Determination of bioequivalence using *in-vitro* techniques

Approaches to obtaining a bio-waiver

RACI

Wednesday, 25th August 2010
Why we want to determine bioequivalence?

- Determine whether changes in the manufacturing process have changed the bioavailability of the drug product.
- Determine whether two formulations will have similar efficacy.
- Whether the bioavailability of a drug changes if the product is manufactured in a different dose.
- Whether the product to be registered has the same bioavailability as the product used in the clinical trial.
- Biowaivers have the potential to dramatically reduce the cost of determining bioequivalence, and therefore reduce the cost of registration of a product, accompanied by significant time saving.
Using dissolution testing to demonstrate bioequivalence.

1. Are two profiles the same – objective measures for comparison.
2. Calculating similarity and difference factors.
3. How much data and how many conditions do I need?
4. Taking the leap – my profiles are the same but are they bioequivalent? Can I use the data to obtain a biowaiver?
5. Biopharmaceutical classification scheme.
6. Is it harder than you think – is my *in-vitro* model valid?
7. Sometimes its easier than you think.
Objective measures for comparing dissolution profiles.

Any statistically valid approach can be used to demonstrate whether profiles are equivalent.

- Acceptance criteria must be defined prior to carrying out the test.

The most widely accepted approach uses difference factors ($f_1$) or similarity factors ($f_2$).

Profiles considered equivalent if:

- $f_1$ between 0 and 15
- $f_2$ between 50 and 100
Calculating similarity and difference factors

Calculations are carried out on the mean value for each batch at each timepoint.

**Difference Factor:**

\[
f_1 = \left\{\left[\frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t}\right]\right\} \cdot 100
\]

**Similarity Factor:**

\[
f_2 = 50 \cdot \log \left\{\left[1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2\right]^{-0.5}\right\} \cdot 100
\]
Calculating similarity and difference factors

Dissolution profile obtained for reference and test product using USP Apparatus 2.
## Calculating similarity and difference factors

<table>
<thead>
<tr>
<th>t</th>
<th>R</th>
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<th>R-T</th>
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<th>ΣR</th>
<th>(R-T)^2</th>
<th>Σ(R-T)^2</th>
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Calculating similarity and difference factors

| t   | R     | T     | |R-T|   | ΣR    | (R-T)^2 | Σ(R-T)^2 | l/n | t   | Point | Cumulative |
|-----|-------|-------|-------|------|-------|--------|---------|------|-----|-------|------------|
|     |       |       |       |      |       |        |         |      |     |       |            |
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|     |       |       |       |      |       |        |         |      |     |       |            |

- **t**: Time in minutes
- **R**: Reference value
- **T**: Test value
- **|R-T|**: Absolute difference
- **ΣR**: Sum of reference values
- **(R-T)^2**: Square of difference
- **Σ(R-T)^2**: Sum of squares of differences
- **l/n**: Inverse of standard deviation
- **F1**: First factor
- **F2**: Second factor
- **Cumulative**: Cumulative value
## Calculating similarity and difference factors

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How much data and how many conditions do I need?


- 3 conditions – pH 1.0 – 1.2, pH 4.5 and pH 6.8 with specific requirements for make up of the medium including no surfactants.

- A minimum of 3 timepoints with only 1 timepoint >85% dissolved.

- 12 individual measurements for each timepoint for each formulation.

- %RSD <20% for the first timepoint and <10% for 2nd to last timepoint.
How much data and how many conditions do I need?


Similar to EMEA, less fussy about makeup of media – “If the drug being considered is poorly soluble, appropriate concentrations of surfactants are recommended.”
How much data and how many conditions do I need?

“Bioequivalence Guidelines for Veterinary Chemical Products”, APVMA

- Refers to FDA Guidance document.
- Minimum of 6 dosage units tested according to pharmacopeial method.
- At least 3 timepoints collecting data until almost complete dissolution.
Taking the leap

Does in-vitro equivalence mean bioequivalence?

Equivalent profiles

Bioequivalence
The biopharmaceutical classification scheme (BCS)

- Indicates when in-vitro equivalence can be taken as bioequivalent.


*Amidon et al* use a mathematical model and human permeability results to show that **solubility** and **permeability** are of primary importance in drug absorption.

The BCS used in both FDA and European (EMEA) guidance documents.
The biopharmaceutical classification scheme (BCS)

<table>
<thead>
<tr>
<th>Class</th>
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<tbody>
<tr>
<td>Class 1</td>
<td>High permeability, high solubility</td>
</tr>
<tr>
<td>Class 2</td>
<td>High permeability, low solubility</td>
</tr>
<tr>
<td>Class 3</td>
<td>Low permeability, high solubility</td>
</tr>
<tr>
<td>Class 4</td>
<td>Low solubility, low permeability</td>
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</table>

- A highly soluble drug is defined as where the dose is soluble in 250 mL over a pH range of 1.0 to 7.5.
- “Highly permeable”- drugs which have >90% absorption (check most relevant guideline)
The biopharmaceutical classification scheme (BCS)

- EMEA 2010 “The BCS based biowaiver approach is meant to reduce *in vivo* bioequivalence studies.”

- BCS based biowaivers are applicable BCS Class 1 drugs – high solubility, high permeability and also BCS Class 3 drugs – high solubility, low permeability.

- This is different to the FDA Guidelines, where the BCS approach is only applicable to BCS Class 1 drugs.
  - New to the EMEA 2010 document.
  - May apply to different salts provided that both salts have the same BCS classification.
  - Not applicable to drugs with a narrow therapeutic range.
  - Include risk assessment in case of “bioinequivalence”.
Is it harder than you think?

Is it possible to demonstrate bioequivalence without any *in-vivo* data?
Do I first need to demonstrate an *in vitro-in vivo* correlation before I can use *in vitro* data to show bioequivalence?

**CDER March 2003:**
“When an *in vivo-in vitro* correlation or association is available, the *in-vitro* test can serve not only as a quality control specification for the manufacturing process, but also as an indicator of how the product will perform *in-vivo*."

**EMEA 2010:**
“In *vivo* bioequivalence studies may be exempted if an assumption of bioequivalence in *in vivo* performance can be justified by satisfactory *in vitro* data.”
Sometimes its easier than you think...

For rapidly dissolving drugs the rate limiting step in absorption is the rate of emptying of the stomach, the “gastric emptying rate”.
Sometimes its easier than you think...

With gastric emptying being rate limiting, drug absorption is no longer dependent on dissolution of the drug, and is therefore formulation independent.

If 85% dissolution is achieved in <15 minutes, their profiles are considered equivalent. Only a single timepoint is required.

Some caution required in considering excipients.

Although applicable to a limited number of drug products, provides the most clear cut route to a biowaiver.
Conclusion

- Dissolution testing can be used to reduce the amount of *in vitro* testing required, and in some cases can replace it. This can result in significant cost and time savings.

- There are a complex range of issues which need to be addressed when designing, implementing and executing *in vitro* bioequivalence studies. Always refer directly to the most relevant publications and guidelines.
Acknowledgements

Karl McCunnie (QA Manager, Chemika)

Preparation of spreadsheets for calculation of similarity and difference factors.