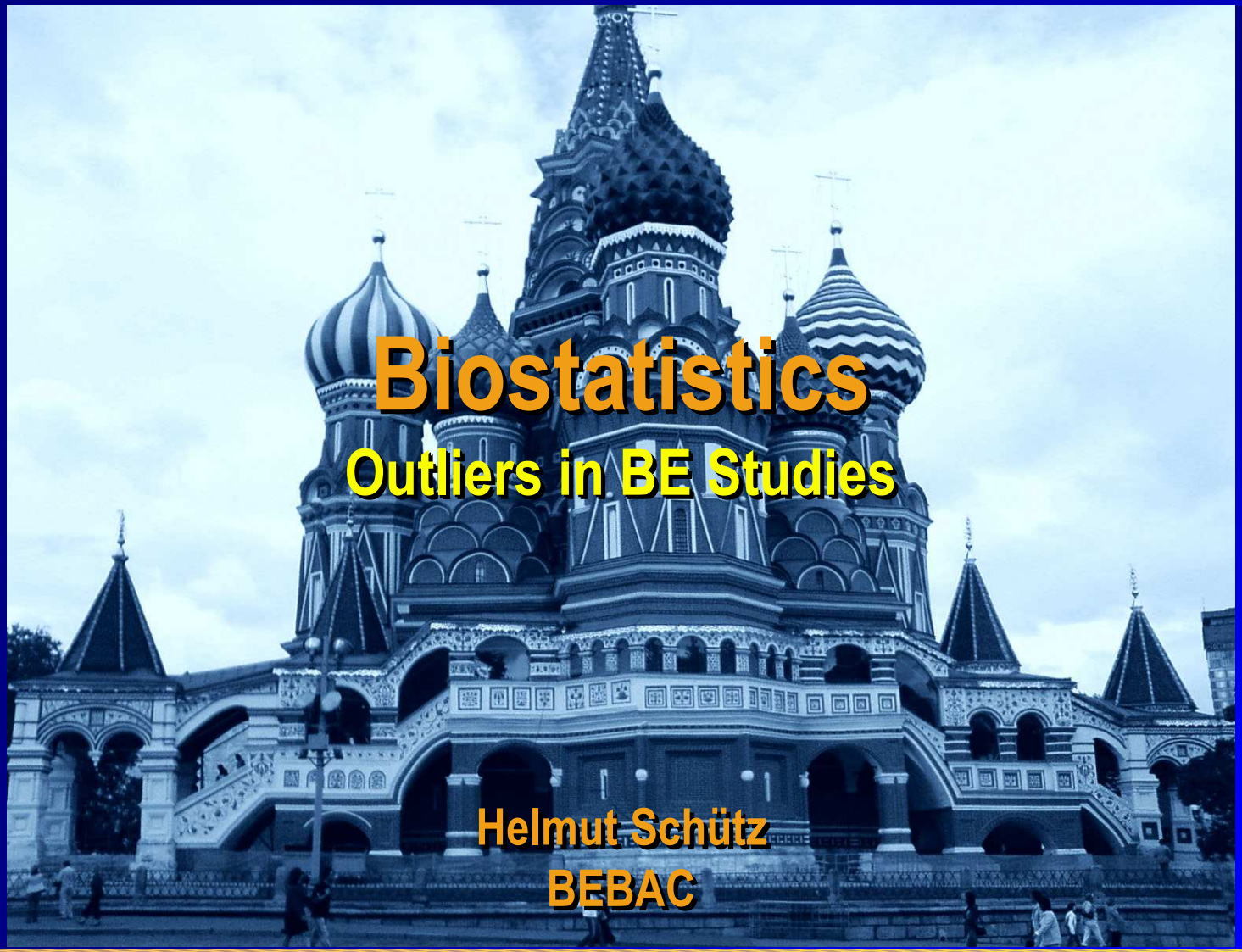

Biostatistics

Outliers in BE Studies

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BEBAC

Outliers

- **Problems**
  - Parametric methods (ANOVA, GLM, LMEM) 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 can be 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 chromatography);
      - Not acceptable if only based on statistical grounds.

