Exploration the Potential Impact of Batch-to-Batch Variability of Inhalation Powder Drug Products on Pharmacokinetic Bioequivalence Study Power

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INTRODUCTION

- Batch-to-batch variability has been reported for inhalation powder products and may pose a challenge for generics development.
- This study explored the effect of batch-to-batch variability on the determination of bioequivalence (BE) for the reference (R) inhalation powder drug products (denoted as R_1, R_2).
- Advair Diskus (100/50 µg inhalation) was used as a model drug product.

METHOD

- The effect of the total number of subjects included and the batch-to-batch variability on pharmacokinetic (PK) BE study power were explored using model-based simulation. The batch variability was quantified as the different bioavailability between batches. Model structures, parameters, and variability were adopted from previous work.[1]
- Between-subject variability (BSV) and within-subject variability (WSV) were set to be 25% in order to match with the observed variability.
- Two-sequence and two-periods (2x2) crossover study was replicated for 500 times to calculate the power for each scenario.
- Criteria for BE determination was based on the 90% confidence interval of both maximum concentration C_{max} and total exposure (area-under-curve AUC_{inf}) within 80%-125%.

RESULTS

- Forty-eight subjects were required to reach 95% power in a 2x2 crossover study without any batch-to-batch variability (N=48, WSV=25%, R_1/R_2 = 1). (Figure 1)
- Power was reduced from 95% to 80% with 5% batch variability (N=48, WSV=25%, R_1/R_2 = 0.95), and to 30% with 10% batch variability (N=48, WSV=25%, R_1/R_2 = 0.9). (Figure 2)
- Eighty-four subjects were needed to reach 80% power with 10% batch variability (N = 84, WSV=25%, R_1/R_2 = 0.9).

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.

How much batch-to-batch variability affects PK BE study power and sample size?

With 10% of batch variability:

- *70% chance of PK BE study failure*
- *Double the needed subjects to achieve 80% power*

Scan me for more info!

Effects of the bioavailability ratio and absorption rate constant on study power are in the supplemental material (scan the barcode).

RESULTS

Figure 1. Relationship between total number of subjects with 2x2 crossover study power with no batch-to-batch variability

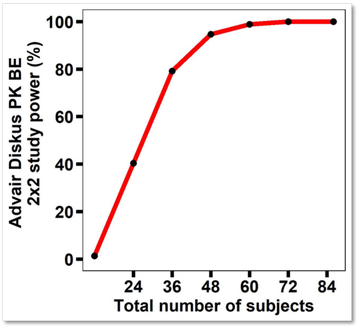
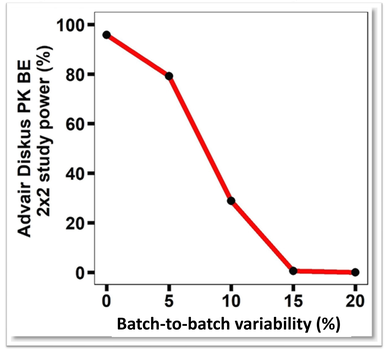


Figure 2. Effects of batch-to-batch variability on 2x2 crossover study power with 48 subjects



DISCUSSION & CONCLUSION

- A batch variability of 10% could cause 60% (95% to 30%) lost of power given a certain design (48 subjects 2x2 crossover) (Figure 2).
- This work suggests that batch variability has a significant impact on BE study power. The appropriate batch selection is critical for the pivotal PK BE study when batch variability presents.

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