

Case Studies

Helmut Schütz

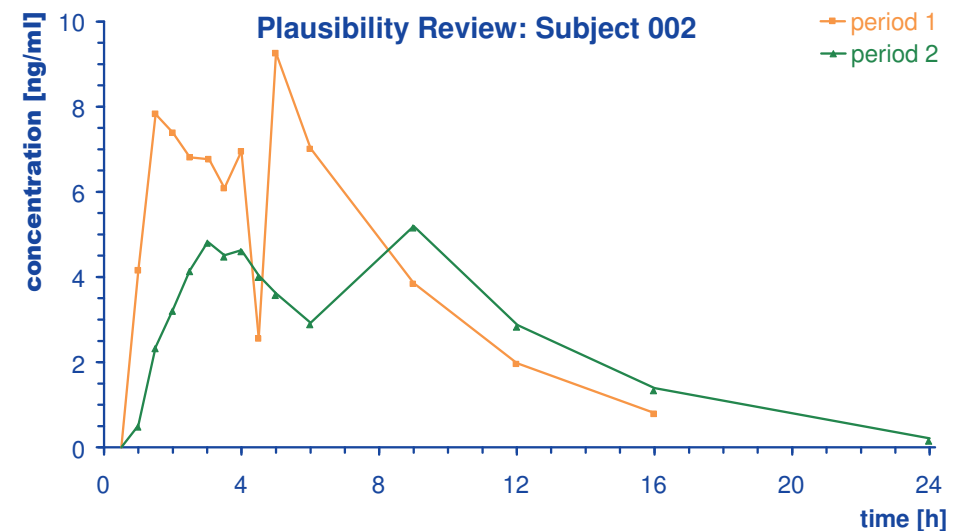
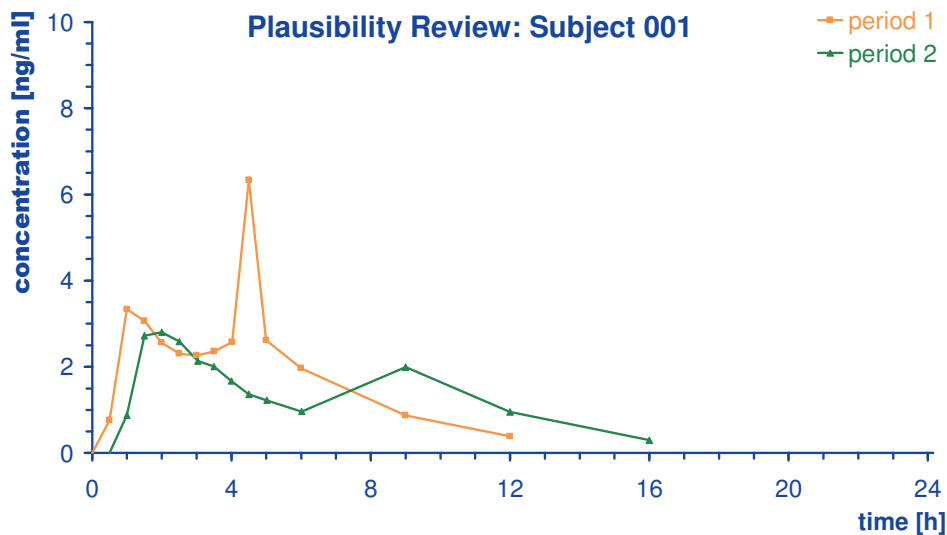


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Case Study 1

Sample mix-up.

