

# 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

# 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

# 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

# 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)

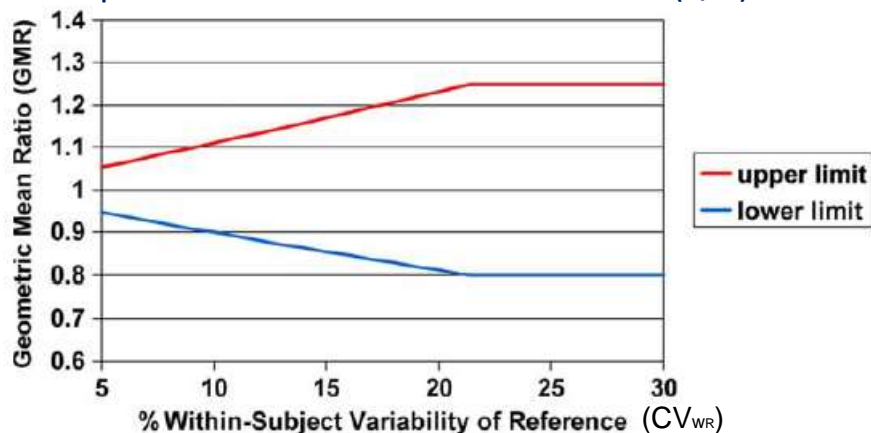
# BE Method and Limit for NTI Drugs



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 <sub>WR</sub> %	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](https://doi.org/10.1002/cpt.28)

# 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

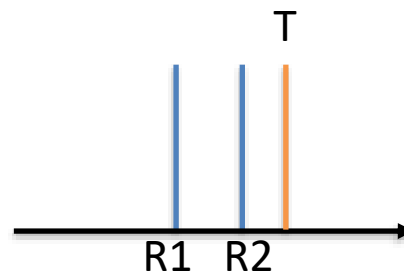
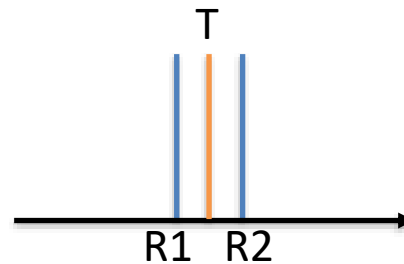
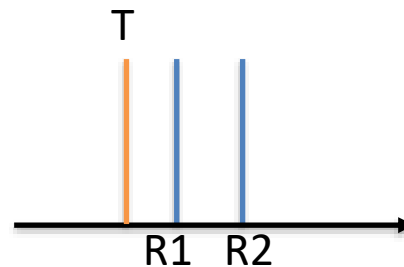
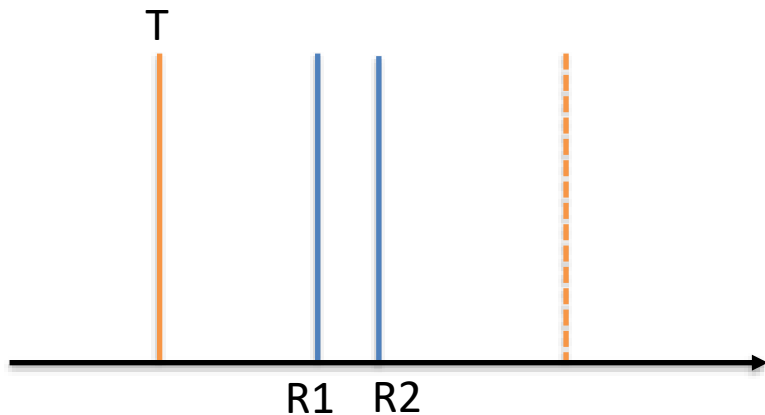
R1 only:

	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



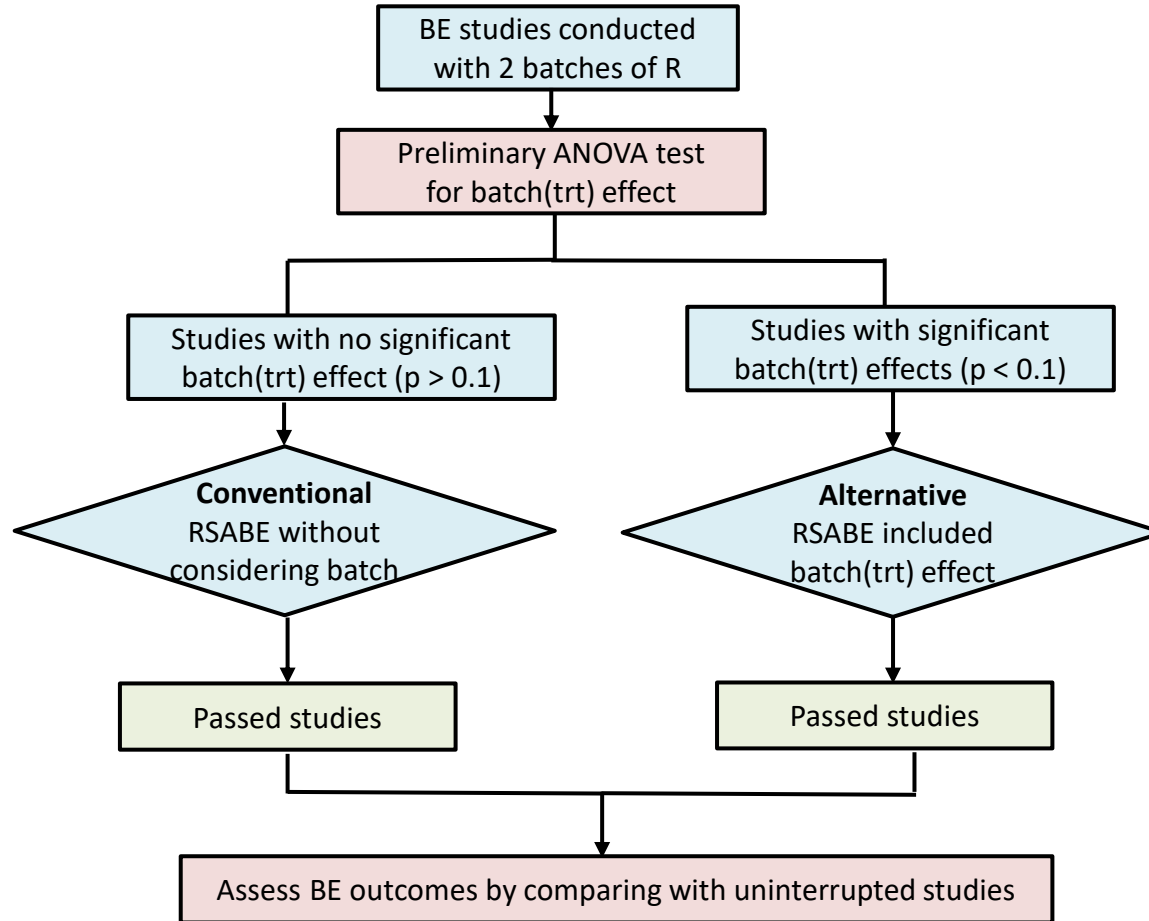
Simulation cover:

- 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 to batch variations (%)				
		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 to batch variation (%)				
		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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