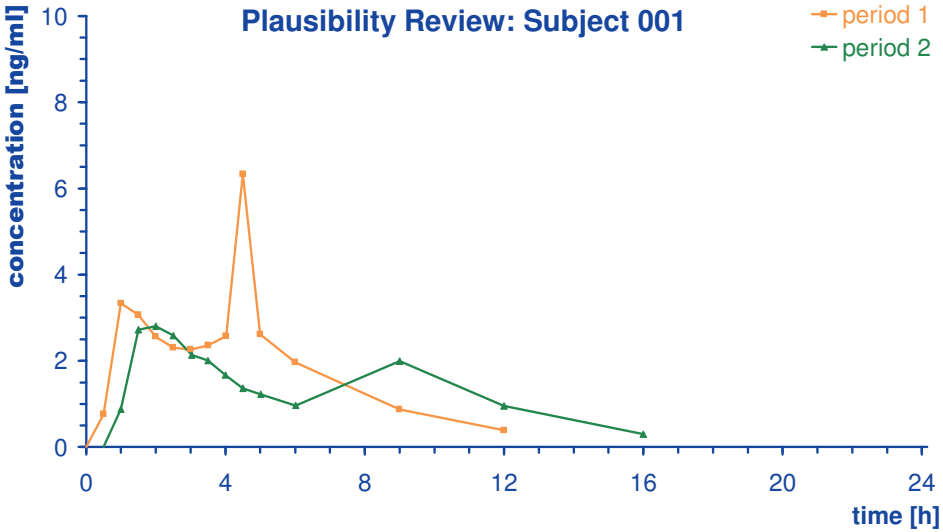
Case Studies

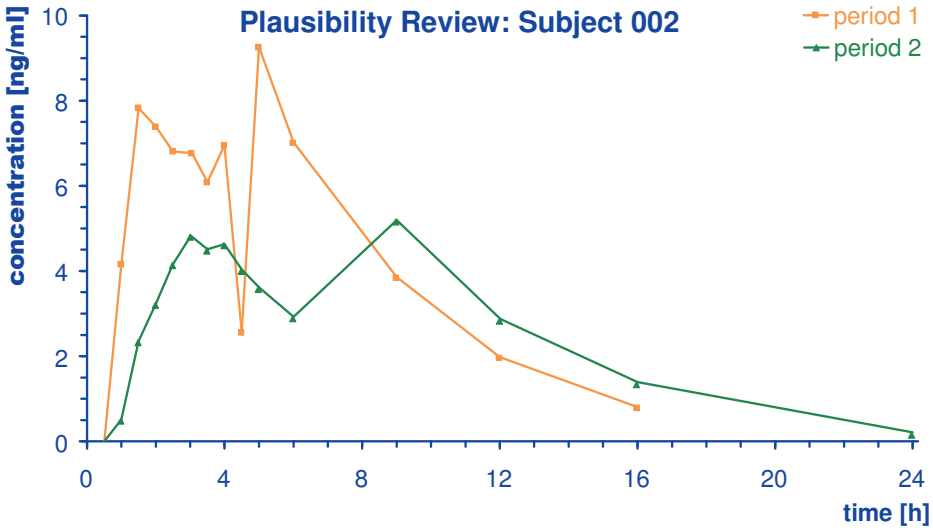
Helmut Schütz

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).

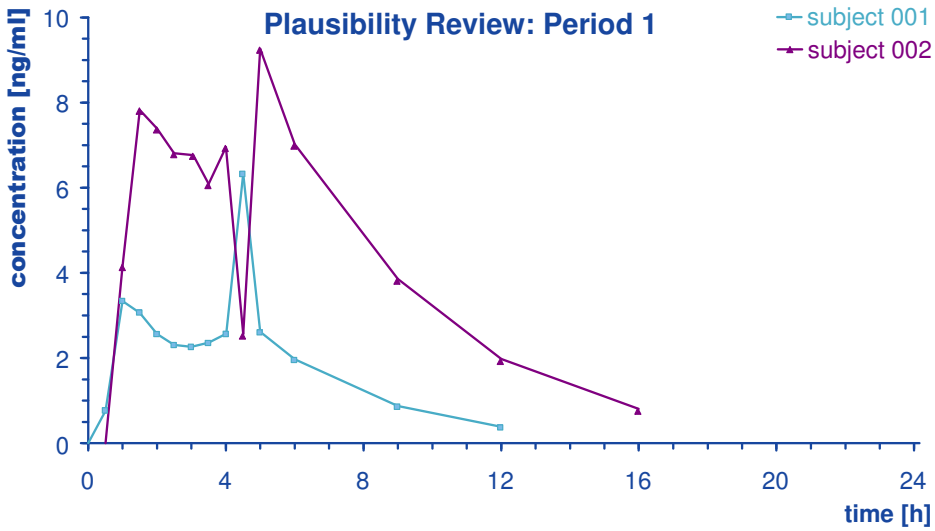




Case Study 1

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* ≤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.

