previous Lecture

Bioavailability / Bioequivalence

- Selection of CROs
- Selection of a Reference Product
- Metrics (AUC, C_{max}/t_{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**

previous Lecture

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

previous Lecture

Bioavailability / Bioequivalence

- **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.

previous Lecture

Bioavailability / Bioequivalence

- **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…)

previous Lecture

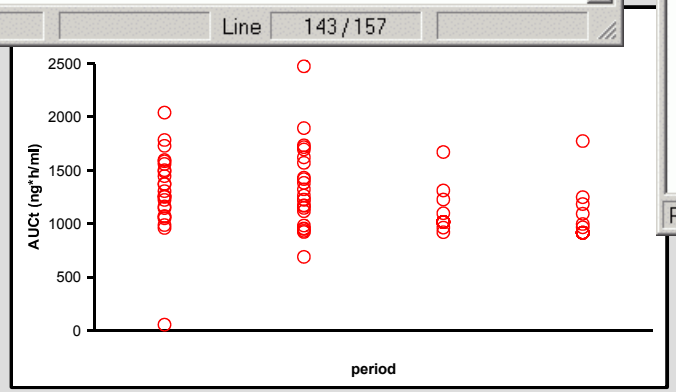
Bioavailability / Bioequivalence

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

Bioequivalence Text - [Untitled11]

```
Bioequivalence Statistics

User-Specified Confidence Level for CI's and Power = 90.0000
Percent of Reference to Detect for 2-1 Tests and Power = 20.0%
A.H.Lower =  0.800   A.H.Upper =  1.250

Formulation variable: formulation
Reference: R   LSMean=    7.085698  SE=    0.104041  GeoLSM= 1194.756651
--------------------------------------------------------------------------

Test:      T   LSMean=    7.129902  SE=    0.104041  GeoLSM= 1248.754167

    Difference =     0.0442,  Diff_SE=    0.1321,  df= 22.0
    Ratio(%Ref) =   104.5195

                        Classical                Westlake
    CI  80% = (   87.7732,  124.4610)  (   80.9169,  119.0831)
    CI  90% = (   83.2969,  131.1493)  (   74.5939,  125.4061)
    CI  95% = (   79.4604,  137.4815)  (   68.4657,  131.5343)
    Failed to show average bioequivalence for confidence=90.00 and percent=20.0.

                      Two One-Sided T-tests

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

Read Only | Line 143 / 157



Bioequivalence Text - [Untitled10]

```
Bioequivalence Statistics

User-Specified Confidence Level for CI's and Power = 90.0000
Percent of Reference to Detect for 2-1 Tests and Power = 20.0%
A.H.Lower =  0.800   A.H.Upper =  1.250

Formulation variable: formulation
Reference: R   LSMean=    7.106774  SE=    0.109442  GeoLSM= 1220.204475
--------------------------------------------------------------------------

Test:      T   LSMean=    7.137202  SE=    0.052715  GeoLSM= 1257.903871

    Difference =     0.0304,  Diff_SE=    0.1017,  df= 28.7
    Ratio(%Ref) =   103.0896

                        Classical                Westlake
    CI  80% = (   90.2172,  117.7987)  (   85.7333,  114.2667)
    CI  90% = (   86.7263,  122.5403)  (   81.2107,  118.7893)
    CI  95% = (   83.7240,  126.9345)  (   76.9552,  123.0448)
    Average bioequivalence shown for confidence=90.00 and percent=20.0.

                      Two One-Sided T-tests

    Prob(< 80%)=0.0093  Prob(> 125%)=0.0341  Max=0.0341  Total=0.0434
```

Read Only | Line 211 / 225

previous Lecture

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

previous Lecture

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 optaining a second opinion from an independent expert
    - prepare a defence strategy beforehand (response times may be rather tight)

previous Lecture

Bioavailability / Bioequivalence

- **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!

previous Lecture

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 clearify ambiguous questions, or
      - ➔ a formal Hearing at the Regulatory Authority.

previous Lecture

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

previous Lecture

Bioavailability / Bioequivalence

- **Repetition of Studies**
  - may be unavoidable due to *e.g.*,
    - *Suprabioavailability* (if Bio***in***equivalence 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.

previous Lecture

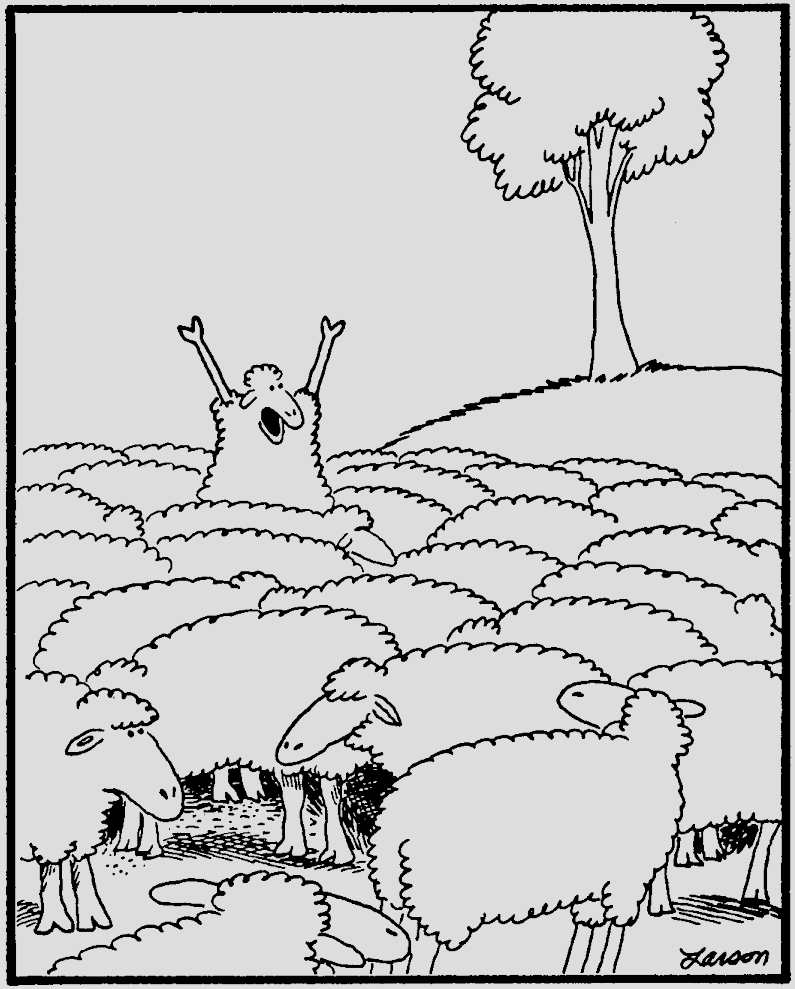
Bioavailability / Bioequivalence

- **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!**

previous Lecture

Bioavailability / Bioequivalence

- **Exchange Expiriences**



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

previous Lecture

Bioavailability / Bioequivalence

- **Exchange Expiriences**
  - David Bourne's (Uni. Oklahoma) E-Mail List
    - 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
  - BA and BE Forum (BEBAC Vienna)
    - http://forum.bebac.at/
      - Specialized in dissolution / BA / BE / bioanalytics.
      - No registration necessary to read posts.
      - Registration page http://forum.bebac.at/register.php

previous Lecture

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

Health Sciences
Diagnosis. Emergency & Long Term Solutions for Health Business

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Teşekkür ederim!