Clinically Relevant Dissolution Specifications: FDA Perspective and Initiatives

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Outline

• Division Organization and Responsibilities
• Current State
• Desired State
• Initiatives
• Additional Considerations
• Conclusions
• Questions
Organization

THE OFFICE OF PHARMACEUTICAL QUALITY

Immediate Office
PMAS Staff

Office of Program and Regulatory Operations

Office of Policy for Pharmaceutical Quality

Office of Biotechnology Products

Office of New Drug Products

Office of Lifecycle Drug Products

Office of Testing and Research

Office of Surveillance

Office of Process and Facilities
Organization

- 2 Primary Review Branches
- 1 Support and Research Branch
- Review Branches Organized by Therapeutic Area
- Support and Research Branch focuses on issues that support review functions (e.g. in silico modelling, IVIVC/R, PKPD, PBPK)
Program Responsibilities

- PDUFA and GDUFA related Biopharmaceutics Reviews
  - NDAs
  - NDA supplements
  - INDs
    - ANDAs (QC In-Vitro Release)
    - ANDA supplements
    - Control Documents (QC In-Vitro Release)
    - Consults (OGD, CDRH, Citizen Petitions)
Why Clinical Relevance?

• Evaluate risks based on clinically relevant product attributes, which impact the drug safety and efficacy

• Consistent safety and efficacy performance for the marketed product compared to those for the clinical trial formulation

• From a Biopharmaceutics perspective, this impacts in-vitro release testing (e.g. Dissolution)
Why Clinical Relevance?

- Better understanding of critical quality attributes and manufacturing processes
- Helps link the product quality (e.g. formulation science, chemistry, manufacturing) to the safety and efficacy of the product (i.e. Bioequivalence)
- Enhanced lifecycle management (e.g. post approval changes)
- CDER Organizational Strategy: Clinically Relevant Quality Standards
Biopharmaceutics Approach

In Vivo

In Silico

In Vitro

Biopharmaceutics
Biopharmaceutics Approach
Current State
Current State

Dissolution assessment often independent of in vivo assessment

Dissolution methodology sometimes oversimplified for higher risk products (e.g. apparatus selection, media, etc.)
Desired State

Early product method development data → In Vivo Data ← In Vitro Data → In Silico Data

Clinically Relevant In Vitro Acceptance Criteria
Initiatives: How do we get there?

• Currently focusing on higher risk products
  – Modified Release Formulations
• Encourage IVIVC Applications
• Encourage QBD applications/concepts
• Plans for leveraging FDA knowledgebase if applicable (e.g. physiological parameters/mechanistic approach/physicochemical attributes)
• In Silico Modeling and Analysis
Requests for additional information:

- Solubility data for the drug substance covering the pH range

- Formulation dependent dissolution method development encouraged. Method development showing selection of optimal test method (e.g. selection of the equipment/apparatus, media, agitation/rotation speed, pH, assay, sink conditions, surfactant selection criteria, etc.)

- Any testing conducted to demonstrate the discriminating ability of the selected dissolution method for the drug product manufactured under target conditions vs. the drug products that are intentionally manufactured with clinically meaningful variations (i.e. aberrant formulations and manufacturing conditions) for the most relevant manufacturing variables
Additional Considerations

• If it ain’t broke…

• Open to different dissolution apparatuses with justification
Additional Considerations

• “Bio-Relevant Dissolution”
  – Apparatus?
  – Media?
  – In-Vivo Correlated?

From QC perspective, could be none or all of these. Application/Product specific. Open to consideration with justification.
Additional Considerations

• Exploring the use of IVIVR (when IVIVC has failed)
  – Can provide a rank-order relationship b/w dissolution and systemic exposure
  – While not a surrogate for BE, could provide determination of clinically relevant specifications
Conclusions

• Evolving thought processes
• Open to exploring new approaches/methodologies
• Clinically relevant specs could:
  – Allow for wider in vitro release acceptance criteria
  – Provide more insight during post approval changes
  – Increased confidence in release and stability data
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Questions?