Sample Size Estimation and Passing Rate Analysis for Highly Variable Drugs Using FDA’s Scaled Average Bioequivalence Approach

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Purpose
The sample size required for a bioequivalence (BE) study is driven by the intra-subject coefficient of variation (ISCV), the Geometric mean ratio (GMR) and the target statistical power to meet bioequivalence limits. For highly variable drugs (HVDs) defined by an ISCV $\geq$30%, it is difficult to demonstrate BE unless many subjects are enrolled. The US FDA proposes using a reference replicate study design to scale up the acceptance criteria limit considering the reference drug for both Cmax and AUC parameters for HVDs. The advantage of the scaled average BE (SABE) approach is that it lowers the sample size requirements to achieve sufficient power to meet bioequivalence limits. With the SABE approach of FDA, there is no straightforward formula to calculate the sample size as it is the case for ISCV lower than 30%. The purpose of this presentation:
1. To provide sample sizes and likelihood of passing which will be useful for designing BE studies for HVDs for FDA submission.
2. To elucidate at different ISCVs, the relationship between sample size and the likelihood of passing for BE studies for HVDs
3. To get a better understanding of when the use of the reference replicate approach may be most beneficial to the Sponsor.

Methods
The statistical power of demonstrating BE from published simulated semi-replicate and fully replicate data were evaluated. Based on this data, the sample size required for designing a BE study at various ISCV of 30%-35%, 35%-40%, 40-60% and >60%, and at 5% and 10% formulation differences (FD) to yield 80%-90% probability of passing were determined.

Results
When the ISCV was between 35%-40% and the FD was within 5%, the sample size of 28 subjects (fully replicate) and 30 subjects (partial replicate) should lead to a likelihood (power) of 90%. The same sample size was required to achieve 80% power when the ISCV was 30%-35% and FD was 10%. When the ISCV was between 40%-60% while the FD was within 5% the sample size of 32 subjects for a fully replicate and 36 subjects for a partial replicated led to a power of 90%. Similar sample size was required to achieve 80% likelihood of passing when ISCV was 35%-40% and FD is up to 10%. When the ISCV was >60% with 5% FD or if it was 40%-60% and FD was 10%, more than 36 subjects were needed to achieve at least 80% likelihood of passing.
Consequently, when ISCV is 30-35% and FD is within 5%, there may not be real advantage for replicate design. It was suggested that the inclusion of at least 24 subject to complete should be considered as an absolute minimum for FDA BE studies for HVDs. Our analysis shows that if ISCV is <35% and FD was 5%, going with the replicate design is not the best option when comparing the number of subjects needed for unscaled 2-way versus SABE approach (2-way = 44 subjects vs 4-way = 28 subjects). However, the FDA SABE approach should be considered and beneficial when ISCV is 35%-40% or higher with 5% FD or when ISCV is 30%-35% with FD = 10%.

Conclusion
Overall there are advantages with scaling from using the FDA SABE approach when ISCV was 35%-40% or higher with 5% FD or when ISCV was 30%-35% with FD = 10%. When the ISCV was 30%-35% and FD was 5%, scaling may not provide real advantage and so the use of the SABE approach may not be the best option. If the ISCV is expected to be >40%, and assuming the FD is within 10%, a SABE study should be selected. When the ISCV is border-line (i.e, 30%-35%), proceeding with the standard 2-way crossover using unscaled BE may be more beneficial if there is confidence about the formulation (FD = 5%). If there are questions about the FD, the safest way would be to use the SABE approach.