Discussion of

‘MULTIPLICITY CORRECTIONS IN BIOEQUIVALENCE TRIALS’

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Question for discussion

‘As per currently valid Guideline on Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr), in studies with more than two treatment arms, the analysis for each comparison should be conducted excluding the data from the treatments that are not relevant for the comparison in question.

Which statistical procedure(s) to preserve the overall type I error would be compatible/acceptable with the requirement of separate analyses?

Context-related comments

- Recommendation in CPMP/EWP/QWP/1401/98 Rev.1/Corr) to exclude ‘non-relevant’ data primarily to handle situations with
  - 2+ reference compounds (e.g. US/EU)
  - Different administration modalities (fasting/fed) in one trial

- Nevertheless, from regulators point of view, recommendation to exclude ‘non-relevant’ data for particular comparison also applicable for designs comparing 2+ test formulations vs. one reference
  - Main concern (indeed) the use of the MSE from the ‘full-data‘ model to compute test statistics for (all) pairwise comparison(s)

Question:

Which statistical procedure(s) to preserve the overall type I error would be compatible/acceptable with the requirement of separate analyses?

Assumed situation:

- Many-to-one testing problem of H_{01}, ... H_{0k}
- Equal relative importance of hypothesis → no hierarchy
- BE to be demonstrated for at least one of the test formulations
- Strong control of the FWER

Answer & further comments

- In principle, any MCP based on p-values coming from k separate ANOVAs controlling the FWER (strong) might be acceptable
- In the particular situation:
  - Bonferroni, or
  - sequentially rejective method e.g. Bonferroni-Holm, (Hochberg)
  - As long as hypotheses are of equal rel. importance → fixed sequence tests, fallback strategies and gatekeeping procedures are not considered primary candidates

- *Zheng, Wang & Zhao:* Testing bioequivalence for multiple formulations with power and sample size calculations. *Pharmaceutical Statistics, Vol 11, Issue 4, p334–341, July/August 2012* → use of 'full-data' ANOVA using one MSE for all test statistics → recommend Hochberg

- Need to reflect '2-endpoint' situation
- Optimality might be design-dependent
- CIs corresponding to Holm/Hochberg tests are asymmetric on the ln scale