Statistical Design and Analysis II

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Sample Size Estimation

- Minimum Sample Size
  - 12 – WHO, EU, CAN, NZ, AUS, Malaysia, Argentina, ASEAN States, South Africa (20 for MR)
  - 24 – Saudia Arabia (12 – 24 if statistically justifiable)
  - 24 – Brazil

Sample Size Estimation

- Rationale for Pilot Studies (FDA/CDER, BA/BE Studies – General Considerations, 2003)
  - Validation of analytical methodology
  - Assessment of variability
  - Optimization of sample collection time intervals
  - A pilot study that documents BE can be appropriate, provided its design and execution are suitable and a sufficient number of subjects (*e.g.*, 12) have completed the study.

Sample Size Estimation

- Maximum Sample Size
  - New Zealand

    'If the calculated number of subjects appears to be higher than is ethically justifiable, it may be necessary to accept a statistical power which is less than desirable. Normally it is not practical to use more than about 40 subjects in a bioavailability study.'
  - All others

    Not specified in Guidelines (judged by IEC/IRB or local Authorities);

    ICH E9 (Section 3.5) applies: 'The number of subjects in a clinical trial should always be large enough to provide a reliable answer to the questions addressed.'

Sample Size Estimation

- EU NfG on the Investigation of BA/BE (2001)
  - The number of subjects required is determined by
    - the error variance associated with the primary characteristic to be studied as estimated from
      - a pilot experiment,
      - previous studies, or
      - published data,
    - the significance level desired,
    - the expected deviation (Δ) from the reference product compatible with BE and,
    - the required power.

Sample Size Estimation

- NfG on the Investigation of BA/BE
  - Problems/solutions
    - … the error variance associated with the *primary characteristic* to be studied …
      - Since BE must be shown both for AUC and C_{max}, and,
      - if you plan your sample size only for the 'primary characteristic' (*e.g.*, AUC), in many cases you will fail for the secondary parameter (*e.g.*, C_{max}), which most likely shows higher variability – your study will be 'underpowered'.
      - Based on the assumption, that CV is identical for test and reference (what if only the reference formulation has high variability, *e.g.*, some formulations of PPIs?).

Sample Size Estimation

- NfG on the Investigation of BA/BE
  - Problems/solutions
    - … as estimated from
      - a *pilot experiment*,
      - *previous studies*, or
      - *published data*,
    - The correct order should read:

      1. previous studies → 2. pilot study → 3. published data
         - Only in the first case you ‘know’ all constraints resulting in variability
         - Pilot studies are often too small to get *reliable* estimates of variability
         - Advisable only if you have data from a couple of studies

Sample Size Estimation

- NfG on the Investigation of BA/BE
  - Problems/solutions
    - … the *significance level desired* …
      - Throughout the NfG the significance level (α, error type I: patient's risk to be treated with a bio***in***equivalent drug) is fixed to 5% (corresponding to a 90% confidence interval)
      - You may *desire* a higher significance level, but such a procedure is not considered acceptable
      - In special cases (*e.g.*, dose proportionality testing), a correction for multiplicity may be necessary
      - In some legislations (*e.g.*, Brazil's ANVISA), α must be tightened to 2.5% for NTIDs (95% confidence interval)

Sample Size Estimation

- NfG on the Investigation of BA/BE
  - Problems/solutions
    - … the *required power*.
      - Generally the power is set to at least 80 % (β, error type II: producers's risk to get no approval for a bioequivalent drug; power = 1 – β).
        Remember: *1 out of 5 studies will fail just by chance!*
      - If you plan for power of less than 70 %, problems with the ethics committee are likely (ICH E9).
      - If you plan for power of more than 90 % (especially with low variability drugs), problems with the regulator are possible ('forced bioequivalence').
      - Add subjects ('alternates') according to the expected drop-out rate!

Sample Size Estimation

- NfG on the Investigation of BA/BE
  - Problems/solutions
    - … the *expected deviation (Δ) from the reference* …
      - Reliable estimate only from a previous full-sized study
      - If you are using data from a pilot study, allow for a safety margin
      - If no data are available, commonly a GMR (geometric test/reference-ratio) of 0.95 (Δ = 5%) is used
      - If more than Δ = 10% is expected, questions from the ethics committee are likely
      - BE Draft (2008) batches must not differ more than 5%.

Sample Size Estimation

- Sample size planning (EMEA Draft BE Guideline, 2008)
  - The number of subjects to be included in the study should be based on an *appropriate* sample size calculation.

Cookbook?

Sample Size Estimation

- Literature search for CV%
  - Preferably other BE studies (the bigger, the better)
  - PK interaction studies (Cave: mainly in steady state! Generally lower CV than after SD)
  - Food studies
  - If CV_{intra} is not given (quite often), a little algebra helps. All you need is the 90% geometric confidence interval and the sample size.
    - Point estimate (PE) from the CI

$$PE = \sqrt{CL_{lo} \cdot CL_{hi}}$$

Sample Size Estimation

- Calculation of CV_{intra} from CI
  - Estimate the number of subjects / sequence (example 2×2 cross-over)
    - If total sample size (N) is an even number, *assume* (!) $n_1 = n_2 = ½N$
    - If N is an odd number, *assume* (!) $n_1 = ½N + ½$, $n_2 = ½N - ½$ (*not* $n_1 = n_2 = ½N$!)
  - Difference between one CL and the PE in log-scale; use the CL which is given with more significant digits

$$\Delta_{CL} = \ln PE - \ln CL_{lo} \quad or \quad \Delta_{CL} = \ln CL_{hi} - \ln PE$$

Sample Size Estimation

- Calculation of CV_{intra} from CI
  - Calculate the Mean Square Error (MSE)

$$MSE = 2\left(\frac{\Delta_{CL}}{\sqrt{\left(\frac{1}{n_1}+\frac{1}{n_2}\right)}\cdot t_{1-2\cdot\alpha,n_1+n_2-2}}\right)^2$$

  - CV_{intra} from MSE as usual

$$CV_{\text{intra}}\% = 100\cdot\sqrt{e^{MSE}-1}$$

Sample Size Estimation

- Calculation of CV_{intra} from CI
  - Example: 90% CI [0.91 – 1.15], N 21 (n_1 = 11, n_2 = 10)

$$PE = \sqrt{0.91 \cdot 1.15} = 1.023$$

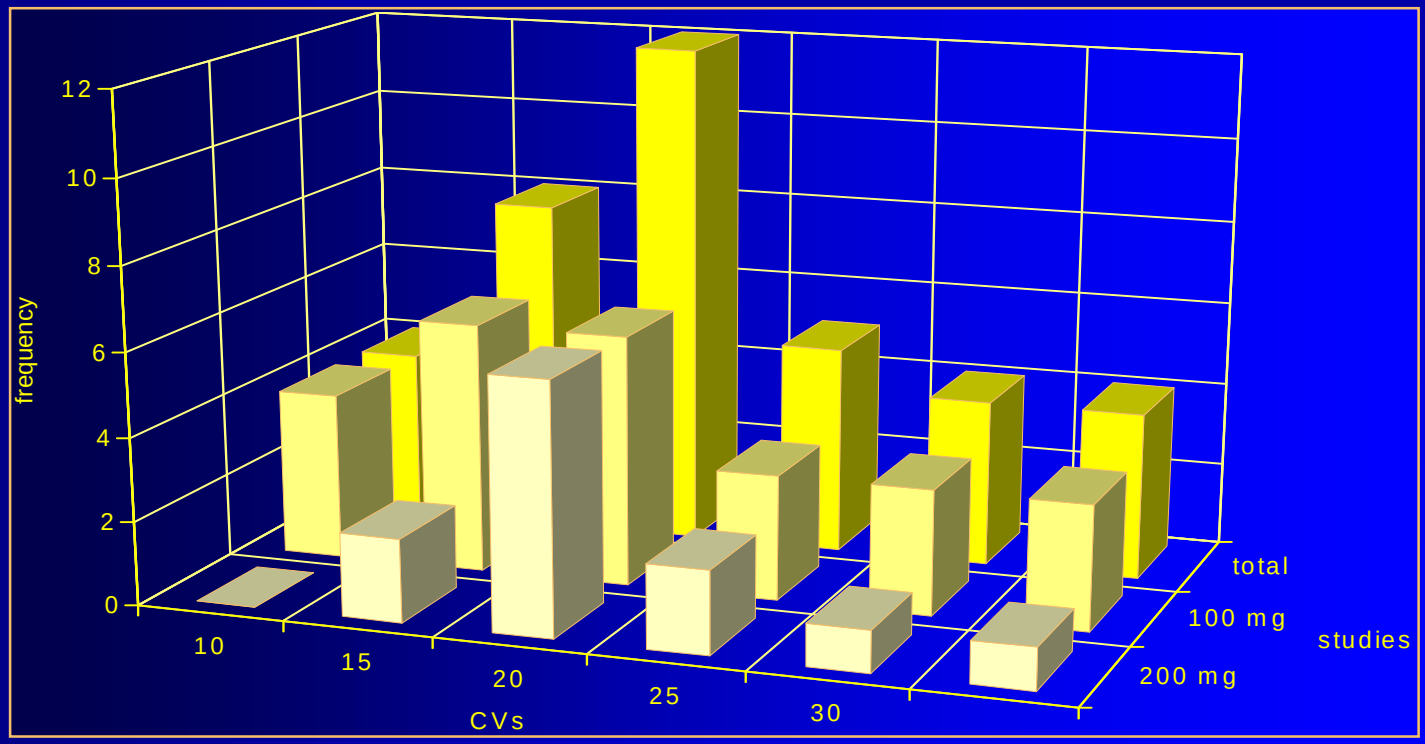
$$\Delta_{CL} = \ln 1.15 - \ln 1.023 = 0.11702$$

