

Biostatistics

Outliers in BE Studies

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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 $2 \times t_{\max}$ 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

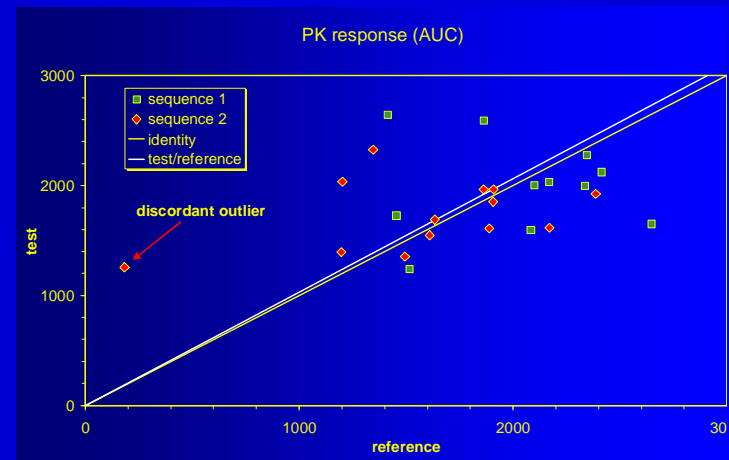
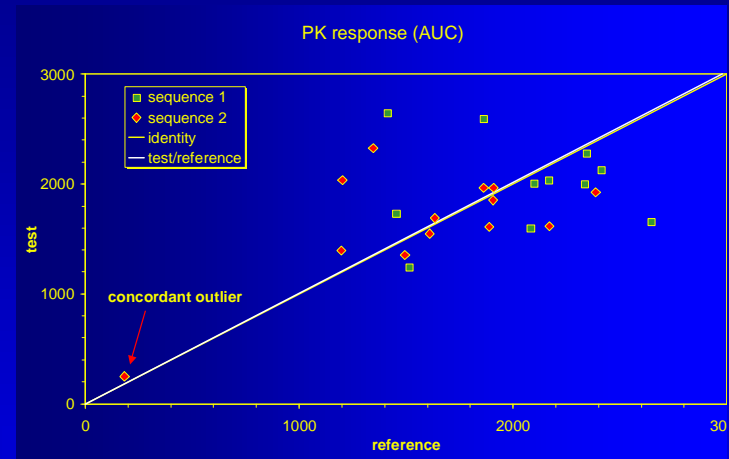
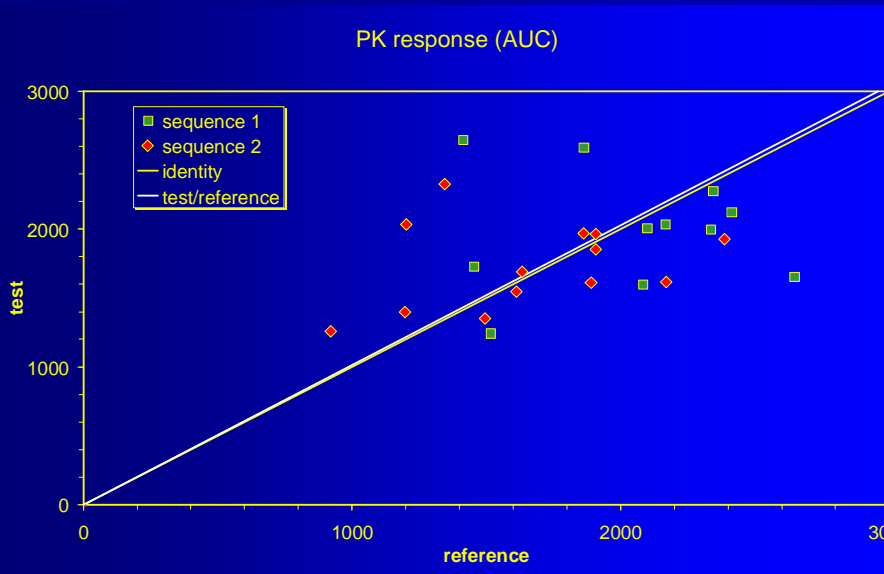
The PK response for *both* test and reference deviates from the majority of the study sample.

- 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?)

