구연 1

Average Bioequivalence Test using Non-Parametric Methods; Experiences on Bootstrap Bioequivalence

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Background: Ninety percent confidence intervals (CI) obtained from average bioequivalence (ABE) tests are based upon the assumption that log-transformed AUC and Cmax are normally distributed. To compare the CI with those obtained from non-parametric methods, we performed repeated estimation of bootstrapped datasets SAS and NONMEM.

Methods: Three original datasets of AUC and Cmax (2 bioequivalence and 1 bioinequivalence results) were used for this study. Bootstrap resampling was repeated for 1,000 times using MACRO function of SAS for each original dataset. ABE tests (PROC MIXED, SAS) were performed for these 1,000 resampled datasets to find the distribution of formulation effect values. The formulation effects were also estimated using NONMEM (Ver.6) for the same resampled datasets. Medians and 90 percentiles of formulation effects thereafter were compared with the 90% CI of the original datasets.

Results: We could not find any significant differences in the formulation effect estimates between SAS and NONMEM. In contrast with the original 90% CI's, the 90% CI's from 1,000 resampled datasets were narrower for all of the three original datasets. The shapes of histograms and density curves of bootstrapped formula effects of log(AUC) and log(Cmax) were similar to those of normal distribution.

Conclusion: Although the current 80-125% rule on the 90% CI is widely used, the narrower 90% CI's obtained from repeated tests on the resampled datasets presented herein deserve further research for its application to regulatory process.