Establishing Clinically Relevant Drug Product Specifications: FDA Perspective

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Outline

➢ Definition of Clinically Relevant Drug Product Specifications

➢ The Role of Biopharmaceutics
  o BA/BE Studies
  o Dissolution

➢ Approaches for Setting Clinically Relevant Drug Product Specifications
  o Approach 1
  o Approach 2
  o Approach 3
    ▪ Case Study

  o Summary

  o Conclusions
What Are Clinically Relevant Specifications (CRS)?

CRS are those specifications that take into consideration the clinical impact of variations in the critical quality attributes (CQA) and process parameters assuring a consistent safety and efficacy profile.
CRS Implies Establishing a Link

Relevant Quality Attributes

IN VIVO PERFORMANCE

BIOPHARMACEUTICS

Compression
Particle size
Dissolution
Blending
Why is the Use of Biopharmaceutics Relevant?

Dissolution ($f_2$ testing)

Clinical Studies

BA/BE

Design Space
Why is it Important to Determine the *in vivo* Impact?

- When manufacturing changes are linked to *meaningful in vitro tests*, it enables the development of science and risk based specifications.

- Consistent *in vivo* product performance (safety and efficacy profiles) for the marketed product relative to the clinical trial formulation.
The Relevance of Dissolution

- A quality control tool
  - Batch-to-batch consistency
  - Provide quality assurance
    - The only test that can monitor if the rate of drug solubilization is impacted by product storage conditions

- Guide formulation development
  - The only product test that truly measures the effect of formulation and physical properties of the API on the rate of drug solubilization

- Dissolution has being identified as a surrogate for bioavailability
  - Some manufacturing changes can be approved based only on the comparability of their dissolution profiles without having to conduct in vivo studies
The Relevance of Dissolution

Clinically meaningful dissolution specifications

- Compression
- Particle size
- Blending
- Water content
How are clinically relevant drug product specifications established?
Approaches for Establishing CRS

- **Approach 1:**
  - Range established based on batches tested in pivotal phase 3 clinical trials

- **Approach 2:**
  - Range established based on a range of release characteristics resulting in bioequivalence

- **Approach 3:**
  - Range established based on predictive and robust in vivo in vitro correlations
Approach 1:
Range established based on batches tested in pivotal phase 3 clinical trials
Approach 1

- Dissolution is a CQA

- No data linking formulation variants with different release characteristics to plasma levels

- Assume the use of a discriminating dissolution method and dissolution acceptance criterion

- Regulatory flexibility limited/determined by the dissolution acceptance criterion/ $f_2$ statistical test
What is a Discriminating Dissolution Method?

- A method that is able to differentiate drug products manufactured under target conditions vs. drug products that are intentionally manufactured with meaningful variations (i.e. aberrant formulations and manufacturing conditions) for the most relevant manufacturing variables (e.g. drug substance particle size, compression force, tablet hardness, etc.)
Dissolution Profiles of Tablets with Varying Bulk Density (BD) and Particle Size (PS)

Discriminating ability is not only determined by the dissolution method conditions, but also by the timing of the acceptance criterion.
Clinically Relevant Particle Size Ranges

Batch D failed $f_2$ testing (<50)

Clinical batch

Discriminating Dissolution spec: $Q = 80\%$ at 15 min.

Non-discriminating dissolution spec: $Q = 80\%$ at 20 min.

Batch A
Batch B
Batch C
Batch D

Drug Dissolved (%) vs. Time (minutes)

Upper bound

Lower bound
What Are the Limitations of Approach 1?

- Regulatory flexibility is limited and determined by the dissolution acceptance criterion and $f_2$ statistical test.

- One cannot really determine if the dissolution method and acceptance criteria are under- or over-discriminating:
  - No data available to determine if the method and acceptance criterion are able to reject for batches that are not BE.

Clinical relevance may not always be assured.
Approach 2:
Established range of release characteristics resulting in bioequivalence
Approach 2

1. Manufacture product variants with different release characteristics
2. Select Optimal dissolution method with adequate discriminating power
3. Determine bioavailability for product variants
4. Determine dissolution rates resulting in similar in vivo performance
5. CRS specifications chosen to ensure similar (BE) product performance
What are the Advantages of Approach 2?

- Assures the establishment of clinically relevant dissolution method and acceptance criterion
  - Direct link to in vivo performance

- An in vivo performance similar to the target profile is always assured within the ranges tested

- Regulatory flexibility resulting in wider specifications
Illustration of the Advantages

Batches A, B, C, D, and Clinical were BE

Approach 1: Q= 80% at 15 min.

Approach 2: Q= 80% at 20 min.
What Are the Limitations of Approach 2?

Clinical performance can be assured for the following CMC changes:

- Those evaluated in the bioequivalence study
- Those changes whose dissolution profiles fall within the extremes of dissolution profiles for batches that were BE
- Other changes typically evaluated by $f_2$ statistical test
Illustration of the Limitation

- Batches B through F were BE to clinical Batch

- Batch X not part of BE study. However, $f_2$ value is > 50

- $f_2$ value for batch Y is < 50
Do the CMC Changes to Batch Y Have an Impact on the Efficacy and Safety of the Drug?

