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

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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.

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

Karl R. Popper

Leslie Z. Benet
Sequence Effect

Better: Unequal carry-over

• Standard $2 \times 2 \times 2$ 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’

- Was applied in the past
  - Test at $\alpha = 0.10$ (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 $2 \times 2 \times 2$: 0.8074
      - power of first period’s data: 0.001585 (!)

- Procedure was demonstrated statistically flawed.
  - Inflated Type I Error.
  - Biased estimate.

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 $C_{max}$
  - $2 \times 2 \times 2$ studies ($n=324$, $\alpha = 0.10$)
    - $AUC$ 34 (10.5%)
    - $C_{max}$ 37 (11.4%)
  - $6 \times 3$ studies ($n=96$, $\alpha = 0.05$)
    - $AUC$ 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 domain and 165 from BEBAC’s database; $AUC$).

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.  

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

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

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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