Bioavailability / Bioequivalence

- Selection of CROs
- Selection of a Reference Product
- Metrics ($\text{AUC, } C_{\text{max}}/t_{\text{max}}$, Shape of Profile)
- Acceptance Ranges (0.80 – 1.25 and beyond)
- Sample Size Planning (Literature References, Pilot Studies)
- Steps in bioanalytical Validation (Validation Plan, Pre-Study Validation, In-Study Validation)
- Study Designs
- Protocol Issues
- Evaluation of Studies
- Advanced Topics
- Avoiding Pitfalls
Bioavailability / Bioequivalence

- Avoiding Pitfalls
  - Matrix-Effects in LC/MS
  - Missing Plausibility Review of Data
  - Exclusion of Outliers / Re-testing of Subjects
  - Dealing with Deficiency Letters
  - Repetition of Studies
Exclusion of Outliers / Re-testing of Subjects

- Parametric methods are sensitive to Outliers
  - see lecture 5 (slides 26/27)
    - Identification preferably *prior* to confirmatory statistics (e.g., Grubbs-test on individual BA-ratios, inter-quartil-range,…)
    - Reasons for exclusion must be defined in the Protocol (e.g., lacking compliance, vomiting, analytics, pre-dose concentrations,…)
    - if you suspect an outlier and cannot identify a clear reason, continue according to protocol:
      - change to a nonparametric method, or
      - calculate ANOVA both for the Full Data Set and the Reduced Data Set.
Exclusion of Outliers / Re-testing of Subjects

- Parametric methods are sensitive to Outliers
  - if you suspect a product failure of the reference formulation, you may consider Re-testing;
    - the outlying subject should be re-tested,
      - at least with the reference,
      - preferably with both the test and reference.
    - include also at least five subjects, who showed ‘normal’ responses in the main study (i.e., size of re-tested group ≥6).
  - expect questions from Regulators anyway (although sometimes accepted by the FDA, not covered in any guideline; the statistical evaluation is not trivial…)}
Bioavailability / Bioequivalence

- **Exclusion of Outliers / Re-testing of Subjects**

![Graph showing bioavailability and bioequivalence](image)

<table>
<thead>
<tr>
<th>Test</th>
<th>T</th>
<th>LSN=7.129502</th>
<th>SE=0.104041</th>
<th>GeoLSN=1240.754167</th>
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</thead>
<tbody>
<tr>
<td><strong>Difference</strong></td>
<td>0.0442</td>
<td><strong>Diff_SE</strong>=0.1331</td>
<td>df=22.0</td>
<td></td>
</tr>
<tr>
<td><strong>Ratio(95%)</strong></td>
<td>104.5185</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Period

<table>
<thead>
<tr>
<th>Classical</th>
<th>Westlake</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI 80%</td>
<td>(87.7732, 124.4610)</td>
</tr>
<tr>
<td>CI 90%</td>
<td>(90.0209, 121.4403)</td>
</tr>
<tr>
<td>CI 95%</td>
<td>(85.4004, 127.4015)</td>
</tr>
</tbody>
</table>

Failed to show average bioequivalence for confidence=90.0% and percent=20.0.

Two One-Sided T-tests

Prob(< 80%)=0.0277 Prob(> 125%)=0.0947 Max=0.0947 Total=0.1224

---

<table>
<thead>
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<th>T</th>
<th>LSN=7.137202</th>
<th>SE=0.052215</th>
<th>GeoLSN=1237.903871</th>
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</thead>
<tbody>
<tr>
<td><strong>Difference</strong></td>
<td>0.0304</td>
<td><strong>Diff_SE</strong>=0.1017</td>
<td>df=28.7</td>
<td></td>
</tr>
<tr>
<td><strong>Ratio(95%)</strong></td>
<td>103.0898</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Period

<table>
<thead>
<tr>
<th>Classical</th>
<th>Westlake</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI 80%</td>
<td>(89.2172, 117.7357)</td>
</tr>
<tr>
<td>CI 90%</td>
<td>(88.9363, 117.5493)</td>
</tr>
<tr>
<td>CI 95%</td>
<td>(83.7260, 126.9345)</td>
</tr>
</tbody>
</table>

Average bioequivalence shown for confidence=90.0% and percent=20.0.

