FDA Experience on the Application of Modeling and Simulation in Setting Clinically Relevant Drug Product Specifications

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OUTLINE

- The meaning of setting Clinically Relevant Drug Product Specifications (CRDPS)

- History of CRDPS setting
  - Past, present, what to expect in the future

- Approaches in setting CRDPS
  - Based on BCS Classification
  - Based on the type of clinical data available

- Case studies for drug products comprising BCS class 2/4 compounds:
  - IVIVR
  - IVIVC
  - In silico PBPK Oral Absorption Modeling and Simulation

- Concluding remarks
Setting CRDPS Requires the Establishment of a Bridge

Without the use of dissolution, it would be rather impractical to verify every variation in the CMAs/CPPs through the conduct of efficacy and safety and/or BA/BE studies.

The development of a dissolution method that is not only discriminating but also biopredictive becomes critical.
What Are the Consequences of the Lack of an In Vivo Link?

- CRDPS can still be established in the absence of a direct link (i.e. via PK studies)

- However, without understating the relationship between variations in the quality attributes and clinical outcome for **BCS class 2/4 drugs**, drug product acceptance criteria limits may be overly wide, unnecessarily tight or completely irrelevant to clinical performance

- As such, variations in the identified critical quality attributes, which are within the approved limits may pose unknown, but **potentially significant risks to patients**

Adapted from S. Suarez, *The Relevance of Biopredictive Dissolution Testing*. DIA 2016, Annual meeting
….. “determining the relationship between critical manufacturing variables and a response surface derived from an in vitro dissolution profile and an in vivo bioavailability data set. ....... the goal is to develop product specifications that will ensure bioequivalence of future batches”......
Applicant's Proposed Dissolution Acceptance Criterion, Another Story

<table>
<thead>
<tr>
<th>Items</th>
<th>Dissolution at 30 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of batches</td>
<td>34&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Average</td>
<td>91.2%</td>
</tr>
<tr>
<td>Standard Deviation (SD)</td>
<td>3.7%</td>
</tr>
<tr>
<td>x-k<em>s (average -2.549</em> SD)</td>
<td>81.8%</td>
</tr>
<tr>
<td>Calculated Q value Q(%)=x-ks-5</td>
<td>76.8%</td>
</tr>
<tr>
<td>Proposed Q value</td>
<td>75%</td>
</tr>
</tbody>
</table>

Example of dissolution acceptance criterion setting proposal based on a parametric approach rather than a response surface methodology linking in vitro to in vivo performance.
Approaches for Establishing CRDPS: Where Are We Now?

- **Approach 1:**
  - Limits established based on the characteristics of batches tested in pivotal phase 3 clinical trials

- **Approach 2:**
  - Limits established based on a range of release characteristics resulting in BE

- **Approach 3**
  - Limits established based on predictive and robust in vivo in vitro correlations

S. Suarez, Establishing clinically relevant drug product specifications. AAPS 2012, Annual meeting
**Approaches for Establishing CRDPS: Where are we now? Cont.**

**APPROACH 1**

- **No PK data available** linking variations in CMAs/CPPs to dissolution/clinical performance
- Ranges established based on batches tested in pivotal phase 3 clinical trials
- Clinically relevance **assured** for drug products comprising BCS class **1/3** compounds
- **Clinically relevance not always assured** for drug products comprising BCS class **2/4** compounds

No regulatory flexibility for BCS Class 2/4 drugs as ranges are established based on ranges/ in process controls from batches tested in Pivotal Phase 3 Trials.
Approaches for Establishing CRDPS: Where are we now?, Cont.

**APPROACH 2**  
(IVIVR/Response surface Methodology)

- **PK data available** linking variations in CMAs/CPPs to dissolution/clinical performance  
  - rank order relationship

- CRDP limits established based on a range of release characteristics resulting in bioequivalence

Regulatory flexibility limited to the extremes of dissolution profiles for batches that were BE
APPROACH 3 (IVIVC)

PK data available linking variations in CMAs/CPPs to dissolution/clinical performance
- rank order relationship resulting in either:
  - Level A IVIVC
  - Multiple Level C IVIVC

CRDP limits established based on model predictions

Multiple Level C IVIVC may not be applicable to waive major CMC changes requiring BE, but could be useful in supporting the establishment of CRDPS

Regulatory flexibility limited by ranges in release rate used in the construction of the model (no extrapolation)
What are the Challenges in Setting CRDPS?

