Symposium 8:
Harmonization of the Bioequivalence Assessments for Narrow Therapeutic Index Drugs:
Delivering the Promise to Patients

U.S. FOOD & DRUG ADMINISTRATION

Data-driven & Science-based Recommendation on Harmonization of Bioequivalence Standards for Narrow Therapeutic Index Drugs

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Advancing Clinical Care through Pharmacology
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"Transformative Solutions:
Delivering on the Promise of Clinical Pharmacology for Patient Care"

Key Questions to Address for Harmonization

1. Tighten bioequivalence (BE) criteria by reference scaled approach or direct tightening?

2. If reference scaling is used, which regulatory constant is more appropriate?

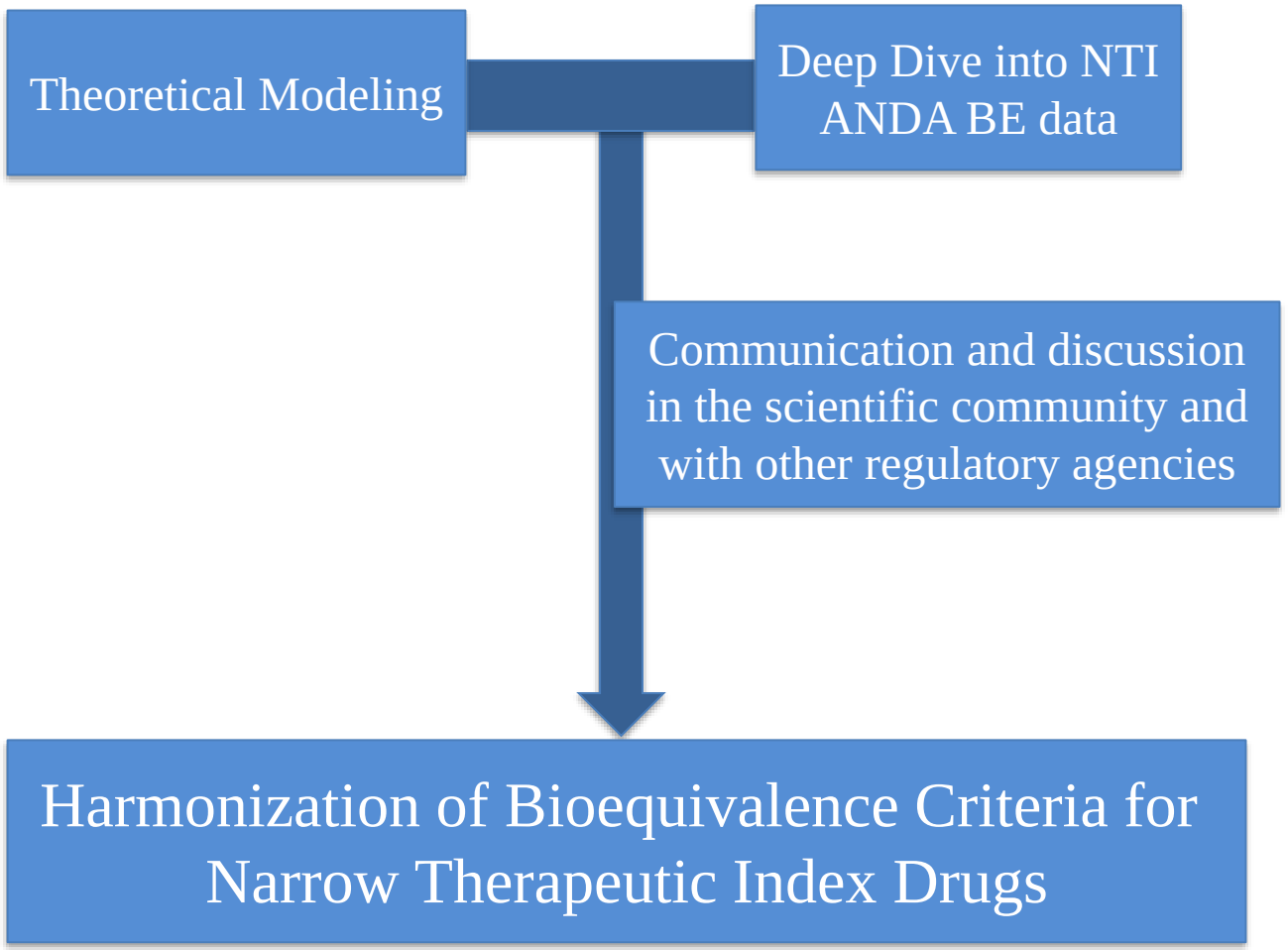
3. Capping BE limits at the lower within-subject variability (sWR) range?

