Designs for a Robust Outcome in Pharmacokinetic Bioequivalence Testing of Orally-Inhaled Drug Products with Batch-to-Batch Variability

IPAC-RS PK Batch-to-Batch Variability Working Group

Hayden Beresford[1], Christopher Wiggenhorn[1], Beth Morgan[2], Alessandro Cavecchi[3], Helen Strickland[4], Dave Christopher[5], Scott Haughie[6] , Elise Burmeister Getz[7], Svetlana Lyapustina[8]

INTRODUCTION

Pharmacokinetic (PK) bioequivalence (BE) of orally-inhaled drug products (OIDPs) has proved to be a challenging hurdle, partly due to variability among manufacturing batches even for well-developed products whose inherent variability is consistent with demonstrated clinical safety and efficacy. The goal is a PK BE test that is interpretable as a comparison of products, both at the development pilot stage and for pivotal registration studies, despite logistically-limited sampling (# batches).

Pharmacokinetic Variability Among Batches of OIDPs

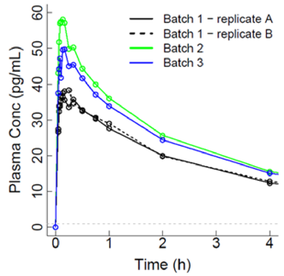


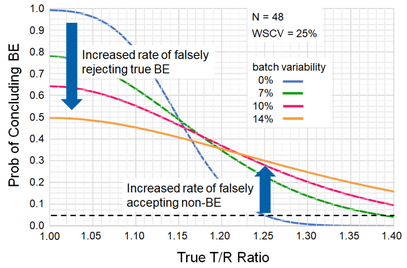
Figure 1. PK profiles for fluticasone propionate administered as Advair Diskus 100/50 following single-dose oral inhalation to healthy adults. Adapted from [1].

In **Figure 1**, between-batch variability was estimated among three batches of Advair Diskus 100/50 as 23% (Cmax) and 14% (AUC)[1].

PK between-batch variability for OIDPs has been acknowledged by industry and regulators for about a decade[1-6].

Performance of the PK BE Test When Batches Differ

Figure 2. Operating curve of the 2-way PK BE study comparing one batch of Test (T) with one batch of Reference (R). Adapted from [7].



Between-batch variability erodes performance of the PK BE test. With 10% batch variability, for example, the probability of selecting batches from *identical* products that pass PK BE is <65% **(Figure 2).**

Uncertainty when # Batches = 1

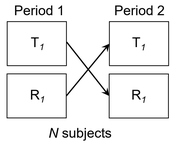
Risk (uncertainty) enters the PK BE assessment during: #1) estimation of the Test/Reference ratio, and #2) construction of the confidence interval around the product ratio. **The PK BE alternative approaches described here use multiple batches to address #1 – T/R point estimate accuracy.**

Approach	*How multiple batches are incorporated into the PK BE test*
Batch as ANOVA fixed effect	Directly into the study design and statistical model
Superbatch	Directly into the study design
Targeted batch	In-vitro screening to select a 'typical' batch for PK BE

PK BE ALTERNATIVE DESIGN / ANALYSIS APPROACHES

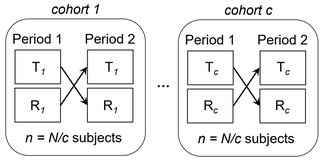
PK BE design / analysis alternatives use multiple batches to improve the T/R point estimate.

Baseline PK BE Approach



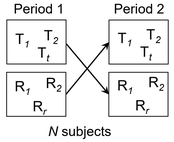
Description	Compares a single randomly-selected batch of Test (T_1) and Reference (R_1)
Key Advantage	History of success for assessing PK BE of systemically-acting drugs[5]
Key Disadvantage	Performance is negatively impacted when batches within a product differ

Batch as a Fixed ANOVA Effect



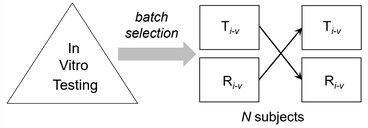
Description	Subset 'cohorts' of the study population receive different batches. T/R estimate arises as the weighted average across the cohorts.
Key Advantage	Outcome not highly dependent on the selected batch.
Key Disadvantage	Requires modification to the statistical model to remove variability due to batch from the ANOVA residual error.

Superbatch Approach



Description	For each subject, the Test and Reference treatments are chosen from a pool of *t* Test and *r* Reference batches. Conceptualized by D Sandell[6,9,10]
Key Advantage	Simplicity of application – no change to the statistical model. Outcome not highly dependent on the selected batch.
Key Disadvantage	Power is relatively less than for the other approaches because batch and measurement variability are confounded.

Targeted Batch Approach



Description	Many batches tested *in vitro*, a single representative (*e.g.*, median) batch is selected for PK BE
Key Advantage	Allows relatively low-cost observation of many batches
Key Disadvantage	Cost depends on resource needed for IVIVC definition. Performance depends on IVIVC quality.

Two additional approaches use multiple batches to also estimate between-batch variability, and incorporate this variability component into the confidence interval (Batch as a Random ANOVA Effect) and/or equivalence criterion (Population Bioequivalence). These two approaches are outside the initial scope of work because they are more complex to implement.