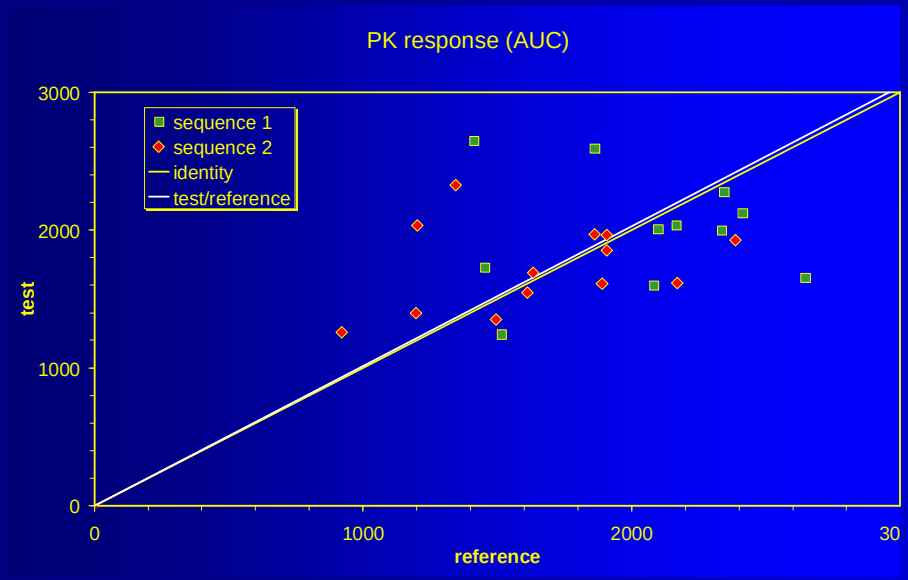
Outliers

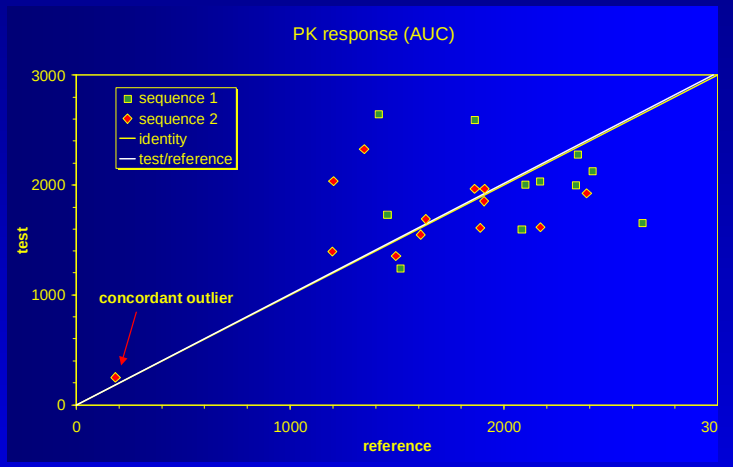
- Types
  - I. Concordant outlier

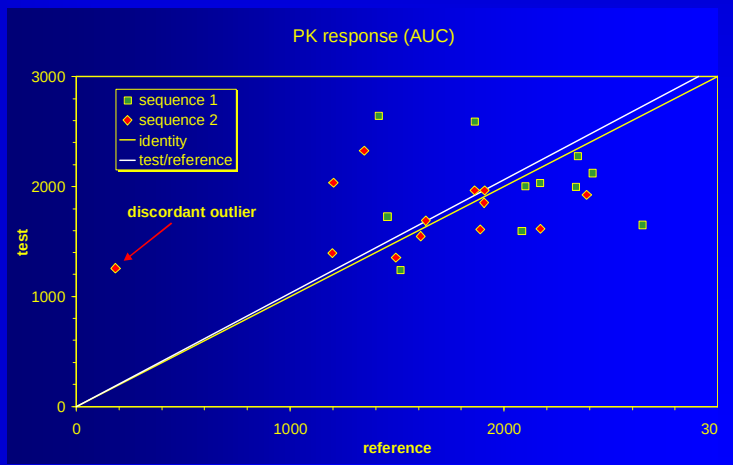
    The PK response for *both* test and reference deviates from the majority of the study sample.
    - Poor metabolizers may lead to high concentrations in 5–10% of subjects.
    - *Does not* effect the BE-assessment in a cross-over study, but should be discussed (polymorphism known?)
  - II. Discordant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

    The PK response of *either* test or reference deviates form the majority of the study sample.

