Quantitative Methods and Modeling to Evaluate Alternative Approaches for COVID-19 Interrupted Bioequivalence Studies

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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

Outline

- Impact of COVID-19 pandemic on bioequivalence (BE) studies
- Work flow
  - To address issues as a result of COVID-19-related study interruptions
- A case demonstration and the proposed regulatory framework
  - To showcase the development of a science-based regulatory framework for establishing BE
- Overall Summary

The COVID-19 Pandemic Impacts on BE Studies

- Study interruptions can arise from
  - Quarantines, site closures, travel limitations, interruptions to the supply chain for the proposed generic products or the reference listed drug (RLD) products; Other situations include if site personnel or study subjects become infected with COVID-19
- Interrupting and restarting BE studies for abbreviated new drug applications (ANDAs) may require protocol revisions and impact the collection of information needed to establish bioequivalence
- Office of Generic Drugs (OGD) has received numerous controlled correspondences regarding interruptions to BE studies as a result of the COVID-19 pandemic

OGD Responses to Address Emerging Questions Related to COVID-19

- Bringing together multiple disciplines to provide consistent, timely, and scientifically sound advice
- COVID-19-related guidances
  - https://www.fda.gov/drugs/emergency-preparedness-drugs/coronavirus-covid-19-drugs
- Refer to Dr. Tao Bai's talk for OGD's approach

Workflow to Develop Alternative Approaches for COVID-19 Interrupted Studies

- Collect and categorize study interruption issues
- Triage issues to be addressed based on the nature and prevalence
- Evaluate scientific solutions and develop science-based framework to inform assessment of affected ANDAs and other relevant inquiries

Summary of COVID-19-Related Questions

- **Category 1: "Test (T)/RLD Availability" Inquiries**
  - E.g., Usage of Multiple Reference Batches (Lots) in a Single PK BE Study
- **Category 2: "Protocol Revision" Inquiries, e.g.**
  - 2-1. Interim analysis
  - 2-2. Shortening study duration; Truncated approach
  - 2-3. Change of the study design (e.g., crossover to parallel)
- **Category 3: Others**
  - 3-1. Partial in vivo study (fasting study only):
  - 3-2. In vitro study only

