Biopharmaceutics Risk Assessment in Product Development

An industry perspective from members of AAM and IQ

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Why dissolution testing?

*Drug absorption from a solid dosage form after oral administration depends on the release of the drug substance from the drug product, the dissolution or solubilization of the drug under physiological conditions, and the permeability across the gastrointestinal tract. Because of the critical nature of the first two of these steps, in vitro dissolution **may be** relevant to the prediction of in vivo performance. Based on this general consideration, in vitro dissolution tests for immediate release solid oral dosage forms, such as tablets and capsules, are used to (1) assess the lot-to-lot quality of a drug product; (2) guide development of new formulations; and (3) ensure continuing product quality and performance after certain changes, such as changes in the formulation, the manufacturing process, the site of manufacture, and the scale-up of the manufacturing process.*

From: Guidance for Industry Dissolution Testing of Immediate Release Solid Oral Dosage Forms, 1997; U.S. Department of Health and Human Services Food and Drug Administration (CDER)

What is dissolution used for in practice?

PRE-APPROVAL

- "Guide development of new formulations" → Currently, sponsor decides which in vitro approaches can be used.
  - "best practice" approach to answer biopharmaceutics questions using in vitro or in vivo (animal and/or human exploratory PK and in silico methods

POST-APPROVAL

- "Assess the lot-to-lot quality of a drug product" → All* IR solid oral dosage forms (SODs) must have a QC dissolution specification
  - ICH Q6A and regional guidance
    - Justification of specification often challenged → what does the test need to detect?
  - Approved QC dissolution method for solid oral dosage forms containing poorly soluble API likely overly discriminative → unnecessary product discards (M-CERSI 2017)
- "Impact of postapproval changes" → Prescribed dissolution conditions are <u>assumed</u> a priori "bio predictive" and "changes" are considered a "risk".
  - Follow regional guidance
  - Dissolution profile comparison criteria met or BE (M-CERSI 2019)

* Disintegration may be approved or BCS1 very rapidly dissolving drugs

Guidance for Industry

Q8(R2) Pharmaceutical Development

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

November 2009
ICH

Revision 2

Guidance for Industry

Q9(R1) Quality Risk Management

U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
May 2023
ICH-Quality

Potential drug product CQAs derived from the quality target product profile and/or prior knowledge are used to guide the product and process development. The list of potential CQAs can be modified when the formulation and manufacturing process are selected and as product knowledge and process understanding increase. Quality risk management can be used to prioritize the list of potential CQAs for subsequent evaluation. Relevant CQAs can be identified by an iterative process of quality risk management and experimentation that assesses the extent to which their variation can have an impact on the quality of the drug product.

Biopharm Risk Assessment

Definitions of Hazard, Risk and CBAs

Hazard: Potential Source of Harm → Drug with unknown/inconsistent bioavailability caused by dissolution impacting efficacy or safety

Risk: The *probability* of harm to occur and magnitude of potential harm* ("R ~P x M")

- The probability of harm depends on the *inherent* biopharmaceutics properties of the API and formulation/process factors along with PK/PD relationship
- Magnitude depends on target disease, patient, PK/PD, etc.

Critical Bioavailability Attribute (CBA): FDA defined CBA as a formulation or process variable that is expected to critically impact the bioavailability of a drug product.**