$$MSE = 2\left(\frac{0.11702}{\sqrt{\left(\frac{1}{11}+\frac{1}{10}\right)}\cdot 1.729}\right)^2 = 0.04798$$

$$CV_{\text{intra}}\% = 100 \cdot \sqrt{e^{0.04798} - 1} = 22.2\%$$

Sample Size Estimation

Literature data…



Doxicycline (37 studies from **Blume/Mutschler**, *Bioäquivalenz: Qualitätsbewertung wirkstoffgleicher Fertigarzneimittel*, GOVI-Verlag, Frankfurt am Main/Eschborn, 1989-1996)

Pooling of CV%

- Intra-subject CV from different studies can be pooled
  - Do not use the arithmetic mean (or the geometric mean either) of CVs
  - In the parametric model of log-transformed data, additivity of variances (not of CVs!) apply
  - Before pooling variances must be weighted acccording to the sample size
    - Calculate the variance from CV

$$\sigma_W^2 = \ln(CV_{\text{intra}}{}^2 + 1)$$

Pooling of CV%

- Intra-subject CV from different studies
  - Calculate the total variance weighted by degrees of freedom

$$\sum \sigma_w^2 df$$

  - Calculate the pooled CV from total variance

$$CV = \sqrt{e^{\sum \sigma_w^2 df / \sum df} - 1}$$

  - Optionally calculate an upper (1-α) % confidence limit on the pooled CV (recommended α=0.20)

$$CL_{CV} = \sqrt{e^{\sum \sigma_w^2 df / \chi^2_{1-\alpha, \sum df}} - 1}$$

Pooling of CV%

- Example 1: $n_1=n_2$;
  $CV_{Study1} < CV_{Study2}$

studies	N
2	24

df (total)	α	1-α	total	CV_{pooled}	CV_{mean}
20	0.2	0.8	1.2540	**0.254**	~~0.245~~
		$\chi^2_{(1-\alpha,df)}$	14.578	0.300	+17.8%

CV_{intra}	n	seq.	df (mj)	σw	$\sigma^2 w$	$\sigma^2 w \times df$	$CV_{intra\ /\ pooled}$	$>CL_{upper}$
0.200	**12**	**2**	10	0.198	0.0392	0.3922	78.6%	no
0.300	**12**	**2**	10	0.294	0.0862	0.8618	117.9%	yes

Pooling of CV%

- Example 2: $n_1 < n_2$;
  $CV_{Study1} < CV_{Study2}$

studies	N
2	36

df (total)	α	1-α	total	CV_{pooled}	CV_{mean}
32	0.2	0.8	2.2881	**0.272**	~~0.245~~
		$\chi^2_{(1-\alpha,df)}$	25.148	0.309	+13.4%

CV_{intra}	n	seq.	df (mj)	σw	$\sigma^2 w$	$\sigma^2 w \times df$	$CV_{intra\ /\ pooled}$	$>CL_{upper}$
0.200	**12**	**2**	10	0.198	0.0392	0.3922	73.5%	no
0.300	**24**	**2**	22	0.294	0.0862	1.8959	110.2%	no

Pooling of CV%

- Example 3: $n_1 > n_2$;
  $CV_{Study1} < CV_{Study2}$

studies	N
2	36

df (total)	α	1-α	total	CV_{pooled}	CV_{mean}
32	0.2	0.8	1.7246	**0.235**	~~0.245~~
		$\chi^2_{(1-\alpha,df)}$	25.148	0.266	+13.2%

CV_{intra}	n	seq.	df (mj)	σw	$\sigma^2 w$	$\sigma^2 w \times df$	$CV_{intra\ /\ pooled}$	$>CL_{upper}$
0.200	**24**	**2**	22	0.198	0.0392	0.8629	85.0%	no
0.300	**12**	**2**	10	0.294	0.0862	0.8618	127.5%	yes

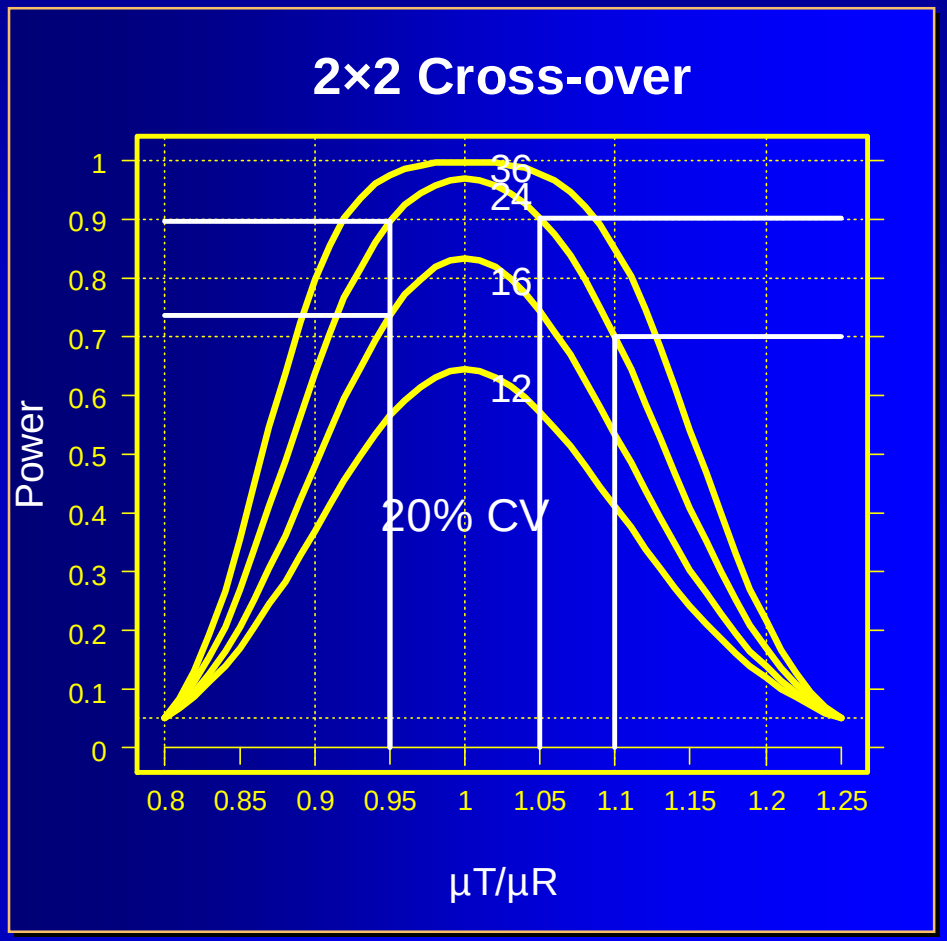
Sample Size Estimation

Power to show BE with 12 – 36 subjects for

CV_{intra} = 20%

n 24 → 16:
power 0.896 → 0.735

μ_T/μ_R 1.05 → 1.10:
power 0.903 → 0.700



Sample Size: Sensitivity Analysis

- ICH E9
  - Section 3.5 Sample Size, paragraph 3
    - The method by which the sample size is calculated should be given in the protocol […]. The basis of these estimates should also be given.
    - It is important to investigate the sensitivity of the sample size estimate to a variety of deviations from these assumptions and this may be facilitated by providing a range of sample sizes appropriate for a reasonable range of deviations from assumptions.
    - In confirmatory trials, assumptions should normally be based on published data or on the results of earlier trials.

