

Industry Perspective On The Current Status And Future Of Dissolution Testing For Product Development And Quality Control

**M-CERSI Workshop - Dissolution and Translational Modelling Strategies Enabling Patient-Centric Product Development,
May 15-17, 2017, Maryland**

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Outline

- Historical and current roles of dissolution and current issues
- Definitions and roles of dissolution methods
 - Relationship between different types of dissolution methods
- Gaps and opportunities to be addressed in this workshop

Evolution of the Pharmaceutical Industry that Expands the Roles of Dissolution

Prior to the 90's

Majority of solid oral dosage forms with low formulation complexity and highly water soluble molecules

Limited roles of dissolution

QC tool to ensure process control and product with consistent *in-vitro* release

Limited correlation to *in vivo* product performance

90's and beyond

Increase of insoluble molecules and enabling technologies; MR for life cycle management

Refinements in “bio-relevant” media and advances in PBPK modeling

BCS, QbD, patient centric, and regulatory guidance with clear expectations for dissolution development

Emerging technologies such as continuous manufacturing

Increasing roles of dissolution – shift toward clinical relevance

Formulation screening (rank ordering)

Assessing potential *in-vivo* challenges (i.e. food effect, DDI effects)

Desire to have method that adequately predicts and ensure acceptable clinical performance as a QC method

Driving Force for Expanded the Roles of Dissolution

New Technologies

- Enabling Technologies and Modified Release
- Continuous Manufacturing and RTR

Shift to clinical relevance

- New apparatus and media and confusion over various methods and terminologies
- Desire to bridge from clinical relevance → QC

Surrogate for Dissolution

- Scenarios where enhanced product understanding justifies alternatives to dissolution How can we achieve global harmonization?

PBPK Modelling

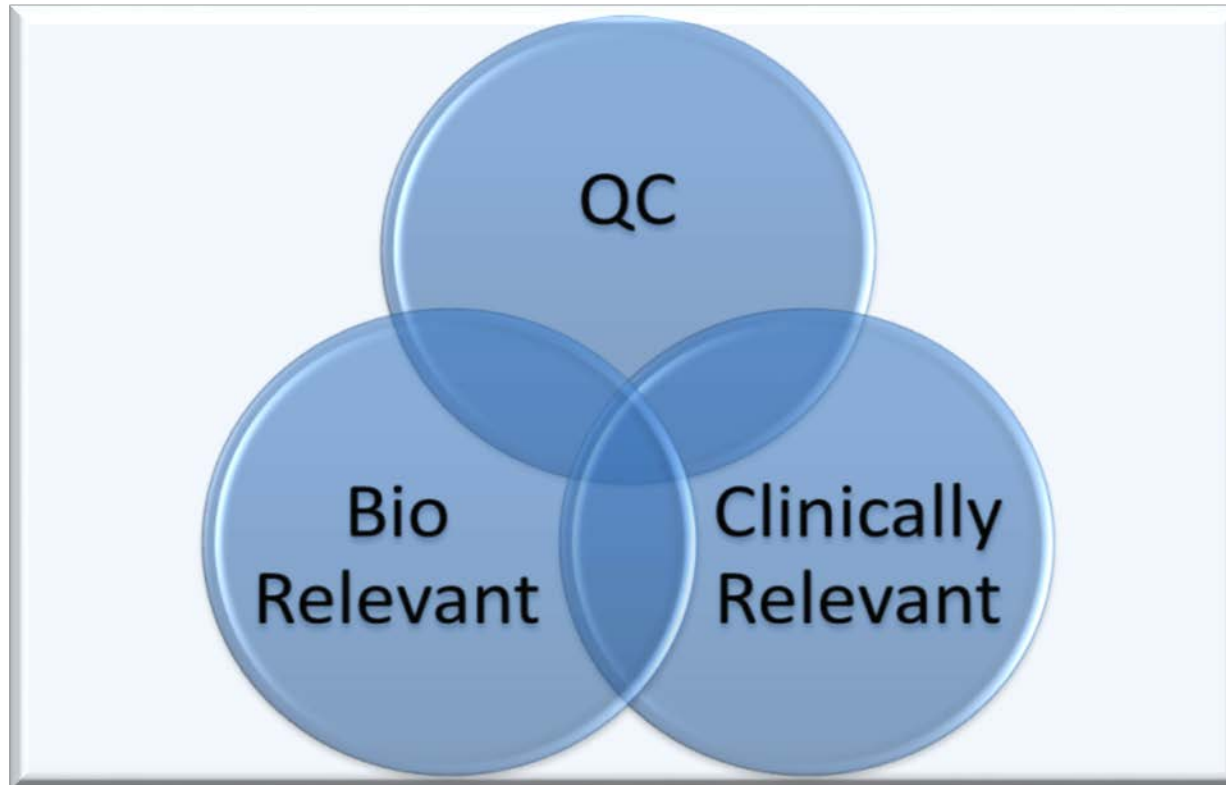
- Expanded use of PBPK modelling for establishing *in vitro-in vivo* Link (Day 2)

Regulatory Expectations

- Clear and harmonized regulatory requirements
- Dialogue between regulatory, industry, and academics