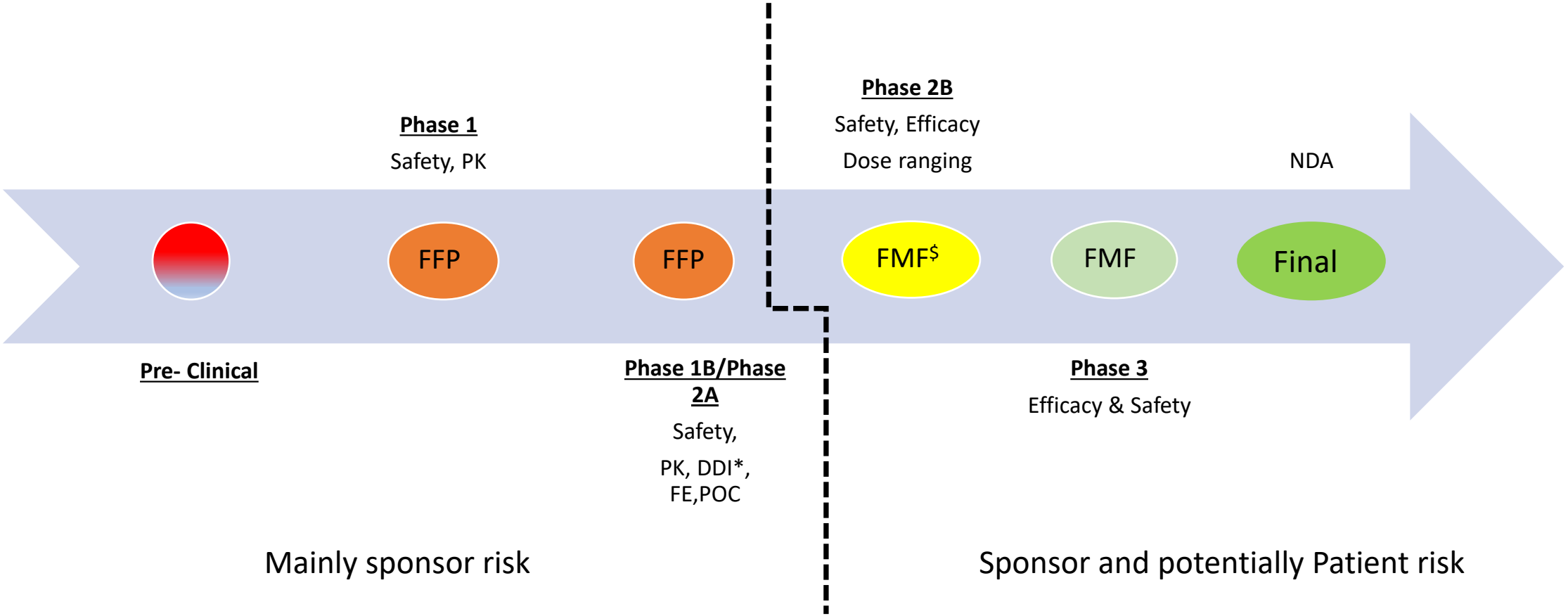
- ***Potential*** CBAs (pCBAs) may be removed/ from the list of influential attributes or confirmed as ***relevant*** *C*BAs that need to be controlled based *on data* generated following ICH principles
    - The relevance of *in vitro* dissolution to assess CBAs needs to be demonstrated

Wikipedia and other online searches

Patient risk and product development

Not achieving desired exposure
LOW RISK for patient (P x M)