Sample Size: Pilot Studies

- Pilot Studies
  - Small pilot studies (sample size <12)
    - are useful in checking the sampling schedule and
    - the appropriateness of the analytical method, but
    - are not suitable for the purpose of sample size planning.

Sample Size: Pilot Studies

- Pilot Studies (cont'd)
  - Moderate sized pilot studies (sample size ~12–24) lead to more consistent results (both CV_{intra} and PE).
    - If you stated a procedure in your protocol, even BE may be claimed in the pilot study, and no further study will be necessary.
    - You may also use an upper confidence limit of CV_{intra} in sample size estimation.
    - If you have some previous hints of high intra-subject variability (>30%), a pilot study size of at least 24 subjects is reasonable.
      A Sequential Design may also avoid an unnecessary large pivotal study.

Two-Stage Design

- EMEA Draft BE Guideline(2008)
  - Section 4.1.8
    - Initial group of subjects treated and data analysed.
    - If BE not been demonstrated an additional group can be recruited and the results from both groups combined in a final analysis.
    - Appropriate steps to preserve the overall type I error (patient's risk).
    - First stage data should be treated as an interim analysis.

'Internal Pilot Study Design'

Two-Stage Design

- EMEA Draft BE Guideline (2008)
  - Section 4.1.8 (cont'd)
    - Both analyses conducted at adjusted significance levels (with the confidence intervals accordingly using an adjusted coverage probability which will be higher than 90%).
    - Plan to use a two-stage approach must be pre-specified in the protocol along with the adjusted significance levels to be used for each of the analyses.

Two-Stage Design

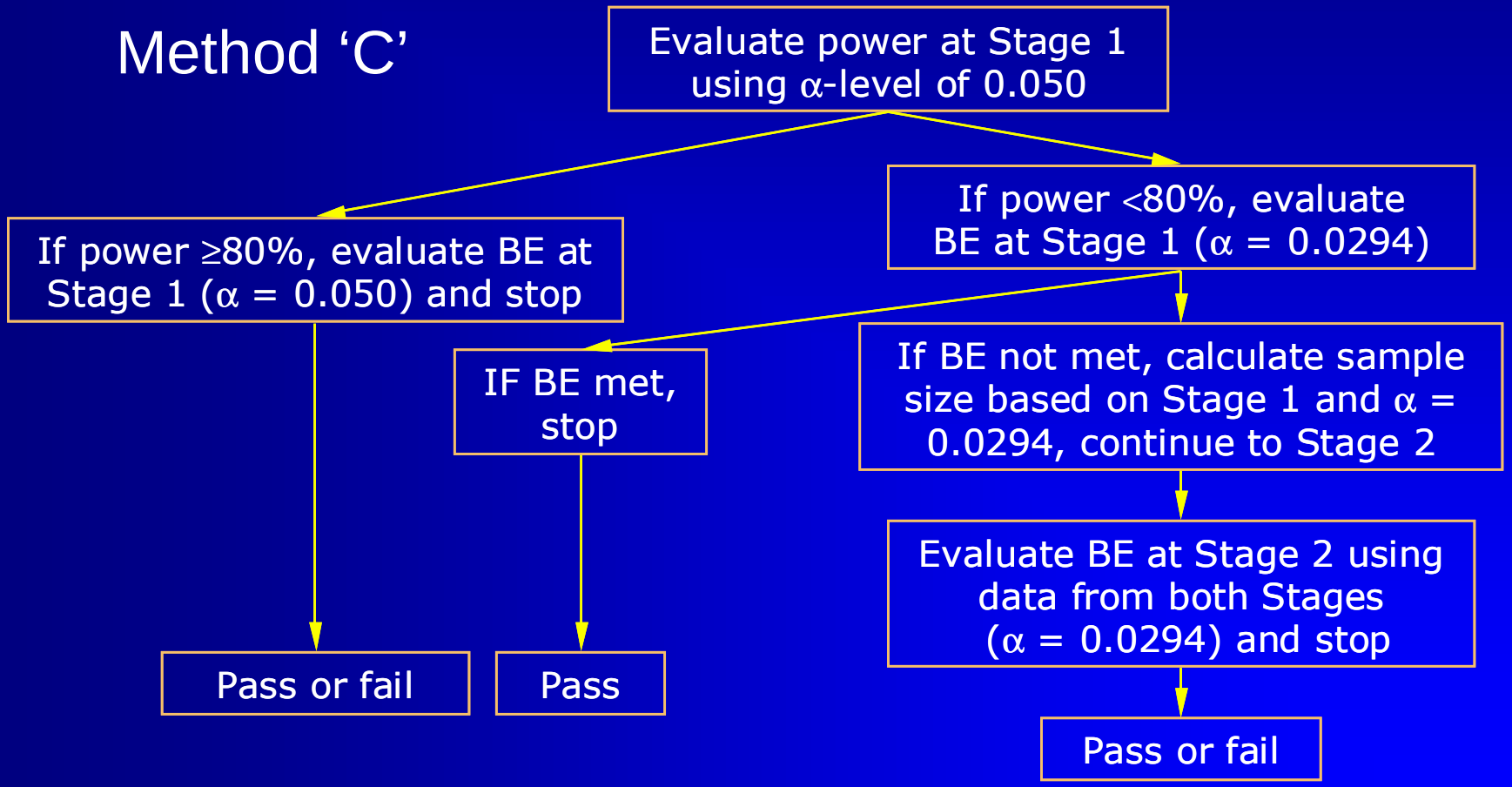
- Critical Remarks
  - 'BE not been demonstrated' in initial group:
    If test at $\alpha \leq 0.05$, patient's risk already 'spent'!
  - 'Adjusted significance levels':
    Bonferroni not validated in BE setting; patient's risk may be inflated (>0.05)!

likely to be implemented by US-FDA and Canada's HPB

Potvin D, Diliberti CE, Hauck WW, Parr AF, Schuirmann DJ, and RA Smith
Sequential design approaches for bioequivalence studies with crossover designs
Pharmaceut Statist (2007), DOI: 10.1002/pst.294
http://www3.interscience.wiley.com/cgi-bin/abstract/115805765/ABSTRACT

Sequential Design

Method 'C'



