

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**

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▪ 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

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- **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.

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- **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...)

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■ 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)

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■ 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!

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■ 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.

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■ 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.

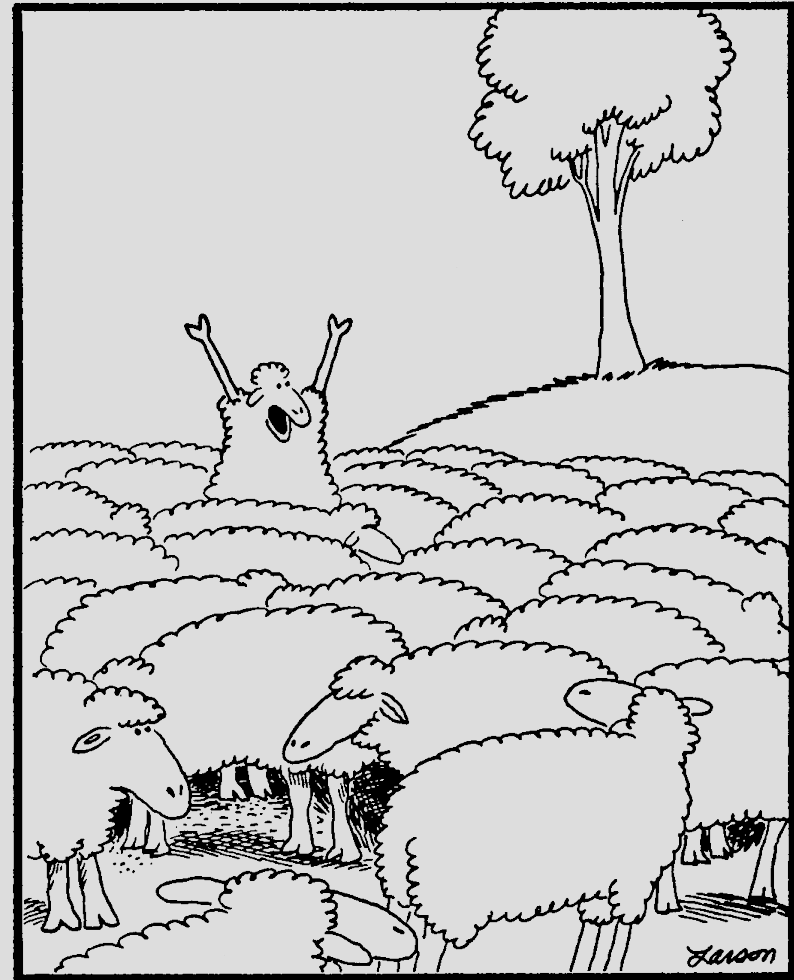
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▪ Repetition of Studies

- 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!**

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- Exchange Experiences



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

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■ Exchange Experiences

- 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>

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- **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



BE
BAC

Teşekkür ederim!