- Lack of efficient strategies for the development of in vitro dissolution methods that are predictive of in vivo performance

- No inclusion of dissolution testing in DoE studies for the selection of CMAs and CPPs and for the verification of design spaces ranges

- Challenges in conducting dedicated in vivo PK studies with aberrant product variants

- An ideal approach in setting CRDPS is via IVIVC or IVIVR implementation. However, the overall acceptance rate of the IVIVC submissions is about 40%. Moreover, the number of IVIVC studies seen in the submissions per year is not increasing*

Are we there yet? What are the current emerging trends?
The Utility of In Silico PBPK M&S

Development of IVIVC

Biopredictive Dissolution Testing

Risk assessment/Establishment of CRDPS

In silico PBPK Modeling and Simulation

Prototype Dissolution Testing
CASE STUDY 1:

The Application of IVIVR/Bracketing Approach to Inform CRDP Acceptance Criteria for Drug Product A (IR Tablet Comprising BCS Class 2 Compound)
Effect of PSD of the API on In Vitro/In Vivo Performance

Bracketed releasing profiles are BE

Target Formulation

BA Study

Drug Dissolved (%)

Time

Single dose (linear scale)
Setting Clinically Relevant Limits for Dissolution and Particle Size (PS)

- Lower bound of PS
- Target Formulation
- Upper bound of PS

Not BE batch

Slowest releasing profile used to set dissolution acceptance criterion
CASE STUDY 2:

The Application of IVIVC in Establishing CRDP Dissolution Acceptance Criteria for Extended Release Drug Product B
Wider than Standard (±10%) In Vitro Release Limits for Drug Product B

Convolution

Applicant's proposed ± 15%
Target (mean profile)
Target ± 10%

Predicted plasma concentrations (ng/mL)

- Applicant's high pred
- Applicant's low pred
- Target
- Target+10
- Target-10

Fraction Dissolved

Time (hrs)

0 5 10 15 20

0.0
0.2
0.4
0.6
0.8
1.0

0
10
20
30
40
50
60
70
80
90

Time (hrs)
**Wider than Standard (±10%) In Vitro Release Acceptance Criteria, cont.**

<table>
<thead>
<tr>
<th></th>
<th>Cmax (ng/mL)</th>
<th>AUC (ng*hr/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% difference (high vs. low)</td>
<td>% difference (high vs. low)</td>
<td></td>
</tr>
<tr>
<td>Target -10%</td>
<td>17%</td>
<td>15%</td>
</tr>
<tr>
<td>Target +10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Target -15%</td>
<td>19%</td>
<td>17%</td>
</tr>
<tr>
<td>Target +15%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dissolution acceptance criteria were set based on the mean dissolution values for the pivotal clinical batches ± 15% variation.

Wider dissolution acceptance criteria foster regulatory flexibility for those CMAs/CPPs impacting dissolution.
CASE STUDY 3:

The Use of IVIVC in Establishing Drug Product Specification Ranges to Ensure Appropriate Cmax Levels for Drug Product C (IR Tablet Formulation)
Dissolution Profiles of Batches Used in the Construction of a Multiple Level C IVIVC (IR Tablet, BCS Class 2)

- **Target Cmax = 7.5 uM**
- **Cmax = 10 uM**
- **Cmax = 5 uM**
- **Cmax = 2 uM**

**Batch A:** Target: 22 kp, Dissolved: 15 kp

**Batch D:** Target: 22 kp, Dissolved: 32 kp

**Batch E:** Target: 22 kp, Dissolved: 38 kp

D and C not BE to Target

Q=80% in 20 min
IVIVC Predicted Border Line for Establishing BE to the Target Formulation

IVIVC approach: Q=75% at 30 min

Predicted Borderline profile
Design Space for Down Stream Process (e.g. Compression Force)

Tensile strength limits: based on IVIVC predictions

Corresponding tablet hardness ranges: linear correlations of tensile strength vs. hardness

Compression DS
### Hardness Limits for all Drug Product C Images as Established by IVIVC Boundaries

<table>
<thead>
<tr>
<th>Drug Product C Image</th>
<th>Hardness Limit (kp)</th>
<th>Hardness Limit (kp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>15</td>
<td>25</td>
</tr>
<tr>
<td>b</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>c</td>
<td>9</td>
<td>22</td>
</tr>
<tr>
<td>d</td>
<td>20</td>
<td>30</td>
</tr>
</tbody>
</table>