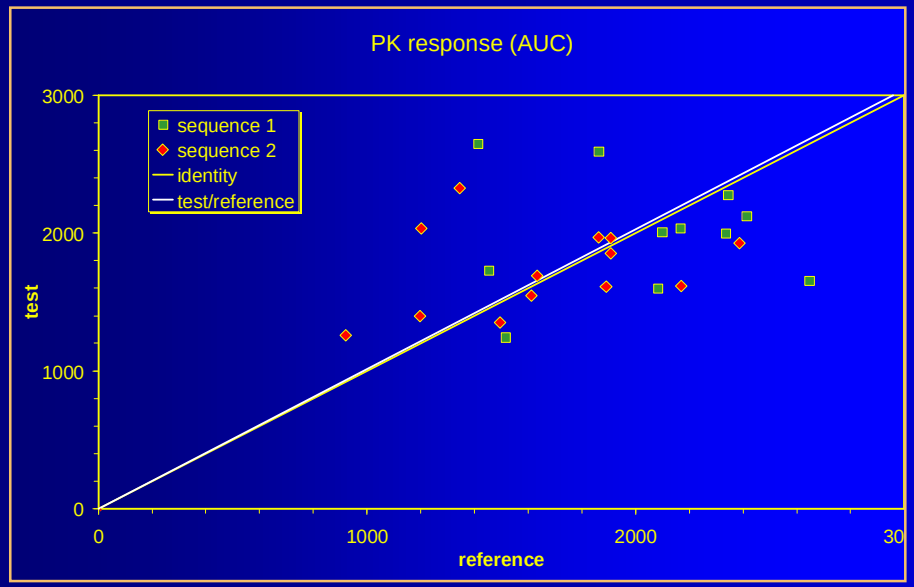
Outliers

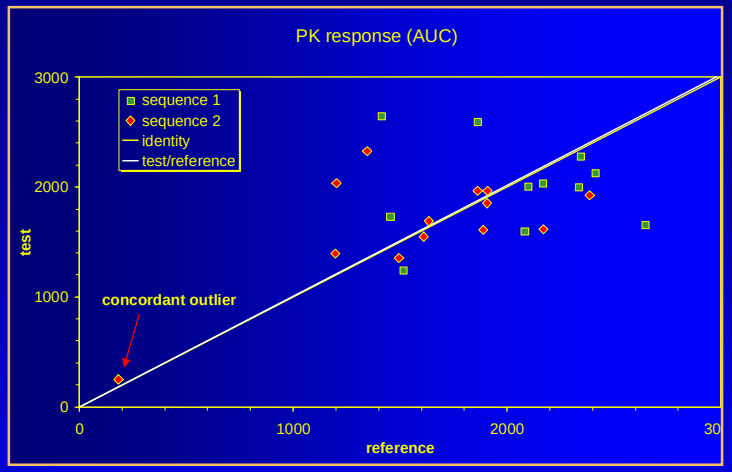
- Problems
  - Parametric methods (ANOVA, GLM) are very sensitive to outliers
    - A single outlier may underpower a properly sized study!
    - Exclusion of outliers only possible if procedure stated in the protocol, and reason is justified, *e.g.*,
      - Lacking compliance (subject did not take the medication),
      - Vomiting (up to 2 × t_{max} for IR, at all times for MR),
      - Analytical problems (*e.g.*, interferences in chromato-graphy);
      - Not acceptable if only based on statistical grounds.

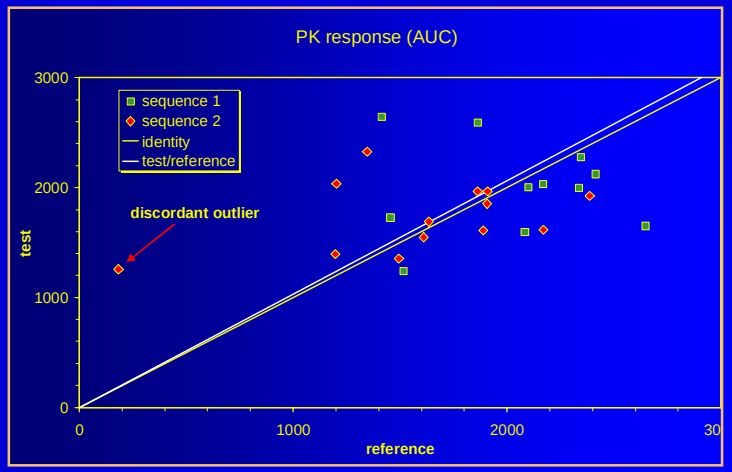
Outliers

- Types
  I. Concordant outlier
  The PK response for both test and reference deviates from the majority of the study sample.
    - Poor metabolizers may lead to high concentrations in 5–10% of subjects.
    - Does not effect the BE-assessment, but should be discussed (polymorphism known?)
  II. Discordant outlier
  The PK response of either test or reference deviates form the majority of the study sample.

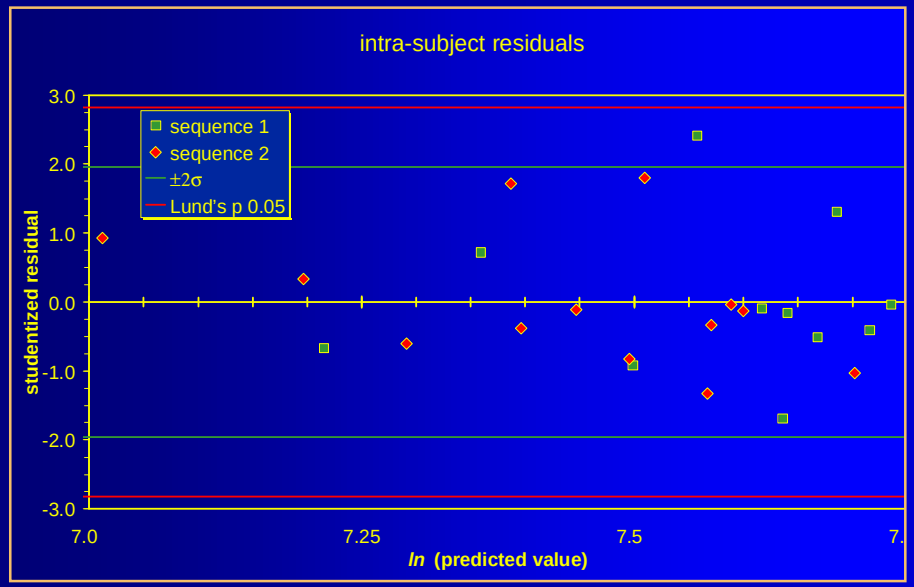
Outliers

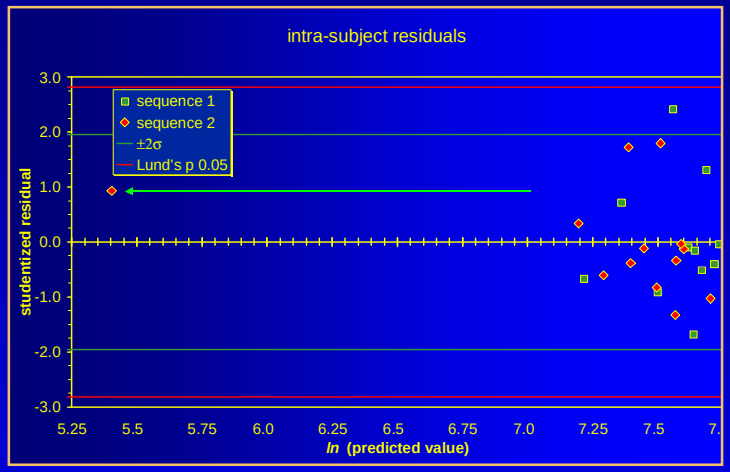

PK response (AUC)
sequence 1
sequence 2
identity
test/reference
test
reference
0
1000
2000
3000

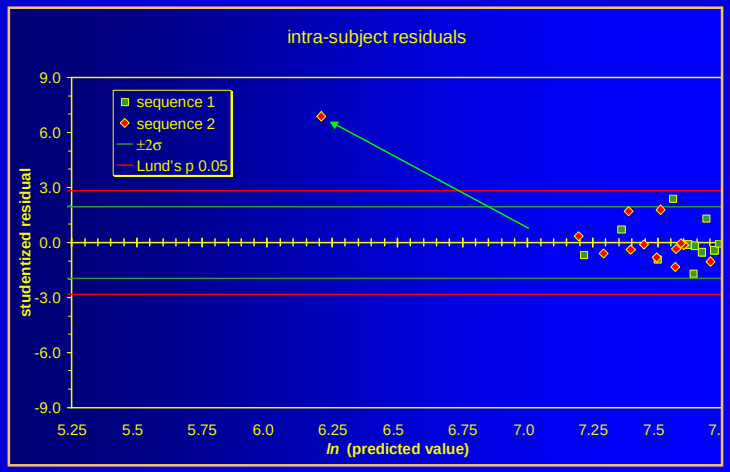

PK response (AUC)
sequence 1
sequence 2
identity
test/reference
concordant outlier
test
reference
0
1000
2000
3000


PK response (AUC)
sequence 1
sequence 2
identity
test/reference
discordant outlier
test
reference
0
1000
2000
3000

