

Planning crossover bioequivalence trials: Systematic review and application of assurance

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Background

The aim of Bioequivalence (BE) trials is to demonstrate the similarity of the pharmacokinetic metrics AUC and C_{max} of two formulations (Test T and Reference R) of a drug.

The sample size of BE trials is usually determined by a power calculation, based on the intrasubject variability CV and the T/R ratio θ of the endpoints. While good estimates of the CV can often be obtained from previous pharmacokinetic trials of the drug, there is limited reasoning for selecting a particular value of the T/R-ratio. Some sponsors take a value of 1.00, others choose a value that deviates from unity by up to 10%.

Our approach is to describe the uncertainty as a (normal) distribution of the log(T/R-ratio), with true mean ratio of 1.00, and a new parameter, the standard deviation σ_u which shall quantify the uncertainty. We evaluate the statistical properties of this bioequivalence assurance concept.

Methods

This investigation has been performed in two parts. Part A was a systematic review on published BE trials of the last 5 years, aiming to evaluate the different assumptions on the T/R-ratio θ in the literature.

Part B is the application of the assurance concept for BE trials by integrating the power over the uncertainty distribution of the T/R-ratio. Simulations have been performed to determine the assurance for various scenarios of input parameters, and to compare the outcomes with those of traditional power calculations. The simulations used the R-package PowerTOST.

Results

Systematic Review: In total, 188 reports were screened, with 109 reporting actual clinical trials without duplication. In only 55 (50.5%) reports, sufficient information was provided to verify the sample size calculation. Of them, 16 (47%) had chosen a value of 1.00 for the T/R-Ratio, 29 (53%) had chosen a single value different from 1.00.

Simulation studies: The relationships of sample size to power and to assurance are quite similar when $\sigma_u = \log(\theta)$, as long as $0.95 \leq \theta \leq 1.05$ (which is similar to $\sigma_u \leq 0.05$). When σ_u becomes larger, then the impact of the tail of the uncertainty distribution leads to substantial loss of assurance.

Conclusion

The advantage of the assurance concept for BE trials is the direct expression of the uncertainty as a parameter of variability, not indirectly via assuming a fixed value of the T/R-ratio different from 1.00. Further developments, e.g. incorporating the uncertainty of CV, will be discussed at the workshop.

Reference

Labes D, Schütz H, Lang B. PowerTOST: Power and Sample Size Based on Two One-Sided t-Tests (TOST) for (Bio)Equivalence Studies. <https://CRAN.R-project.org/package=PowerTOST>. Ver 1.4-7.