Determining Similarity of Products - $F_2$ Criterion and Variability of Dissolution Test

Vivian Gray
V. A. Gray Consulting
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Bioequivalence Testing, using the Dissolution Profile

- Establishes procedure for granting biowaivers
  - New drug and generic drug application
  - Higher strengths
  - Lowers strengths
- Assures product sameness under FDA, WHO, Japanese and European guidances
Bioequivalence Tool

- $f_1$
  - Calculates the percent difference between the two dissolution profiles at each time point and is a measurement of the relative error between the two curves
- $f_2$ or similarity factor
  - Predict bioequivalence from dissolution and examines waivers for BE studies

Dissolution Profile Comparison

\[ f_2 = 50 \cdot \log \left[ 1 + \left( \frac{1}{n} \sum (R_t - T_t)^2 \right)^{-0.5} \right] \cdot 100 \]
F2

- Similarity factor is a logarithmic reciprocal square root transformation of the sum of the squared error.

Definition of Terms

- Term $n$ is number of time points
- $R_1$ is the Dissolution value of the reference (pre-change) batch at time $t$
- $T_1$ is the dissolution value of the test (post change) batch at time $t$
FDA Guidances

- Dissolution Testing of Immediate Release Solid Oral Dosage Forms - 1997

FDA Guidances

FDA Guidances


- Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on Biopharmaceutics Classification System -2000
F2 Rules

- N=12 of reference and test or post-change product
- Results of 50 or greater indicate bioequivalence or similarity
- RSD should be NMT 20% at < 15 minutes
- RSD NMT 10% for all other points

F2 not needed when....

- Dissolution rate of product is 85% in fifteen minutes in all three media
>85% timepoint

- Wording slightly different in the guidances.
- FDA “Only one measurement should be considered after 85% dissolution of both the products”

85% (continued)

- Follow-up article from FDA says “Because f2 values are sensitive to the number of dissolution time points, only one measurement should be considered after 85% dissolution of the product”
85%

- EMEA says “not more than one mean value of >85% dissolved for each formulation”

WHO

- “...maximum of one time-point should be considered after 85% dissolution of the comparator (Brand/Reference/Innovator) product has been reached”
# Examples F2

<table>
<thead>
<tr>
<th>Time</th>
<th>Point</th>
<th>Test Prod</th>
<th>Ref Prod</th>
<th>Delta</th>
<th>Delta**2</th>
</tr>
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<tbody>
<tr>
<td>15</td>
<td></td>
<td>78</td>
<td>83</td>
<td>-5</td>
<td>25</td>
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<td>90</td>
<td>-3</td>
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</tr>
</tbody>
</table>

ave delta2 | F2
12.66667 | 0.270501 | 71.60843
<table>
<thead>
<tr>
<th>Time Point</th>
<th>Test Prod</th>
<th>Ref Prod</th>
<th>Delta</th>
<th>Delta**2</th>
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</thead>
<tbody>
<tr>
<td>15</td>
<td>78</td>
<td>83</td>
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<tr>
<td>45</td>
<td>90</td>
<td>88</td>
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<td>4</td>
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</table>

ave delta^2 | F2  
--- | ---  
10 | 0.301511 | 73.96518
<table>
<thead>
<tr>
<th>Time</th>
<th>% released R</th>
<th>% released T</th>
<th>IR-T</th>
<th>(IR-T)^2</th>
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<tr>
<td>10</td>
<td>10</td>
<td>16</td>
<td>0</td>
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</tbody>
</table>

Difference factor f1: 13.28

Similarity factor f2: 54.05

Examples F2

- Although f1 and f2 suggest similarity, the comparison is not suitable because the profiles display different release kinetics.
EMEA Guidance

- Note for Guidance on the Investigation of Bioavailability and Bioequivalence
- Differences from the FDA guidance
  - Media
    - pH 1.2 (0.1 N HCl or SGF w/o enzymes)
    - pH 4.5
    - pH 6.8 or SIF w/o enzyme

Japan and FDA BCS

- PMDA does not recognize the BCS
- Biowaiver allowed for any class drug
- Article comparing Biowaivers in US, EU, and Japan in American Pharmaceutical Review
Japan and FDA BCS

- PDMA guidelines combine the BCS waiver concept with the SUPAC (scale up and post approval changes) and include Modified Release dosage forms.
- Drug substance and Product characteristics and pH of media and apparatus are important.
- Achlorhydria accounts for careful review throughout the pH range.
- No recognition of a IVIVC (in vitro and in vivo correlation) for bioequivalence.