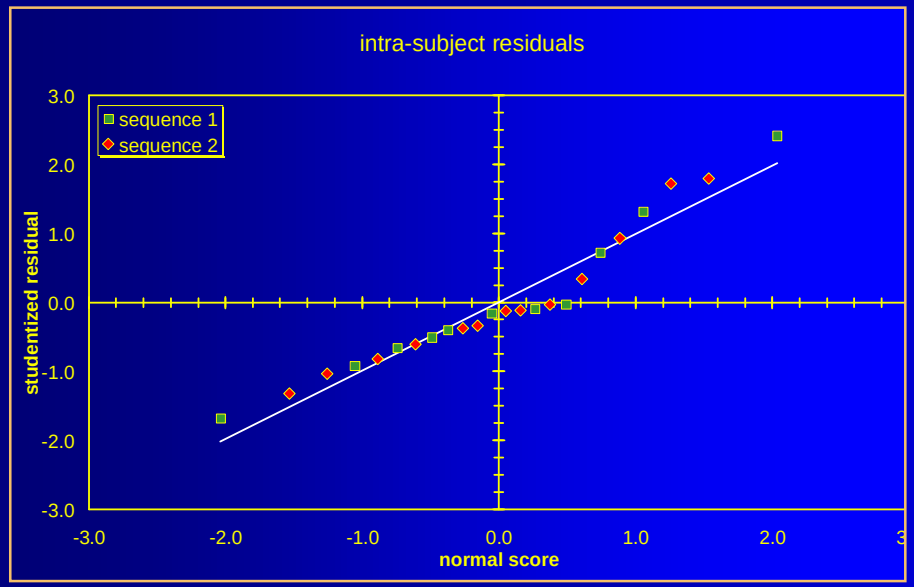
Outliers

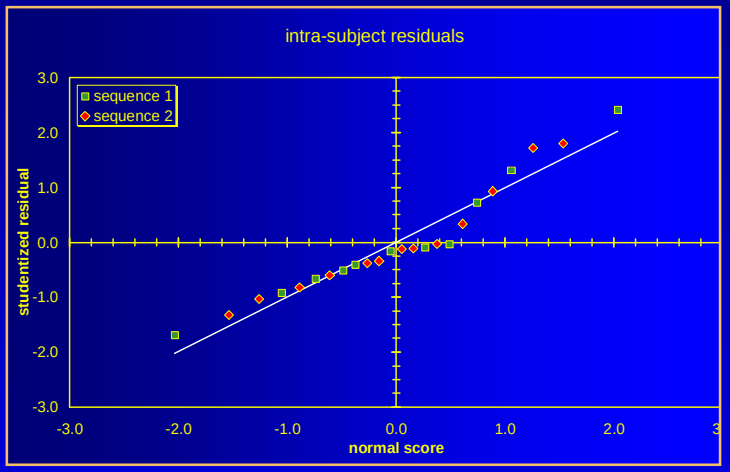

intra-subject residuals
sequence 1
sequence 2
±2σ
Lund's p 0.05
studentized residual
3.0
2.0
1.0
0.0
-1.0
-2.0
-3.0
7.0
7.25
7.5
ln (predicted value)

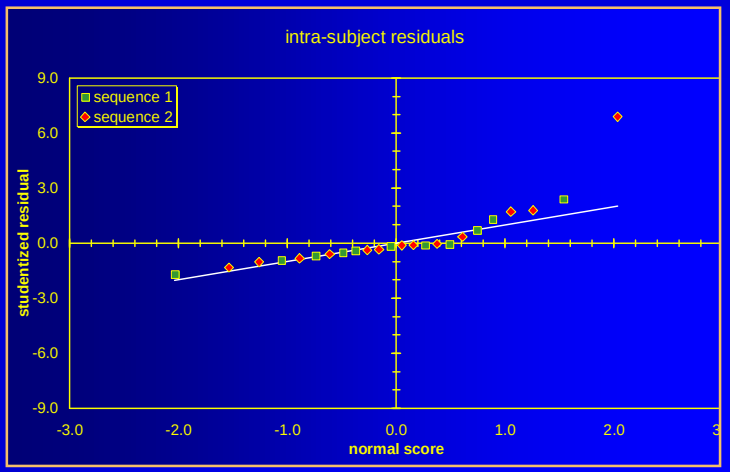

intra-subject residuals
sequence 1
sequence 2
±2σ
Lund's p 0.05
studentized residual
3.0
2.0
1.0
0.0
-1.0
-2.0
-3.0
5.25
5.5
5.75
6.0
6.25
6.5
6.75
7.0
7.25
7.5
ln (predicted value)


intra-subject residuals
sequence 1
sequence 2
±2σ
Lund's p 0.05
studentized residual
9.0
6.0
3.0
0.0
-3.0
-6.0
-9.0
5.25
5.5
5.75
6.0
6.25
6.5
6.75
7.0
7.25
7.5
ln (predicted value)

Outliers


intra-subject residuals
sequence 1
sequence 2
studentized residual
normal score
3.0
2.0
1.0
0.0
-1.0
-2.0
-3.0
-3.0
-2.0
-1.0
0.0
1.0
2.0


intra-subject residuals
sequence 1
sequence 2
studentized residual
normal score
3.0
2.0
1.0
0.0
-1.0
-2.0
-3.0
-3.0
-2.0
-1.0
0.0
1.0
2.0


intra-subject residuals
sequence 1
sequence 2
studentized residual
normal score
9.0
6.0
3.0
0.0
-3.0
-6.0
-9.0
-3.0
-2.0
-1.0
0.0
1.0
2.0

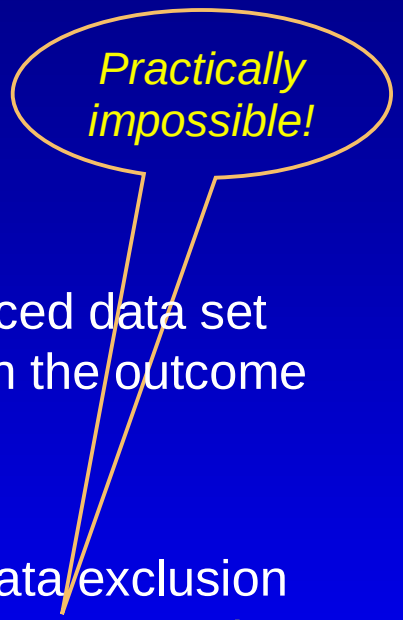
Outliers

- Strategies / Solutions
  - Be prepared to face the unexpected!
  - Examples of drugs/formulations with documented product failures:
    - Drugs sensitive to low pH (gastric resistance!),
    - Monolithic MR products,
    - …
  - Include available information (PK, literature, former studies) in the protocol.
  - Develop a statistical contingency plan.

Outliers

- Solution I
  - Since assumptions of the parametric statistical model are violated, you may apply a statistical method which does not rely on those!
  - Drawback: Lacking regulatory acceptance of nonparametric methods in many countries…
    - ☺ WHO (Technical Report Series No. 937, Annex 9, Section 6.8, May 2006)
    - ☺ Japan NIHS (Bioequivalence Studies for Generic Products, Q&A Document, November 2006)
    - ☹ All other regulatory agencies

Outliers



- Solution II
  - Stay with the parametric method, but
    - evaluate both the full data set and the reduced data set (outliers excluded) and discuss influence on the outcome of the study.
  - In accordance with EMEA's Q&A #3:
    - Exceptional reasons may justify post-hoc data exclusion […]. In such a case, the *applicant must demonstrate that the condition stated to cause the deviation is present in the outlier(s) only* and absence of this condition has been investigated using the same criteria for all other subjects.
    - Results of statistical analyses with and without the group of excluded subjects should be provided.

