Quantitative Modeling and Simulation to Evaluate Alternative Approaches to Be Used in COVID-19 Interrupted Bioequivalence Studies

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INTRODUCTION

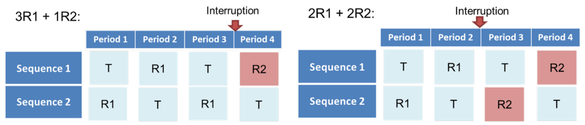
- The emergence of coronavirus disease 2019 (COVID-19) has caused a large outbreak and became a major public health emergency.
- Many ongoing clinical trials are interrupted due to national guidelines and restrictive measures, including government lockdown, site closures, quarantines, and travel restrictions.
- The COVID-19 pandemic may lead to difficulties in meeting protocol-specified procedures for clinical trial execution, including those for Abbreviated New Drug Applications (ANDAs).

OBJECTIVES

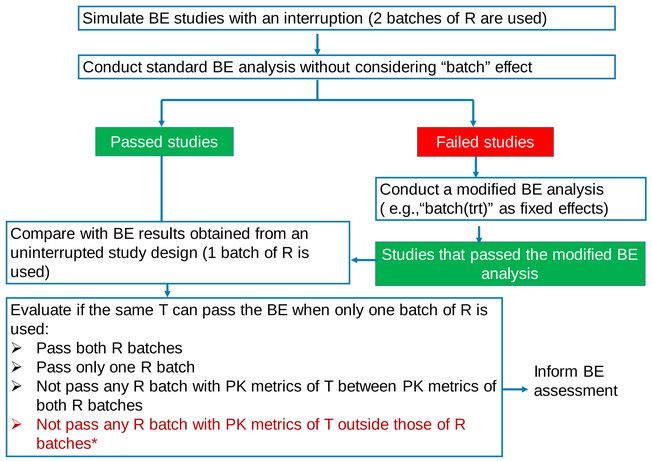
- The purpose of this study is to use a modeling and simulation approach to evaluate the impact of using more than one batch of a Reference Listed Drug (RLD) in a pharmacokinetic (PK) bioequivalence (BE) study due to RLD expiration with study interruption.

METHODS

- Simulations were performed with a hypothetical orally administered product using a two-compartment model to mimic possible COVID-19 interruption scenarios. The investigated scenarios are 4-way fully replicated crossover study design with two types of interruptions.



R1: RLD batch #1, R2: RLD batch #2



*BE failure scenario.

For interrupted 4-way fully replicated crossover studies that are conducted with two RLD batches and pass BE evaluations with standard BE analyses without considering batch information, they would also pass BE if they were conducted without an interruption.

Table 1. Analyses of interrupted studies that passed the standard BE evaluation

Interruptions	BE Evaluation Results	Batch Difference				
		5%	10%	15%	20%	30%
3R1 + 1R2	BE to both R1 and R2 if used alone	62%	31%	6%	0	0
	BE to only one batch of R (R1 or R2)	35%	68%	82%	65%	35%
	BE to neither of the R batches but with PK between R1 and R2	2%	1%	12%	35%	65%
	BE to neither of the R batches & with PK not between R1 and R2*	1%	0	0	0	0
2R1 + 2R2	BE to both R1 and R2 if used alone	63%	31%	6%	0	0
	BE to only one batch of R (R1 or R2)	34%	68%	80%	53%	4%
	BE to neither of the R batches but with PK between R1 and R2	2%	1%	14%	47%	96%
	BE to neither of the R batches & with PK not between R1 and R2*	1%	0	0	0	0

Note: % indicates the frequency observed in each category. *BE failure scenario.

- If the T can pass the standard BE in an interrupted study (2 batches of an RLD used), when the study is conducted without interruption (1 batch of an RLD used), T would be 1) BE to at least one batch of the R; or 2) not BE to either R batches, but the PK metrics of T is between the metrics for the two R batches when the batch difference is large compared with implied BE limits on T/R ratios. The chance of studies that fell into the BE failure scenario was close or equal to 0 across all the investigated batch differences. The BE results obtained from a standard method are acceptable.

For interrupted studies that cannot pass a standard BE evaluation without considering batch information, using a modified approach such as incorporating "batch(trt)" as a fixed effect may provide a more accurate estimate of the T/R ratio and can potentially make studies pass. Under this circumstance, whether the BE establishment with a modified BE approach is acceptable would be case specific.

Table 2. Analysis of interrupted studies that passed the modified BE evaluation while not passing the standard BE evaluation

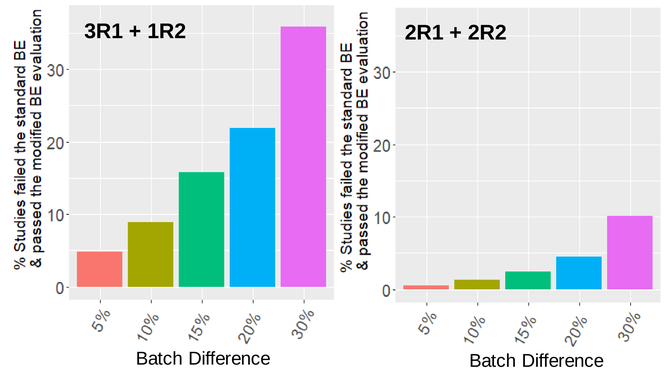
Interruptions	BE Evaluation Results	Batch Difference				
		5%	10%	15%	20%	30%
3R1 + 1R2	BE to both R1 and R2 if used alone	10%	1%	0	0	0
	BE to only one batch of R (R1 or R2)	64%	94%	92%	64%	8%
	BE to neither of the R batches but with PK between R1 and R2	5%	3%	8%	36%	92%
	BE to neither of the R batches & with PK not between R1 and R2*	21%	2%	0	0	0
2R1 + 2R2	BE to both R1 and R2 if used alone	14%	2%	0	0	0
	BE to only one batch of R (R1 or R2)	73%	93%	99%	90%	14%
	BE to neither of the R batches but with PK between R1 and R2	13%	5%	1%	10%	86%
	BE to neither of the R batches & with PK not between R1 and R2*	0	0	0	0	0

Note: % indicates the frequency observed in each category. *BE failure scenario.

- If the T failed to pass the standard BE but can pass the modified BE in the interrupted study (2 batches of an RLD used), when the study is conducted without interruption (1 batch of an RLD used), under most circumstances, T would be 1) BE to at least one batch of R; or 2) not BE to either R batches, but the PK metrics of T is between the 2 R batches. However, the chance of studies fell into the BE failure scenario is more than 5% when batch difference is small (i.e. 5%) and interrupted by a 3 to 1 R batch division. The acceptability of BE results conducted with a modified approach would be case specific.

RESULTS

Figure 1. Percentage of studies that passed the modified BE evaluation while not passing the standard BE evaluation



- For studies that cannot pass a standard BE evaluation without considering batch information, using a modified approach such as incorporating "batch(trt)" as a fixed effect may provide a more accurate estimate of the T/R ratio and can potentially make studies pass.

REFERENCES

FDA Guidance for Industry - Statistical Approaches to Establishing Bioequivalence (January 2001). Available at: https://www.fda.gov/downloads/drugs/guidances/ucm070244.pdf

FDA Draft Guidance on Warfarin Sodium (recommended Dec 2012). Available at: https://www.accessdata.fda.gov/drugsatfda_docs/psg/Warfarin_Sodium_tab_09218_RC12-12.pdf

FDA COVID-19-Related Guidance Documents:

https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders

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