Statistical Aspects of Revision of CHMP Bioequivalence Guidelines

David Brown
MHRA

Disclaimer

The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to Drug Information Association, Inc. (“DIA”), its directors, officers, employees, volunteers, members, chapters, councils, Special Interest Area Communities or affiliates, or any organization with which the presenter is employed or affiliated.

These PowerPoint slides are the intellectual property of the individual presenter and are protected under the copyright laws of the United States of America and other countries. Used by permission. All rights reserved. Drug Information Association, DIA and DIA logo are registered trademarks or trademarks of Drug Information Association Inc. All other trademarks are the property of their respective owners.
Bioequivalence

Generic product same substance as originator, at same dose usually in same type of formulation e.g. tablet, capsule.

Intention to use the new formulation interchangeably with originator, usually with much lower price.

Need to test if it is the same or similar to originator, but full development programme excessive.

Can tell chemically that the substance is the same – just need to test if the formulation releases the substance in the same way.

Bioequivalence

Compare pharmacokinetics

If pharmacokinetic profile similar – then assumption is that efficacy/safety will be similar
Acceptance criteria

It is very difficult to test whether two curves are sufficiently similar

So various descriptive statistics e.g. AUC, Cmax, used to characterise the curve

If one is different, but others the same – the curve has a different shape

Acceptance criteria

Idea is that the mean AUC and Cmax for the test compared to the reference do not differ by more than 8:10

- $8/10 = 0.80$
- $10/8 = 1.25$

90% confidence intervals for the ratios should be contained within (0.80-1.25) – then we can be fairly sure that the 8:10 difference is not exceeded
Study Design

Standard design is a 2 treatment, 2 period crossover design

Other designs possible – parallel group, additional periods

Open-label

<table>
<thead>
<tr>
<th>GROUP 1</th>
<th>GROUP 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>PERIOD 1</td>
<td>TEST</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>PERIOD 2</td>
<td>REFERENCE</td>
</tr>
</tbody>
</table>

Design

Sequence 1

1. Receives test product

2. Plasma levels measured

3. Washout

4. Receives reference product

5. Plasma levels measured
Analysis

Standard analysis is established as ANOVA using log transformed data with terms for sequence, subject within sequence, period and formulation.

Resulting 90% confidence intervals are then back-transformed to gain a confidence interval for the ratio (test/reference).

CHMP guidelines

Note for Guidance on the investigation of bioavailability and bioequivalence – January 2002

Questions & Answers on the Bioavailability and Bioequivalence Guideline – July 2006

Both to be replaced by:

Guideline on the investigation of bioequivalence – draft released July 2008
CHMP guidelines

New guideline aims to make things more explicit, to make it clearer to applicants what is required, and to make assessments more consistent between EU countries.

Text quoted here is from the draft version and subject to change before the final version.

Topic 1 – Sample size

The number of subjects to be included in the study should be based on an appropriate sample size calculation. The minimum number of subjects in a cross-over study should be 12.

1. Minimum number?
2. Sample size calculation?
Topic 2 – Acceptance limits

Confidence intervals should be presented to two decimal places. To be inside the acceptance interval the lower bound should be \( \geq 80.00 \) and the upper bound should be \( \leq 125.00 \).

1. Arbitrary, seemingly finickity, but necessary.

When results are close, e.g. (0.79-1.17) there is a temptation to accept them – but where do you draw the line?

---

Topic 3 – Carry-over effects

A test for carry-over should not be performed and no decisions regarding the analysis (e.g. analysis of the first period, only) should be made on the basis of such a test.

The potential for carry-over can be directly addressed by examination of the pre-treatment plasma concentrations in period 2.

If there are any subjects for whom the pre-dose concentration is greater than 5 percent of the Cmax value for the subject in that period, the statistical analysis should be repeated with those subjects excluded.
**Topic 3 – Carry-over effects**

1. There was a tendency for people to test for a carry-over effect and make decisions based on that – but this is inefficient and could lead to needless rejection of period 2 data.

2. Unlike in other settings, we can directly check for the existence of carry-over here.

---

**Topic 4 – Two-stage design**

It is acceptable to use a two-stage approach when attempting to demonstrate bioequivalence. An initial group of subjects can be treated and their data analysed. If bioequivalence has not been demonstrated an additional group can be recruited and the results from both groups combined in a final analysis.

If this approach is taken appropriate steps must be taken to preserve the overall type I error of the experiment. The analysis of the first stage data should be treated as an interim analysis and both analyses conducted at adjusted significance levels (with the confidence intervals accordingly using an adjusted coverage probability which will be higher than 90%).

The plan to use a two-stage approach must be prespecified in the protocol along with the adjusted significance levels to be used for each of the analyses.
Topic 4 – Two-stage design

1. Interim analyses and sample size re-estimation are possible in other trials – this new text allows them in the bioequivalence setting

2. Allows companies to learn about variability etc. during the course of the study and helps with powering.

3. Actually less problems with this in bioequivalence than in other settings – objective measures etc.

4. Theoretically more than two stages could be allowed, but would not seem a sensible or practical approach

Topic 5 – Data from more than one study

If the application contains some studies which demonstrate bioequivalence and others that do not, the documentation must be considered as a whole.