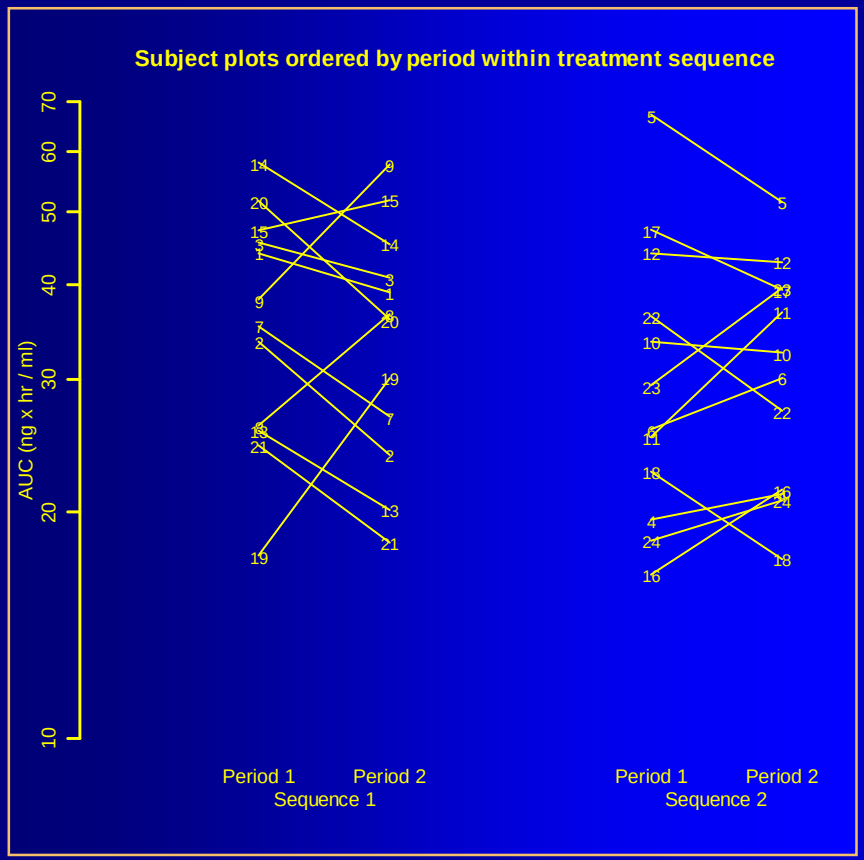
Re-testing of subjects

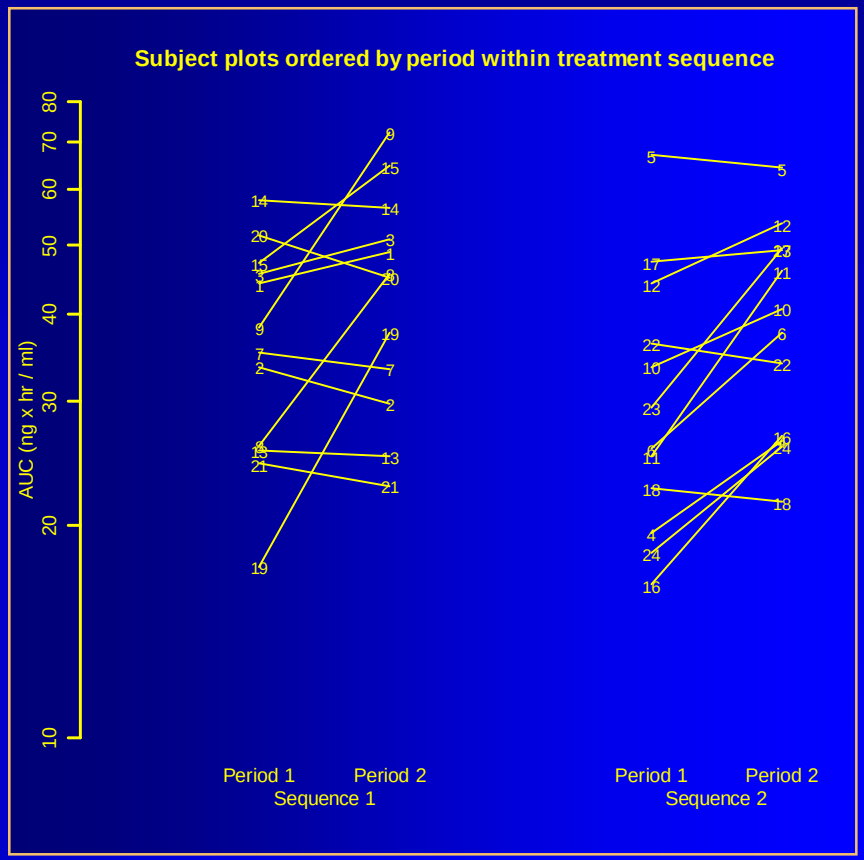
- If you suspect a product failure of the reference formulation, you may consider re-testing
  - The outlying subject should be re-tested
    - with *both* the test and reference.
    - Include ≥5 subjects, who showed 'normal' responses in the main study (*i.e.*, size of re-tested group ≥6 or 20% of subjects, whichever is larger).

Re-testing of subjects

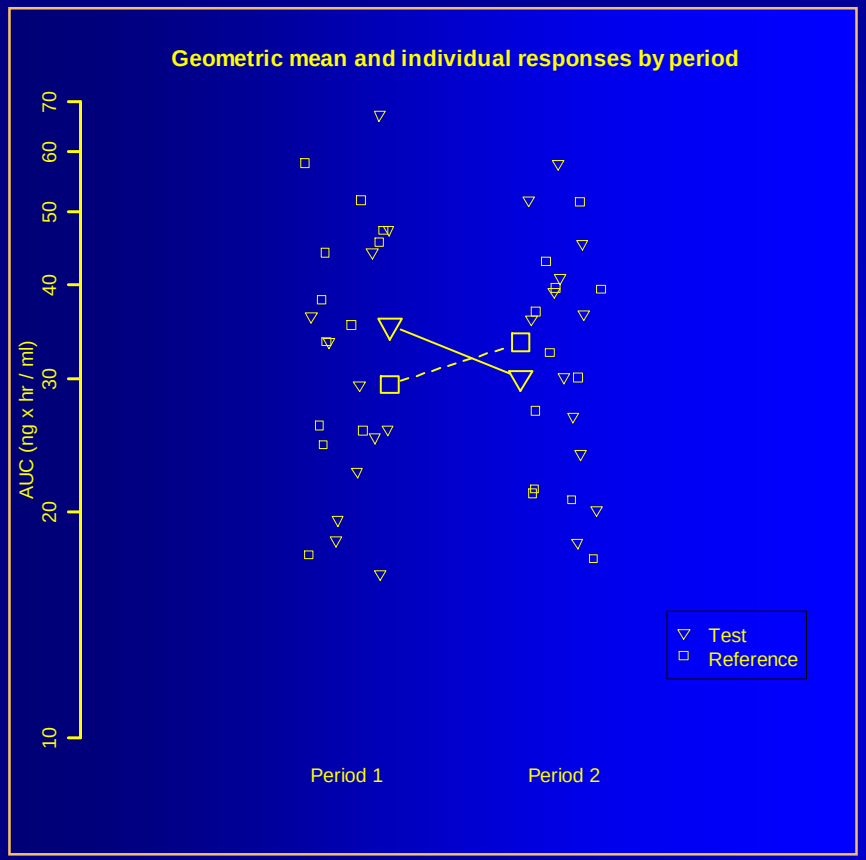
- Evaluation
  - Expect questions anyway!
    - Procedure *sometimes* suggested by the FDA:
      - If the subject shows a ‘normal’ response in re-testing, the original value may be exluded from the main study.
      - Substitution of original values with results from the re-test study not allowed
      - No pooling of data
    - Not covered in any guideline
    - Suggested by EGA (and many others) in comments to the drafted EU BE-guideline