4. Is point estimate constraint (PEC) (90.00-111.11%) necessary?

5. Apply alpha adjustment?

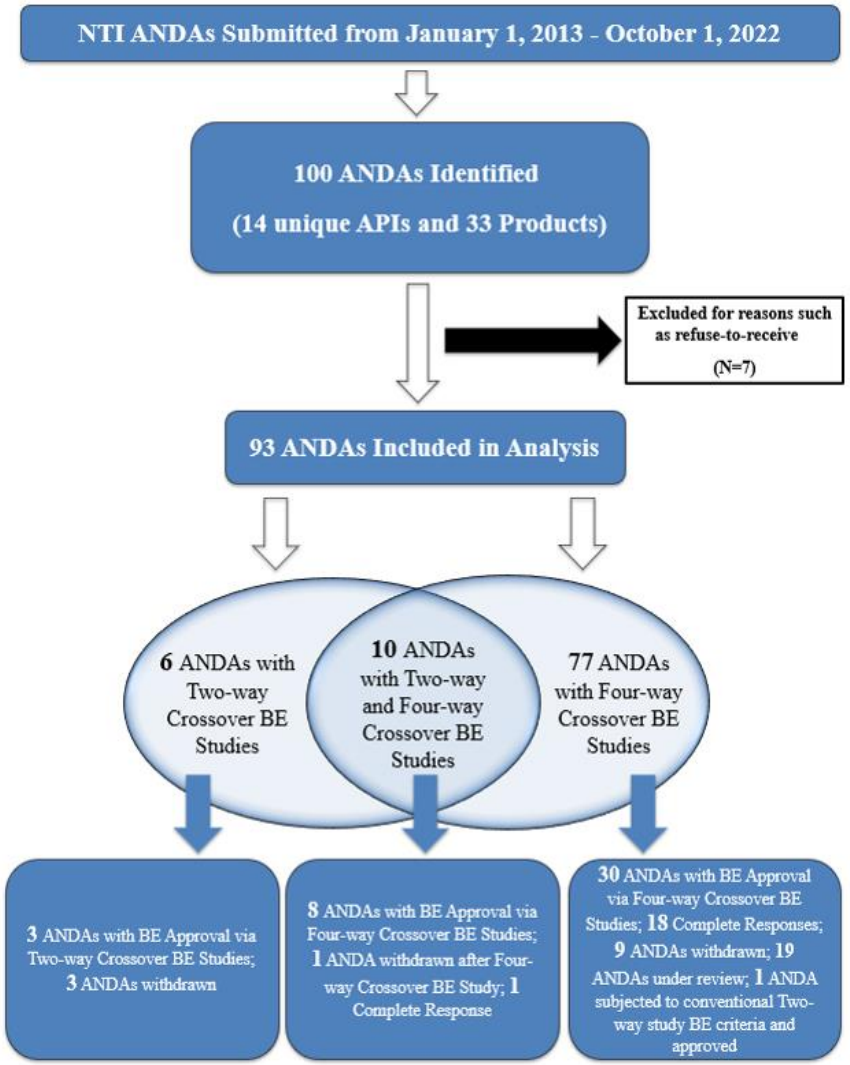
6. Is variability comparison necessary?

