Biorelevant Dissolution Testing for In Vitro In vivo Correlation/Relationship (IVIVC/R) Development: Regulatory Perspective

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IVIVC/R Concept

• IVIVC: “a predictive mathematical model describing the relationship between an in vitro property of a dosage form (e.g., the rate or extent of drug dissolution or release) and a relevant in vivo response (e.g., plasma drug concentration or amount of drug absorbed)”

• IVIVR: a semi-quantitative or rank-order relationship between an in vitro property of a dosage form (e.g., the rate or extent of drug dissolution or release) and a relevant in vivo response (e.g., plasma drug concentration or amount of drug absorbed)

• IVIVC/R applications:
  • Biowaiver (IVIVC)
  • Clinically relevant dissolution specification
  • Risk assessment and clinically relevant design space/specifications in QbD
Current Status of IVIVC Studies in the NDA and IND Submissions

- Submission rate is very low

Analyzing Root Causes for Underutilized Status/Low Success Rate of IVIVC/R

• It is very challenging for IVIVC development meeting regulatory requirements (e.g., 3 release rates; cross-over studies; fasted conditions)

• Low success rate of IVIVC studies is discouraging
  ➢ It could be very challenging to correlate in vitro dissolution vs in vivo absorption which is a complex integration of in vivo dissolution, GI transition, degradation, GI absorption, first-pass metabolism etc.)

  ➢ The conventional IVIVC methodologies (e.g., two-stage) take insufficient considerations on drug in vivo dissolution and absorption mechanisms under physiological state

  ➢ The compendial in vitro dissolution test may not be bio-predictive
Biorelevant Dissolution Testing

A biorelevant dissolution test can be defined as an in vitro test that reflects physiological environment in the test conditions with a purpose of correlating in vitro with in vivo drug absorption.

**Biorelevance**

**Medium:**
- SGF w/o pepsin
- SIF w/o pancreatin
- FaSSGF/FeSSGF
- FaSSIF/FeSSIF

**Device:**
- Artificial Dynamics GI System
- Dissolution/permeation System
- Two-compartment apparatus (artificial stomach and Duodenum; FloVitro)
- Two-phase Dissolution apparatus (water: organic)

**Others:**
- Hydrodynamics
- Real-time testing for long acting formulations
Opportunities and Challenges of Biorelevant Dissolution

• **Opportunities:** streamline product development and lead to time and cost savings during product development
  - Pre-clinical development: screen active pharmaceutical ingredient; select/develop formulation selection; guide quality control method development
  - Clinical development: correlate with in vivo dissolution; support clinical trial design; investigate food effect; explore IVIVC/R; assess the risk and impact of CMC on the in vivo performance; clinically relevant specifications and control strategies; bridging formulations; etc.
  - Lifecycle: support post-approval changes (via IVIVC/R)

• **Challenges:**
  - Complex medium/device/procedures
  - Unrealistic for quality control purposes
  - May not guarantee a correlation with the in vivo
Current Status of Biorelevant Dissolution Testing in the Submissions of IVIVCs

- 5 out of 53 IVIVCs used biorelevant media in the dissolution testing

<table>
<thead>
<tr>
<th>Drug product</th>
<th>Dosage form</th>
<th>Dissolution method</th>
<th>Development strategy</th>
<th>Acceptable or not</th>
<th>Deficiencies</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>IR tablet</td>
<td>Apparatus I; rpm 100; pH1.2 mSGF without pepsin; 900 mL</td>
<td>Two-Stage</td>
<td>No</td>
<td>1. In vivo studies were conducted in fed condition while food has significant effect on drug absorption; 2. Excluding 4 subjects' in vivo data from a total 16 subjects without acceptable justifications; 3. inconclusive predictability</td>
</tr>
<tr>
<td>B</td>
<td>ER tablet</td>
<td>Apparatus II; rpm 100; pH 6.8 SIF without pancreatin; 900 mL</td>
<td>One-Stage</td>
<td>No</td>
<td>1. Non-mechanistic term was included in the model without reasonable justification; 2. Mean in vivo data instead of individual data was used</td>
</tr>
<tr>
<td>C</td>
<td>ER capsule</td>
<td>Apparatus I; rpm 75; SGF for 2 hrs followed by pH7.0 buffer for 4 hrs; 900 mL</td>
<td>Two-Stage</td>
<td>No</td>
<td>1. No difference in the in vitro release rate between formulations; 2. In vitro and in vivo data were not from the same batch</td>
</tr>
<tr>
<td>D</td>
<td>ER tablet</td>
<td>Apparatus II; 50 rpm; SGF without pepsin, pH 1.2; 900 mL</td>
<td>Two-Stage</td>
<td>No</td>
<td>No submissions of the in vivo/vitro data, model files and IVIVC study report</td>
</tr>
<tr>
<td>E</td>
<td>ER capsule</td>
<td>Apparatus I; rpm 100; pH1.2  SGF without pepsin; 900 mL; 12 hrs</td>
<td>Two-Stage</td>
<td>Yes</td>
<td>N/A</td>
</tr>
</tbody>
</table>

- Use of biorelevant medium alone may not lead to increased success rate of IVIVCs
- The failure of IVIVC models was due to common deficiencies in IVIVC development
Case Study: Drug Product E