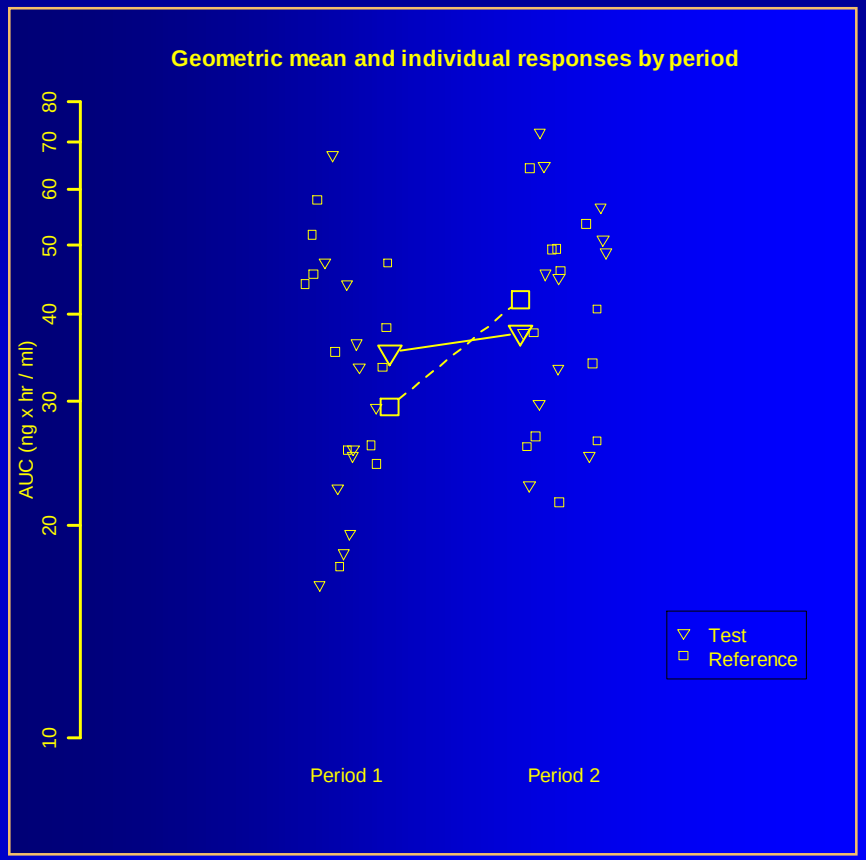
Nuisance: period effect





Nuisance: period effect

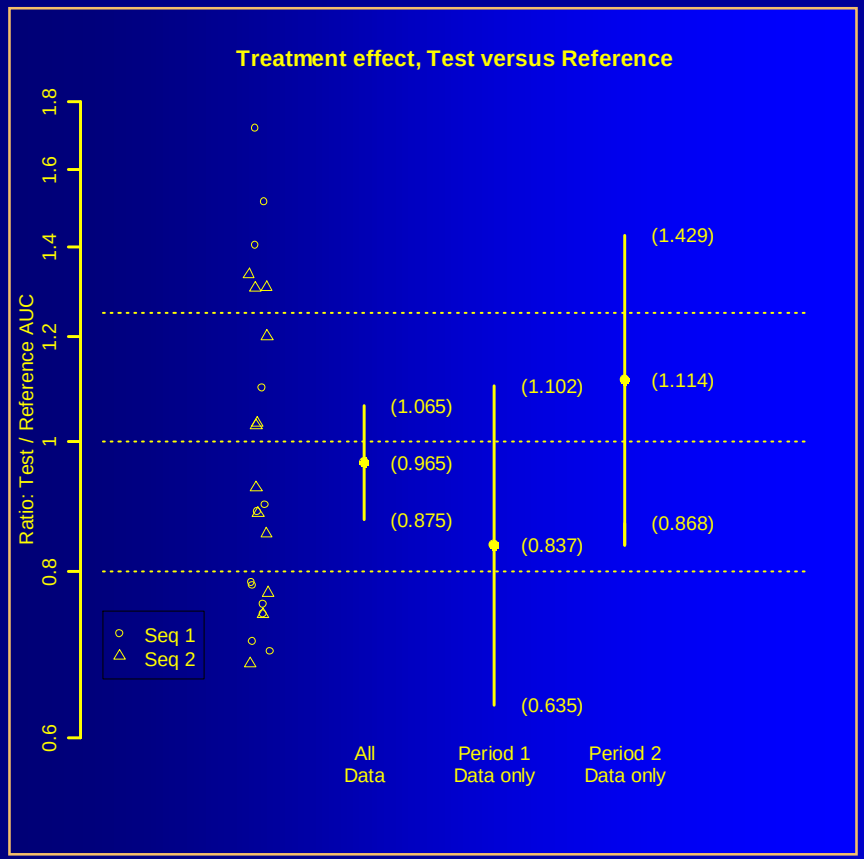


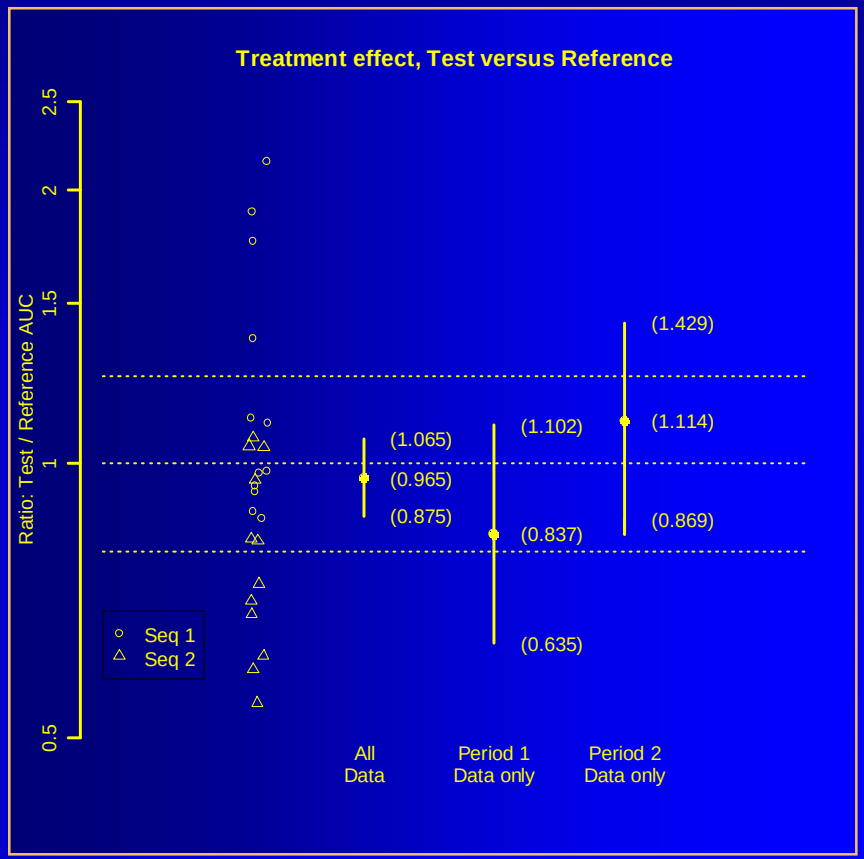


Nuisance: period effect

- Original data
  - AUC(p_2/p_1): 98.4%
  - Period: *p* 0.7856 (95% CI: 87.4% –110.8%)
  - Sequence: *p* 0.3239 (95% CI: 86.0% –154.8%)
  - GMR: 96.5% (90% CI: 87.5% –106.5%)
- Modified data (p_2 125% of original values)
  - AUC(p_2/p_1): 123.0%
  - Period: *p* 0.0015 (95% CI: 109.3% –138.5%)
  - Sequence: *p* 0.3239 (95% CI: 86.0% –154.8%)
  - GMR: 96.5% (90% CI: 87.5% –106.5%)

Nuisance: period effect





Nuisance: sequence effect

- In a ‘standard’ 2×2 cross-over design
  - the sequence effect is confounded with
    - the carry-over effect, and
    - the formulation-by-period interaction.
  - Therefore, a statistically significant sequence effect could indicate that there is
    - a true sequence effect,
    - a true carryover effect,
    - a true formulation by period interaction, or
    - a failure of randomization.

Nuisance: sequence effect

- 'Two-stage analysis'[1)] was – and regrettably still is – often applied.
  - Test for a significant sequence effect at α 0.10
  - If a significant sequence effect is found, evaluation of the first period as a parallel design
- This procedure was shown to be statistically flawed.[2)]

1) **JE Grizzle**
The two-period change over design and ist use in clinical trials
Biometrics 21: 467-480 (1965)

2) **P Freeman**
The performance of the two-stage analysis of two-treatment, two-period cross-over trials
Statistics in Medicine 8: 1421-1432 (1989)

