LIKELIHOOD APPROACH FOR EVALUATING BIOEQUIVALENCE OF HIGHLY VARIABLE DRUGS

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Bioequivalence (BE) is required for approval of generic drugs by the US FDA and other countries’ regulatory authorities. A test drug should be bioequivalent to a reference drug for pharmacokinetic parameters such as the area under the blood concentration-time curve (AUC) and the peak concentration (Cmax). To test the average BE, the Two-One-Sided-Test (TOST, equivalently, the 90% confidence interval) has been used as the mainstream methodology. However, for highly variable drugs (HVDs, %CV>30%), it is difficult to demonstrate BE in a standard cross-over study with the typical subject number of 24 to 36. Recently, the FDA and the European Medicines Agency (EMA) recommend similar but not identical reference scaled average bioequivalence approaches (RSABE). Although the power is improved, the new approaches still may not guarantee high level of confidence for the true mean difference of the two drugs being at the BE boundaries. It is also difficult for these approaches to address the population BE (PBE) and the individual BE (IBE) issues.

Choi et al. (2008) advocated the likelihood approach for representing and interpreting BE data as evidence. In this thesis, we extended this likelihood approach to HVDs. Using an example data from a full replicate 2 × 4 cross-over study, we demonstrated how to present evidence for BE or bioinequivalence (BIE) using the profile likelihoods for the mean difference and standard deviation ratios of the two drugs for log AUC and log Cmax. We recommend interpreting the evidence using Zhang’s generalized likelihood ratio (Zhang et al. 2013) for interval hypotheses in BE testing. Using the likelihood approach, we may present evidence for PBE or IBE by considering the evidence from the mean and standard deviation (total or within-subject) together within a unified framework. Our simulations showed that the operating characteristics of the profile likelihood approach are comparable with the FDA and EMA RSABEs when the same criteria are applied to the likelihood intervals.

Wednesday, October 2nd, 2013
1:30 - 2:30pm
MRBIII  Conference Room 1220