High priority and internal research was conducted

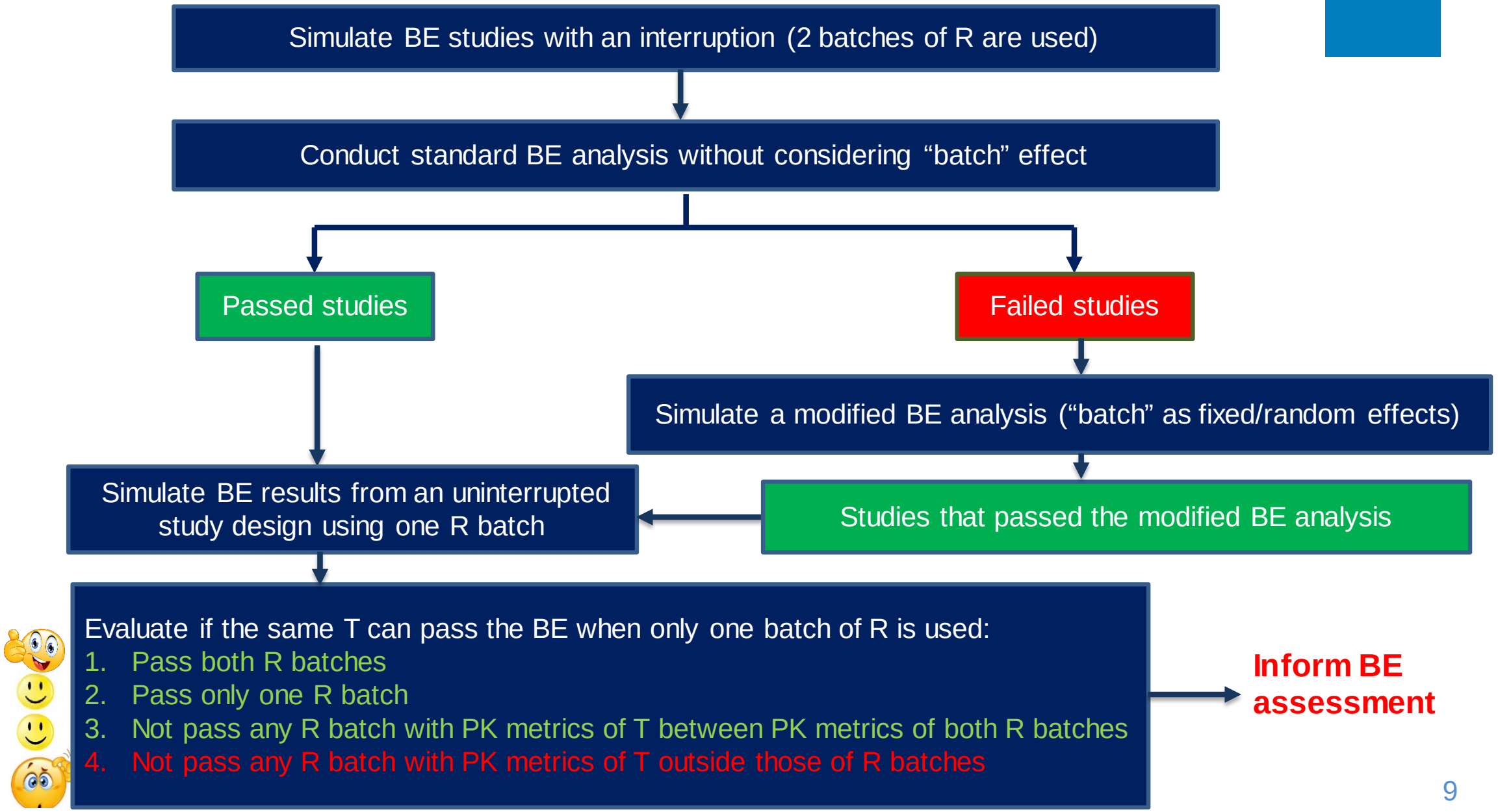
Adaptive designs and model-based analysis plan can be useful to support protocol revisions by generic applicants
CPT Commentary: Applications of Adaptive Designs in Generic Drug Development https://ascpt.onlinelibrary.wiley.com/doi/abs/10.1002/cpt.2050?af=R

