Statistical Internship in Bioequivalence Studies for Generic Drugs

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Abstract:
This summer I worked as an ORISE Fellow at CDER, FDA. My primary research project is Adaptive Clinical Endpoint Bioequivalence (BE) Studies with Sample Size Re-estimation based on a Nuisance Parameter. A clinical endpoint bioequivalence (BE) study is often used to establish bioequivalence (BE) between a locally acting generic drug (T) and reference drug (R), where a pharmacokinetic (PK) study is uninformative. Typical study design is a double-blind, randomized three-arm (T, R and placebo: P) parallel clinical trial. BE between T and R can be established if two superiority tests (T vs. P, R vs. P) and one equivalence test (T vs. R) all pass. During study design, accurate estimate of the nuisance parameter (e.g. variance of the outcome variable) is essential in determining an adequate sample size to attain sufficient power. However, due to variations in the study design and procedures between NDA and Abbreviated NDA studies, as well as the high variability of clinical endpoints, the nuisance parameter is often under or over-estimated, resulting in unnecessary extra costs with a too large sample size or insufficient power with a too small sample size. Recently, Potvin et al (2017) proposed a two-stage adaptive design which allows sample size re-estimation based on the estimated variance from the first stage data. Potvin et al, however, only evaluated power and type 1 error of an equivalence test (T vs R), and did not assess family-wise type 1 error or power by incorporating the two superiority tests (T vs P, R vs P). In this work, we propose four sample size re-estimation approaches when assumed homogeneity: 1) lumped variance with a naïve t test; 2) lumped variance with a stratified t test; 3) Gould's variance estimate with a naïve t test; 4) pooled variance with a naïve t test. Approaches 3, 4 and Approach 5, sample variances for active drugs and placebo with an unequal variance t test, are further evaluated when assumed heterogeneity. Unrestricted design (i.e., re-estimated sample size can increase or decrease from the original sample size) is adopted. Normal distribution is assumed with homogeneous or heterogeneous variances among treatment groups. Simulation studies are conducted to compare the five approaches in family-wise type 1 error rate inflation, family-wise power, point estimate of mean ratio T/R and the coverage of 90% confidence interval for T/R under different scenarios. Simulation results show that Approaches 3 and 4 have more accurate estimate of sample size, sufficient power and negligible type 1 error inflation for homogeneous variances; and slight loss of power and negligible type 1 error inflation is observed for heterogeneous variances.

Keywords: Bioequivalence, Sample size re-estimation, Nuisance parameter, Adaptive design