How Can we Answer this Question?
The Role of Models in Setting Clinically Relevant Specifications

- Validated models (e.g., IVIVC) can provide the means for predicting/determining the clinical impact of CMC changes without the need for additional in vivo studies
Approach 3: 
*Predictive and robust in vivo in vitro correlations*
The Purpose of IVIVC

- Reduction of regulatory burden: IVIVC in lieu of required *in vivo* studies, leading to:
  - Time/Cost savings during product development
    - Less testing in humans
  - Permits setting wider than standard (±10%) *in vitro* release acceptance criteria
  - Permits the setting of specifications based on targeted clinically relevant plasma concentrations
  - If available, could support the approval of a design space
    - Prediction/determination of the clinical impact of “movements” within the design space without the need for additional *in vivo* studies
    - Regulatory flexibility resulting in wider specifications
Case Study

Establishment of an IVIVC Model to Support Design Space Development
Drug Product A

- BCS 2 Drug Substance
- Immediate Release Tablet
- Several strengths
Data Used for the Construction of the IVIVC Model

- Dedicated PK study to determine the effect of hardness on Bioavailability
  - Four batches with different hardness values
  - Targeted value (clinical batch) included

- QC Dissolution Method
**Dissolution Profiles of Batches Used in the Construction of a Multiple Level C IVIVC**

![Graph showing dissolution profiles of batches with different Cmax values and target Cmax=1.48 uM. Batch A: 15 kp, Batch D: 32 kp, Batch E: 38 kp. Approach 2: Q=80% in 20 min. D and C not BE to Target.]
IVIVC Predicted Borderline for BE to the Target Formulation

Approach 3: Q=75% at 30 min

Predicted borderline profile

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dissolved (%)</th>
<th>Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>100</td>
<td>30</td>
</tr>
<tr>
<td>Target</td>
<td>93</td>
<td>30</td>
</tr>
<tr>
<td>D</td>
<td>85</td>
<td>30</td>
</tr>
<tr>
<td>E</td>
<td>90</td>
<td>30</td>
</tr>
<tr>
<td>Test</td>
<td>87</td>
<td>30</td>
</tr>
</tbody>
</table>

Cmax values:
- A: 1.67µM
- Target: 1.52µM
- D: 1.39µM
- E: 1.29µM
- Test: 1.42µM
Fishbone Diagram for “Drug Product A” (Downstream Process)

- Blending
  - Composite Assay, Content Uniformity
- Lubrication
  - Composite Assay, Content Uniformity, Elegance, Dissolution
- Film Coated Tablet Quality Attributes
  - Composite Assay, Content Uniformity, Drug Substance Phase/Form Stability, Elegance, Dissolution

- Compression
  - Composite Assay, Content Uniformity, Elegance, Dissolution
- Film Coating
  - Drug Substance Phase/Form Stability, Elegance, Dissolution
Design Space (DS) for Down Stream Process

Tensile strength limits: based on IVIVC predictions

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

Tablet friability

Compression

Lubrication
Percent Dissolved at 15 minutes Versus Tablet Tensile Strength for all Drug A Images

![Graph showing the relationship between percent dissolved at 15 minutes and tensile strength.](image-url)
### Tablet Tensile Strength Limits for all Drug Product A Images as Established by IVIVC Boundaries

<table>
<thead>
<tr>
<th>Drug Product A Image</th>
<th>Lower Tensile Strength Limit (MPa)</th>
<th>Upper Tensile Strength Limit (MPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>1.4</td>
<td>3.05</td>
</tr>
<tr>
<td>b</td>
<td>1.4</td>
<td>2.63</td>
</tr>
<tr>
<td>c</td>
<td>1.4</td>
<td>2.47</td>
</tr>
<tr>
<td>d</td>
<td>1.4</td>
<td>2.12</td>
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</tbody>
</table>
Tablet Hardness versus Tablet Tensile Strength for All Drug A Images
# Tablet Hardness Limits for all Drug Product A Images as Established by IVIVC Boundaries

<table>
<thead>
<tr>
<th>Drug Product A Image</th>
<th>Hardness Limit (kp)</th>
<th>Hardness Limit (kp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>b</td>
<td>8.5</td>
<td>16.5</td>
</tr>
<tr>
<td>c</td>
<td>8.5</td>
<td>19.5</td>
</tr>
<tr>
<td>d</td>
<td>15</td>
<td>27.5</td>
</tr>
</tbody>
</table>

Approach 2: hardness = 22 Kp
Regulatory Flexibility

Approach 1
Approach 2
Approach 3

Regulatory Flexibility
Summary

Setting clinically relevant specifications starts with the development of a clinically relevant (predictive) dissolution method and dissolution acceptance criterion

- Setting clinically relevant dissolution specifications
- Clinically relevant drug product specifications

Three approaches for setting clinically relevant dissolution specifications

- **Approach 1:**
  - Less desirable approach
  - Discriminating ability is crucial
  - There is no relationship established between in vitro release and plasma levels
  - Clinical relevance not always assured
  - Limited regulatory flexibility
  - Determined by the dissolution acceptance criterion/ $f_2$, statistical test
Summary, cont.

- **Approach 2:**
  - There is a relationship between in vitro release and plasma levels
  - Clinical relevancy is assured
    - Those manufacturing changes resulting in dissolution profiles that fall within the extremes of dissolution profiles for batches that were BE
  - Regulatory flexibility

- **Approach 3:**
  - Most desirable approach
  - There is a correlation between in vitro release and plasma levels
  - Clinical relevance is assured
  - Regulatory flexibility resulting in wider specifications

- The ultimate goal is to assure consistent in vivo product performance (safety and efficacy) for the marketed product relative to the clinical trial formulation
Conclusions

FDA encourages the conduct of dedicated BA/BE studies during product development to establish the relationship between drug products variants with different release characteristics and plasma levels:

- Mechanistic understanding of the critical manufacturing variables
- Establishment of clinically relevant drug product specifications
- Potential for developing IVIVC models
- Potential for wider drug product specifications
- Stronger link between *in vivo* and *in vitro* performance as compared to using $f_2$, statistical test
- Regulatory flexibility within the QbD frame-work
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