- CPT: Clinical Pharmacology & Therapeutics
- RLD: Reference listed Drug

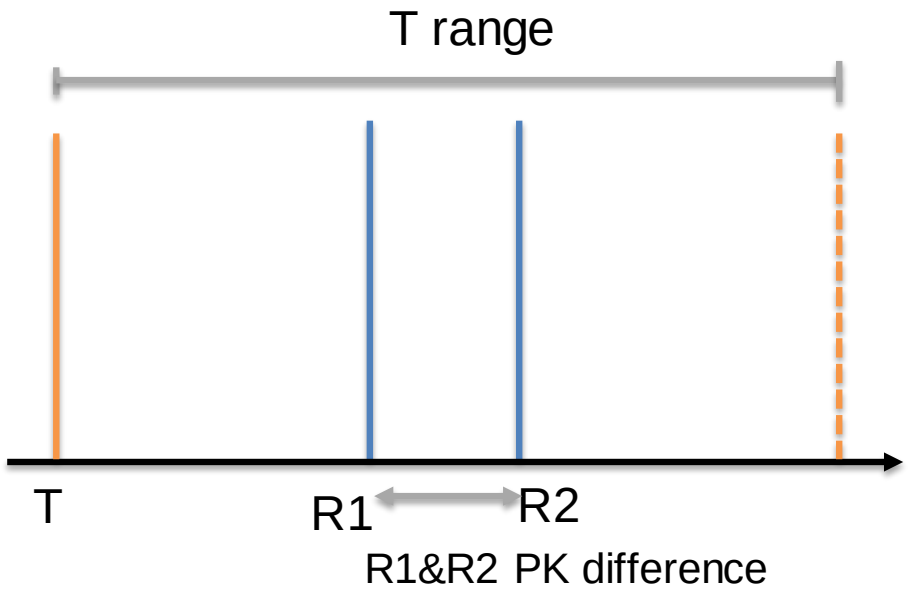
Re-Frame the Question

- Situation: Reference product expires in an ongoing BE study interrupted due to COVID-19 pandemic
  - Use one batch in one period and a different batch in the other period
- **Question: If two Reference (R) batches are used in the pivotal PK BE study, how will FDA assess the BE results?**

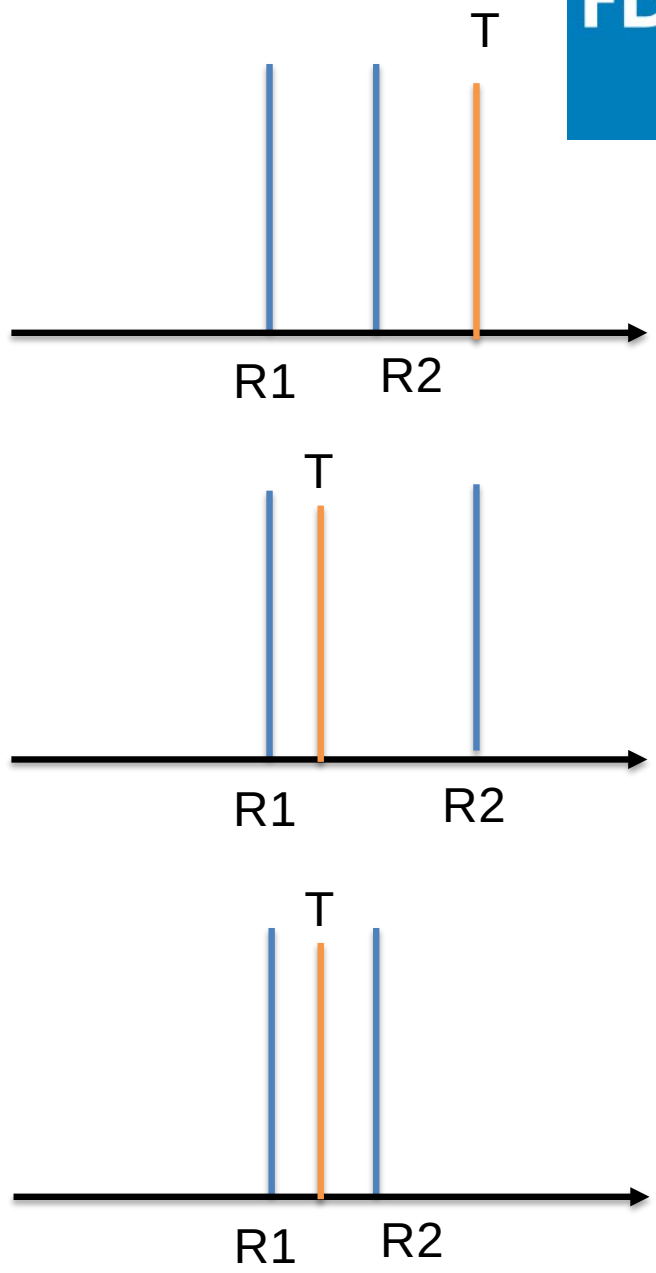
Analysis Scheme



Simulation Scheme



Simulations =>



- Simulate all potential BE scenarios
  - A range of underlying R batch differences (R1: batch 1; R2: batch 2)
  - All potential T/R1 and T/R2 ratios
  - A range of intra-subject variabilities for PK metrics
  - Different sample size
- Compare BE results
  - A study without interruption: T vs R1 or R2 with only one batch in the simulated dataset
  - A study with interruption: T vs R1 and R2 with both batches in the simulated dataset

Example I: 2-way Crossover BE Study

BE Interruption Simulation

Interrupted Studies:

