Alternative BE Approaches for Data Analysis Due To COVID-19 Related Study Interruptions

SBIA 2021: Advancing Generic Drug Development: Translating Science to Approval

Day 1, Session 1: COVID-19 Impact

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The Disclaimer

- This presentation represents the views and perspectives of the speaker and does not necessarily reflect the views of the U.S. FDA.

Learning Objectives

- Describe common challenges for conducting bioequivalence (BE) studies during the COVID-19 pandemic
- Discuss how OGD can help prospective applicants for their COVID-19 interrupted studies
- Explain a case demonstration of using alternative data analysis approaches for COVID-19 interrupted in vivo BE studies

BE Study Challenges During COVID-19

- The COVID-19 pandemic may interrupt the conduct of BE studies intended for submission in Abbreviated New Drug Applications (ANDAs)
- Study interruptions may arise from:


Exposure risk


Travel limitations


Site closures


Product availability

- The process of interrupting and restarting BE studies for ANDAs may require protocol revisions and impact the collection of information needed to establish BE

For more information: https://www.fda.gov/drugs/coronavirus-covid-19-drugs/bioequivalence-studies-submission-andas-during-covid-19-pandemic

OGD's Responses to Address Emerging Questions Related to COVID-19

- OGD published guidance regarding the conduct of in vivo BE studies during the COVID-19:
  - *Guidance for Industry: Protecting Participants in Bioequivalence Studies for Abbreviated New Drug Applications During the COVID-19 Public Health Emergency* (January 2021)
- OGD brings together multiple disciplines to provide consistent, timely, and scientifically sound advice

Questions to OGD on Interrupted Studies

- Prospective applicants should submit specific questions related to their impacted BE studies via the controlled correspondence process or other appropriate avenues
- Questions may relate to proposed protocol modifications, including:
  - Alternative statistical analysis plans as supported by modeling and simulation.
  - Modifications to incorporate adaptive designs that may allow recruitment of additional subjects

For more information: https://www.fda.gov/drugs/coronavirus-covid-19-drugs/bioequivalence-studies-submission-andas-during-covid-19-pandemic

Alternative Analysis Approaches for COVID-19 Interrupted Studies

- FDA encourages prospective applicants to find and perform alternative analysis approaches for COVID-19 interrupted studies
- Any protocol or statistical analysis plan changes should be accompanied with adequate justifications and not lead to biased equivalence determination
- Protocol and statistical analysis plan changes should be made prior to data lock and unblinding

For more information: *Guidance for Industry: Protecting Participants in Bioequivalence Studies for Abbreviated New Drug Applications During the COVID-19 Public Health Emergency* (January 2021)

Common Questions Due to COVID-19

Test/Reference Availability

- Product expirations
- Usage of multiple batches (lots) of the product in a single pharmacokinetics (PK) study
- Usage of multiple batches of the product between fed and fasting study

Protocol Revision

- Interim analysis; Adaptive design
- Shortening study duration; Truncated approach
- Change of the study design (e.g., crossover to parallel)

Others

- Study with large missing data
- Partial in vivo study (e.g., fasting study only)
- In vitro study only

*Summarized from received inquiries

A Case Demonstration

-- Quantitative Methods and Modeling to Assess COVID-19-Interrupted in vivo PK BE Studies with Two Reference Batches

A Case Question from Common Challenges

Test (T)/Reference (R) Availability

- Product expirations
- Usage of multiple batches (lots) of the product in a single pharmacokinetics (PK) study
- Usage of multiple batches of the product between fed and fasting study

- Reference product expires in an ongoing BE study due to COVID-19 related interruptions
  - Use one batch in one period and a different batch in the other period

If two R batches (lots) are used in a pivotal PK BE study, how can we assess the BE results?

