FDA’s current practice and challenges in the evaluation of dissolution profile comparisons in support of minor/moderate product quality changes

Om Anand, Ph.D.
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality
CDER, US-FDA

M-CERSI Workshop
May 21-22, 2019,
University of Maryland, Baltimore

This presentation reflects the views of the presenter and should not be construed to represent FDA’s views or policies
Are these profiles similar?
Dissolution Profile Comparisons

Dissolution profiles may be considered similar by virtue of (i) overall profile similarity and (ii) similarity at every dissolution sample time point.

Two Approaches to demonstrate the similarity:

Model Independent Approach:
- Similarity Factor ($f_2$)
- Multivariate Confidence Region

Model Dependent Approaches
Regulatory Application of the Dissolution Profile Comparisons in the Life cycle of a Drug Product
Dissolution Profile Comparison

Model Independent Approach Using Similarity Factor ($f_2$)

$$f_2 = 50 \cdot \log \left\{ 1 + \left( \frac{1}{n} \sum (R_t - T_t)^2 \right)^{-0.5} \cdot 100 \right\}$$

$n = \text{number of time points}$

$R(t) = \text{mean \% API dissolved of reference product at time point } x$

$T(t) = \text{mean \% API dissolved of test product at time point } x$

Minimum of 3 time points (zero excluded)

12 units (each in own dissolution vessel) for each product

Only one measurement should be considered after 85\% dissolution of both the products

\%RSD at earlier time points (e.g., 15 minutes) $\leq$ 20\%

\%RSD at higher time points $\leq$ 10\%

“$f_2$ values greater than 50 (50-100) ensure sameness of the two curves and, thus, of the performance of the test (post-change) and reference (pre-change) products.”
Similarity Factor ($f_2$)- SUPAC MR Guidance

- The average difference at any dissolution sampling time point should not be greater than 15% between the changed drug product and the bio-batch or marketed batch (unchanged drug product) dissolution profiles.
**Is \( f_2 \) Applicable to All Dosage Forms?**

- **Oral simple dosage forms**
  - Immediate release
  \( f_2 \) applicable

- **Oral complex dosage forms**
  - Modified release (DR, ER)
  - Combination-IR/IR, IR/MR, MR/MR
  \( f_2 \) applicable

- **Non-oral dosage forms**
  - Transdermal Drug Delivery Systems
  - Drug-Device Combination Products
  \( f_2 \) applicable

- **Other dosage forms**
  - For example topical etc.
  \( f_2 \) metric NOT applicable
Cases When $f_2$ Cannot be Used

- When the percent coefficient of variation is higher than 20% requirement for earlier time points (i.e., 15 min) or higher than 10% for the other time points the $f_2$ test cannot be used.
  - Alternative methods to estimate profiles similarity should be used
    - $f_2$ with Bootstrap method
    - Multivariate approach
Cases When $f_2$ may not be Used

- In general, the $f_2$ test should not be used when there is an IVIVC model available/established “safe space”
  - The IVIVC model must be used to estimate AUC and Cmax
Cases When $f_2$ Cannot be Used cont..

In Vitro Metric Evaluated - Drug Release Rate (mcg/day)

$f_2$ metric cannot be used to estimate the similarity of drug release rate data (mg/day etc.).
Case Studies
Case study 1: Discriminating method

BCS class 2 drug product

\[ f_2 = 76^* \]

Very rapid dissolution, \( f_2 \) should not be calculated

Method not discriminating/ drug particle size

In an in vivo study Test 1 and Test 2 were found not bio-equivalent

*Applicant calculated
Case study 1: Discriminating method...

BCS class 2 drug product- **New method**

\( f_2 = 40 \)

Method discriminating/ drug particle size
Case study 1: Discriminating method...

**f₂ limitations:** f₂ has no application for very rapid dissolution.
The outcome of f₂ test is uncertain if the method is not discriminating.

**Lesson learnt:** For a meaningful/reliable calculation of f₂, the dissolution method should be discriminating/meaningful.
Case study 2: site change

Alternate Manufacturing Site
Low solubility drug

Pre Change
Post change

\[ f_2 = 46 \]
Case study 2: site change...

\(f_2 < 50\), was justified and found acceptable

- Previously, a PK study showed no difference in BA between a tablet vs. suspension formulations of the same drug. Plasma levels peaks in approximately four hours.

- The dissolution profile of the post-change batch was within those observed for the tablet and suspension.

- Slightly faster dissolution and the lower value of \(f_2\) should not have affect on the efficacy/safety of the drug product.

- Based on totality of information provided, the change in the site was accepted even though the dissolution was faster and the \(f_2\) was slightly lower than 50.
Case study 2: site change...

**f₂ limitations:** f₂ similarity may have limited application for very rapid dissolving products.

**Lesson learnt:** An f₂ value less than 50 does not necessarily indicate lack of similarity. Risk-based assessment on the potential effect of the proposed change(s) on bioavailability should be conducted.
Case study 3: Multiple process changes

Post approval, multiple, Level 1 changes in the process to improve the stability of the drug product.

Low solubility drug

\[ f_2 = 58 \]
Case study 3: Multiple process changes..

The Applicant was asked to provide dissolution data with additional time points at early phase

\[ f_2 = 40 \]

Based on the totality of the information and potential effect of the manufacturing changes on the bioavailability, the Application was asked to conduct a BE study.
Case study 3: Multiple process changes ...