7. Tighter limits applied to AUC~~,~~ only on Cmax if it is of clinical significance to safety and efficacy?



NTI ANDA Analysis

Survey pharmacokinetic BE data of abbreviated new drug applications (ANDAs) of NTI drugs submitted to the FDA to identify the impact of FDA's current BE approach on generic NTI approval.

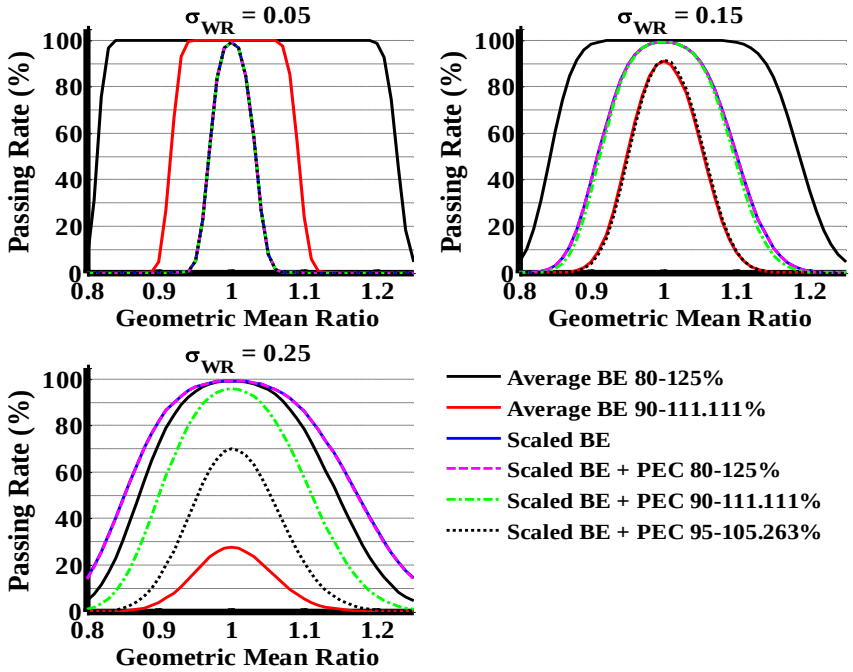


1. Analyze distribution of passed and failed four-way crossover BE studies
2. Investigate reasons for failure
3. Understand the sWR of different NTI drug products
4. Subject the BE data of ANDAs of NTI drug products received by the FDA to NTI BE criteria from different regulatory agencies, literature proposed, and newly modified criteria to compare the passing rate

Direct Tightening of BE Criteria vs Current FDA Reference Scaled Criteria

Simulation

$\sigma_{WT}=\sigma_{WR}$, n = 24 Δ = 1.11, σ_{W0} = 0.10



Current FDA Criteria: GMR=0.95, $\sigma_{WT}=\sigma_{WR}$, Power=0.8

σ_{WR}	Sample size
0.05	>1000
0.075	68
0.1	34
0.15	20
0.2	18
0.25	18
0.3	22

- When applying direct tightening of BE limits to 90-111.11%, low power of passing (unreasonably stringent) at medium within subject variability.
- For the current FDA reference scaled criteria: lower power of passing (unreasonably stringent) at extremely low σ_{WR} <0.05, suggesting the need for capping BE limits at lower σ_{WR}.