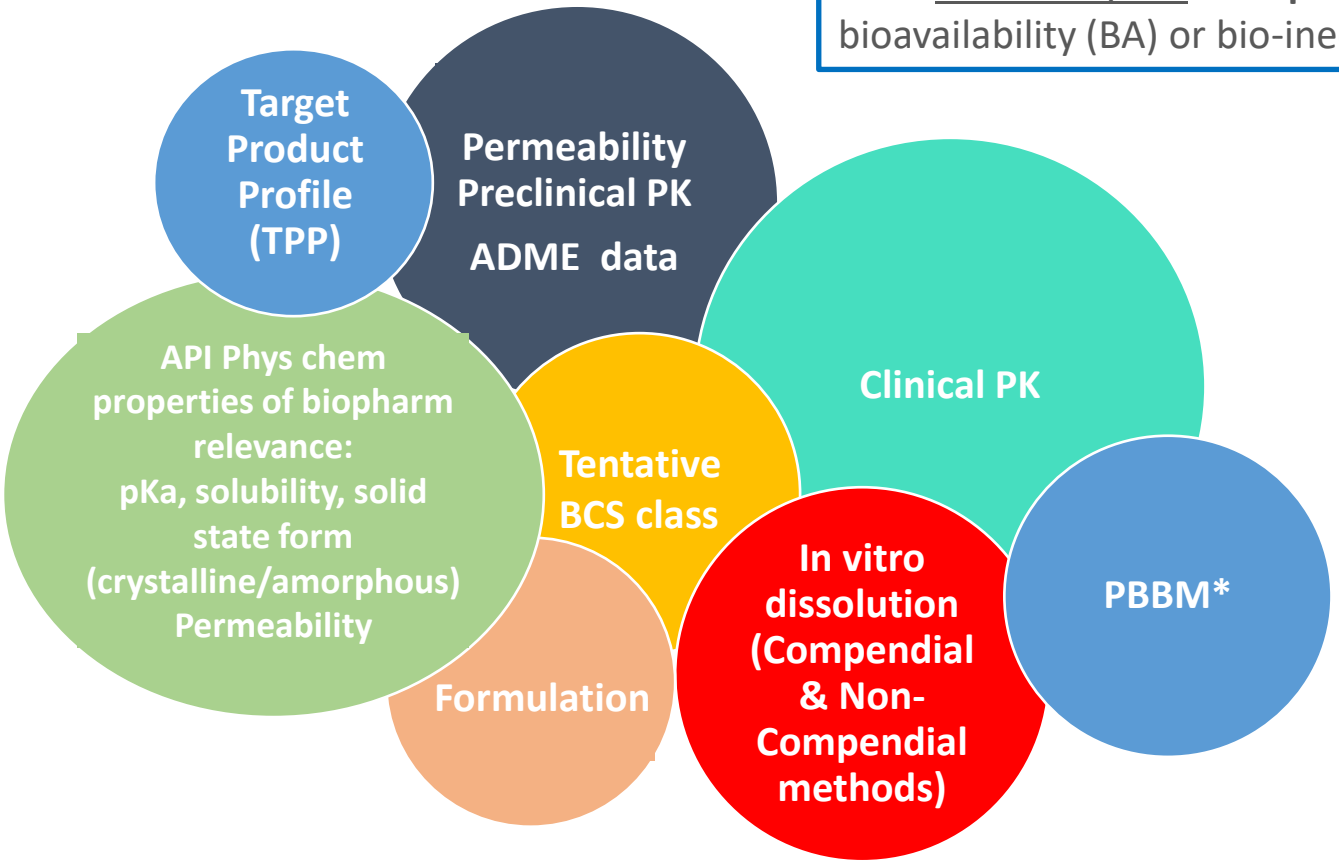
Inconsistent exposure
Increased Risk (P x M)



FFP = fit for purpose, FMF = final market formulation

Biopharmaceutics risk assessment in development

RISK: Probability of **inadequate clinical performance. E.g.: unacceptable** bioavailability (BA) or bio-inequivalence (BE).



- **Applicable to oral immediate release formulations throughout drug product development**
- **Clinical experience (i.e., from studies evaluating Safety/ efficacy, prior experience) as part of hazard and risk assessment**
- **Risk assessment process is an iteratively process applied throughout development**

Expected Biopharm risk mitigation

Very Low & Low Risk	BCS 1 & 3 and drugs/ drug products showing high solubility in physiologically relevant media: Risk assessment supported by *in vitro* dissolution following current guidance for BCS 1&3/SUPAC. Mitgation: Control process and material attributes to assure acceptable dissolution performance.
Medium Risk	BCS 2 & 4, *absorption limiting factors known*: Mechanistic understanding of in vitro dissolution as well as biopharm failure modes. Risk assessment supported by dissolution, PBBM* and clinical experience. Mitigation: CPPs and CMAs impacting dissolution controlled via in-process controls. Follow SUPAC
High Risk	*BCS 2 & 4, absorption limiting factors not understood or difficult to detect.* Acceptable CBA ranges are justified by clinical data (traditional IVIVR/PBBM). Mitigation: In-process controls to control CMAs/CPPS that impact CBAs. Dissolution as input to IVIVR/C or PBBM* to assess changes if CMAs/CPPs ranges need to be expanded.

