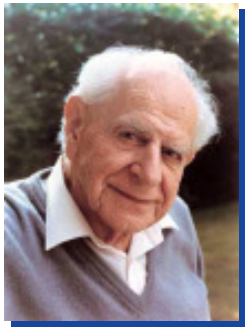
Unequal carry-over – “solved” in BE but still an Issue in Assessing Biosimilarity?

Helmut Schütz

To bear in Remembrance...

Whenever a theory appears to you as the only possible one, take this as a sign that you have neither understood the theory nor the problem which it was intended to solve.



Karl R. Popper

Even though it's *applied* science we're dealin' with, it still is – *science*!

Leslie Z. Benet

Sequence Effect

Better: Unequal carry-over

- Standard 2×2×2 cross-over design
  - Subjects' responses in the second period in sequence RT are different from the ones in sequence TR.
  - 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 carry-over effect,
  - true formulation by period interaction, or
  - a failure of randomization.

Sequence Effect

'Two-stage analysis' [1]

- Was applied in the past
  - Test at α 0.10 (low sensitivity since this is a between-subject term).
  - If $p < 0.1$, evaluation of the first period's data as a parallel design.
  - Extreme loss in power.
    - Example: CV_w 0.25, CV_p 0.50, GMR 0.95, n 28
      power of 2×2×2: 0.8074
      power of first period's data: 0.001585 (!)
- Procedure was demonstrated statistically flawed. [2]
  - Inflated Type I Error.
  - Biased estimate.

1. Grizzle JE. *The Two-Period Change-Over Design and Its Use in Clinical Trials.* Biometrics. 1965;21(2):467–80. doi:10.2307/2528104.
2. Freeman P. *The performance of the two-stage analysis of two-treatment, two-period cross-over trials.* Stat Med. 1989;8(12):1421–32. doi:10.1002/sim.4780081202.

Sequence Effect

Nuisance

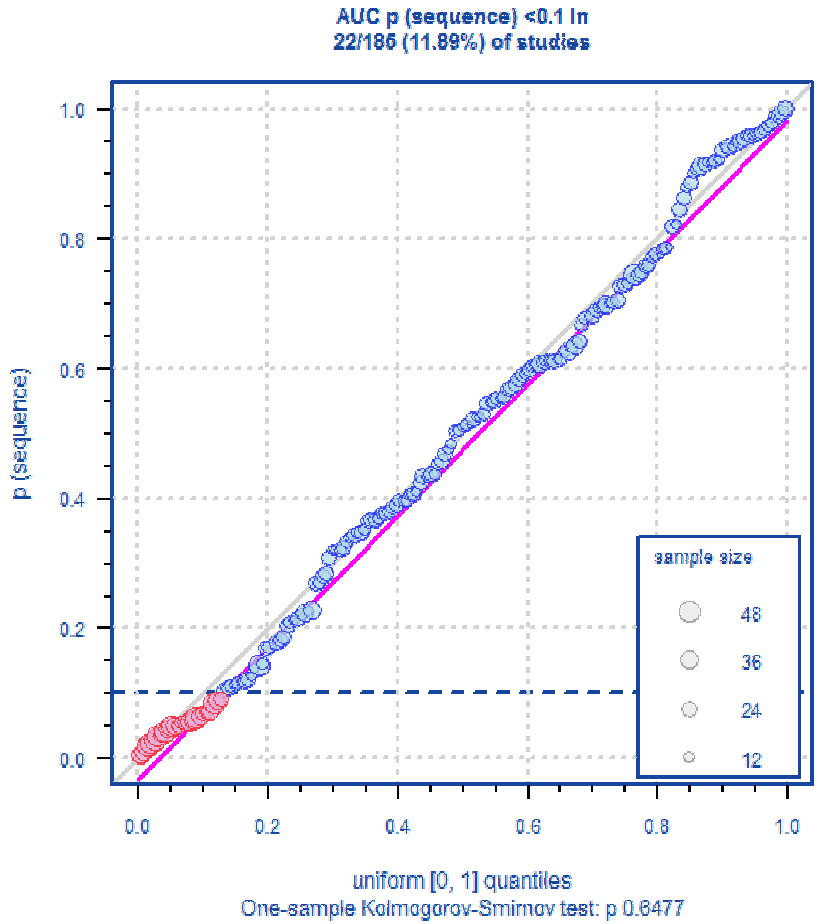
- No procedure exists to correct for a true sequence / unequal carry-over effect. [2,3]
- Significant sequence effects were found in a large metastudy [4] at about the level of the test, both for *AUC* and C_{max}.
  - 2×2×2 studies (n=324, α 0.10)
    AUC 34 (10.5%) C_{max} 37 (11.4%)
  - 6×3 studies (n=96, α 0.05)
    AUC 4 (4.2%) C_{max} 4 (4.2%)
  - As expected, the distribution of *p* values followed closely uniform [0, 1].
- Confirmed (20 studies from the public doamin and 165 from BEBAC's database; *AUC*).