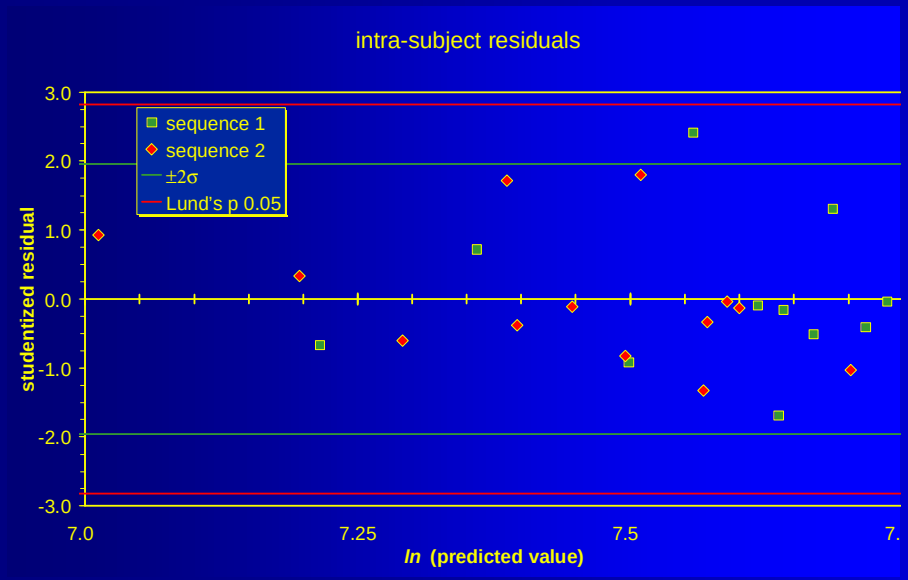
Type I/II

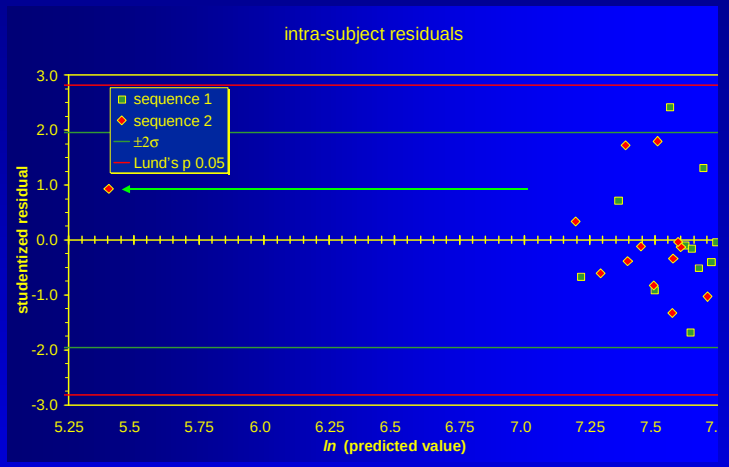

PK response (AUC)
sequence 1
sequence 2
identity
test/reference
test
reference
0
1000
2000
3000

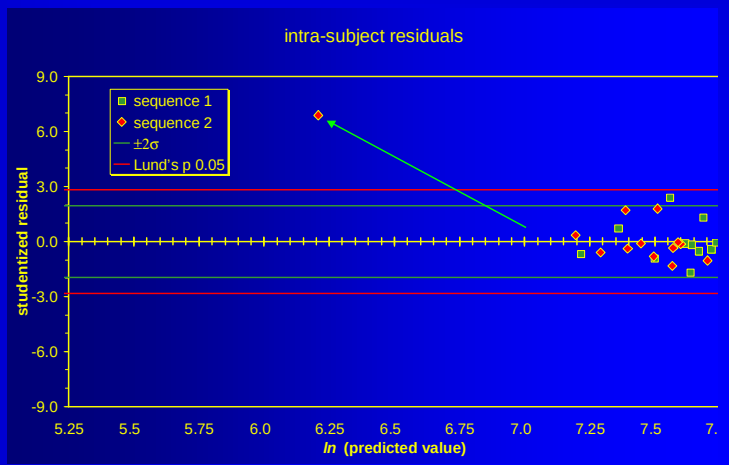

PK response (AUC)
sequence 1
sequence 2
identity
test/reference
concordant outlier
test
reference
0
1000
2000
3000


