Establishment of bioequivalence has generally been relied on the comparison of estimated population averages of rate ($C_{\text{max}}$) and extent of absorption (AUC) of drug from different pharmaceutical equivalents. The concepts of individual bioequivalence (IBE), introduced in 1990s for drug switchability and population bioequivalence (PBE) for drug prescribability assessed through limited sequence, four period, replicate, crossover design made possible estimation of not only inter-subject variation but also intra-subject variability due to subject-by-formulation interaction. More interestingly, such designs often provide a more accurate and reliable assessment of Average Bioequivalence (ABE) than that obtained from traditional 2-period crossover studies.

An analysis of relative merits and demerits of ABE, IBE and PBE will be carried out in the presentation. Application of mixed effect models for analysis of replicate studies and understanding the variabilities will be discussed. A case study of a semi-simulated, replicate, crossover study of alverine citrate 120 mg capsules in 48 healthy volunteers will also be presented. In this study, two formulations of alverine were found to be average bioequivalent as 90% CI for AUC and $C_{\text{max}}$ were entirely within 80-125%. Very interestingly, population and individual bioequivalence were also demonstrated for these formulations as the upper bound of 90% CI, as calculated by a mixed effect ANOVA model, was a negative value. However, one has to be careful as the results obtained from different softwares (e.g., MS Excel, SAS and WinNonlin) can be different owing to model optimization and treatment of missing data.