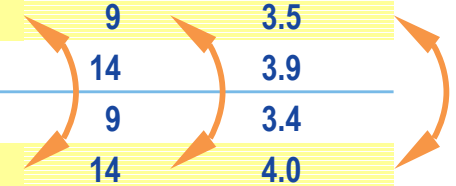


Case Study 1

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

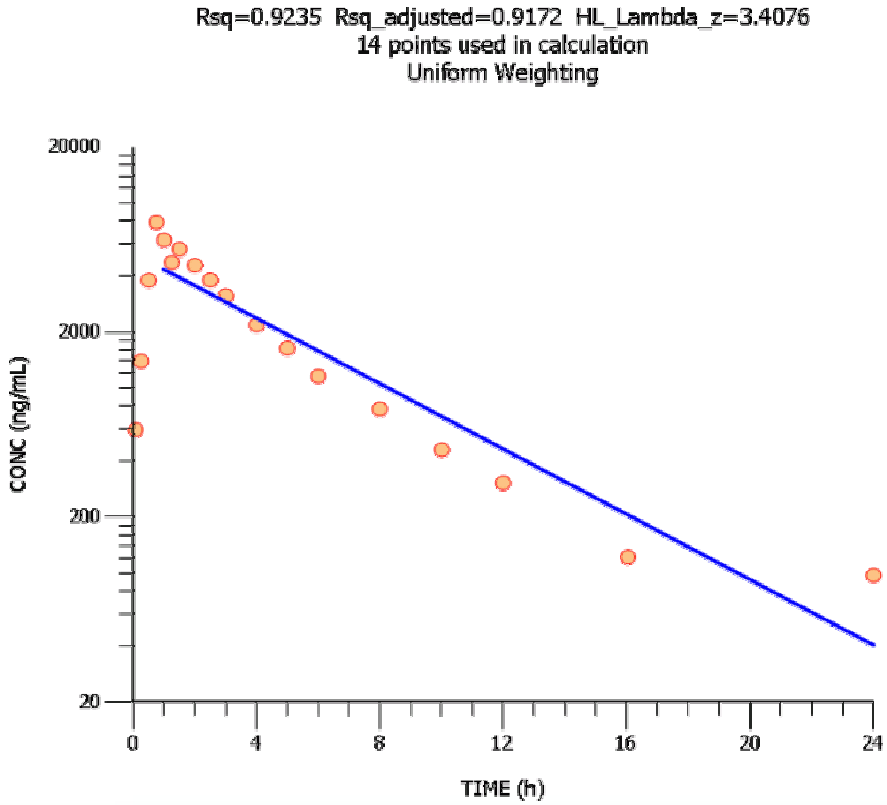
Sample mix-up.

- 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 were 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 the 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

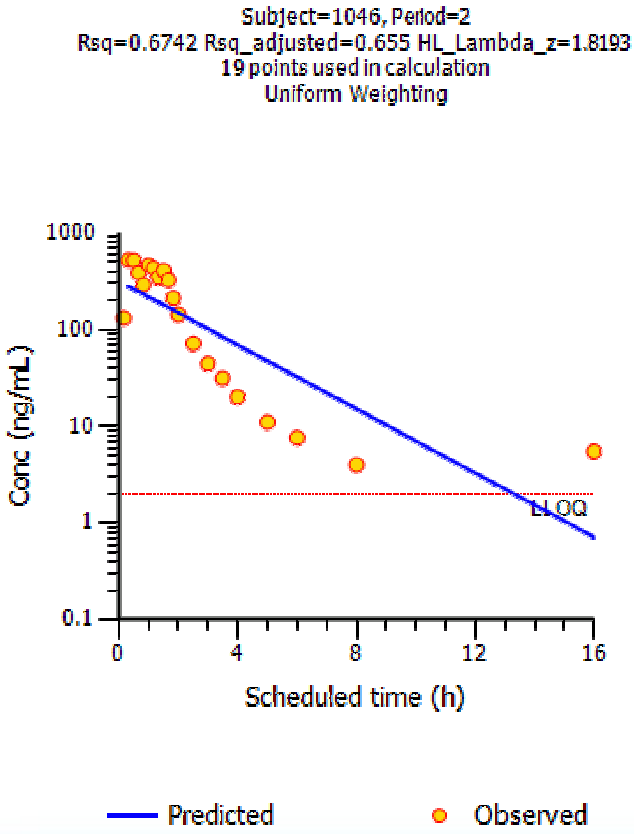
NCA (estimating λ_z).