- **Drug product information:**
  - ER capsules: polymer-based delivery system
  - BCS Class I
  - Multiple strengths: compositionally proportional

- **Objectives of the IVIVC study**
  - To request the waiver of the in vivo BE for the lower strengths (the four strengths are dose proportional)
  - To support dissolution specification

- **Formulations for IVIVC development**
  - Different release rates were produced by varied ratio of coated ER beads
Level A Two-Stage IVIVC Flow Chart

Data exploration (in vitro and in vivo) → In vitro dissolution modeling → Deconvolution to obtain %absorbed versus time profiles → Construct IVIVC Model %absorbed vs %dissolved → Applications → Validation

UIR generation from the IR formulation → Justify the proposed dissolution acceptance criteria

Support biowaiver request for lower strengths
In Vitro Dissolution Data and Modeling

- In vitro dissolution method (same as the QC method):
  - USP Apparatus I
  - rpm 100
  - 900 mL Simulated Gastric Fluid without pepsin, pH 1.2
  - Drug dissolution was demonstrated condition independent (pH 1.2, 5.0 and 6.8; rpm 50, 100, and 150), indicating one release rate for IVIVC model development may be sufficient per IVIVC Guidance

Makoid Banakar model was selected based on AIC, CV%, residual plot, predicted vs. observed plot
In Vivo Data and IVIVC Model Development

- **In vivo data from a single dose cross-over study including:**
  - Unit impulse response (UIR) generated from IR tablet
  - Slow and fast release formulations used for model construction (deconvolution-based) and internal validation
  - To-be-marketed formulation was used for external validation

- **Individual deconvolution**

- **Linear IVIVC model:** \( \text{Fabs} = \text{AbsScale} \times \text{Diss}(T\text{scale} \times T\text{vivo}) \)

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% Absorbed vs Time  
% Absorbed vs % Dissolved  
Tvivo vs Tvitro

- Fast  
- Slow
# Model Validation

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Parameter</th>
<th>% P.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast release</td>
<td>AUC</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td>Cmax</td>
<td>5.27</td>
</tr>
<tr>
<td>Slow release</td>
<td>AUC</td>
<td>1.71</td>
</tr>
<tr>
<td></td>
<td>Cmax</td>
<td>8.22</td>
</tr>
<tr>
<td>Avg Internal</td>
<td>AUC</td>
<td>1.21</td>
</tr>
<tr>
<td></td>
<td>Cmax</td>
<td>6.75</td>
</tr>
<tr>
<td>External</td>
<td>AUC</td>
<td>8.4</td>
</tr>
<tr>
<td></td>
<td>Cmax</td>
<td>0.8</td>
</tr>
</tbody>
</table>

**Validation acceptance criteria (per IVIVC guidance):**

Internal validation: average absolute percent prediction error (% PE) of 10% or less for Cmax and AUC and the % PE for each formulation should not exceed 15%

External validation:% PE of 10% or less for Cmax and AUC
**IVIVC Application 1: Biowaiver**

Step 1: Collect dissolution profiles of primary batches at lower strengths

Step 2: In vitro dissolution profile modeling (same model as IVIVC construction)

Step 3: Predict plasma drug concentration time profiles for the lower strengths based on convolution using the IVIVC model

Step 4: Evaluate BE using predicted PK parameters (after dose normalization)

<table>
<thead>
<tr>
<th>Strength</th>
<th>Parameter</th>
<th>Ratio of predicted to the target</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>AUClast</td>
<td>1.19</td>
</tr>
<tr>
<td></td>
<td>Cmax</td>
<td>1.05</td>
</tr>
<tr>
<td>S2</td>
<td>AUClast</td>
<td>1.18</td>
</tr>
<tr>
<td></td>
<td>Cmax</td>
<td>1.04</td>
</tr>
<tr>
<td>S3</td>
<td>AUClast</td>
<td>1.18</td>
</tr>
<tr>
<td></td>
<td>Cmax</td>
<td>1.04</td>
</tr>
</tbody>
</table>

*Biowaiver of all lower strengths were granted*
**IVIVC Application 2: Dissolution Acceptance Criteria**

Current practice for ER products:

- at least three time points covering the initial, middle, and terminal phases of the complete dissolution profile
- the selection of acceptance criteria ranges is based on mean target value +10% and NLT 80% for the last specification time-point
- wider specification ranges may be acceptable if justified with IVIVC

In vitro dissolution

<table>
<thead>
<tr>
<th>Deviation from Target</th>
<th>Ratio of Predicted to Target</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cmax</td>
</tr>
<tr>
<td>-10%</td>
<td>0.90</td>
</tr>
<tr>
<td>+10%</td>
<td>1.06</td>
</tr>
<tr>
<td>-13%</td>
<td>0.87</td>
</tr>
<tr>
<td>+13%</td>
<td>1.08</td>
</tr>
</tbody>
</table>
Summary

- It could be very challenging for IVIVC/R development indicated by low submission/success rate of IVIVCs in the new drug applications
- Biorelevant dissolution method was not often considered in the IVIVC/R development
- The use of biorelevant medium alone may not lead to increased success rate of IVIVCs
- New modeling approaches are needed to guide bio-predictive dissolution method development and support IVIVC establishment (e.g., PBPK absorption modeling and simulation)
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