Japan and F2

- Guideline for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms
  - Section 5 and Appendix 1-Very complex and case by case. Example F2 of 42 allowed instead of 50.
Japan and F2

- Japan uses different passing criteria for f2 depending on the dissolution profile of the reference formulation and whether dissolution is to support a clinical BE
  - Passing f2 values (42 [fast] -61[slow]) or biowaiver (50-61)
  - There are criteria for passing dissolution, even if you go into the clinic
  - 42 is passing, but not for a biowaiver
  - Sometimes, 50 is not enough for a Biowaiver

WHO

- WHO Technical Report Series
- “WHO Expert Committee on Specifications for Pharmaceutical Preparations”. Fortieth Report
WHO

- Extension of Biowaivers to...
  - BCS Class 3 if 85% in 15 minutes with the three media
  - BCS 2, weak acids if the API has a dose solubility ratio of 250 mL or less at pH 6.8 and the multi source product is rapidly dissolving (no less than 85% in pH 6.8 in 30 minutes) and has a similar F2 at all pH's
  - Paddle allowed at 75 RPM

Failure to meet F2
Failure to meet F2

- Are products the same age (especially with capsules)?
- Innovator lots may give different profiles—how do you pick a lot for F2
- Solubility differences (particle size, excipient matrix)
- Disintegration properties

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Failure to meet F2

- Observations can be a clue
  - Visual representation of Release mechanism
- Should be run together – 3 and 3 in same six unit run to reduce differences
Capsule dissolution lag time

In Japan you can account for lag time... not seen in other guidances.
Problem with overencapsulation of comparators is often due to lag time.

Failure to meet F2-Possible Problems if run separately

- Filtration – Validation of filter type, stick with it
- Automation-Going from manual to automated—Big issue
  - Filter
  - Deaeration
  - Cleaning
- Deaeration technique-Primary suspect
- Sinkers-Must be the same design
Trouble

- Standard preparation method
  - Alcohol used, sonication time
- Purity of reagents
  - Especially surfactant—use the purest grade
  - Check stability of media
- Poorly soluble drugs most trouble

Trouble

- Equipment comparisons
  - Brand to brand differences
    - Baths run “hot” or “cool”
  - Age differences
  - Maintenance history
  - Prednisone Tablet probe is the best with paddle at 50 rpm.
Other uses of F2

- Fed and fasted comparisons
- Formulation development
- Comparators
- IVIVC is better than F2 for Extended Release
- Validation studies criteria
  - Deaeration versus Non-deaerated

Preferred Validation Criteria

- From <1092> The Dissolution Procedure: Method Development and Validation
- Usual criteria
  - 5-10% absolute difference for early time points with more variable data
  - 3-5% absolute difference for later points with >80% dissolved
### F2 and Method Development

- BCS class 2 and 4
- BCS class 1 and 3 that do not dissolve in 3 media at 85% in 15 minutes
- Need this three point profile as a first step to a discriminating profile.
  - Critical Quality Attributes-Factors responsible for the release mechanism

### Selection of Test Conditions

- Basics for method
  - Need low variability
  - Good profile-- May need to add earlier time points (5, 10 minutes)
  - Should pick up changes
- Hydrodynamic aspects- Observations
  - Minimize artifacts- sticking, coning, clogging, floating
Typical Dissolution Curve

![Typical Dissolution Curve](image)

Problems with F2

- Product profiles are too fast
  - May need to add earlier time points (5, 10 minutes)
- Too variable, RSD requirements too restrictive especially for earlier time points-Bootstrap method?
- 50 may be too stringent
  - FDA may consider a lower value on case-by-case basis as determined by prudent justification
A story from the Generic scandal in US

- Generic company had product that showed a different dissolution rate than the innovator product—much faster
- Clinical study used overencapsulated innovator product—Got caught
- Innovator product was a very old formulation with Shellac in coating
- Dissolution gave false impression of BE

F2

- Calculation everyone loves to hate
- Although it has drawbacks, nothing else seems better as a practical, routine choice—apparently here to stay
- A big obstacle to a new harmonized alternative is consensus on criteria and the need for special statistical expertise.
Acknowledgments

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- Gregg Kelly, Pfizer
- Lawrence Xu, FDA, Generics
- Patrick Marroum, FDA, Biopharm
- Vinod Shah, Consultant, formerly FDA

References

- Biowaivers in the United States, European Union, and Japan
  Gregg Kelly, Ph.D., Pfizer
References

- Dissolution Profile Comparison Using Similarity Factor, f2
  Vinod P. Shah, Yi Tsong, Pradeep Sathe and Roger L. Williams
  http://www.dissolutiontech.com/DTresour/899Art/DissProfile.html

References

- In Vitro Dissolution Profile Comparison—Statistics and Analysis of the Similarity Factor
  Vinod Shah, Ti Tsong, Pradeep Sathe, and Jen-Pei Liu
  Pharmaceutical Research, Vol. 15, No. 6, 1998
Dissolution Resources

Websites

Dissolution Technologies at www.dissolutiontech.com
www.fda.gov/cder
www.ich.org
www.usp.org

FDA Data base of Dissolution Methods

- FDA has made public the database containing the dissolution conditions for products approved by the agency. The website was created on November 2, 2005
- The website address is www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm
Dissolution Resources

- FDA, JAPAN, WHO and European Guidances
- USP General Chapters and Stimuli Articles and Revisions
  - New <1092> Dissolution validation and method development
- ICH Documents

Dissolution Resources

- “Pharmaceutical Dissolution Testing”, Edited by Dressman and Kramer
- “Dissolution Theory, Methodology and Testing”, Edited by A. Palmieri
- Journal of the Controlled Release Society