* Clinical development phase appropriate model

Past M-CERSI discussions - the issue with dissolution testing

Any in vitro dissolution testing is a surrogate for in vivo dissolution

- In this context: “All dissolution tests are wrong – some are useful”*

Need to understand what impacts dissolution in vitro and in vivo– not just assume! (MCERSI 2017)
In vitro rate and extend of drug release depends on product and the method (instrument, media, operator, etc.)

For small molecules, other analytical techniques are much more definitive (e.g., assay, impurities)

* (that is NOT how George Box referred to statistical models)

Risk- and Science- based Dissolution Specification Development

BCS, formulation complexity and QRM based *in vitro*, *in vivo* and *in silico* efforts in support of Biopharm risk assessment and mitigation

Available tools listed in order of complexity

BCS 1/3/2a IR products

BCS 2/4 Conventional IR products

"Enabling" Technologies (e.g. ASDs, Lipids)

MR products

"BCS" Dissolution
If >80% in 30 min at pH 6.8, low probability of in vivo impact

Dissolution Experiments to Identify Critical Dissolution Step (for any formulation technology)
E.g. API vs granule vs tablet dissolution to assess impact of API PSD, assessment of polymorphic form, etc. Experiments may include media with surfactant/multimedia/biorelevant media or biorelevant setups – selection of tool depends on formulation characteristics

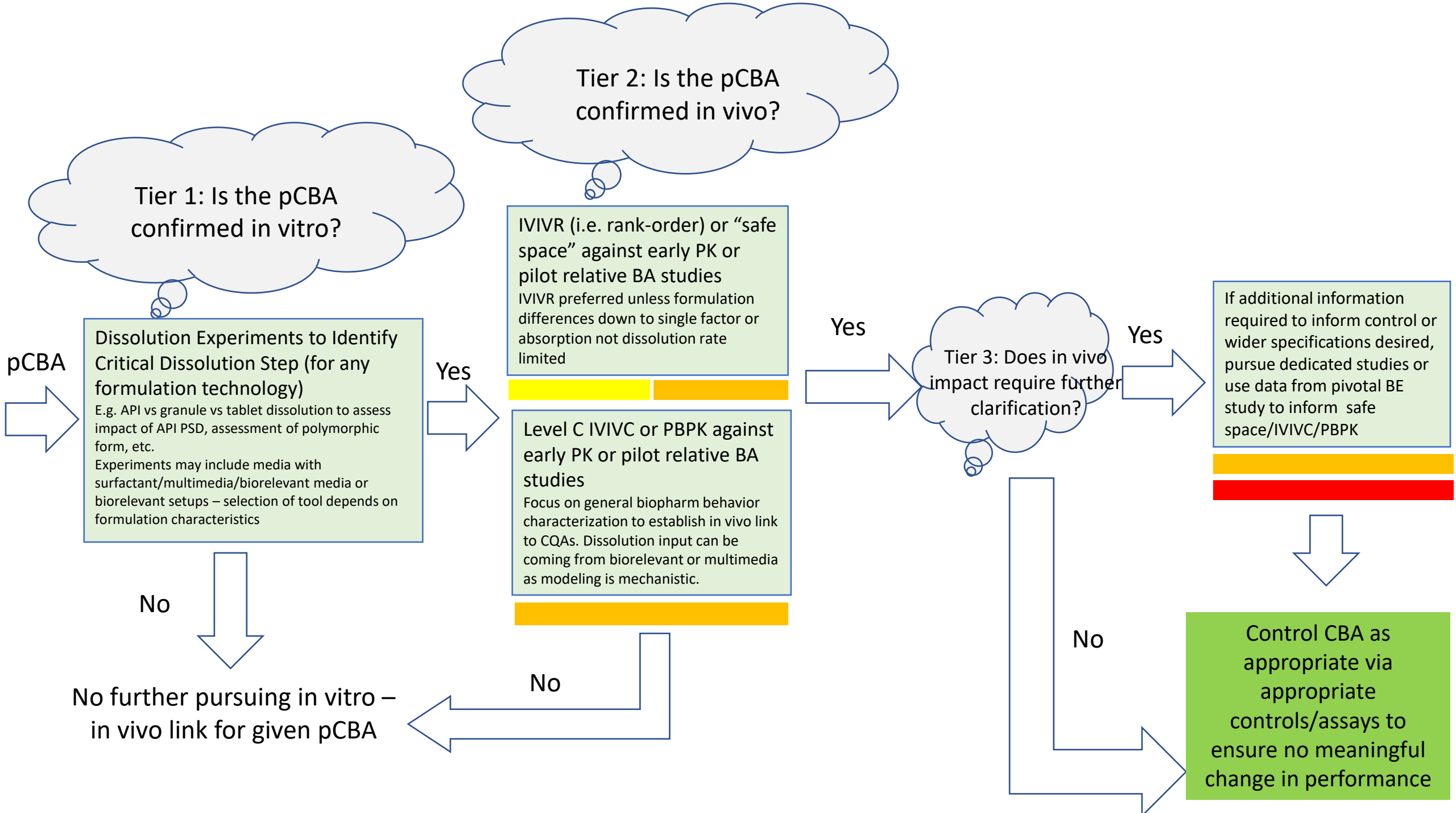
IVIVR (i.e., rank-order) or "safe space" against early PK or pilot relative BA studies
IVIVR preferred unless formulation differences down to single factor or absorption not dissolution rate limited