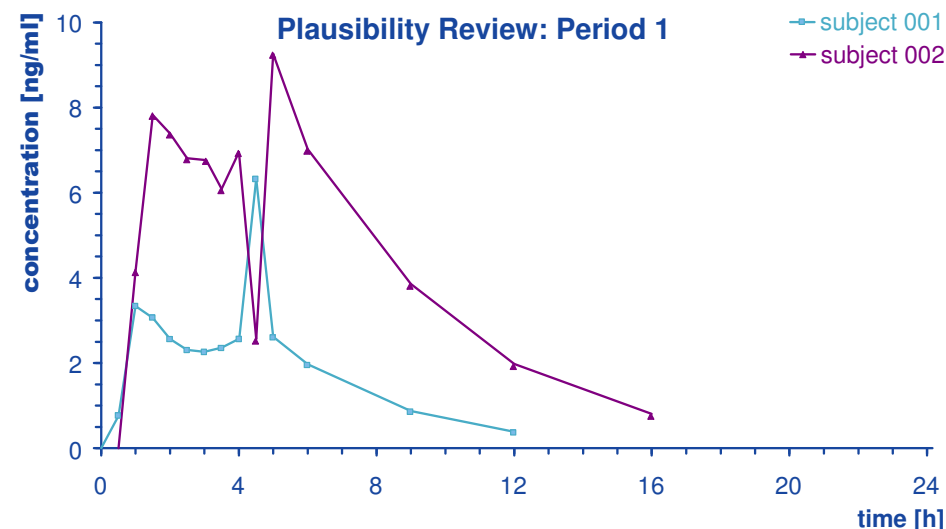
- Very large CRO (study performed in 2008). Common drug, biphasic MR formulations, pilot study (suboptimal sampling between 6 – 14 h).



Case Study 1

Sample mix-up.

- Barcode-system out of order in the first period.
 - No bail-out procedure (e.g., four eyes principle).
 - Suspected sample mix-up at 4.5 h.
 - Concentrations confirmed.
 - No deviation documented in clinical phase.
 - Drug has very low intra-subject CV ($AUC \leq 10\%$, C_{max} 10–15%) and high inter-subject CV (>50%) due to polymorphism.
- Pivotal studies are generally performed in only 14 subjects.
- A single mixed-up sample close to t_{max} could ruin an entire study.



Case Study 1

Sample mix-up.

- We tried to confirm the mix-up by comparing lab-values of the suspect samples (and each of the two neighbouring ones in each profile).
- Anticoagulant was citrate for GC/MS.
- With this anticoagulant the analyzer was validated only for γ -GT and albumine.

subject	time [h]	analyte [ng/ml]	γ -GT [U/l]	albumine [g/dl]
001	4.0	2.572	13	3.8
001	4.5	6.330	9	3.5
001	5.0	2.615	14	3.9
002	4.0	6.956	9	3.4
002	4.5	2.561	14	4.0
002	5.0	9.262	8	3.4

- γ -GT and albumine showed a similar pattern like the analyte.
 - Mean values of γ -GT in the pre- and post-study lab exams were 14 U/dl (# 001) and 9 U/dl (# 002). Means of albumine were 3.9 g/dl (# 001) and 3.4 g/dl (# 002).
 - Luckily subjects differed in their values. Pilot study only supportive...

Case Study 1

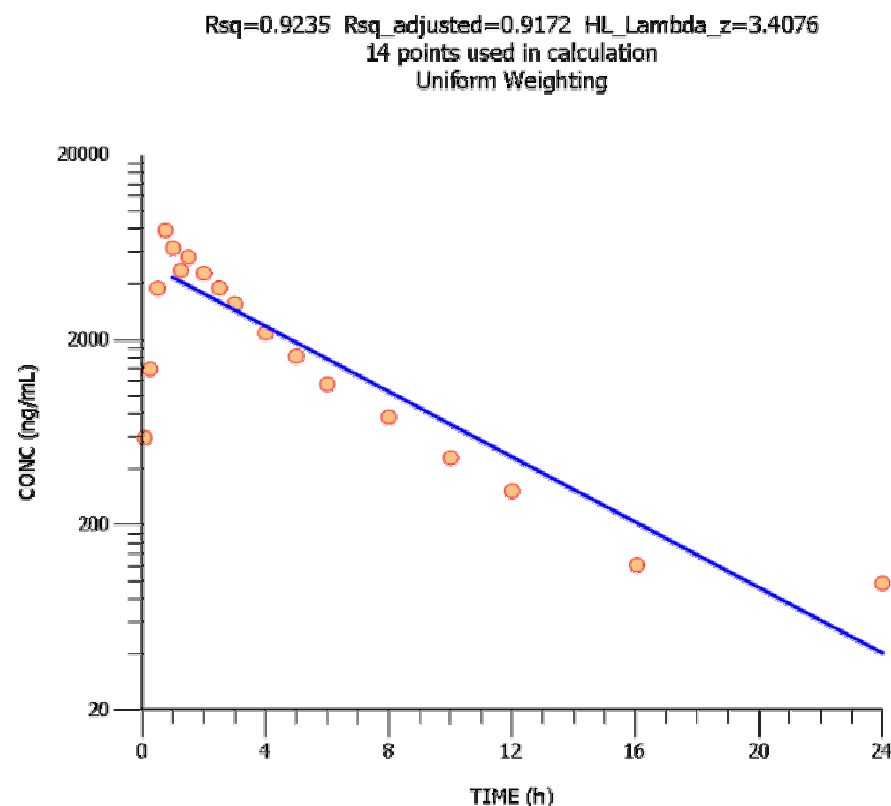
Sample mix-up.