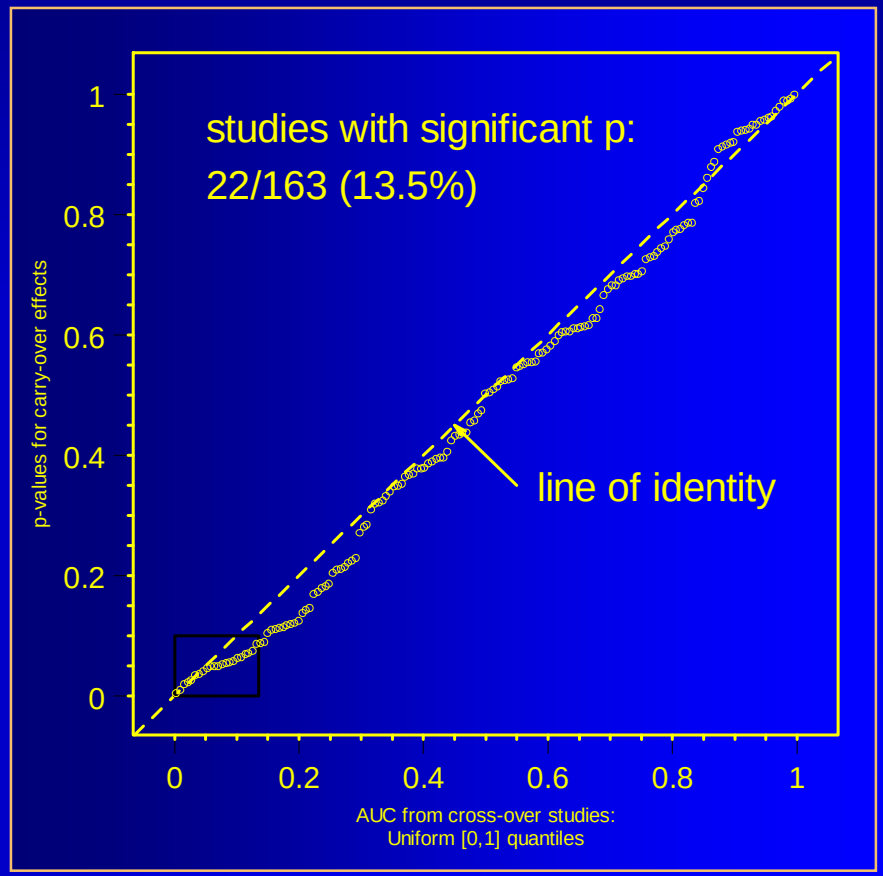
Nuisance: sequence effect

- In a large metastudy (n=420) significant sequence effects were found at ≈ α, both for AUC and C_{max}.*)
  - 2×2 studies (n=324)
    AUC: 34/324 (10.5%) C_{max}: 37/324 (11.4%)
  - 6×3 studies (n=96)
    AUC: 4/96 (4.2%) C_{max}: 4/96 (4.2%)
  - For both metrics the distribution of *p* values followed closely Uniform [0,1]

*) **D'Angelo G, Potvin D and J Turgeon**
Carry-over effects in bioequivalence studies
J Biopharm Stat 11: 35-43 (2001)

Nuisance: sequence effect

- These results could be confirmed (20 published studies, 143 studies from BEBAC's database; AUC):
  - Significant sequence effects in 22/163 studies (13.5%)
- Significant sequence effects in properly planned studies should be considered a statistical artefact (significant results are obtained in α of studies)



Nuisance: sequence effect

- Conclusions
  - No valid procedure exists to *correct* for a true sequence/carry-over effect
  - A true sequence/carry-over is *highly unlikely* in a BE study if
    - the study is performed in healthy subjects,
    - the drug is not an endogenous entity, and
    - an adequate washout period (no predose concentrations) was maintained.
  - Testing for a sequence effect is futile!

Nuisance: sequence effect

- Conclusions (cont'd)
  - EMEA Draft GL on BE (2008)

    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 (and beyond if applicable).

Nuisance: sequence effect

- Conclusions (cont'd)
  - EMEA Draft GL on BE (2008)

    […] *tests for difference and the respective confidence intervals for the treatment effect, the period effect, and the sequence effect should be reported for descriptive assessment.*
    - Tests for the treatment effect are meaningless in BE!
    - BE assessment is not influenced by the period effect.
    - Sequence effect again?!

Nuisance: group effect

- More than one group of subjects
  - ‘If a crossover study is carried out in two or more groups of subjects (*e.g.*, if for logistical reasons only a limited number of subjects can be studied at one time), the statistical model should be modified to reflect the multigroup nature of the study. In particular, the model should reflect the fact that the periods for the first group are different from the periods for the second group.’

FDA, Center for Drug Evaluation and Research (CDER)
Guidance for Industry: Statistical Approaches to Establishing Bioequivalence (2001)

Nuisance: group effect

- More than one group of subjects
  - Cases where '… the study is carried out in two or more groups and those groups are studied at different clinical sites, or at the same site but greatly separated in time (months apart, for example) […] should be discussed with the appropriate CDER review division.'
  - EMEA BA/BE (2001), BE Draft (2008)
    - The study should be designed in such a way that the formulation effect can be distinguished from other effects.

Nuisance: group effect

- Increasing number of referrals (deficiency letters) from
  - Canada
  - Gulf States (Saudia Arabia, Emirates, Oman)
- Extended Statistical model (fixed effects in ANOVA)
  - Group
  - Group × Treatment Interaction
  - If both terms are not significant ($p>0.05$), pooling of groups is justified.

Nuisance: group effect

- Recommendations
  - If possible, multiple groups should be avoided.
  - Keep the time interval between groups as short as possible.
  - Do not split the study into equally sized groups.
    - Perform at least one group in the maximum capacity of the clinical site (*e.g.*, 24+8 instead of 16+16 for a total of 32).
    - If a significant group and/or group × treatment interaction is found (preventing a pooled analysis), it may still be possible to demonstrate BE in the largest group only.

Are we making progress?

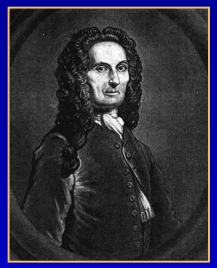
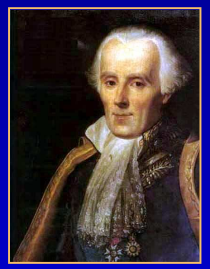
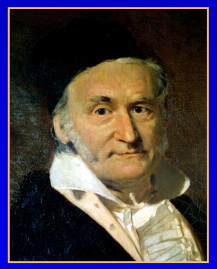
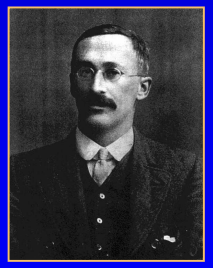
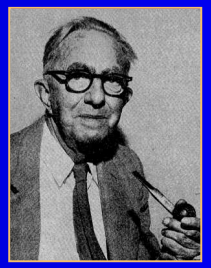
- About 3 000 – 10 000 BE studies / year are conducted worldwide; only ~ 1 – 5% of them are published.
- Although a standard for publishing data of BE studies was already suggested in 1992,[1)]
  - a review in 2002 found only 17 complete data sets on AUC and 12 on C_{max}.[2)]
  - Since no 'real world' data are available, proposed methods (*e.g.*, reference-scaled ABE) rely entirely on simulations!
  - Studies seen by regulators are 'selection biased'.

1) **Sauter R, Steinijans VW, Diletti E, Böhm E and H-U Schulz**
Int J Clin Pharm Ther Toxicol 30/Suppl.1, S7-S30 (1992)

2) **Nakai K, Fujita M and M Tomita**
Int J Clin Pharmacol Ther 40, 431-438 (2002)

Bell curve (and beyond?)

- Abraham de Moivre (1667-1754), Pierre-Simon Laplace (1749-1827)
  Central limit theorem 1733, 1812
- Carl F. Gauß (1777-1855)
  Normal distribution 1795
- William S. Gosset, aka Student (1876-1937)
  t-distribution 1908
- Frank Wilcoxon (1892-1965)
  Nonparametric tests 1945

Thank You!
Statistical Design and Analysis II
Open Questions?

(References in your handouts)

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  - E8: General Considerations for Clinical Trials (1997)
  - E9: Statistical Principles for Clinical Trials (1998)
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  - Guidelines for GCP for trials on pharmaceutical products (WHO Technical Report Series No. 850, Annex 3, 1995)
  - Handbook for GCP (2005)
  - WHO Expert Committee on Specifications for Pharmaceutical Preparations, Fortieth Report (WHO Technical Report Series No. 937, Annex 9: Additional guidance for organizations performing *in vivo* bioequivalence studies. 2006)
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  - 21CFR320: BA and BE Requirements (Revision 2008)
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  Procedure for Conducting GCP Inspections requested by the EMEA
  - Annex I: Investigator Site (2007)
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  - NfG on the Investigation of BA/BE (2001)
  - Points to Consider on Multiplicity Issues in Clinical Trials (2002)
  - BA/BE for HVDs/HVDPs: Concept Paper (2006); removed form EMEA's website in Oct 2007. Available at http://bebac.at/downloads/14723106en.pdf
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  - Draft Guideline on the Investigation of BE (2008)
  - Questions & Answers : Positions on specific questions addressed to the EWP therapeutic subgroup on Pharmacokinetics (2009)