Three Types of Dissolution Methods

- Different roles in product development
- Degree of overlap depending on the product



Definition and Roles: QC Dissolution

- **Definition:** A method capable of detecting variations during routine product manufacture and/or changes during product storage that might negatively impact product performance.
- **Purpose:** Quality Control for:
 - lot-to-lot consistency , stability, and unacceptable product changes.
- **Key features:**
 - Standard and robust with global acceptance
 - Desired to have appropriate discrimination power
- **Current status:**
 - Not much changed over the years from an experimental perspective
 - Increased regulatory expectations lead to stronger integration of dissolution into product development and quality control strategy
 - Deeper process understanding enables the identification of CMAs and CPPs that allow predicting dissolution performance of the product



Definition and Roles: Biorelevant Methods

- **Definition:** A method designed to model the different physiological environments that the drug will experience within human gastrointestinal tract and to study the drug dissolution in gastric, intestinal, colonic conditions or under the influence of food , i.e., fed vs. fasted state
- **Purpose:** formulation screening/rank-ordering, optimization and BE assessment
- **Key features:**
 - Discriminative and sensitive to formulation variations
 - Experimentally, these methods can be challenging, as they are often not robust, not performed under “standard” conditions including media and apparatus
- **Current status:**
 - Fertile ground for dissolution innovation, such as new media, apparatus, and combined evaluation of dissolution and absorption
 - Great opportunities for incorporating modeling/simulation with dissolution testing



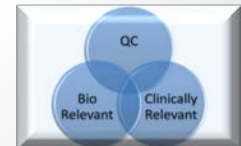
Definition and Roles: Clinically Relevant (Bio-predictive) Method

- **Definition:** A method capable of linking *in vitro* dissolution data with *in vivo* PK data, creating an *in-vitro in-vivo* correlation or relationship (IVIVC or IVIVR).
- **Purpose:** To ensure product quality with a clear link to performance in humans that can be potentially used to justify clinical relevant specs, CMAs, CPPs, or biowaiver.
- **Key features:**
 - May require a more complex/non-standard experimental approach with similar challenges as mentioned for biorelevant media
- **Current status:**
 - Increased focus on CRS as the desired state for QC dissolution
 - Concerns over global acceptability



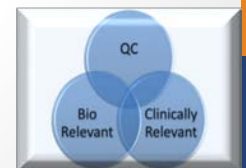
Definition: Discriminating

- Definition: The ability of a method to differentiate (1) API properties (e.g., particle size), (2) formulation variables (e.g., excipient type or level, composition), or (3) process variables (e.g., process duration, temperature, blending speed, and compression force).
- Key features:
 - Bio-relevant, clinically relevant, or QC methods can have some degree of discrimination.
 - “Discriminating power” can be ambiguous – this is recognized and hence desirable to address the “right” level of discrimination.



Overall Relationship of various Dissolution Methods

- Do QC methods need to be biorelevant?
 - **Not necessarily, indeed** it is rate if not none at all.
- Do clinically relevant methods need to be biorelevant?
 - **Not necessarily**, although some are the same
- Do QC methods need to be clinically relevant (bio-predictive)?
 - It's desired to have strong link between clinically relevant and QC methods, but less with biorelevant
 - However, it can be challenging for a QC method to be clinically relevant
 - See more in Day 1 presentations



Opportunity 1: scenarios where surrogate for dissolution can be used as part of a comprehensive control strategy

Scenario 1:

- Disintegration test can be used in place of dissolution when certain criteria/info is met/available.
- But, global acceptance remains a challenge.

Scenario 2:

- When dissolution \gg permeability or a sufficiently wide range of dissolution profile leads to BE.
- Is dissolution even needed?

Opportunity 2: use PBPK modelling to justify clinically relevant methods and specifications (Confidence, limitations, and challenges for PBPK applications to Absorption, food effect, and formulation prediction, Jones et al, 2015)

BCS	Level of Confidence	Limitations and challenges
BCS I	High	No significant limitations or challenges for absorption prediction in fasted or fed state.
BCS II	Medium to Low	Need to ensure that in vitro data and/or in vivo models for solubility, dissolution, and precipitation are relevant for humans.
BCS III	Low	Role of food on bile-micelle binding, P-gp and permeability can be unclear.
BCS IV	Low	Complex interplay between multiple factors, including solubility, permeability, and transporter interactions. Difficult to verify model as multiple mechanisms involved cannot be verified independent of each other.

How PBPK modeling can be used to justify dissolution is not critical or waived?

Opportunity 3: More Clear and More Harmonized Regulatory Requirements

- Stakeholders agree upon issues and pain points
- Open dialogue on issues/pain points with an attempt to find common grounds on
 - Definitions and roles of various methods (Day 1)
 - applications and limitation of PBPK modelling (Day 2)
 - recommendations for revising the dissolution requirements in SUPAC
 - Framework for developing clinically relevant methods and specifications (Day 3)
 - Gain acceptance for the option that IVIVC/R dissolution methods for biowaiver or post-approval change evaluation only, not for QC if lack of robustness (Days 1 and 3)

Thanks.

Any immediate questions?