Level C IVIVC or PBPK against early PK or pilot relative BA studies
Focus on general biopharm behavior characterization to establish in vivo link to CQAs. Dissolution input can be coming from biorelevant or multimedia as modeling is mechanistic.

Safe space against dedicated BA study with formulation variants or pivotal BE study

Level C or PBPK against dedicated relative BA study with formulation variants or pivotal BE study
Non-BE batch may be required for significantly wider specifications

Level A Full IVIVC against dedicated relative BA study with formulation variants

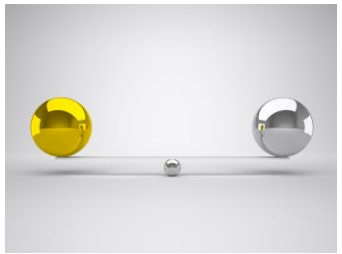

Tier 2: Is the pCBA confirmed in vivo?
Tier 1: Is the pCBA confirmed in vitro?
IVIVR (i.e. rank-order) or "safe space" against early PK or pilot relative BA studies
IVIVR preferred unless formulation differences down to single factor or absorption not dissolution rate limited
pCBA
Dissolution Experiments to Identify Critical Dissolution Step (for any formulation technology)
E.g. API vs granule vs tablet dissolution to assess impact of API PSD, assessment of polymorphic form, etc.
Experiments may include media with surfactant/multimedia/biorelevant media or biorelevant setups – selection of tool depends on formulation characteristics
Yes
Level C IVIVC or PBPK against early PK or pilot relative BA studies
Focus on general biopharm behavior characterization to establish in vivo link to CQAs. Dissolution input can be coming from biorelevant or multimedia as modeling is mechanistic.
Yes
Tier 3: Does in vivo impact require further clarification?
Yes
If additional information required to inform control or wider specifications desired, pursue dedicated studies or use data from pivotal BE study to inform safe space/IVIVC/PBPK
No
No
No further pursuing in vitro – in vivo link for given pCBA
No
Control CBA as appropriate via appropriate controls/assays to ensure no meaningful change in performance

What is a “meaningful” change?

