EVALUATING NOVEL PILOT PHARMACOKINETIC BIOEQUIVALENCE STUDY FOR INHALATION POWDER DRUG PRODUCTS EXHIBITING BATCH-TO-BATCH VARIABILITY

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Purpose

Batch-to-batch variability for both the reference listed drugs (RLDs) and generic products poses challenges to the generic product development. This study proposed and evaluated a novel pharmacokinetics (PK) bioequivalence (BE) study design using oral inhalation products as an example, with the aim of elucidating a rational framework for selecting batches of RLD and generic products for PK BE studies.

Methods

A two-phase study framework utilizing a pilot study prior to a full 2x2 crossover BE pivotal study was proposed. Multiple batches of the reference product (R, e.g., R1, R2, R3) and the test product (T, e.g., T1, T2, T3) were evaluated in the pilot study with the aim of finding the most desirable T-R batch pair (e.g., T2-R3) for the pivotal study. Various pilot study designs were explored.

From the pilot study results, the point estimates (PE) of the geometric mean ratio and their uncertainty (standard error-SE) for each T-R batch pair were obtained and were used to select the batch pair. Conditional power of a pivotal study here is defined as the BE passing rate calculated from the model-based simulation using the PE and SE of a certain batch pair from the pilot study. Hence, criteria based on the conditional power obtained from different PE and SE of batch pairs were proposed to choose the most appropriate batch pair for the pivotal study (details in Figure 1). The models and parameters used in the simulation mentioned above were adopted from our other related work.[1] Final simulation models were built and qualified using a four-sequence, four-period crossover BE study data with 60 healthy subjects administering two batches from each of reference and test oral inhaled products.

To evaluate the two-phase framework, BE passing rate was calculated as the study power using 200 replicated simulations. The 90% confidence interval (CI) of both C_{max} and AUC_{inf} falling within 80%-125% was used as criteria for BE.

Results

Framework and Criteria The two-phase study framework and criteria are proposed in Figure 1. A successful PK BE study generally requires the geometric mean T/R ratio deviating not more than 5-10% from the unity in order for the 90% CI to be within 80%-125%. Therefore, PE within [0.9, 1.11] was chosen as the first criteria to exclude those futile T-R batch pairs.

Results Cont.

For the T-R batch pairs meeting the first criteria, their conditional power was ranked, and the one with the highest conditional power was determined as the most desirable batch pair for the pivotal study. If the conditional power among batch pairs were closed by, the probability of PE within [0.9,1.11] could then be used to finalize the batch pair for the pivotal study.

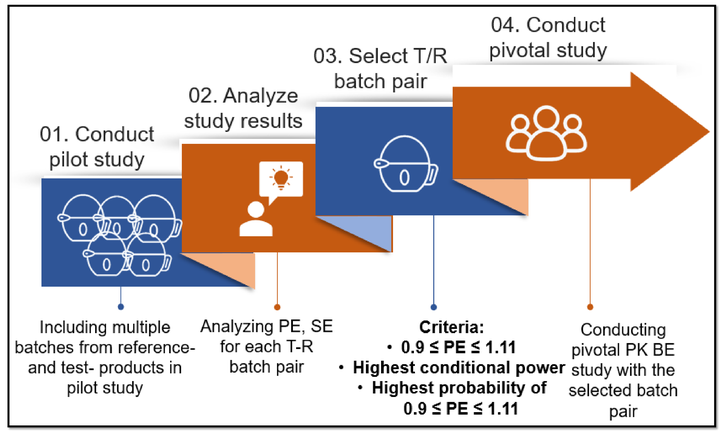

Figure 1. Two-phase study framework: pilot study results were used to select the T-R batch pair for the pivotal PK BE study based on the listed criteria. Abbreviations: T- test products; R- reference products; PE- point estimate.

Pilot study design The PE uncertainty - standard error (SE) for some pilot study designs with different numbers of subjects is listed in Table 1, in which three batches from each of test and reference products were evaluated.

Table 1. Median uncertainty (CV%) for various pilot study designs with different numbers of subjects

Designs (sequences x periods)	Parallel (6 x 1)		William (6 x 6)		Crossover (2 x 6)	
# of subjects per sequence	Nsubj total	Uncertainty	Nsubj total	Uncertainty	Nsubj total	Uncertainty
6	36	14.9%	36	6.0%	12	9.9%
10	60	11.3%	60	4.8%	20	8.1%
12	72	10.4%	72	4.4%	24	7.4%

As shown in Table 1, the study designs with more periods or sequences had lower uncertainty but had a longer study duration. The parallel design (6 x 1) has a shorter study duration, while the results were associated with higher uncertainty.

Results Cont.

Pilot study design options Including more subjects or conducting the pilot study with more periods or sequences gets better type I error control and has a higher power (results not shown). However, these require extra time and higher cost. Therefore, pilot study design should be chosen based on real-life conditions, including the number of batches to be studied, amount of time, amount of budget, etc. An adaptive type of design can be considered using the same approach being demonstrated here, e.g., if many batches need to be tested, a parallel study could be used first to filter out the futile batches, followed by a crossover study to confirm the most promising batches with sufficient certainty.

Pivotal study conditional power The conditional power here is the simulated power of a potential pivotal study incorporating the PE and SE results obtained from the proposed pilot study. The pivotal study conditional power for batch pairs with various uncertainty are shown in Figure 2. For example, a batch pair with PE of 1.0 and SE of 10% will have a conditional power of 80% in a pivotal study (2 x 2) using 48 subjects. A batch pair with PE of 0.9 and SE of 10% will have a conditional power of 70% in the same pivotal design; therefore, the former batch pair would be determined to be more desirable for a pivotal study.

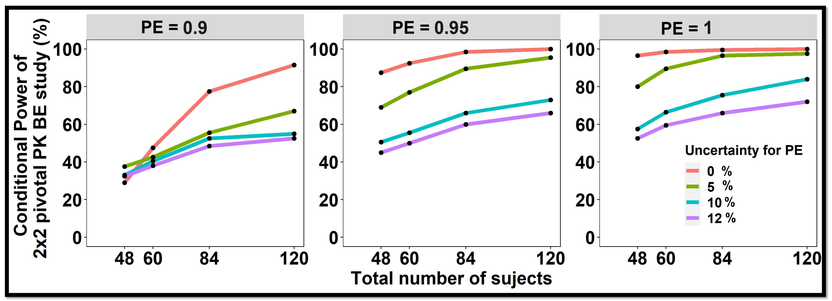

Figure 2. Conditional power of a pivotal study for batch pairs with various uncertainty using point estimates (PE) of 0.9, 0.95, 1.0 as the example.

Conclusions

These results suggest that an informed selection of the test and reference batches leveraging PK pilot studies could be helpful in addressing the challenges of batch variability in PK BE studies for inhalation powder drug products.

Acknowledgement & Disclaimer

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1. Li et.al. Population Pharmacokinetic Modeling for Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder in a Bioequivalence Study. ASCPT 2022 Annual Meeting Abstract ID 1113679.