Two One-Sided T-tests

Prob(< 80%)=0.0093 Prob(> 125%)=0.0341 Max=0.0341 Total=0.0454
Avoiding Pitfalls

- Matrix-Effects in LC/MS
- Missing Plausibility Review of Data
- Exclusion of Outliers / Re-testing of Subjects
- **Dealing with Deficiency Letters**
- Repetition of Studies

Bioavailability / Bioequivalence
Dealing with Deficiency Letters

- If you experience ‘strange results’ in your study, you already should prepare for a Deficiency Letter.
  - identify ‘weak points’
  - consider obtaining a second opinion from an independent expert
  - prepare a defence strategy beforehand (response times may be rather tight)
Dealing with Deficiency Letters

- Answers to Deficiency Letters
  - must cover all quoted points (may sound trivial, but sometimes ambiguous questions are simply ignored…)
  - keep the exact order of questions
  - since reports (especially listings of rawdata and hardcopies from bioanalytics, statistical output) are often complex, the question may already have been answered!
  - try to answer as objective as possible – don’t prepare a promotional!
  - stay polite – don’t try to prove the Reviewer’s ignorance!
Bioavailability / Bioequivalence

- Dealing with Deficiency Letters
  - Answers to Deficiency Letters
    - consider to include a ‘second opinion’ – may be helpful; but don’t drown the Reviewer in addenda!
    - if possible consider
      → a telephone conference in order to clarify ambiguous questions, or
      → a formal Hearing at the Regulatory Authority.
Bioavailability / Bioequivalence

- Avoiding Pitfalls
  - Matrix-Effects in LC/MS
  - Missing Plausibility Review of Data
  - Exclusion of Outliers / Re-testing of Subjects
  - Dealing with Deficiency Letters
  - Repetition of Studies
Bioavailability / Bioequivalence

- Repetition of Studies
  - may be unavoidable due to e.g.,
    - *Suprabioavailability* (if Bio\textit{ine}quivalence was demonstrated: point estimate of BA higher than the upper limit of acceptance)
      - Reformulation
    - Product failure of the test formulation (re-testing of subjects as in the case of the reference is not acceptable)
      - if possible, try to identify a potential reason (e.g., problems with gastric resistance for delayed release formulations), and
      - consider reformulation.
Bioavailability / Bioequivalence

- Repetition of Studies
  - may be unavoidable due to e.g.,
    - Non-acceptance of your defending strategy
      - lacking required standards in the conduct of the study
      - political reasons (yes!)
  - only reasonable, if potential problems could be resolved
    - Never repeat old mistakes, make new ones 😊
    - Positive: sample size estimation should be easy…
    - Assign a different title to the new study (EudraCT!)
    - Good Luck!
Bioavailability / Bioequivalence

- Exchange Expiriences

"Wait! Wait! Listen to me! … We don't HAVE to be just sheep!"
Bioavailability / Bioequivalence

- Exchange Expiriences
  - David Bourne’s (Uni. Oklahoma) E-Mail List
    - [http://www.boomer.org/pkin/](http://www.boomer.org/pkin/)
      - A rather active list (2800 members, about 50 posts/week) devoted to nearly everything about PK / PD / BA…
      - Search page
        [http://www.boomer.org/pkin/simple.html](http://www.boomer.org/pkin/simple.html)
  - BA and BE Forum (BEBAC Vienna)
    - [http://forum.bebac.at/](http://forum.bebac.at/)
      - Specialized in dissolution / BA / BE / bioanalytics.
      - No registration necessary to read posts.
      - Registration page
Bioavailability / Bioequivalence

- Stay Up-to-date with EMEA
  - Subscribe to the ‘Human Medicine Regulatory Guidance’ E-Mail List
    - http://list.emea.eu.int/mailman/listinfo/human_medicinal_regulatory_guidance
Regulatory Update and Overview of BE and BA Testing with an Industry Perspective

Istanbul, 7-8 March 2006

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