**BE study results**

<table>
<thead>
<tr>
<th></th>
<th>Ratio*</th>
<th>90 % CI#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax</td>
<td>146</td>
<td>135</td>
</tr>
<tr>
<td>AUC(_{0-t})</td>
<td>110</td>
<td>103</td>
</tr>
</tbody>
</table>

*Point estimate of Geometric mean ratio

# 90% Geometric Confidence Interval using log transformed data

Based on the BE study results, the Applicant withdrew the supplement
Case study 3: Multiple process changes..

$f_2$ limitations: the selection of sampling time points (both number and sampling time distribution) are critical for a robust conclusion on the similarity results.

Lesson learnt: To evaluate the similarity of the drug product performance, it is important to assess the totality of the information. $f_2$ values are only one part of the total information.
The use of $f_2$ in “Safe Space”

If “**Safe Space**” [all batches are assumed to be bioequivalent] is established, through IVIVC, BE studies, IVIVR, virtual BE studies etc., similarity in the dissolution profiles is not needed, if the dissolution profiles are within in the “safe space”. 
Case study 4: Site and process change.

Manufacturing site change and minor changes to the manufacturing procedure. No change in the IR formulation. Drug substance has very low aqueous solubility

\[ f_2 = 38 \]
Case study 4: “Safe Space”

Bio-Test 1 and Bio-Test 2 were bioequivalent
Case study 4: change with in the “safe space”...

\textbf{f_2 limitations}: “Safe space” supersedes \textit{f}_2 similarity testing.

\textbf{Lesson learnt}: An \textit{f}_2 value less than 50 does not necessarily indicate lack of similarity. If product changes are occurring with in the “safe space’, an \textit{f}_2 value less <50 is superseded by “safe space” boundaries.
Case study 5: variable dissolution

A Modified Release (MR) product.
BE Study on higher strength (strength 1), biowaiver request for the lower strength (strength 2),

\[ f_2 = 57 \]

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength 1</td>
<td>16.8</td>
<td>13.7</td>
<td>8.9</td>
<td>7.1</td>
<td>2.6</td>
</tr>
<tr>
<td>Strength 2</td>
<td>13.1</td>
<td>9.5</td>
<td>6.4</td>
<td>4.5</td>
<td>0.9</td>
</tr>
</tbody>
</table>
Case study 5: variable dissolution...

\[ f_2 = 63 \]

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strength 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\begin{tabular}{|c|c|c|c|c|c|}
\hline
Time (hours) & 1 & 2 & 4 & 6 & 8 \\
\hline
Strength 1   & 11.3 & 8.8 & 6.3 & 5.1 & 3.9 \\
Strength 2   & 14.2 & 11.5 & 8.8 & 6 & 4 \\
\hline
\end{tabular}
Case study 5: variable dissolution.

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>% RSD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% RSD</td>
</tr>
<tr>
<td>Strength 1</td>
<td>19.1</td>
</tr>
<tr>
<td>Strength 2</td>
<td>16.5</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>15.7</td>
</tr>
<tr>
<td></td>
<td>12.6</td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>10.8</td>
</tr>
<tr>
<td></td>
<td>8.4</td>
</tr>
<tr>
<td></td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>9.5</td>
</tr>
<tr>
<td></td>
<td>3.9</td>
</tr>
</tbody>
</table>

\[ f_2 = 35 \]
Case study 5: variable dissolution.

- Investigate the root cause of high variability; and differences in dissolution profiles in pH 6.8.
- **Response:** No specific reasons for the variability and the differences.
- BE study was recommended.
- BE study failed to meet the 90% CI.
Case study 5: variable dissolution

$f_2$ limitations: Due to high variability in the dissolution data, comparison of mean $f_2$ profiles is not recommended.

what is early timepoint for an ER product?

Lesson learnt: In case of high variability in the dissolution profiles, the root cause of high variability should be determined prior to using alternate approaches to demonstrate the similarity between the profiles.
$f_2$ values are only part of the total information
Question

Should we use $f_2$ for comparing these dissolution profiles?

$f_2 = 52$
Challenges in the Implementation of Similarity Testing

- $f_2$ similarity may have limited or no application for very rapid dissolving products.

- Selection of sampling time points (both number and sampling time distribution) are critical.

- High variability in the dissolution data. An early timepoint for ER products is not defined.

- $f_2$ calculations does not consider shape of the profiles.
Conclusions

- For a reliable calculation of $f_2$, the dissolution method should be discriminating/meaningful.

- To evaluate the similarity of the drug product performance, it is important to assess the totality of the information. $f_2$ values are only the part of the total information.

- In case of high variability in the dissolution profiles, the root cause of high variability should be determined and variability in the data should be reduced, if possible, without compromising on the discriminating ability of the method.
An $f_2$ value less than 50 does not necessarily indicate lack of similarity. The potential effect of the proposed change resulting in differences in dissolution profiles can be justified including additional data to support the claim of similarity, as well as supporting statistical analysis (e.g. 90% confidence interval analysis), and ‘safe space’ etc.
Acknowledgements

• Thanks To:
  – Sandra Suarez Sharp, Ph.D.
  – Angelica Dorantes, Ph.D.
  – Haritha Mandula, Ph.D.
  – Kaushal Dave, Ph.D.
  – Kimberly W. Raines, Ph.D.
  – Poonam Delvadia, Ph.D.
FDA Guidances and Similarity $f_2$ Metric

Several Guidance documents recommend $f_2$ metric to evaluate products sameness:

- Dissolution Testing of Immediate Release Solid Oral Dosage Forms
- Waiver of in vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System
- Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations
Thank you!