BE Study Design

Replicated 4-way crossover design

- A hypothetical narrow therapeutic Index (NTI) drug as an example

	Period 1	Period 2	Period 3	Period 4
Sequence 1	T	R	T	R
Sequence 2	R	T	R	T

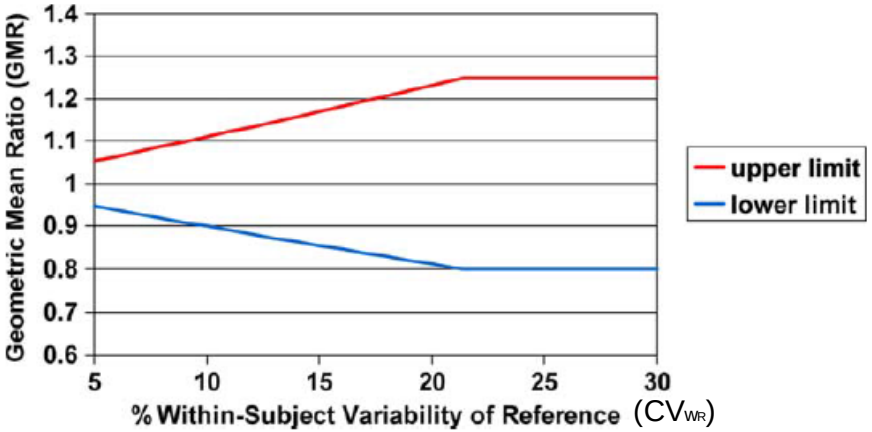
In general, the same lots of the T and R formulations should be used for the replicated administration. (*Guidance for Industry: Statistical Approaches to Establishing Bioequivalence January 2001)*

BE Method and Limit for NTI Drugs

Reference Scaled Average Bioequivalence (RSABE):

- BE limits for these drug products are scaled against the within subject variability and capped at 80-125%

Implied BE limits on Geometric Mean (T/R) Ratios



CV_{WR}%	Implied BE limits on T/R ratios
5	0.95 – 1.05
10	0.90 – 1.11
15	0.85 – 1.17
20	0.81 – 1.23

Yu, L., et al (2015), Clin. Pharmacol. Ther., 97: 286-291. doi:10.1002/cpt.28

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

BE Interruption Simulation

Interrupted studies

3R1 + 1R2:

Interruption

	Period 1	Period 2	Period 3	Period 4
Sequence 1	T	R1	T	R2
Sequence 2	R1	T	R1	T

2R1 + 2R2:

Interruption

	Period 1	Period 2	Period 3	Period 4
Sequence 1	T	R1	T	R2
Sequence 2	R1	T	R2	T

Uninterrupted studies

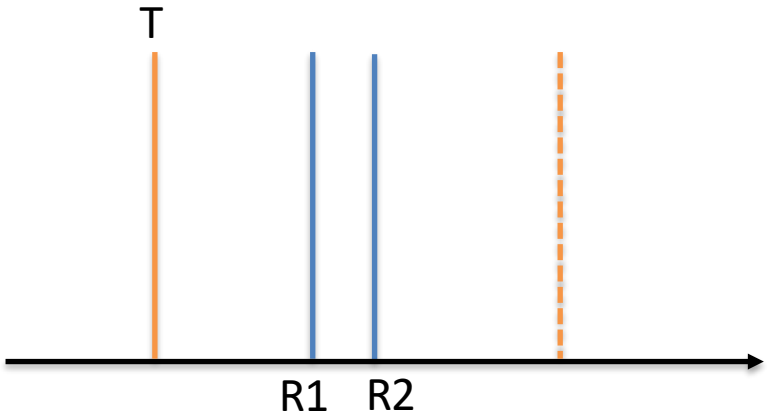
R1 only:

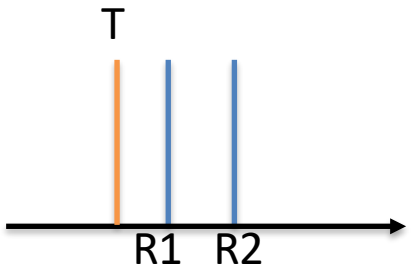
	Period 1	Period 2	Period 3	Period 4
Sequence 1	T	R1	T	R1
Sequence 2	R1	T	R1	T

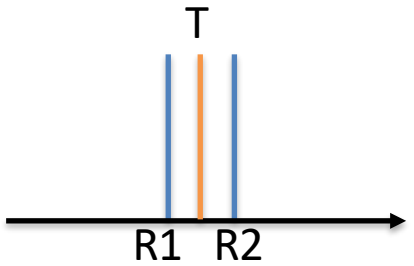
R2 only:

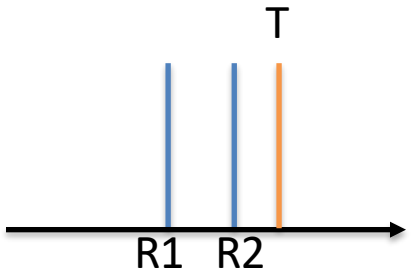
	Period 1	Period 2	Period 3	Period 4
Sequence 1	T	R2	T	R2
Sequence 2	R2	T	R2	T

Simulation









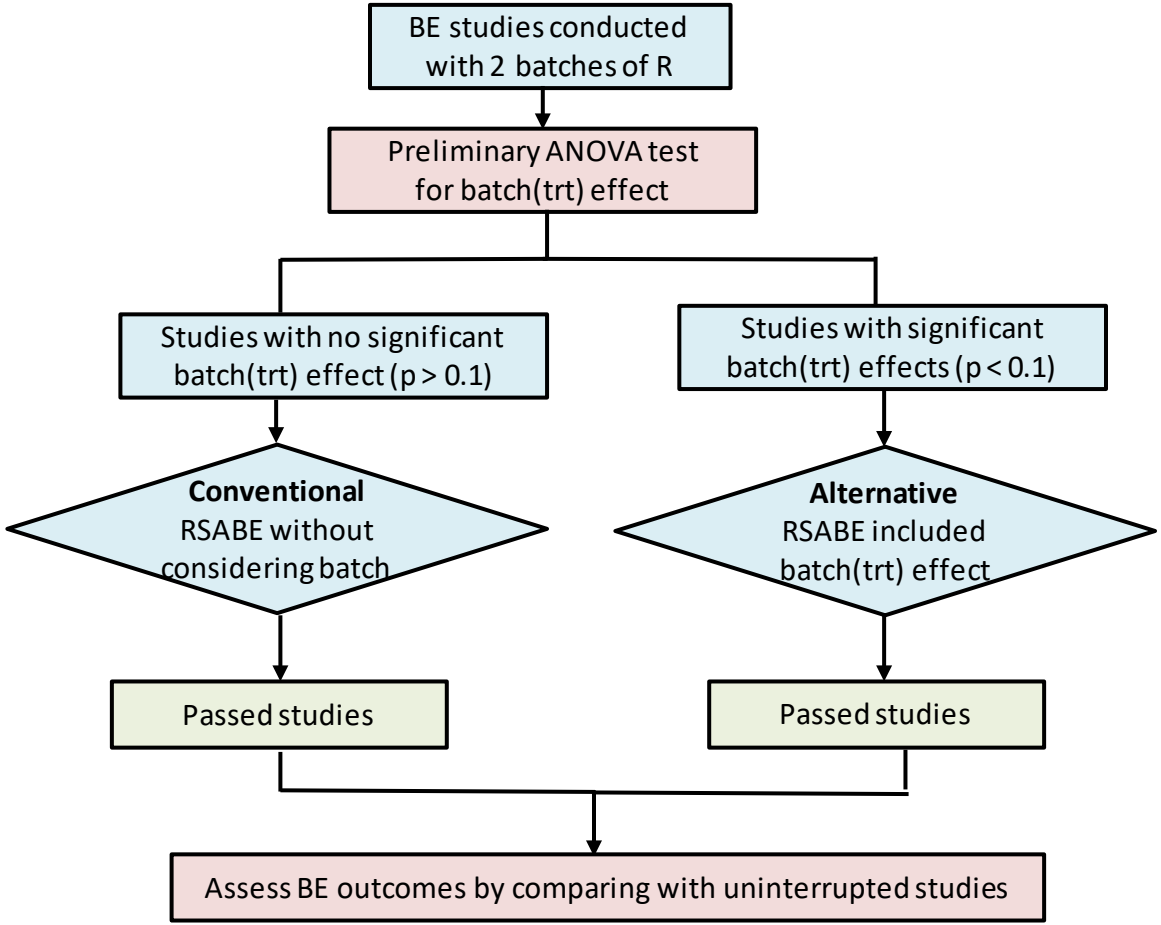
Simulation cover:

- A range of underlying R batch differences (R1: batch 1; R2: batch 2)
- Different scenarios of T/R1 and T/R2 ratios
- A range of intra-subject variabilities for PK metrics

Assessment Criteria

- Compare BE evaluation outcomes between the interrupted and uninterrupted studies
- BE results from uninterrupted studies represent the possible outcomes if there were no interruptions related to COVID-19
  - T can pass BE for both T vs. R1 and T vs. R2 
  - T can pass BE for either T vs. R1 or T vs. R2, but not both 
  - T cannot pass BE for either T vs. R1 or T vs. R2 and PK exposure of T falls within the PK exposures of the two R batches 
  - T cannot pass BE for either T vs. R1 or T vs. R2 and PK exposure of T falls outside those of the two R batches 

Analysis Scheme



Preliminary ANOVA Tests Results

Below results are conducted with average CV_{WR} =10%, similar results hold for other studied CV_{WR} (results not shown)

Interruption types	ANOVA tests results	Batch to batch variations (%)				
		5	10	15	20	30
3R1 + 1R2 (Interruption after the completion of period 3)	Studies with no significant batch(trt) effect	79%	51%	22%	5%	0
	Studies with significant batch(trt) effect	21%	49%	78%	95%	100%
2R1 + 2R2 (Interruption after the completion of period 2)	Studies with no significant batch(trt) effect	68%	27%	4%	0	0
	Studies with significant batch(trt) effect	32%	73%	96%	100%	100%

Note: % indicates the frequency observed in each category; ANOVA, analysis of variance.

- The percentage of studies with significant batch(trt) effect increases with increasing batch-to-batch variation
- When batch-to-batch variation is higher or equal to 20%, more than 95% of interrupted studies show significant batch(trt) effect regardless of types of interruption

Analyses of Interrupted Studies Evaluated with Conventional RSABE with Batch Effect Excluded in the Statistical Model

Interruption types	Comparison with uninterrupted studies	Batch differences (%)				
		5	10	15	20	30
3R1 + 1R2 (Interruption after the completion of period 3)	1. BE to both T vs. R1 and T vs. R2	64%	36%	10%	2%	0
	2. BE to either T vs. R1 or T vs. R2, but not both	33%	63%	82%	68%	0
	3. Not BE to either T vs. R1 or T vs. R2 & PK between R1 and R2	2%	1%	8%	30%	100%
	4.*Not BE to either T vs. R1 or T vs. R2 & PK not between R1 and R2	1%	0	0	0	0
2R1 + 2R2 (Interruption after the completion of period 2)	1. BE to both T vs. R1 and T vs. R2	66%	40%	19%	20%	0
	2. BE to either T vs. R1 or T vs. R2, but not both	31%	59%	77%	50%	0
	3. Not BE to either T vs. R1 or T vs. R2 & PK between R1 and R2	2%	1%	4%	30%	0
	4.*Not BE to either T vs. R1 or T vs. R2 & PK not between R1 and R2	1%	0	0	0	0

Note: % indicates the frequency observed in each category. NTI products are not expected to have high batch-to-batch variability. Simulation conducted for illustration of extreme cases. *BE failure scenario.