- Before the current EMA GLs a blind plausibility review was acceptable (and still is in many regulations like the FDA).
- According to the current EMA GLs re-analyzing of samples is not permitted.
 - Gerald Beuerle of TEVA/ratiopharm (joint EGA/EMA workshop, London 2010) presented an example where due to a single mix-up a study would *pass*.
 - » The study would *fail* to show BE if the results were exchanged.
 - » The study would *fail* to show BE if the two subjects were excluded.
 - » Panelists of the EMA's PKWP confirmed that either procedure is not acceptable and the values have to be used as they are (*i.e.*, the study would *pass*).
 - Helmut Schütz: *'The EMA is a Serious Risk to Public Health!'*
- At the 2nd International Conference of the Global Bioequivalence Harmonization Initiative (Rockville, 15 – 16 September 2016) Session IV was devoted to the issue (*Exclusion of PK Data in the Assessment of IR and MR Products*).

Case Study 2

NCA (estimating λ_z).

- Very large sponsor & CRO (study performed in 2011). Common drug, IR formulation. New sensitive method. PK followed a 2- or 3-compartment model in all subjects.
 - No plots and range of time points used in the estimation given in the report.
 - I had to get them from reported half-lives by trial and error.
 - What was likely going on here – and even more important – *why*?



Case Study 2

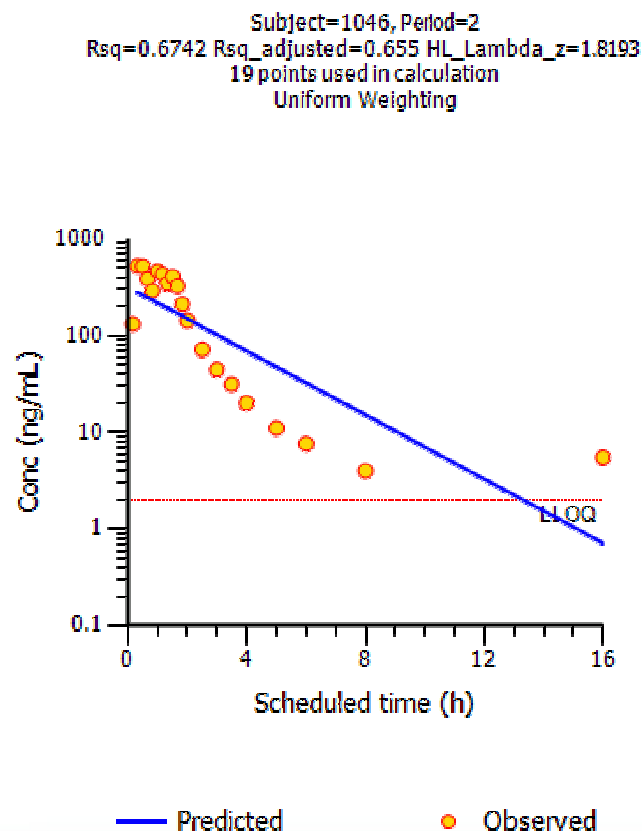
NCA (estimating λ_z).