**Without IVIVC:** hardness = 52 Kp
Verification of Water Activity
Proposed Ranges

Upper limit on the final tablet moisture: ≤ X % RH
CASE STUDY 4:
The Application of PBPK M&S to Inform CRDP Acceptance Criteria for dissolution and API Particle Size Distribution (PSD) (Drug Product Y)
Model Development/Validation and Application for Drug Product Y (IR Tablet/BCS 2)

MODEL DEVELOPMENT

- Physicochemical properties of drug product Y
- Information on Metabolic pathways and rate
- IV PK Data : Disposition Model
- Oral PK Data from target formulation: Absorption model

MODEL VALIDATION

- Dissolution Profiles from several trials of same formulation
- Dissolution profiles from non-BE batches
  - % PE were less than 10% in all cases

MODEL APPLICATION

1. **Dissolution safe space**: simulations performed using virtual dissolution profiles below/above the proposed specs. Virtual BE of proposed bounds vs. target.

2. **PSD safe ranges**: simulations performed using a virtual drug substance batch with a particle size distribution at the limit of the proposed specification for particle size. Virtual BE for lower/upper bounds of D50 vs. target.
Setting Clinically Relevant Dissolution Acceptance Criterion

Passed BE and Virtual BE

Clinical batch

Failed BE and virtual BE

Passed virtual BE: Slowest releasing profile (virtual) used to set dissolution Acceptance criterion
BE was demonstrated between the biobatch and the same formulation with PSD within proposed specification.

There is a low risk on having a significant effect on in vivo performance when using API within the PSD specification.
## Regulatory Applications of PBPK Absorption Models Submitted to OPQ

<table>
<thead>
<tr>
<th>Applications</th>
<th>Situation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dissolution Method and Acceptance Criteria</strong></td>
<td></td>
</tr>
<tr>
<td>Justify/support bio-predictive dissolution method</td>
<td>Use the verified PBPK/absorption model combined with bioequivalence clinical study and dissolution profiles generated to show that the proposed dissolution method can reject non-BE (bioequivalence) batch</td>
</tr>
<tr>
<td>Set clinically relevant dissolution acceptance criteria</td>
<td>Allow more permissive dissolution acceptance criterion.</td>
</tr>
<tr>
<td></td>
<td>Additional evidence (data) needed to validate model and confirm predictive performance</td>
</tr>
<tr>
<td><strong>Set clinically relevant drug product limits for CMAs and CPPs</strong></td>
<td></td>
</tr>
<tr>
<td>CMAs (e.g. particle size distribution)</td>
<td>Predict particle size distribution (PSD) upper limit which pharmacokinetics would result in similar in vivo performance to the target (clinical batch)</td>
</tr>
<tr>
<td>CPPs (hardness)</td>
<td>Used to justify specification range of compression force based on the predicted in vivo performance</td>
</tr>
</tbody>
</table>
Challenges in Current PBPK Absorption Models

- Few regulatory submissions containing PBPK absorption models in support of setting CRDPS
- Lack of robustness in the input data
- Precipitation of weak bases is not well addressed by commercial software
- Not enough clinical data for robust verification of the model(s)
- No clear regulatory guidance in terms of criteria for model validation
- It seems that there are differences among commercial software in predicting intestinal absorption partially due to “difficulty in separating the influence of modeler bias in selection of input parameter values and in selection of model options...”*

Concluding Remarks

Are we there yet?

- Setting CRDPS for BCS class 2/4 drugs requires establishing a link to in vivo performance
  - Challenges with the conduct of dedicated PK studies
  - The success rate of IVIVC is low
  - PBPK absorption M&S is a promising but underused tool for risk assessment and establishing CRDPS

What is the benefit for Industry?

- Advancement in vivo predictive dissolution and IVIVC combined with PBPK absorption models provides an opportunity for taking a major step in model based drug development and to support regulatory flexibility in drug product specifications

- Use of new approaches in the development of IVIVC
- Use of mechanistic PBPK absorption models to:
  - Guide the development of a biopredictive dissolution method
  - Increase the rate of success of IVIVC
  - Risk assessment for the selection of CMAs and CPPs
  - Verification of the Design Spaces

What to expect in the near future?

With the ultimate goal to setting CRDPS
OPQ Values

Put patients first by balancing risk and availability
Acknowledgments

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