- The chance of studies falling into BE failure scenario was close or equal to 0 across all investigated batch-to-batch variations

Analyses of Interrupted Studies Evaluated with Alternative RSABE with Batch Effect Included in the Statistical Model

Interruption types	Comparison with uninterrupted studies	Batch differences (%)				
		5	10	15	20	30
3R1 + 1R2 (Interruption after the completion of period 3)	1. BE to both T vs. R1 and T vs. R2	53%	26%	5%	0	0
	2. BE to either T vs. R1 or T vs. R2, but not both	39%	71%	79%	54%	7%
	3. Not BE to either T vs. R1 or T vs. R2 & PK between R1 and R2	1%	3%	16%	46%	93%
	4.*Not BE to either T vs. R1 or T vs. R2 & PK not between R1 and R2	7%	<1%	0	0	0
2R1 + 2R2 (Interruption after the completion of period 2)	1. BE to both T vs. R1 and T vs. R2	55%	27%	5%	0	0
	2. BE to either T vs. R1 or T vs. R2, but not both	43%	71%	81%	55%	6%
	3. Not BE to either T vs. R1 or T vs. R2 & PK between R1 and R2	2%	2%	14%	45%	94%
	4.*Not BE to either T vs. R1 or T vs. R2 & PK not between R1 and R2	0	0	0	0	0

*BE failure scenario.

- The chance of studies falling into the BE failure scenario is more than 5% when batch-to-batch variation is small (i.e., 5%) and interrupted by a 3 to 1 R batch division.
- The chance of falling into the BE failure scenario was not observed for studies with a 2 to 2 R batch division.

Conclusions from Case Demonstration

- From simulation results, BE results obtained from interrupted studies with no significant batch(trt) effect seems to be acceptable to use a conventional statistical analysis approach with batch(trt) term excluded

- However, the acceptability of BE outcomes from interrupted studies with significant batch(trt) effect using the alternative statistical approach with batch(trt) term included may be case specific

- In conclusion, the simulated scenarios are only considered as a case demonstration, which cannot be extrapolated to all interrupted studies, the study results could be case specific

Overall Summary

- FDA is proactively evaluating approaches to mitigate study challenges posed by the COVID-19 pandemic
  - Simulation can be one of the approaches to show a modified BE method is acceptable
  - Any protocol or statistical analysis plan changes should be accompanied with adequate justifications and not lead to biased equivalence determination
- Industry can include science-based justifications for alternative approaches to data analysis from interrupted studies
  - Pre-specify analysis plan before analyzing the data
- Proposed framework can be discussed with FDA
  - Controlled Correspondences or other appropriate avenues

Challenge Question #1

Which of the following statements is NOT a common questions on BE studies due to COVID-19?

A. Product expirations; Usage of multiple batches (lots) of the product in a single pharmacokinetics (PK) study

B. Study with large missing data

C. Subjects dropout due to adverse events

D. Shortening study duration; Truncated approach

Challenge Question #2

For COVID-19 related study interruptions:

A. FDA encourages prospective applicants to find and perform alternative analysis approaches for COVID-19 interrupted studies

B. Any protocol or statistical analysis plan changes should be accompanied with adequate justifications and not lead to biased equivalence determination

C. Protocol and statistical analysis plan changes should be made prior to data lock and unblinding

D. All of the above

Resources

- https://www.fda.gov/drugs/coronavirus-covid-19-drugs/bioequivalence-studies-submission-andas-during-covid-19-pandemic
- *Guidance for Industry: Protecting Participants in Bioequivalence Studies for Abbreviated New Drug Applications During the COVID-19 Public Health Emergency* (January 2021)

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