Interruption

	Period 1	Period 2
Sequence 1	T	R2
Sequence 2	R1	T

24 Subjects, CV = 20%
R1&R2 difference = 10%, 15%, 20%, 30%

Uninterrupted Studies:

	Period 1	Period 2
Sequence 1	T	R1
Sequence 2	R1	T

	Period 1	Period 2
Sequence 1	T	R2
Sequence 2	R2	T

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 COVID19

Interrupted BE Studies that Pass the Standard Average BE (ABE) Evaluation

Compare with uninterrupted studies	10% batch difference	15% batch difference	20% batch difference	30% batch difference
BE to both R1 and R2 if used alone	61%	46%	23%	1%
BE to only one batch of R (R1 or R2)	39%	54%	76%	71%
BE to neither of the R batches but with PK between R1 and R2	0%	0%	1%	28%
BE to neither of the R batches & with PK not between R1 and R2	0%	0%	0%	0%

For interrupted studies that pass average BE (ABE) evaluation:

- T would pass the ABE evaluation against at least one R batch if used alone under most circumstances
- For situations when T is not BE to either of the R batches, its PK metrics will be between the two R batches (generally not a concern)

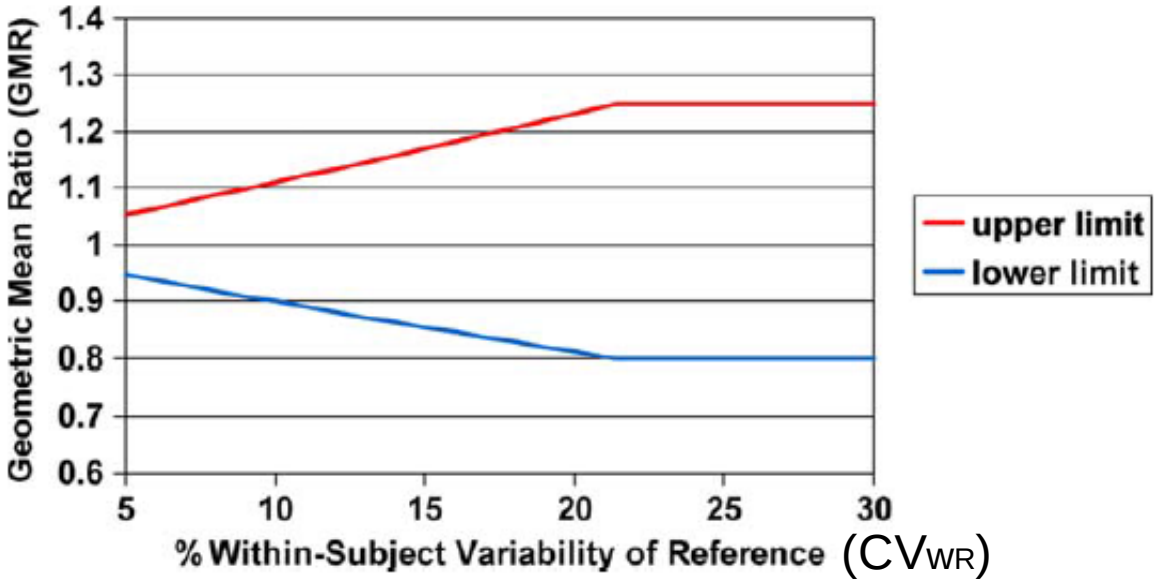
Example II: 4-way Fully Replicated Crossover BE Study, Narrow Therapeutic Index (NTI) Drugs

BE Criteria and Simulation Range 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	$T/R_{average}$ simulation range
5	0.95 – 1.05	0.9 – 1.1
10	0.90 – 1.11	0.8 – 1.2
15	0.85 – 1.17	0.7 – 1.3
20	0.81 – 1.23	0.6 – 1.4

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

*$R_{average}$ -- average of R1 & R2

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

24 Subjects, CV_{WR} = 5%, 10%, 15%, 20%
R1&R2 difference = 5%, 10%, 15%, 20%, 30%

Simulated Interrupted BE 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

Simulated Uninterrupted Studies:

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

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

Analyses of Interrupted BE Studies that Pass the RSABE Evaluation for NTI Drugs

Below results are conducted with CVWR =10%, similar results hold for other studied CVWR (results not shown)

Interruptions	BE Evaluation Results	5% batch difference	10% batch difference	15% batch difference	20% batch difference	30% batch difference
3R1 + 1R2	BE to both R1 and R2 if used alone	60%	31%	7%	0%	0%
	BE to only one batch of R (R1 or R2)	37%	67%	78%	58%	36%
	BE to neither of the R batches but with PK between R1 and R2	3%	2%	15%	42%	64%
	BE to neither of the R batches & with PK not between R1 and R2	0%	0%	0%	0%	0%
2R1 + 2R2	BE to both R1 and R2 if used alone	61%	31%	7%	0%	0%
	BE to only one batch of R (R1 or R2)	35%	68%	77%	48%	8%
	BE to neither of the R batches but with PK between R1 and R2	4%	1%	16%	52%	92%
	BE to neither of the R batches & with PK not between R1 and R2	0%	0%	0%	0%	0%

Note: NTI products are not expected to have high batch-to-batch variability. Simulation conducted just for illustration of extreme cases.

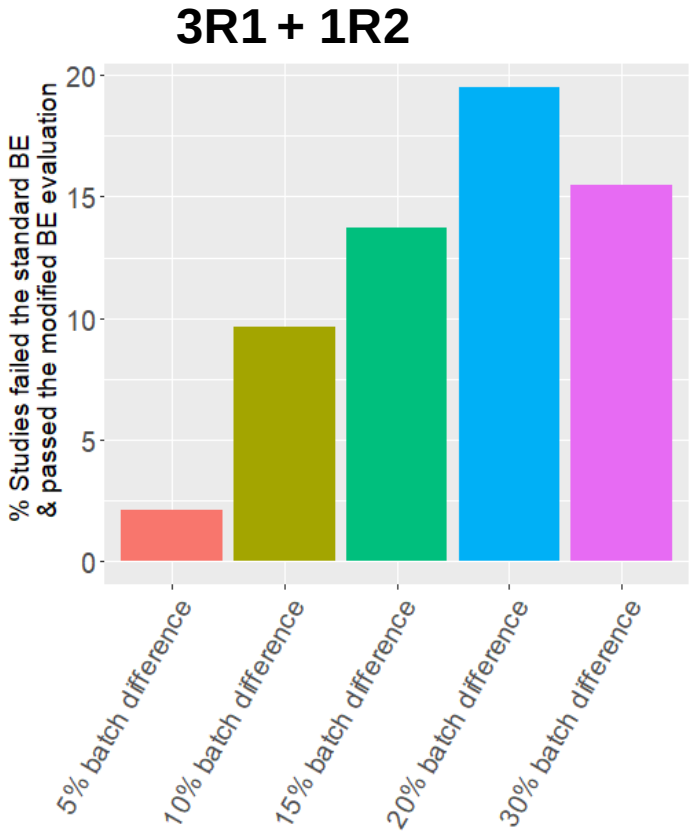
If the T can pass RSABE evaluation for the interrupted study and if study were conducted without an interruption,