- Very large sponsor & CRO (study performed in 2011). Common drug, IR formulation. New sensitive method. PK followed a 2- or 3-compartment model in all subjects.
 - Since this is an ‘old’ drug, the literature – and the label/SmPC – gives the half-life with one to four hours.
 - This range of half-lives was established in the 1980s by HPLC/UV. Only the first (distribution) phase could be detected.
 - With LC/MS-MS a second (and in some subjects a third) slower phase is apparent due to better LLOQ.
 - What I assume:
 - The median reported half-life was 4.61 h (2.49 – 8.34 h, 54 profiles).
 - If including fewer (*i.e.*, only later) time-points I got 5.05 h (2.78 – 8.34 h).
 - Both methods give no problems with residual $AUCs$ (max. 6.2% of AUC_∞).
 - *Anticipatory obedience* (avoiding to report / discuss ‘long’ half-lives)?

Case Study 3

NCA (estimating λ_z).

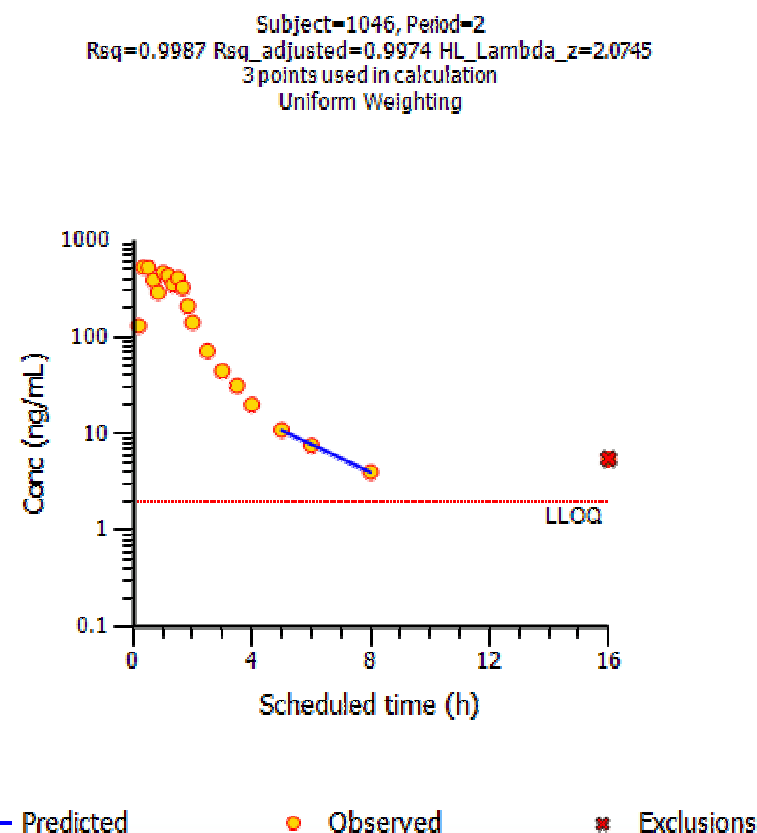
- Large CRO (study performed in 2013). 4-period full replicate; the double peak is specific for the formulation.
 - In four cases the last concentration was *increasing*. The CRO followed EMA's GLs and did not re-analyze samples (PK reason alone not sufficient). Obviously the CRO tried to 'save' the profiles by including more data points...
 - To the right the most extreme case.
 - Two samples (at 10 & 12 h) were BLQ.
 - 5.47 ng/mL ($\sim 2.7 \times$ LLOQ) at 16 h.
 - The first time point for the estimation of λ_z was t_{max} .



Case Study 3

NCA (estimating λ_z).