3. Senn S. *Cross-over Trials in Clinical Research*. Chichester: Wiley; 2nd ed. 2002.
4. D'Angelo G, Potvin D, Turgeon J. *Carry-over effects in bioequivalence studies*. J Biopharm Stat. 2001;11(1–2):35–43. doi:10.1081/BIP-100104196.

Sequence Effect

Nuisance

- Significant sequence effects in properly planned studies could be considered a statistical artifact (significant results are likely false positives).
- 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 was maintained.



Review of Guidelines

EMA

- BE-GL (2010)
  - A test for carry-over is not considered relevant 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).
- Clinical Investigation of the PK of Therapeutic Proteins (2005)
  - The ordinary cross-over design is not appropriate for therapeutic proteins with a long half-life, e.g. therapeutic antibodies and pegylated proteins, or for proteins for which formation of anti-drug antibodies is likely.
- However, in many of the product-specific guidelines a cross-over design is recommended.

Recap

A true sequence/carry-over is highly unlikely if

- **the study is performed in healthy subjects,**
- **the drug is not an endogenous entity …**

Always remember:

> ***Pharmacokinetics*** **may be simply defined as what the body does to the drug, as opposed to** ***pharmacodynamics*** **which may be defined as what the drug does to the body.** [5]

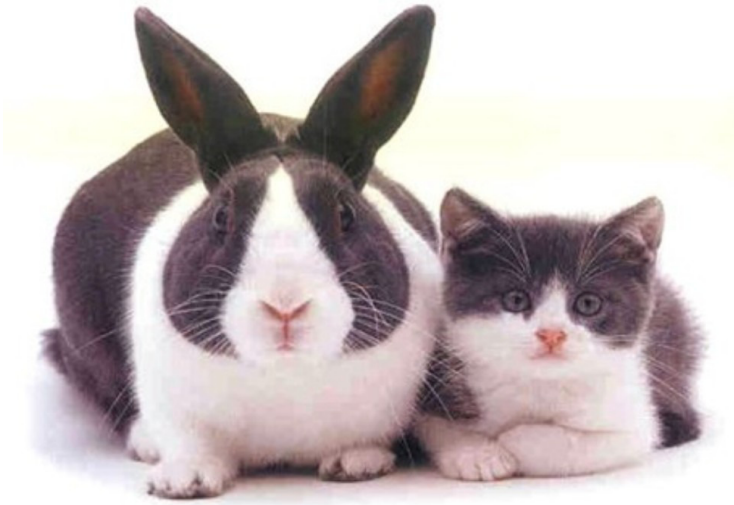
I'll give you my gun when you take it from my cold, dead hands.

5. Benet LZ. *Pharmacokinetics: Basic Principles and Its Use as a Tool in Drug Metabolism.* In: Mitchell JR, Horning MG, editors. *Drug Metabolism and Drug Toxicity*. New York: Raven Press; 1984. p. 199.

Observations / Concerns

Biosimilar Studies in a cross-over

- Observations
  - All I have seen showed a highly (!) significant sequence effect.
  - Almost in all a highly significant sequence effect was observed (János Borvendég, personal communication 2014).
- Concerns
  - I would be very wary performing studies of biosimilars in a cross-over – even if recommended in a product-specific guideline.
  - Absence of evidence ≠ evidence of absence!
  - Assessing relevance? [6]



6. Ocaña J, Sanchez O MP, Carrasco JL. *Carryover negligibility and relevance in bioequivalence studies.* Pharmaceut Stat. 2015;14:400–8. doi:10.1002/pst.1699.

Are Parallel Designs the Solution?

In principle, yes.

- Drawbacks
  - Sample sizes much higher than in cross-overs.
  - Requires careful selection of subjects (anthropometric data, genotyping recommended, …) in order to allow an unbiased estimate of the treatment effect.
  - Doubtful whether agencies would accept reference-scaling.
    The current definition of HVD(P)s is based on within-subject variability.
- For the courageous ones
  - State in the SAP that you will evaluate the study as ‘matched pairs’ (suggested by Stephen Senn).
  - Power close to cross-over.
  - Scientific advisory meeting with the EMA mandatory.

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Thank You!

Open Questions?

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