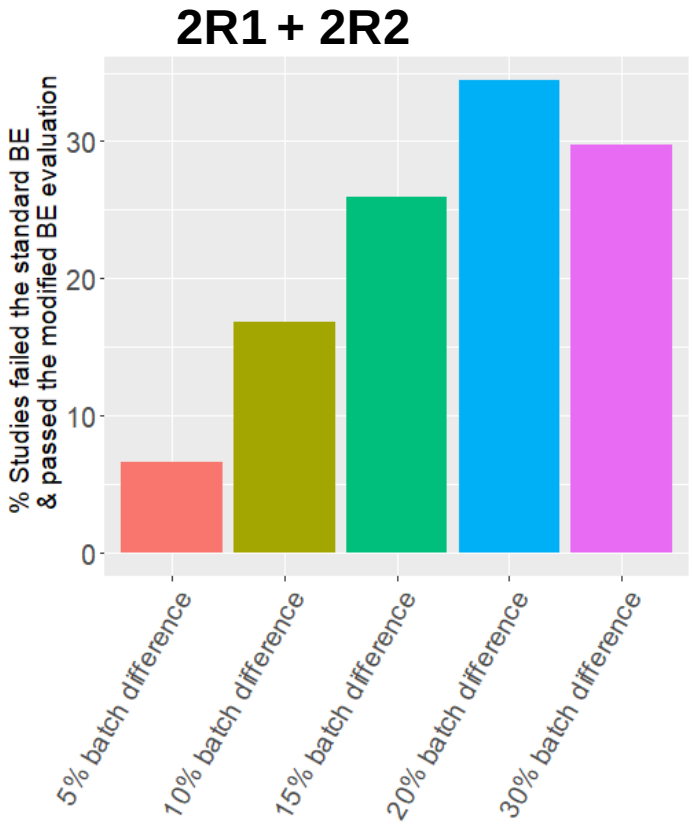
- T would pass BE to at least one batch of R or
- In the event T could not pass BE evaluation to either of the R batches, PK of the T will locate between PKs of the two batches of the R

Re-Analyses of Interrupted BE Studies that Do Not Pass the Standard NTI Evaluation with a Modified Approach

% of studies that fail the RSABE evaluation but pass the modified BE evaluation by incorporating batch as a fixed effect

Similar observations when "batch" used as a random effect





If a BE study cannot pass the standard RSABE evaluation without considering batch effect, adding "batch" as a fixed/random effect as a modified BE assessment provides a more accurate estimate of the T/R ratio

Analyses of Interrupted BE Studies that Fail RSABE Evaluation but Pass the Modified BE Evaluation

CV_{WR} =10%, "batch" as a fixed effect

Interruptions	BE Evaluation Results	5% batch difference	10% batch difference	15% batch difference	20% batch difference	30% batch difference
3R1 + 1R2	BE to both R1 and R2 if used alone	8%	0%	0%	0%	0%
	BE to only one batch of R (R1 or R2)	85%	74%	84%	94%	100%
	BE to neither of the R batches but with PK between R1 and R2	0%	2%	3%	2%	0%
	BE to neither of the R batches & with PK not between R1 and R2	8%	24%	13%	4%	0%
2R1 + 2R2	BE to both R1 and R2 if used alone	5%	1%	0	0	0
	BE to only one batch of R (R1 or R2)	83%	79%	89%	96%	91%
	BE to neither of the R batches but with PK between R1 and R2	0	4%	1%	0	8%
	BE to neither of the R batches & with PK not between R1 and R2	12%	17%	10%	4%	1%

- If only one batch of R were used without study interruption
  - In most of the cases, T would be BE to at least one batch of the R or its exposure would be between R batches
  - However, there could be cases that the T cannot pass either batch of the R, and the PK exposure of T is not between two R batches

Analyses of Interrupted BE Studies that Fail RSABE Evaluation but Pass the Modified BE Evaluation

CV_{WR} =10%, "batch" as a random effect

Interruptions	Compare with uninterrupted studies	5% batch difference	10% batch difference	15% batch difference	20% batch difference	30% batch difference
3R1 + 1R2	BE to both R1 and R2 if used alone	7%	0%	0%	0%	0%
	BE to only one batch of R (R1 or R2)	79%	74%	84%	93%	100%
	BE to neither of the R batches but with PK between R1 and R2	0%	2%	3%	2%	0%
	BE to neither of the R batches & with PK not between R1 and R2	14%	24%	13%	5%	0%
2R1 + 2R2	BE to both R1 and R2 if used alone	5%	1%	0	0	0
	BE to only one batch of R (R1 or R2)	83%	79%	89%	96%	91%
	BE to neither of the R batches but with PK between R1 and R2	0	4%	1%	0	8%
	BE to neither of the R batches & with PK not between R1 and R2	12%	17%	10%	4%	1%

