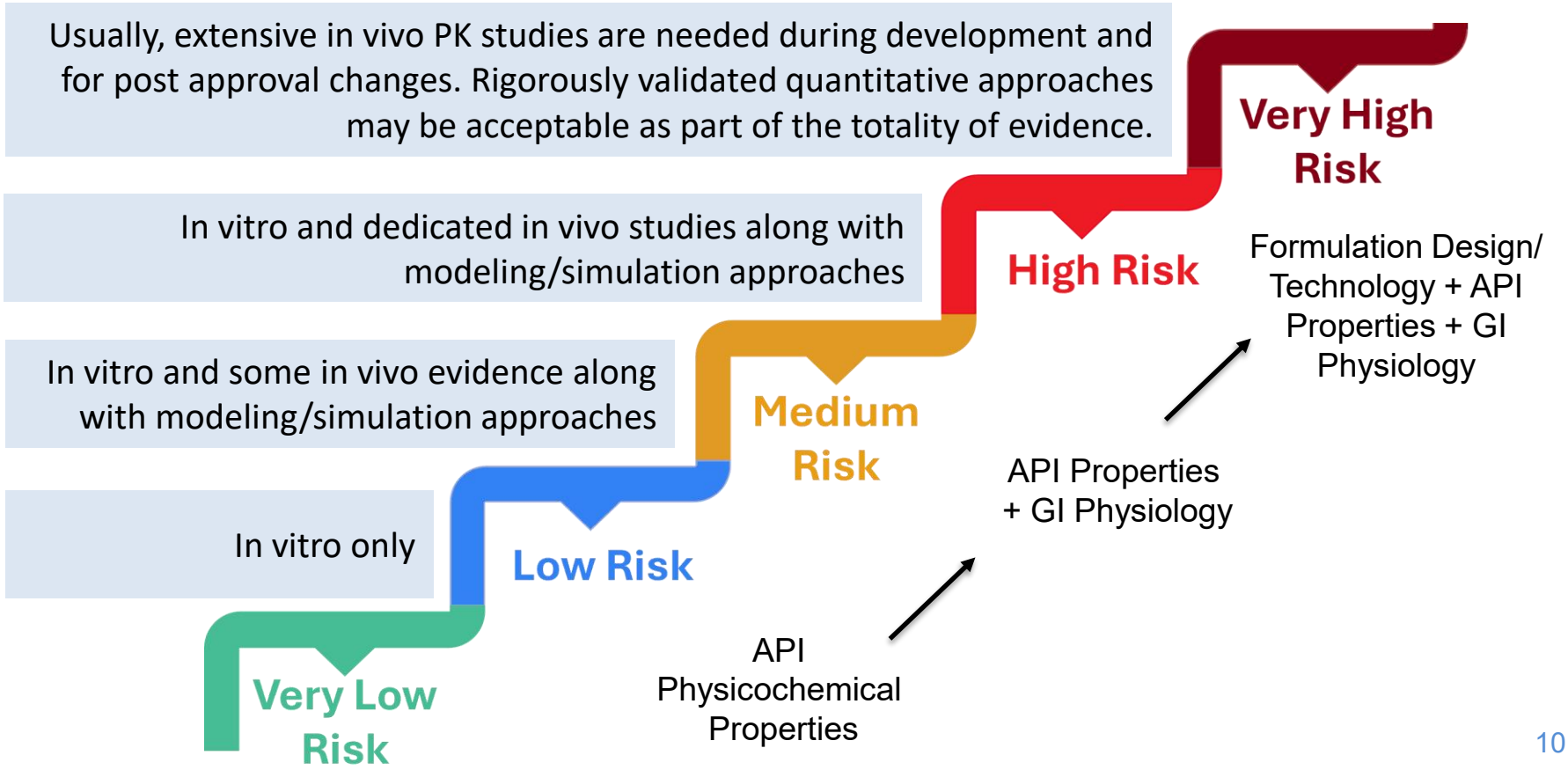
Biopharmaceutics Risk Assessment: Updated Framework

- Ultimate goal remains the same:
  - Dissolution test should be able to predict in vivo performance. i.e., it must distinguish drug product that gives the desired in vivo performance vs. that which doesn't
- Shift in focus from identifying and controlling CBAs via dissolution OR only relying on pivotal clinical batches to understanding the **dynamic interplay** between the API, GI physiology, and the formulation design
- IR and ER oral products included in the same risk assessment framework

Updated Framework: General Principles

- Oral drug products are classified into five distinct risk categories from very low to very high, based on systematic assessment of API properties, effect of GI physiology, and complexity of formulation design / technology
- Risk level dictates the evidence required for a predictive dissolution method