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

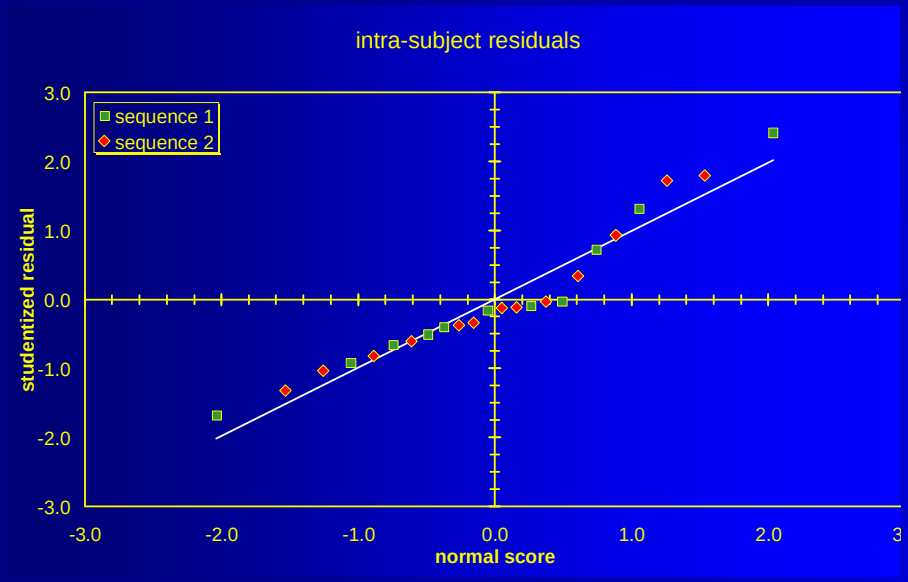
Type I/II

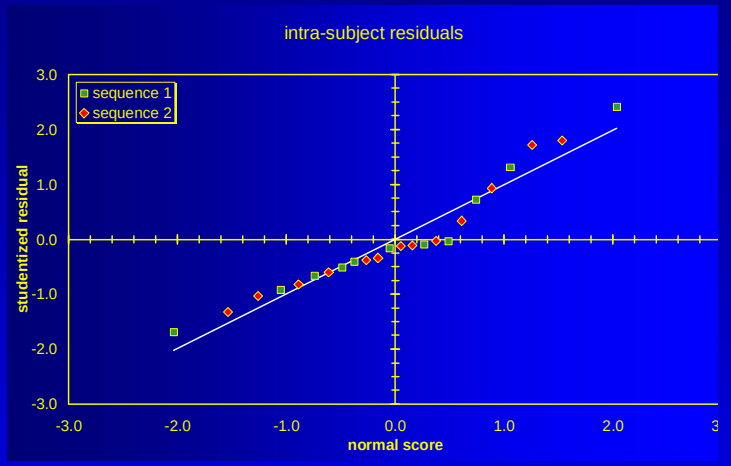

intra-subject residuals
sequence 1
sequence 2
±2σ
Lund's p 0.05
studentized residual
3.0
2.0
1.0
0.0
-1.0
-2.0
-3.0
7.0
7.25
7.5
ln (predicted value)