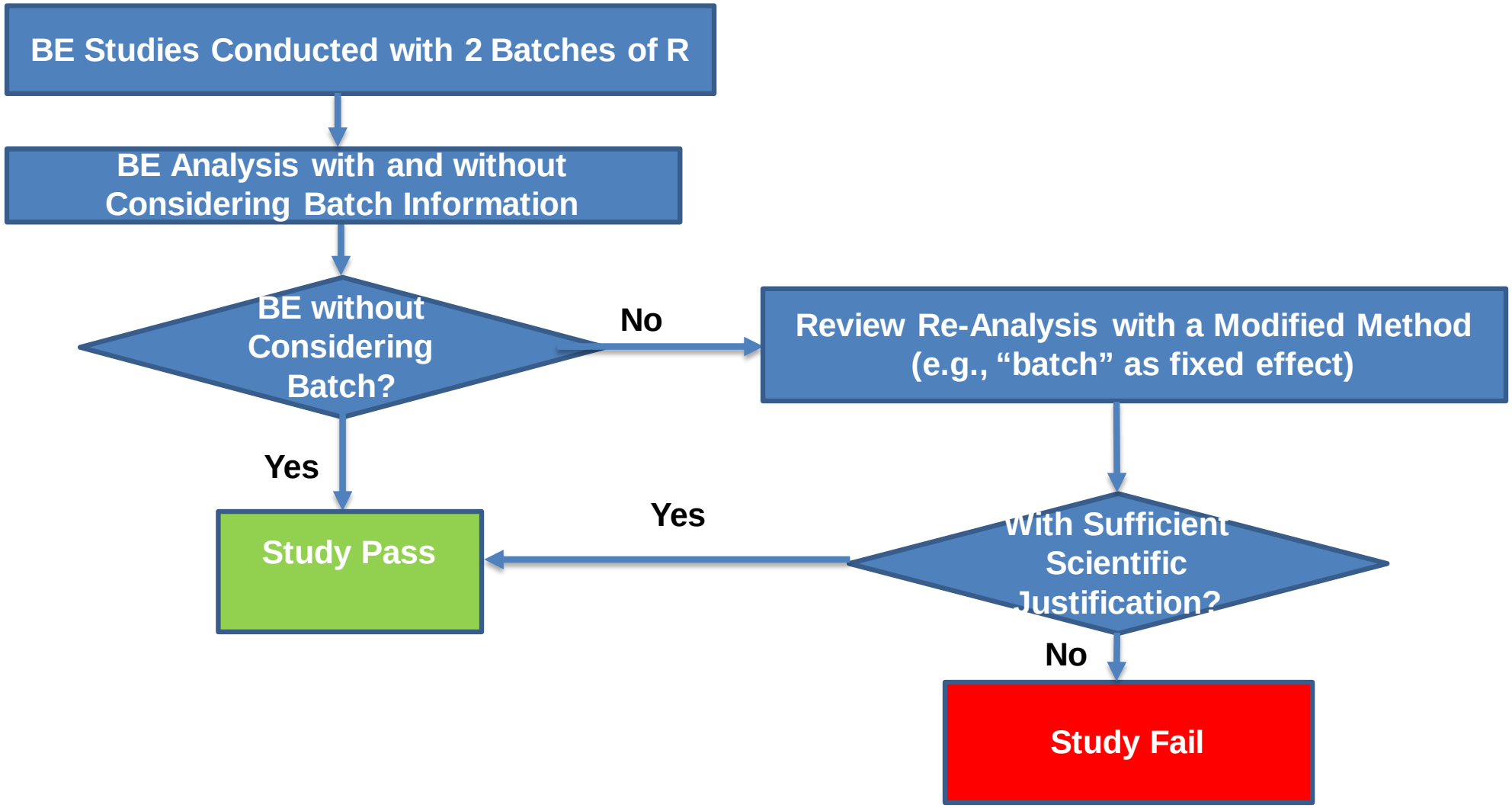
- Similar observations when "batch" is incorporated as a random effect.