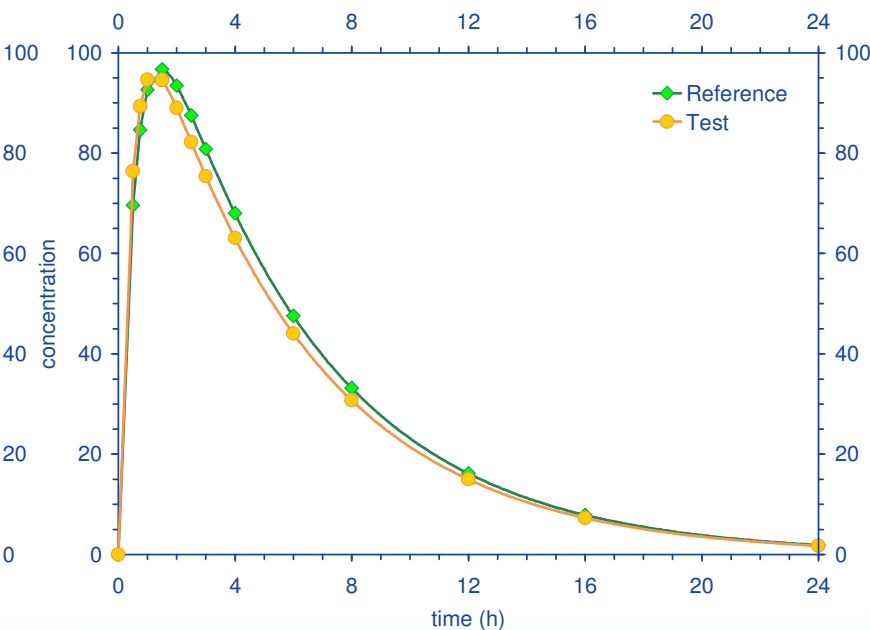
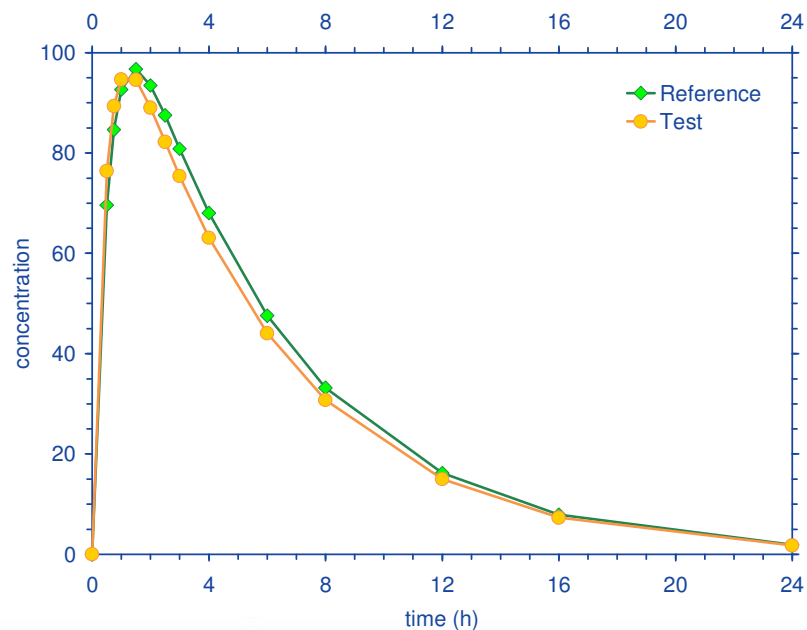
- What I would do (if an SOP allows that). Two options:
 - Exclude the doubtful value from the estimation of λ_z . Justifications:
 - » The estimated half-life of 2.07 h is consistent with the ones of the same subject in the other periods (2.12, 2.00, 2.16 h).
 - » Two values before the doubtful value were BLQ – which agrees with the predicted λ_z .
 - Drop the profile from the *AUC* comparison, but keep C_{max} (higher variability anyway and reference-scaling intended in the protocol).



Case Study 4

NCA (trapezoidal methods).