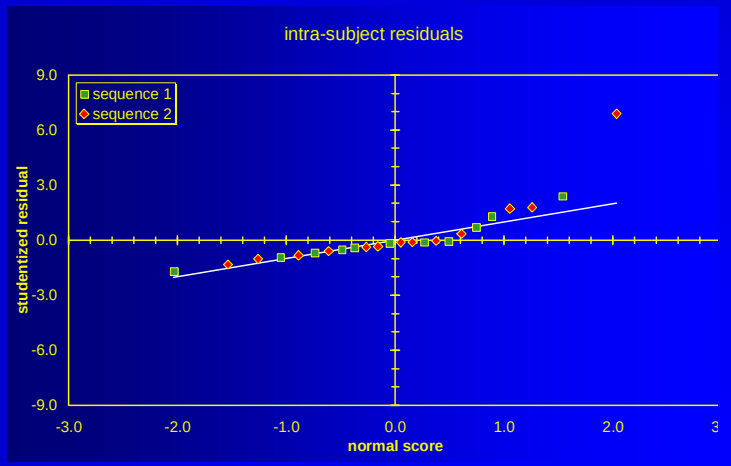

intra-subject residuals
sequence 1
sequence 2
±2σ
Lund's p 0.05
studentized residual
3.0
2.0
1.0
0.0
-1.0
-2.0
-3.0
5.25
5.5
5.75
6.0
6.25
6.5
6.75
7.0
7.25
7.5
ln (predicted value)


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)

Type I/II


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.

Solutions (?)

- 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

Solutions (?)

- **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 EMA'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.

Practically impossible!

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 *excluded* from the main study.
      - *Substitution* of original values with results from the re-test study is not acceptable.
      - No pooling of data.
    - Not covered in any guideline.
    - Suggested by EGA – and many others – in comments to the drafted EU BE-guideline. Was *not* accepted by the EMA.

Reminder (EMA)

- Q&A document (March 2011)
  - Data set I: Full replicate (RTRT | TRTR), 77 subjects, imbalanced, incomplete
    - CV_{WR} 46.96% → apply ABEL (> 30%)
    - Scaled Acceptance Range: 71.23–140.40%
    - Method A: 90% CI 107.11–124.89% ⊂ AR; PE 115.66% ✓
    - Method B: 90% CI 107.17–124.97% ⊂ AR; PE 115.73% ✓

HVDs/HVDPs (EMA)

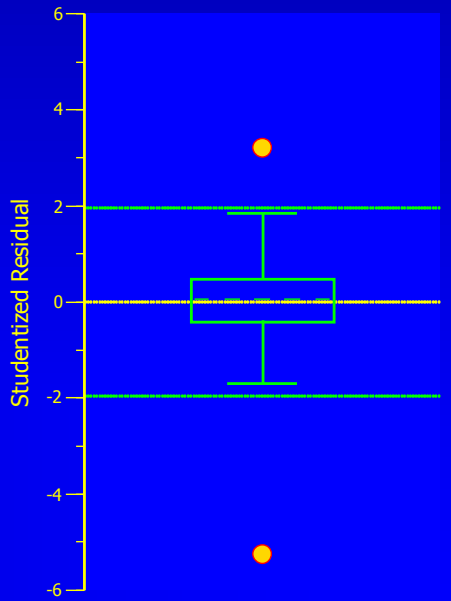
- EMA GL on BE (2010), Section 4.1.10
  - The applicant should justify that the calculated intra-subject variability is a reliable estimate and that it is not the result of outliers.
- EGA/EMA Q&A (2010)
  - Question:
    How should a company proceed if outlier values are observed for the reference product in a replicate design study for a Highly Variable Drug Product (HVDP)?

HVDs/HVDPs (EMA)

- EGA/EMA Q&A (2010)
  - Answer:
    The outlier cannot be removed from evaluation […] but should not be taken into account for calculation of within-subject variability and extension of the acceptance range. An outlier test is not an expectation of the medicines agencies but outliers could be shown by a box plot. This would allow the medicines agencies to compare the data between them.

HVDs/HVDPs (EMA)

- Data set I (full replicate)
  - CV_{WR} 46.96%
    Expanded Limits 71.23 – 140.40%
    Method A: 107.11 – 124.89%
    Method B: 107.17 – 124.97%
  - But there *are* two outliers!
    By excluding subjects 45 and 52
    CV_{WR} drops to 32.16%.
    Expanded Limits 78.79 – 126.93%
    Almost no more gain compared to conventional limits…



Thank You!

Outliers in BE Studies

Open Questions?

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