The existence of a positive study does not mean that negative studies can be ignored.
**Topic 5 – Data from more than one study**

1. Still debate on how to handle this. But it is clear that a large multiplicity issue arises if studies can be repeated until a positive result is seen.

2. It is clear that if a “better” (e.g. larger, better sampling) study is done after a “poor” study was inconclusive, the new study wins out.

3. But what about contradictory studies?

**Topic 6 – exclusion of data**

All treated subjects should be included in the statistical analysis, with the exception of subjects in a crossover trial who do not complete at least one period receiving each of the test and reference products.
The data from all treated subjects should be treated equally. It is not acceptable to have a protocol which specifies that ‘spare’ subjects will be included in the analysis only if needed as replacements for other subjects who have been excluded.

1. This was a very common practice but we would like to see all data, for two reasons:

   a) It seems strange to subject subjects to the study and not use their data

   b) It eliminates any suspicion that the subject for inclusion have been selected in any way

Unbiased assessment of results from randomised studies requires that all subjects are observed and treated according to the same rules, rules that should be independent from treatment or outcome. In consequence, the decision to exclude a subject from the statistical analysis must be made before bioanalysis.

Exclusion of data can never be accepted on the basis of statistical analysis or for pharmacokinetic reasons alone, because it is impossible to distinguish the formulation effects from other effects affecting the pharmacokinetics.
What is an outlier?

Common for applicant to wish to remove outliers

\[ C_{\text{max}} \text{ (ng/ml)} - \text{all differences} > 0.5 \text{ on log scale} \]

<table>
<thead>
<tr>
<th>Subject</th>
<th>Test</th>
<th>Reference</th>
<th>Difference in log values</th>
</tr>
</thead>
<tbody>
<tr>
<td>36</td>
<td>14.533</td>
<td>128.74</td>
<td>-2.181</td>
</tr>
<tr>
<td>1</td>
<td>5.818</td>
<td>18.482</td>
<td>-1.156</td>
</tr>
<tr>
<td>12</td>
<td>16.128</td>
<td>42.915</td>
<td>-0.979</td>
</tr>
<tr>
<td>5</td>
<td>66.962</td>
<td>177.79</td>
<td>-0.977</td>
</tr>
<tr>
<td>24</td>
<td>22.48</td>
<td>58.724</td>
<td>-0.96</td>
</tr>
<tr>
<td>43</td>
<td>52.36</td>
<td>133.62</td>
<td>-0.937</td>
</tr>
<tr>
<td>25</td>
<td>17.796</td>
<td>38.843</td>
<td>-0.781</td>
</tr>
<tr>
<td>18</td>
<td>30.688</td>
<td>55.983</td>
<td>-0.601</td>
</tr>
<tr>
<td>41</td>
<td>75.537</td>
<td>44.731</td>
<td>0.524</td>
</tr>
<tr>
<td>9</td>
<td>40.164</td>
<td>66.863</td>
<td>-0.51</td>
</tr>
</tbody>
</table>

e.g. applicant wanted to remove subjects 1 and 36 as outliers

Reasons for exclusions from analysis

Excluding outliers

- Acceptable if there is a documented physical reason for outlying value, e.g. value is very low and it is documented that patient vomited after taking medication. Decision to remove made before seeing results.

- Acceptable to remove patients with zero concentrations for a period even without documentation (assume didn’t take it).

- Even if a value seems extreme, that fact it has occurred in a small study means it may represent a significant percentage of the population.
Outliers

It is clear that a policy of removing the subjects with larger differences will bias the study towards showing bioequivalence, especially if the extreme values all fall in the same direction – in this case with the test having lower values than the reference.

The purpose of a bioequivalence study is to allow evaluation of whether the test and reference formulations differ from each other. In the absence of a physical explanation it must be assumed that the differences seen are possibly the result of a difference between the formulations; precisely the sort of thing that the bioequivalence trial is being used to look for.

Topic 7 – Highly variable drugs

In certain cases, Cmax is of less importance for clinical efficacy and safety compared with AUC. When this is applicable, the acceptance criteria for Cmax can be widened to 75-133% provided that all of the following are fulfilled:

- the widening has been prospectively defined in the study protocol
- it has been prospectively justified that widening of the acceptance criteria for Cmax does not affect clinical efficacy or safety
- the bioequivalence study is of a replicate design where it has been demonstrated that the within-subject variability for Cmax of the reference compound in the study is >30%.

This approach does not apply to AUC.

It is acceptable to apply either a 3-period or a 4-period crossover scheme in the replicate design study.
Topic 7 – Highly variable drugs

Very difficult issue where agreement was difficult and so a compromise position was used for the draft – but the debate goes on.

See the next two talks!