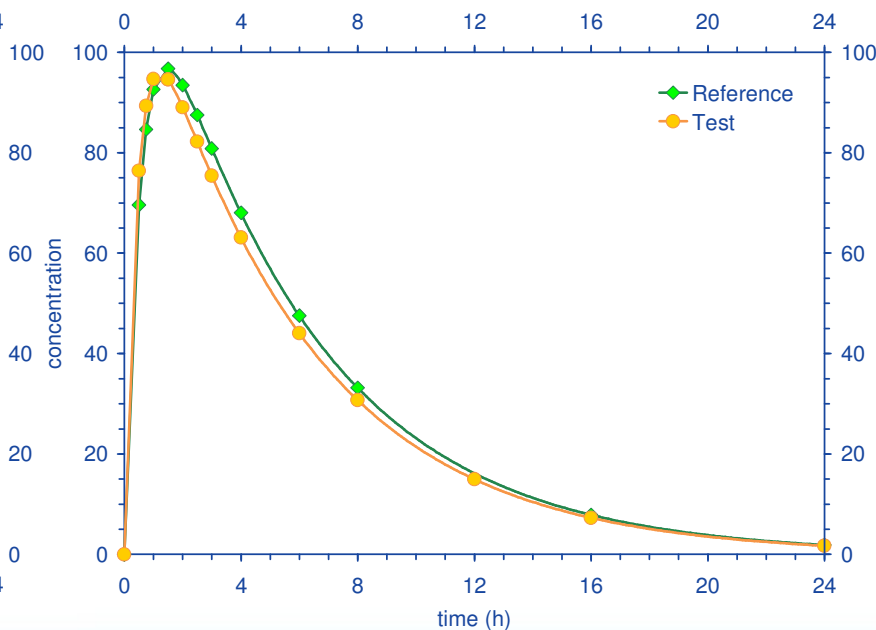
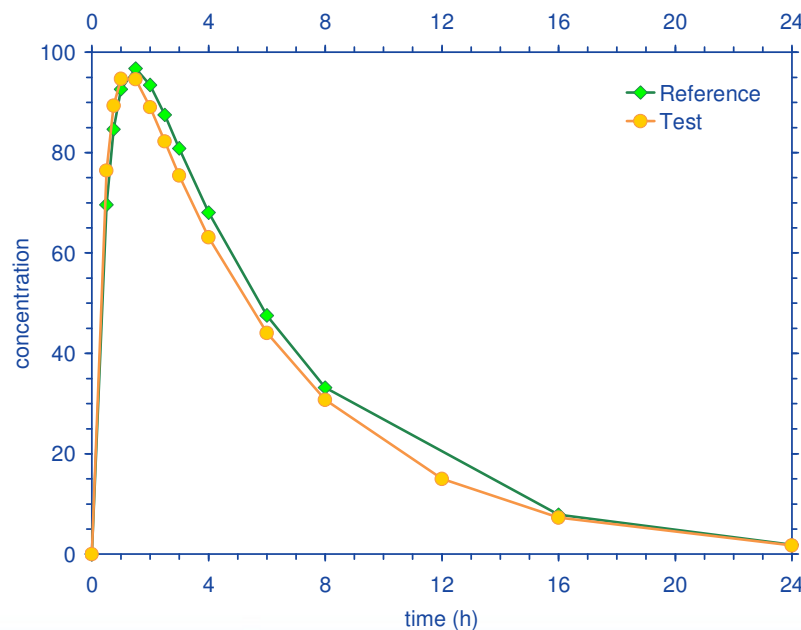
- If all samples are available, there is practically no difference between algorithms.
 - Simulated data. AUC_{∞} 697.8 (Reference), 662.9 (Test), true GMR 95.00%.
 - Linear trapezoidal: 707.6 (R), 670.9 (T); GMR 94.85% (bias **-0.20%**).
 - Lin-up / log-down trapezoidal: 693.7 (R), 658.0 (T); GMR 94.89% (bias **-0.16%**).



Case Study 4

NCA (trapezoidal methods).

- If a sample is missing (e.g., vial broken in centrifugation), the chosen algorithm matters. 12 h sample (R) removed.
 - Simulated data. AUC_{∞} 697.8 (Reference), 662.9 (Test), true GMR 95.00%.
 - Linear trapezoidal: 725.1 (R), 670.9 (T); GMR 92.53% (bias **-2.60%**).
 - Lin-up / log-down trapezoidal: 693.7 (R), 658.0 (T); GMR 94.89% (bias **-0.15%**).



Case Studies

Thank You!
Questions in the Panel Discussion.



Helmut Schütz
BEBAC

Consultancy Services for
Bioequivalence and Bioavailability Studies
1070 Vienna, Austria
helmut.schuetz@bebac.at