- 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 *AUC*s (max. 6.2% of AUC_∞).
    - *Anticipatory obedience* (avoiding to report / discuss 'long' half-lives)?

Case Study 3

NCA (estimating λ_z).

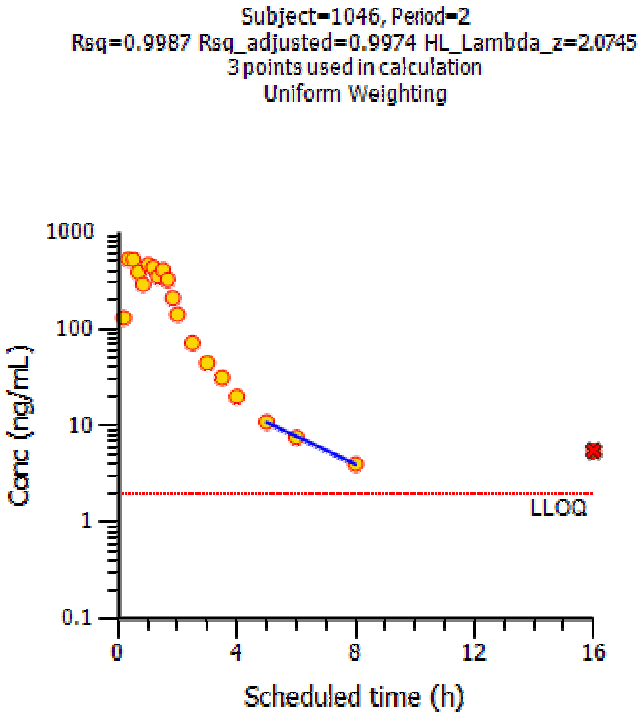
- Large CRO (study performed in 2013). 4-period full replicate; the double peak is specific for the formulation.
  - In four cases the last concentration was *increasing*. The CRO followed EMA's GLs and did not re-analyze samples (PK reason alone not sufficient). Obviously the CRO tried to 'save' the 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 (~2.7× LLOQ) at 16 h.
    - The first time point for the estimation of λ_z was t_{max}.



Case Study 3

NCA (estimating λ_z).

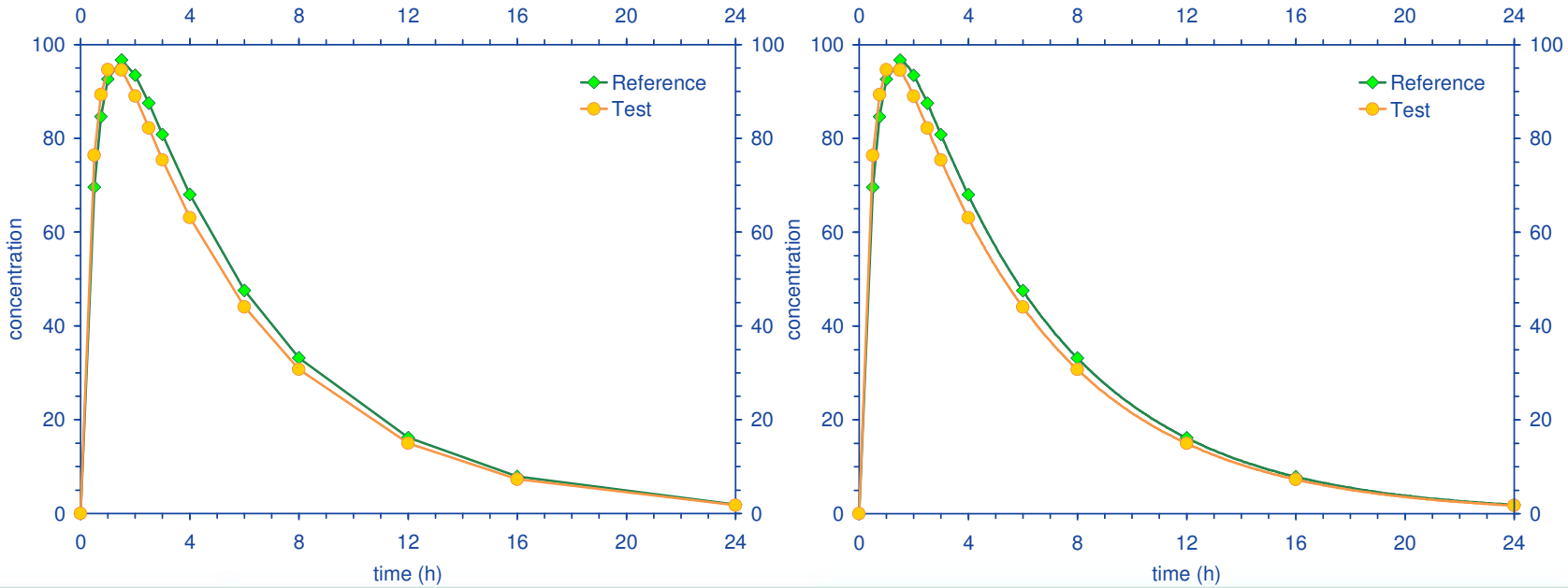
- What I would do (if an SOP allows that). Two options:
  - Exclude the doubtful value from the estimation of λ_z. Justifications:
    - The estimated half-life of 2.07 h is consistent with the ones of the same subject in the other periods (2.12, 2.00, 2.16 h).
    - Two values before the doubtful value 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).