Current state:
Suitability of the dissolution method to indicate unacceptable in vivo performance (fit for purpose) is assessed by demonstration of its sensitivity (“discriminatory power”) towards ***“meaningful change(s)”,*** *defined as +/- variation of potential CMA/CPP/CFVs.*
Current approaches are inconsistent with the “fit for purpose” goal of the dissolution method.

Industry position:

- Demonstrating sensitivity towards arbitrary levels of +/- variations in materials attributes or manufacturing conditions without regard to the established product-specific boundaries is not value added
- In general, CMA/CPP/CFVs are not necessarily CBAs
- *What is the relevance of a method to detect “change” when not considering in vivo impact? A method may be:*
  1) sensitive towards changes in product, but not be able to identify unacceptable product = Consumer Risk
  2) “just right”: unacceptable product is detected when manufacturing conditions change
  3) overly-sensitive (over discriminating) leading to product rejects = Manufacturer Risk



Interpretation of Meaningful Change in context of BRA

Two scenarios:

A. Absorption is in vivo dissolution limited (in vitro dissolution likely to be bio-indicative/predictive)

B. The absorption is not in vivo dissolution rate limited and/or In vivo-in vitro relationship is not available

Scenario A

In vitro – In vivo relationship/correlation is likely*:
→ Changes in CPPs/CMAs that lead to unacceptable in vitro(= in vivo) dissolution can then be considered meaningful

Meaningful change:
Change in a CBA leading to unacceptable bio-performance (e.g., non-BE or exposure level not justified by clinical experience)

Discriminating ability:
Ability of a dissolution method to differentiate between acceptable and non-acceptable batches (for example bio-inequivalent batches, where non-BE is driven by a manufacturing change that affects dissolution)

*IVIVR/C or PBPK is used to assess impact of change on PK and or patient safety

Two scenarios:

A. Absorption is in vivo dissolution limited (in vitro dissolution likely to be bio-indicative/predictive)

B. **Absorption is not in vivo dissolution rate limited and/or In vivo-in vitro relationship is not available**

Scenario B-1

Changes in dissolution rate has limited impact on bioperformance*: In vivo impact of changes in CBAs over a wide range may be acceptable/low but point of failure unknown.

Scenario B-2

No in vitro-in vivo link - changes in CBAs may negatively impact product performance:

"Meaningful" Changes are based on minor/moderate change definitions in SUPAC guidance. Reference for CBA levels (and associated CMAs/CPPs) are representative clinical/biobatches ("precedented conditions**), acceptable changes are assessed via dissolution similarity.

** BCS 1 and 3, 2A usually cited as examples but could include any BCS Class within specific formulation constraints*

***Hermans, A. et al. 2017, AAPSJ, Approaches for Establishing Clinically Relevant Dissolution Specifications for Immediate Release Solid Oral Dosage Forms*

Conclusions

- Biopharm Risks are rigorously identified, tracked, and mitigated during product development.
  - Sponsors are “not interested” in delivering questionable product to patients
  - Sponsor knows what is meaningful and what is not
- Dissolution testing may be useful in guiding product development and to assess and control product in vivo performance (patient risk).
  - Other tests maybe more specific and sensitive
- In case dissolution testing is useful and if it is the only test that can be used to identify “inacceptable” product, then specifications should be established and implemented.
  - These specifications (method and acceptance criteria) should be used in support of postapproval changes depending on level of change
- For “high risk” products IVIVR/C/safe space should be attempted when feasible
  - For some products, traditional PK bracketing may not be possible.
  - Modeling is not necessary in most cases other than MR products
- Primary control of performance is through formulation composition and control strategy
- “Keep it simple”
  - Complexity ≠“accuracy” or “biorelevance”

Acknowledgements

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- Physiologically Based Biopharmaceutics Modelling—Best Scientific Practices to Define Drug Product Performance, Latest Regulatory and Industry Perspectives: Workshop Summary Report (manuscript under review)