Simulation Results

- For studies that are conducted with two R batches and pass BE evaluations with standard BE analyses (i.e., ABE or RSABE) without considering batch information, they would also pass BE if they were conducted without an interruption
- For studies that cannot pass a standard BE evaluation without considering batch information, using a modified approach such as incorporating “batch” as a fixed/random effect can potentially make the studies pass. Under this circumstance, whether the BE establishment with a modified BE approach is acceptable will be case specific

Proposed Framework Based on Simulation Results

Two (2)-way crossover BE studies and 4-way fully replicated crossover BE studies, NTI drugs



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
  - Additional information, e.g., analysis of formulations and manufacturing controls, may be needed as supportive data
  - Control of type one error to limit the risk of demonstrating BE for bioinequivalent products
- Industry can include science-based justifications for alternative approaches to data from interrupted studies
  - Pre-specify analysis plan before analyzing the data!
- Proposed framework can be discussed with FDA
  - Controlled Correspondences and other venues

Acknowledgements

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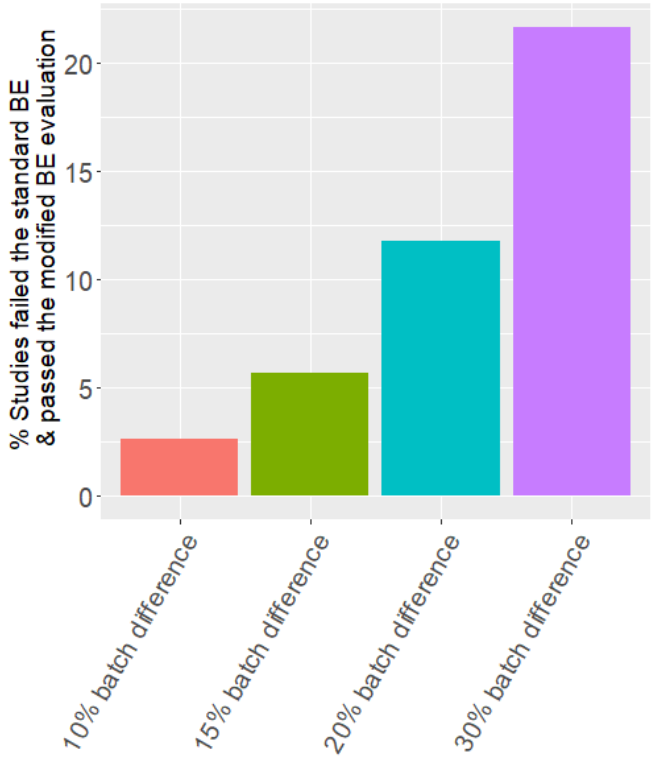
All ORS/OB project team members

Interrupted BE Studies that Do Not Pass the ABE Evaluation

% of studies that fail the ABE evaluation but pass a modified BE evaluation by incorporating batch information as a fixed effect



- If a BE study cannot pass the ABE evaluation with two batches of R, adding “batch” as a fixed effect can potentially provide a more accurate estimate of the T/R ratio and increase study power to demonstrate BE when batch differences are large

Analyses of Interrupted BE Studies that Fail ABE Evaluation but Pass the Modified BE Evaluation

Compare with uninterrupted studies	10% batch difference	15% batch difference	20% batch difference	30% batch difference
BE to both R1 and R2 if used alone	0%	0%	0%	0%
BE to only one batch of R (R1 or R2)	71%	82%	86%	87%
BE to neither of the R batches but with PK between R1 and R2	0%	0%	0%	2%
BE to neither of the R batches & with PK not between R1 and R2	29%	18%	14%	11%

- If only one batch of RLD were used without study interruption
  - In most of the cases, T would be BE to at least one batch of the R or its exposure would be between R batches
  - However, there could be cases that the T cannot pass either batch of the R, and the PK exposure of T is not between two R batches


FDA