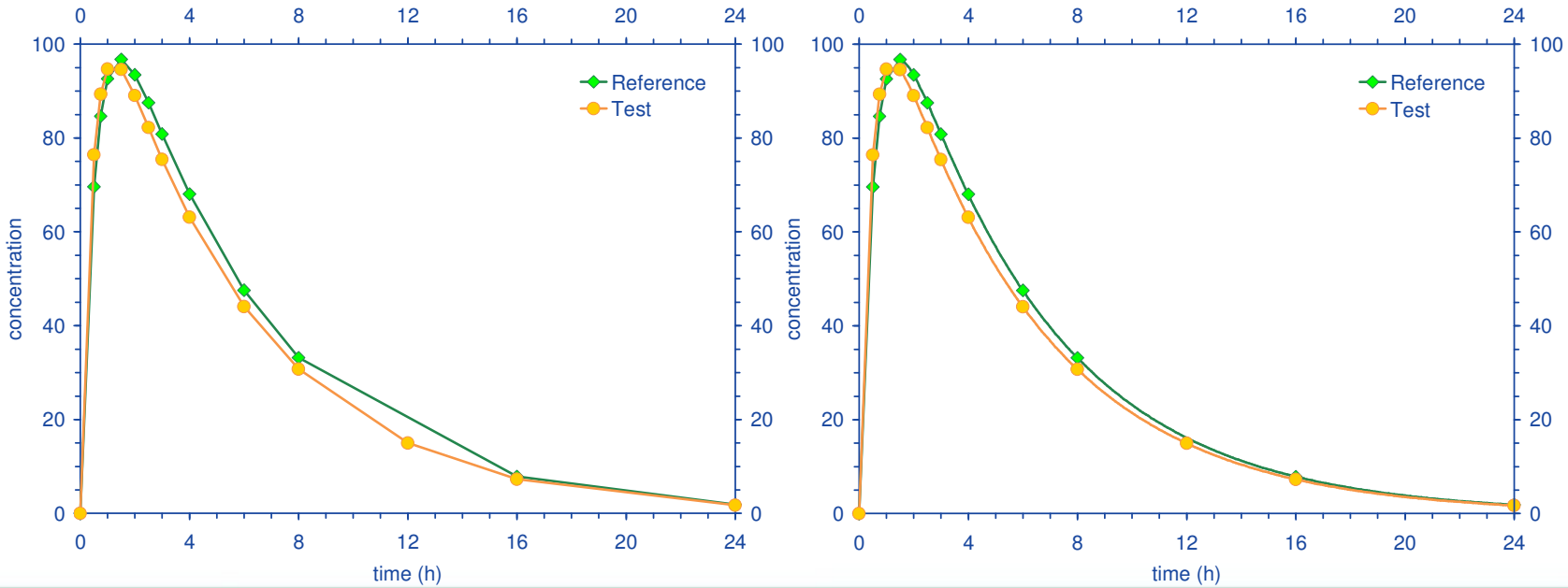
- If all samples are available, there is practically no difference between algorithms.
  - Simulated data. AUC_{∞} 697.8 (Reference), 662.9 (Test), true GMR 95.00%.
    - Linear trapezoidal: 707.6 (R), 670.9 (T); GMR 94.85% (bias –0.20%).
    - Lin-up / log-down trapezoidal: 693.7 (R), 658.0 (T); GMR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



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Thank You!

Questions in the Panel Discussion.

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