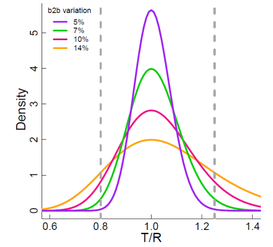
SIMULATION PARAMETER SPACE

Batch Variability and Batch Sample Size (# Batches)

Figure 3. Distribution of single-batch T/R values from comparison of identical products

Performance of PK BE approaches will be explored for log-scale batch-to-batch (b2b) variance of 5%, 7%, 10% and 14%, reflecting low to moderate between-batch variability that may be broadly encountered for OIDPs, notably less than the 23% observed for a marketed DPI (Advair Diskus)[1]. The impact of b2b variability on a comparison of identical products (T/R=1.0) is illustrated in **Figure 3**.

Multiple-batch PK BE approaches respond to b2b variability with, *e.g.*, 2 to 8 (in-vivo) or more (in-vitro) batches of each product.



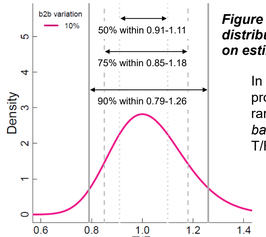


Figure 4. Coverage of the single-batch T/R distribution illustrating the effect of b2b variability on estimating the product ratio: 10% b2b example

In a single-batch PK BE study comparing identical products with 1 batch each of T and R selected at random assuming 10% b2b variability, true *single-batch* T/R values may differ from the true *product* T/R value (1.00):

- 1-in-2 *batch* T/R values outside 0.91 – 1.10
- 1-in-4 *batch* T/R values outside 0.85 – 1.18
- 1-in-10 *batch* T/R values outside 0.79 – 1.26

Even low (≤10%) b2b variability can shift a single-batch PK ratio (one batch of T *vs* one batch of R) substantially away from the true product ratio, increasing the likelihood that truly equivalent products will fail PK BE and that truly non-equivalent products will pass.

Residual Error and Measurement Sample Size (# Subjects)

Performance will be explored using study sizes and log-scale residual variabilities that are amenable to a range of design variations (*e.g.*, 1, 2, 4 or 8 batches; 2-way or 4-way crossover) and pertinent to OIDP PK BE[8,9,11]. Examples in **Table 2**.

Table 2. Example PK BE study sizes that provide adequate (>80%) to high (>95%) probability of success in a 2-way crossover

Description	*Number of subjects*	*Within-subject residual error*	*True T/R*	*Probability of BE in a 2-way crossover**
Baseline scenario	64	20%	0.875	81%
Increased # subjects	128	20%	0.875	97%
Increased residual error relative to b2b	128	29%	0.875	81%

**calculated in R using power.TOST*

DISCUSSION

Can PK BE design and data analysis methods be re-imagined to yield reliable PK BE outcomes in the presence of between-batch variability?

Key objectives of the current work are to:

1. Understand performance of baseline and alternative PK BE approaches when batches vary
2. Present the findings graphically, as quantitative operating curves in the style of Figure 2
3. Summarize key learnings for the pharmaceutical aerosol industry

Between-batch variability may be inherent to OIDP design. The current work is therefore anticipated to be broadly applicable among OIDPs.

OIDP design features potentially contributing to batch variation:

- Low systemic availability – large window of opportunity for PK variability
- Complex formulations – multiple opportunities for variation in physicochemical association among formulation components
- Drug/device interactions also contribute opportunity for variability

PK BE is an established component of the therapeutic equivalence assessment, including FDA's weight-of-evidence paradigm and EMA's step-wise approach. OIDP PK differences arise from product (device, formulation, process) differences, just as for systemically-acting products. FDA notes "it is clear that the connection of PK to product quality is the same whether the site of action is downstream or upstream"[12].

REFERENCES

1. Burmeister Getz E, *et al. Clin Pharmacol Therap.* 2016, 100:223-231. doi:10.1002/cpt.373
2. O'Connor D, *et al. JAMPDD.* 2011, 24:119-135. doi:10.1089/jamp.2011.0878
3. Hochhaus G, *et al. AAPS J.* 2015, 17:769-775. doi:10.1208/s12248-015-9736-6
4. Burmeister Getz E. *et al. Clin Pharmacol Therap.* 2017, 101:331-340. doi:10.1002/cpt.535
5. Låhelmä S, *et al. JAMPDD.* 2015, 28:462-473. doi:10.1089/jamp.2014.1195.
6. Sandell D. *Inhaled Drug Delivery Annual Conference.* November, 2015
7. Benet L, *et al. Clin Pharmacol Therap.* 2019, 105:326-328. doi:10.1002/cpt.1294
8. Davit B, *et al. Ann Pharmcotherap.* 2009, 43:1583-1597. doi:10.1345/aph.1M141
9. Sandell D, *et al. Inhalation Mag.* December 2017.
10. Sandell D, and M Wieczorek. *Respir. Drug Deliv.* 2018, 1:255-264.
11. Haughie S, *et al. JAMPDD.* 2019, 32:1-9. doi:10.1089/jamp.2019.1537.
12. Background information for the Pharmaceutical Science Advisory Committee meeting on locally-acting gastrointestinal drugs. October 2004.

ACKNOWLEDGEMENTS

The authors would like to thank the IPAC-RS Board of Directors for their support of this project.

Corresponding Author: Svetlana Lyapustina (svetlana.lyapustina@faegredrinker.com)

Author Affiliations: [1]3M Health Care, [2]AstraZeneca, [3]Chiesi Farmaceutici S.p.A., [4]GlaxoSmithKline, [5]Merck, [6]Mylan, [7]Sandoz, [8]IPAC-RS Secretariat