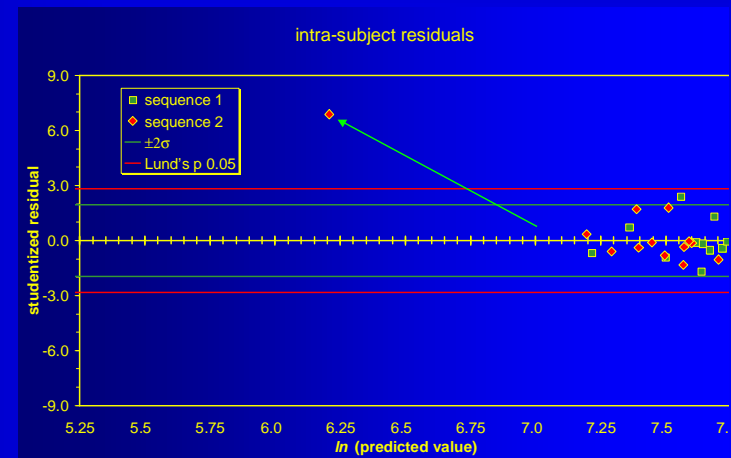
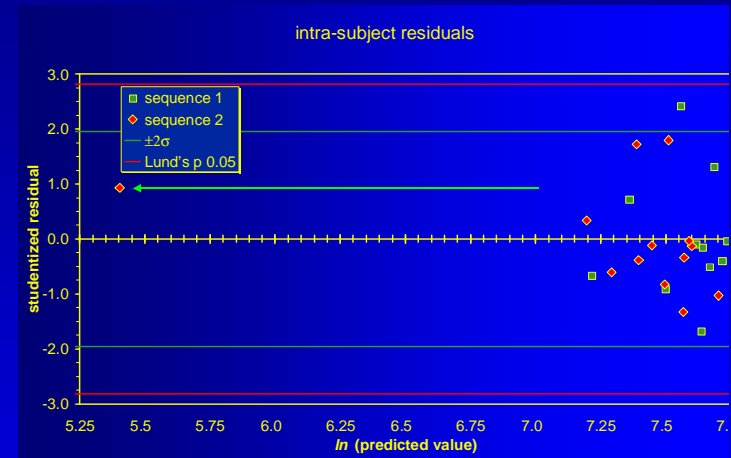
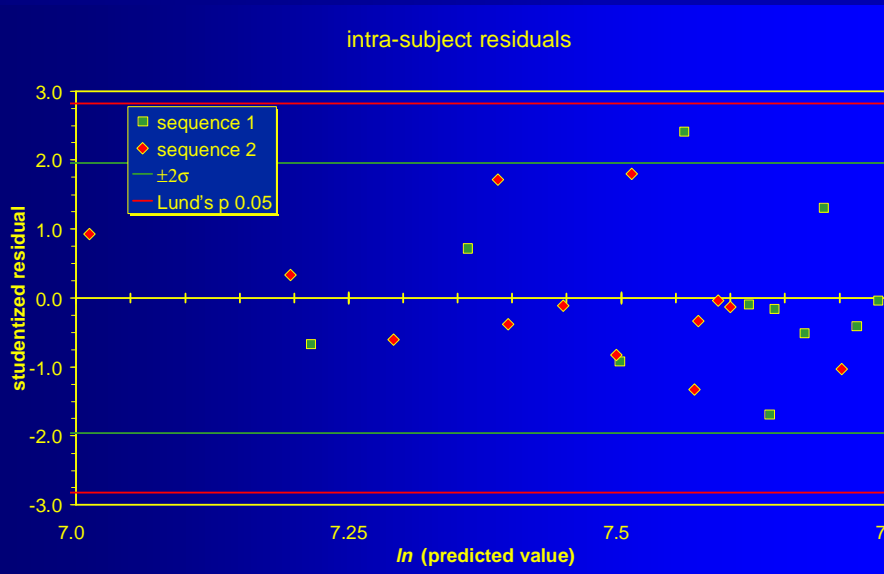
II. Discordant outlier

