Assessment of Repeated Crossover Bioequivalence Design Under Steady State Conditions

Peijue Zhang, Mark Donnelly, Kairui Feng, Yuqing Gong, Xiaolei Liu, Andrew Babiskin, Miyoung Yoon, Liang Zhao, Lanyan Fang

Division of Quantitative Methods and Modeling, Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD

Objectives

Challenges in conducting patient pharmacokinetic (PK) bioequivalence (BE) studies are prevalent particularly for oncology drugs with long half-lives. These challenges include, but are not limited to, recruitment of an adequate sample size, and prolonged study durations, which potentially increases probability of participant dropouts.

A repeated crossover design, which involves consecutive PK measurements under steady state conditions using the sequences of TTRR or RRTT [1], is a potential alternative BE design that can significantly benefit the development of such products by shortening the study period compared to conventional 4-way crossover study, and by increasing study power by extending the 2-way crossover design with only two additional dosing periods. Additionally, this design may potentially enable the use of reference-scaled average bioequivalence (RSABE) approach, particularly applicable to highly variable drugs.

Despite these advantages, the repeated crossover design appears underutilized in generic drug development. In this work, we employ model-based simulations to examine the performance of the repeated crossover design based on study power and type I error control in steady-state PK BE studies, in comparison with conventional crossover designs, including a 2-way or 4-way crossover design.

Methods

Population Pharmacokinetic Model:

A theoretical Population Pharmacokinetic (PPK) model for a long half-life oncology drug is employed to simulate steady-state PK BE studies. This model adopts a one-compartment construct with the integration of a first-order absorption process accompanied by a lag time (Tlag).The half-life of the simulated product is approximately 1.5 days.

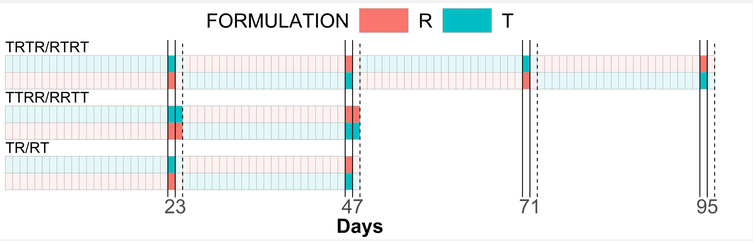
Model-based Simulation:

A formulation effect, introduced as relative bioavailability (F), is used to signify differences between reference and test formulations (T/R ratio). PK parameters other than F are consistent between formulations [3].

Table 1. Simulated Study Designs

Study Sequence	TRTR/RTRT	TTRR/RRTT	TR/RT
Sampling Day	23, 47, 71, 95	23, 24, 47, 48	23, 47

Figure 1. Sampling Scheme for The Simulated Study Designs



Blood Sampling:

Given the necessity of multiple blood samples on consecutive days in the repeated design, it's essential to limit the overall number of samples and the volume of blood collected. To achieve this goal, we investigated various sampling approaches: intensive, moderate, and sparse, which translate to 18, 12, and 8 samples per day, respectively.

Table 2. Blood Sampling Schemes

Schemes	Time of Sampling (hours after dosing)																	
	0	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5	6	7	9	12	15	18	21
Intensive	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Reduced	✓	✓	✓	✓	✓	✓	✓		✓			✓		✓		✓		✓
Sparse	✓	✓	✓		✓		✓						✓		✓			✓

Inter-occasional Variability:

Simulations are conducted with normal and increased inter-occasional variability settings separately to evaluate the performance of the repeated design under these two scenarios. We considered normal inter-occasional variability as inter-occasional variability based solely on the residual errors in the simulations. To emulate the conditions of increased inter-occasional variability, a factor on random effect (rf) is introduced to the relative bioavailability (F) for each occasion (i.e., each dosing period). The rf was constrained to be within the range of 0.5 to 2 times of the rf in previous dosing period to prevent unreasonable jumps between consecutive occasions.

Sample Size and BE Approaches:

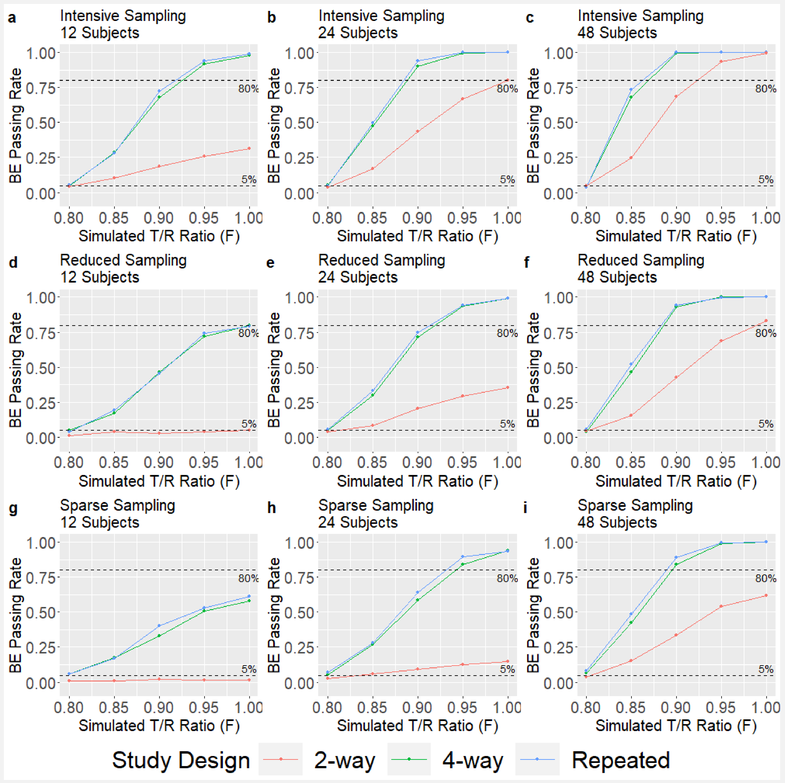
The simulations with normal inter-occasional variability setting are conducted with sample sizes of 12, 24, and 48 subjects. The sample sizes were increased to 24, 48, and 60 subjects in simulations with increased inter-occasional variability. The BE analysis is conducted using average bioequivalence (ABE) or RSABE approaches, as applicable [2].

Results

Simulations with Normal Inter-occasional Variability :

All simulated studies demonstrate within-subject standard deviation (SWR) less than 0.294. Therefore, ABE with standard 80-125% criteria is employed to all the simulated studies. The repeated design demonstrated similar BE pass rate as the 4-way crossover design. Both repeated and 4-way crossover design show higher BE pass rate than the 2-way crossover design (Figure 2). The repeated design is an acceptable alternative design in studies with normal inter-occasional variability, which reduces study duration compared to the conventional 4-way crossover design.

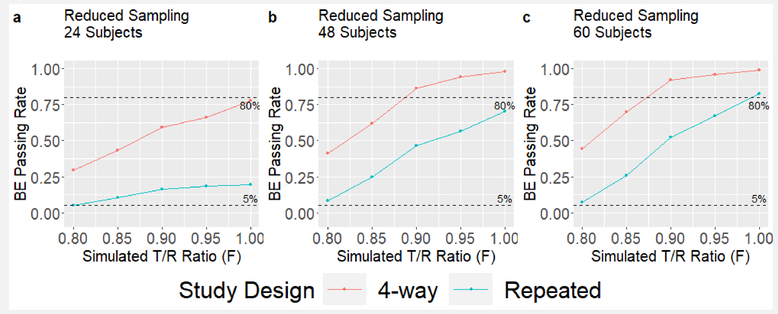
Figure 2. BE Pass Rates in Simulations with Normal Inter-occasional Variability



Simulations with Increased Inter-occasional Variability :

In studies with increased inter-occasional variability, the repeated crossover design exhibited a lower BE pass rate compared to the conventional 4-way crossover design (Figure 3). This discrepancy may be attributed to the smaller estimation of intra-subject variability, given the observation that only 33% of the simulated studies utilizing repeated crossover design demonstrated SWR over 0.294 while this percentage is almost 100% amount the studies utilizing conventional 4-way crossover design. The decreased estimation of intra-subject variability may be a consequence of the correlation within the consecutive sampling schedules in the repeated crossover design compared to the conventional 4-way crossover design, especially in scenarios with high extent of accumulation at steady state condition.

Figure 3. BE Pass Rates in Simulation with Increased Inter-occasional Variability



Conclusions

The repeated crossover design presents distinct advantages when compared to the conventional 2-way crossover design, including enhanced statistical power using the ABE approach and potential expanded BE limits for highly variable drugs. In addition, the repeated crossover design presents advantages over the conventional 4-way crossover design, including a shorter study duration, which may reduce study cost and participant dropouts.

When applying the RSABE approach for highly variable drugs, the repeated crossover design provides adequate control of type-I error. However, the repeated crossover design can yield reduced estimates of intra-subject variability when compared to the conventional 4-way crossover design, primarily due to the correlation of PK parameters between two consecutive sampling periods given the high extent of accumulation. Therefore, it is expected that the scaled BE limits using the repeated crossover design would be tighter than those with conventional 4-way crossover design when using the RSABE approach for highly variable drugs.

Reference

[1] Liu JP. Use of the Repeated Cross-Over Designs in Assessing Bioequivalence. Statistics in Medicine. 1995;14(9-10):1067-78; discussion 79-80. doi: 10.1002/sim.4780140926.

[2] FDA Draft Guidance For Industry: Statistical Approaches to Establishing Bioequivalence. (2022)

[3] Gong Y, Feng K, Zhang P, Lee J, Pan Y, Zhang Z, et al. Quantitative Methods and Modeling to Assess COVID-19-interrupted in Vivo Pharmacokinetic Bioequivalence Studies with Two Reference Batches. CPT Pharmacometrics Syst Pharmacol. 2022;11(7):833-42. doi: 10.1002/psp4.12795.

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