Dissolution – Biopharmaceutics Vision in the Office of New Drug Products

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Outline

• Division Organization and Responsibilities
  – OPQ Standup
  – A historical perspective
• Current state
• Desired state
• Initiatives
• Additional Considerations
• Conclusions/Questions
OPQ Standup

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

Approximately 10 months old!
A historical perspective

• Biopharmaceutics discipline at FDA

OGD
Divisions of Bioequivalence

ONDQA
Biopharmaceutics Review Staff

OPQ/ONDP
Division of Biopharmaceutics
Division 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)
Biopharmaceutics

GDUFA

ANDAs (QC In-Vitro Release)
ANDA supplements
Control Correspondence
Consults

PDUFA

NDAs
NDA supplements
INDs
Consults

Current State
Biopharmaceutics

GDUFA
- QC Release Testing (e.g. dissolution)
- SUPAC Related PAS-dissolution, In-Vitro Release Tests

PDUFA
- b(1) & b(2) Biowaivers
- BCS
- QC dissolution
- IVIVC/R
- SUPAC Related PAS-dissolution
- ER Claim
- MR Integrity (e.g. in vitro EtOH Dumping)
• Biopharmaceutics:
  – The study of the physical and chemical properties of drugs and their proper dosage as related to the onset, duration, and intensity of drug action.¹

• Applying this definition to the regulatory perspective

Challenges

• PDUFA and GDUFA program responsibilities, timelines, and deliverables are markedly different
  – Balancing between the programs is challenging

• Historically, approaches to the review have been different
  – Finding some parity in approach

• Training of new staff
Why Clinical Relevance?

- Conceptually, CRS can apply to any aspect of review. From a Biopharmaceutics perspective, this impacts QC in-vitro release testing (e.g. Dissolution).
- Provide better test methods and acceptance criteria that are able to identify and reject drug product batches that are likely to perform inadequately in the indicated patient population.
- 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.
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

Biopharmaceutics

In-Silico

In-Vitro
Biopharmaceutics Approach
Current State

Biopharmaceutics
Current State

- Dissolution assessment often independent of in vivo assessment
- Dissolution methodology sometimes oversimplified for higher risk products (e.g. apparatus selection, media, etc.)
- Sometimes methodology is overdiscriminating as in vivo results can be “less sensitive”
  - CRS via IVIVC or in silico supported can lead to wider specifications
New Drug Development

- **Discovery**
  - Medicinal Chemistry
  - Target ID
  - Receptor Binding

- **Preclinical Development**
  - PK/PD
  - ADME
  - Safety
  - Pre-formulation
  - Drug Delivery
    - PK Optim.
    - Dosage Form Selection
    - Modeling

- **Clinical Development (Phase 1, 2, 3)**
  - Phase 1-3 Trials
  - Human PK
  - Dose Selection
  - Bioavailability
  - Formulations Bridging

- **Regulatory Decision**
  - Approval / Complete Response
  - Phase IV Commitments

- **Market**

- Agency sees smaller “snapshot”
- Larger datapool often not used
- Misconception where CRS consideration occurs
Generic Drug Development

- Agency sees smaller “snapshot”
- Larger datapool often not used
- Misconception where CRS consideration occurs
Desired State (A/NDA)

- Early product method development data
- In Vivo Data
- In Vitro Data
- In Silico Data

Clinically Relevant
In Vitro Acceptance Criteria
Desired State

• CRS for dissolution is difficult with the in vitro and in vivo data currently contained in a typical ANDA

• Need the extra data not always contained in regulatory submissions (e.g. product/method development data)

• Aims to leverage in silico modeling to handle the extra data and potential for relationships or correlations
Initiatives: How do we get there?

• Currently focusing on higher risk products
  – Modified Release Formulations

• Encourage IVIVC Applications

• Encourage QBD applications/concepts
• 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
Requests for additional information:

• Any IVIVC/R pre-analysis (i.e. correlation studies conducted in development stage, but not submitted) could be submitted.

• Any computational modeling (e.g. mechanistic IVIVC, PBPK absorption/dissolution modeling, simulations) and its related dataset/database could be submitted.
Modifying the Biopharmaceutics Approach

- Plans for leveraging FDA knowledgebase if/where applicable
  - Physicochemical attributes
    - Log P, pKa
  - Relevant physiological parameters
    - GI Transit/Residence Time, pH, biological volumes, absorption parameters, fraction unbound in plasma, blood to plasma ratio, etc.
  - Publicly available information (product labeling, publications, FOIA documents)
    - PK Parameters, Excipient effects, Permeability/absorption
- In Silico Modeling and Analysis
In Silico Modeling

• Many approaches possible
  – Curve fitting exercise (data fit to several models leading to model selection criteria)

• Correlations may not always be possible, but other information can be discerned to make CRS

• Best examples so far include clear, stepwise description of the thought process
Additional Considerations

• Open to different dissolution apparatuses with justification

• “Bio-Relevant Dissolution”
  – Apparatus?
  – Media?
  – In-Vivo Correlated?
  From QC perspective, could be none or all of these. Application/Product specific.

• Various apparatuses often explored in development phase but not seen as “viable” as QC.
  – Could still have relevance in modeling
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
  – Explorations using mechanistic modeling in support of IVIVC/R
Conclusions

• Evolving thought processes/Flexible
• Open to exploring new approaches/methodologies
• More early development data should be submitted in support of QC in vitro release tests
  – Computational modeling a useful tool with larger data pool
• 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?