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

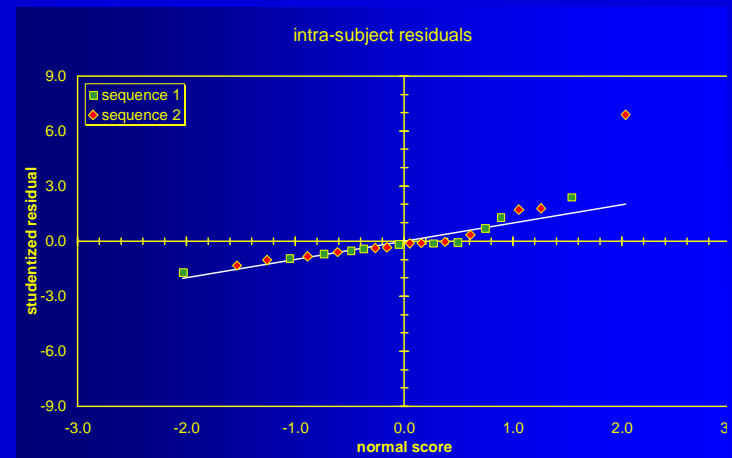
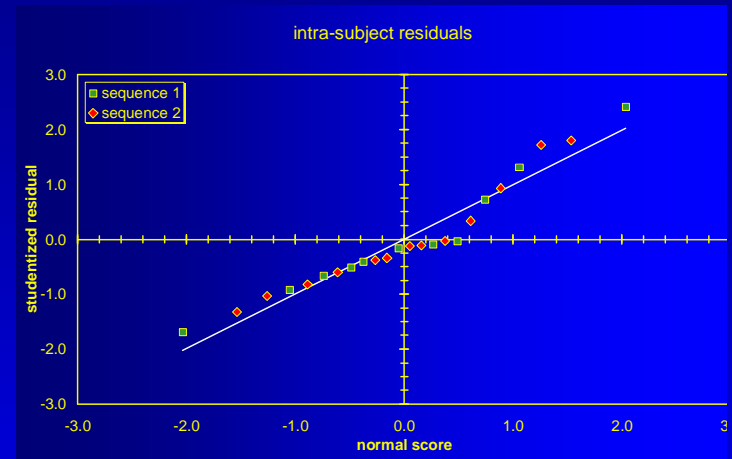
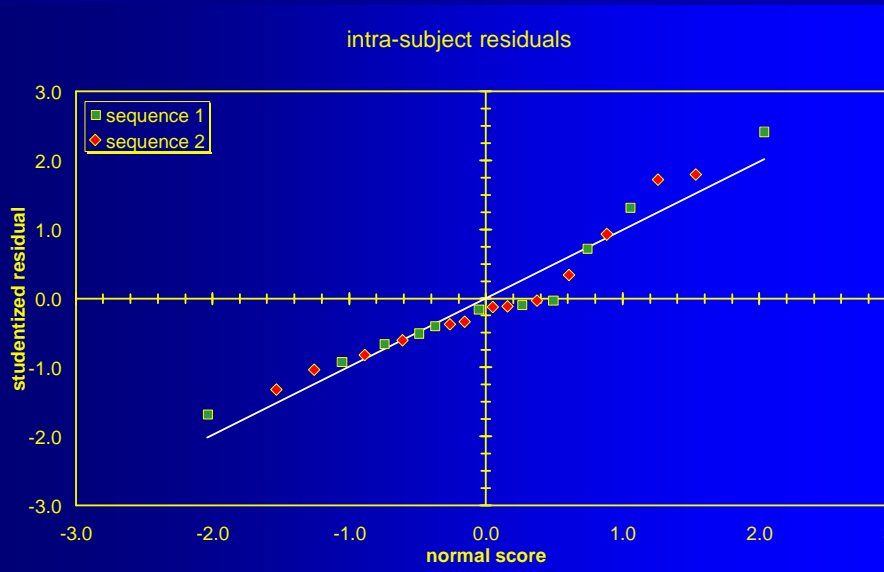
Type III



Type III



Type III



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% \subset AR; PE 115.66% ✓
 - Method B: 90% CI 107.17–124.97% \subset 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.**
- **EMA/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%

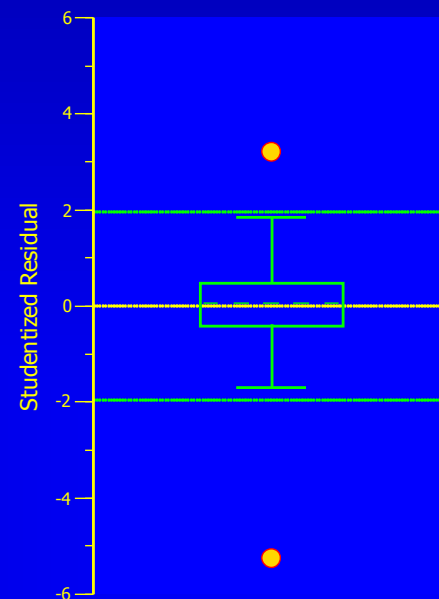
■ But there *are* two outliers!

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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