Risk Categories



Very Low Risk

- High solubility and high permeability drugs (BCS Class I) in IR dosage forms
- In vivo dissolution is independent of formulation and GI physiology; Dissolution is *not* the rate-limiting step
- Minimal evidence needed
  - Demonstration of rapid dissolution (80% in 30 min) under standard dissolution conditions (e.g., 0.1 N HCl at pH 1.2)
  - Dissolution test can be waived if disintegration is consistently correlated with rapid dissolution

Low Risk

- High solubility / low permeability drugs (BCS Class III) OR High Solubility in intestinal pH range (pH>~4.5) with high permeability (BCS Class IIa) weak acids in IR dosage forms
- Permeability is rate limiting for BCS Class III, gastric emptying is likely rate limiting for BCS Class IIa
- Evidence of rapid dissolution (80% in 30 min) at pH 6.8 is sufficient to demonstrate in vivo dissolution is not rate limiting

Medium Risk

- Low solubility in the intestinal region where GI physiological conditions (pH, bile salts, food etc.) can significantly impact in vivo dissolution and absorption
  - Most BCS Class II non-ionized and weakly basic (Class IIb) drugs in IR dosage forms
- Interplay of API properties and GI physiology determines in vivo dissolution
- Significantly more evidence including qualitative (IVIVR or safe space) or quantitative link (e.g., PBBM) to in vivo performance is required to demonstrate predictive nature of the dissolution method
  - Use of biorelevant media (FaSSIF/FeSSIF), physiologically relevant conditions (e.g., pH switch), or other tools that mimic GI physiology may be used to assess CQAs and develop the link to in vivo performance
  - Could incomplete release/dissolution in these media be acceptable as it may be reflective of in vivo situation?
  - Use of available clinical data (pilot studies / food effect studies) or dedicated PK studies with formulations containing variations of CQAs selected based on in vitro studies

High Risk

- Formulation technology controls dissolution or release rate, affecting in vivo performance
  - IR products containing enabling technologies e.g., ASDs, nanoparticles, lipid-based formulations like SMEDDs
  - ER products control release rate to reduce PK fluctuation and dosing frequency
- Quantitative M/S approaches including dedicated in vivo PK studies for the development and validation models are needed to demonstrate predictive nature of the in vitro dissolution test
  - Level C / multiple Level C or validated PBBM based approaches may be pursued for IR products
  - Level A IVIVCs are preferred for ER products

Very High Risk

- Medium or high-risk products may be elevated to very high risk when additional factors warrant highest level of scrutiny
  - Formulation / process complexity
  - NTI drugs OR drugs that require rapid onset
  - Certain safety considerations (e.g., black box warnings)
  - Inability to develop predictive dissolution method
- In vivo PK studies are needed for development and significant post-approval changes
  - Quantitative models may be used if they can be developed and validated rigorously; model predictions may need to be applied conservatively

In vivo Data Requirements for Risk Levels

- In vivo data requirements to link in vitro to in vivo increase with risk levels
- Proactive planning to demonstrate predictive nature of dissolution test is needed

VERY LOW RISK	In vivo data not needed
LOW RISK	In vivo data generally not needed
MEDIUM RISK	In vivo studies are needed; Can be early / pilot PK studies or dedicated PK studies with formulation variants
HIGH RISK	Dedicated in vivo studies are needed to develop and validate quantitative relationship between in vitro and in vivo
VERY HIGH RISK	Extensive in vivo studies are needed to develop and validate quantitative relationship

Risk Reclassification

- With proper evidence of predictive nature of the dissolution test, the risk can be managed at the existing classification level
- Downgrade or upgrade of original risk classification may happen based on totality of evidence when initial risk does not match in vivo data in multiple clinical scenarios

Predictive Biopharmaceutics in Regulatory Context

- Biopharmaceutics risk assessments are used extensively by industry during product development but inconsistently in control strategy
- Biopharmaceutics principles should be integrated as core component into control strategy for solid orals for seamless lifecycle management (initial approval to post-approval changes)
- In vitro dissolution for release and stability testing (used in regulatory control strategy) should
  - provide predictive insight into in vivo performance
  - be able to reject batches with unacceptable in vivo performance

Conclusion

- Development of predictive dissolution methods require upfront investment, especially with increasing risk level (medium and above)
- Predictive dissolution methods and acceptance criteria avoid release of unacceptable batches or failures of acceptable batches
- The return on investment (ROI) is high due to reduced regulatory burden over the product lifecycle

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