Wenlei Jiang[1], Fairouz Makhlouf, Donald J Schuirmann, Xinyuan Zhang, Nan Zheng, Dale Conner, Lawrence X Yu, Robert Lionberger
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Direct Tightening of BE Criteria vs Current FDA Reference Scaled Criteria

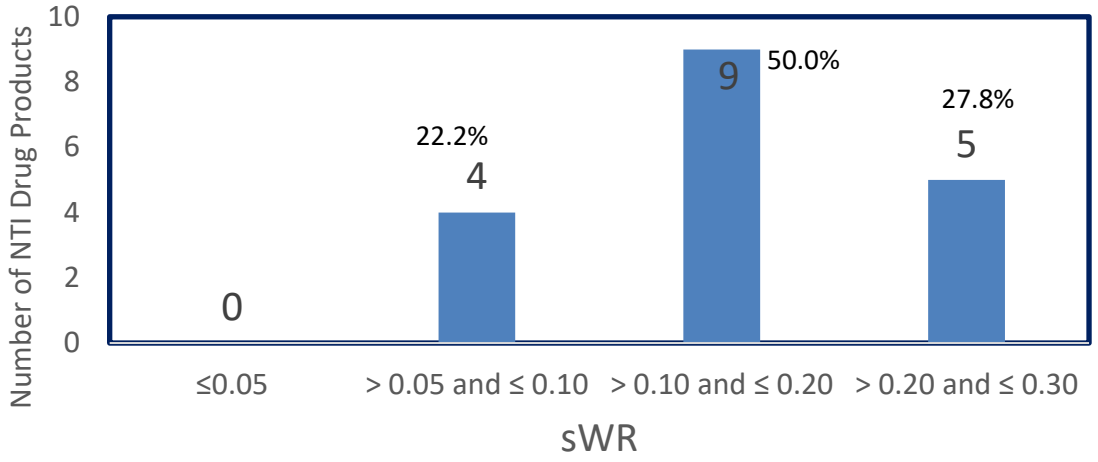
ANDA Analysis

- Current FDA criterion is more stringent at lower sWR range while EMA/Health Canada criteria fail more studies at moderate sWR range.
- Very few products have sWR ≤ 0.05

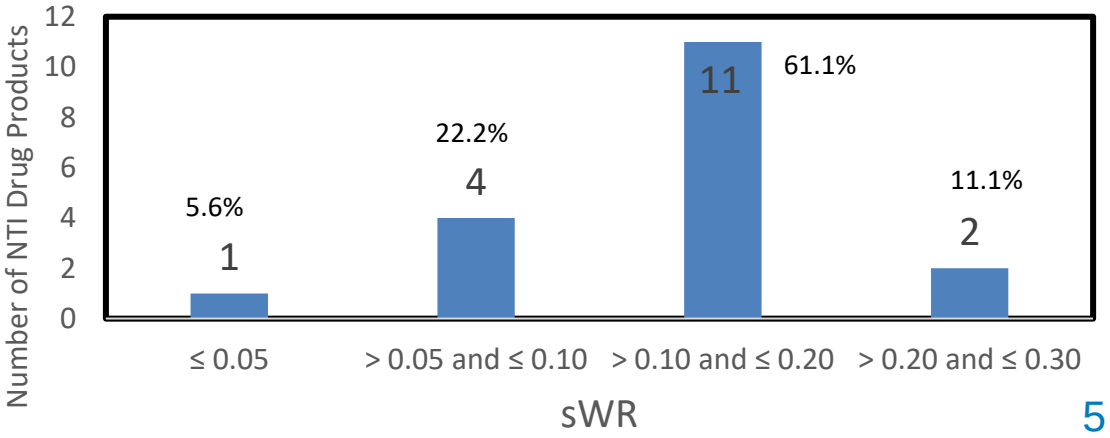
BE Criteria	Passing rates of PK Parameters (AUC_t and C_{max}) [N=352]			
	sWR ≤ 0.05	sWR > 0.05 and ≤ 0.10	sWR > 0.10 and ≤ 0.20	sWR > 0.20
	N=6	N=65	N=200	N=81
EMA	100.00%	96.92%	92.00%	75.31%
Health Canada	100.00%	96.92%	92.50%	77.78%
[Japan] PMDA	100.00%	100.00%	100.00%	98.77%
FDA	66.67%	84.62%	94.00%	98.77%

Passing rate is calculated as the percentage of PK parameters passing BE criteria over the total number of PK parameters.

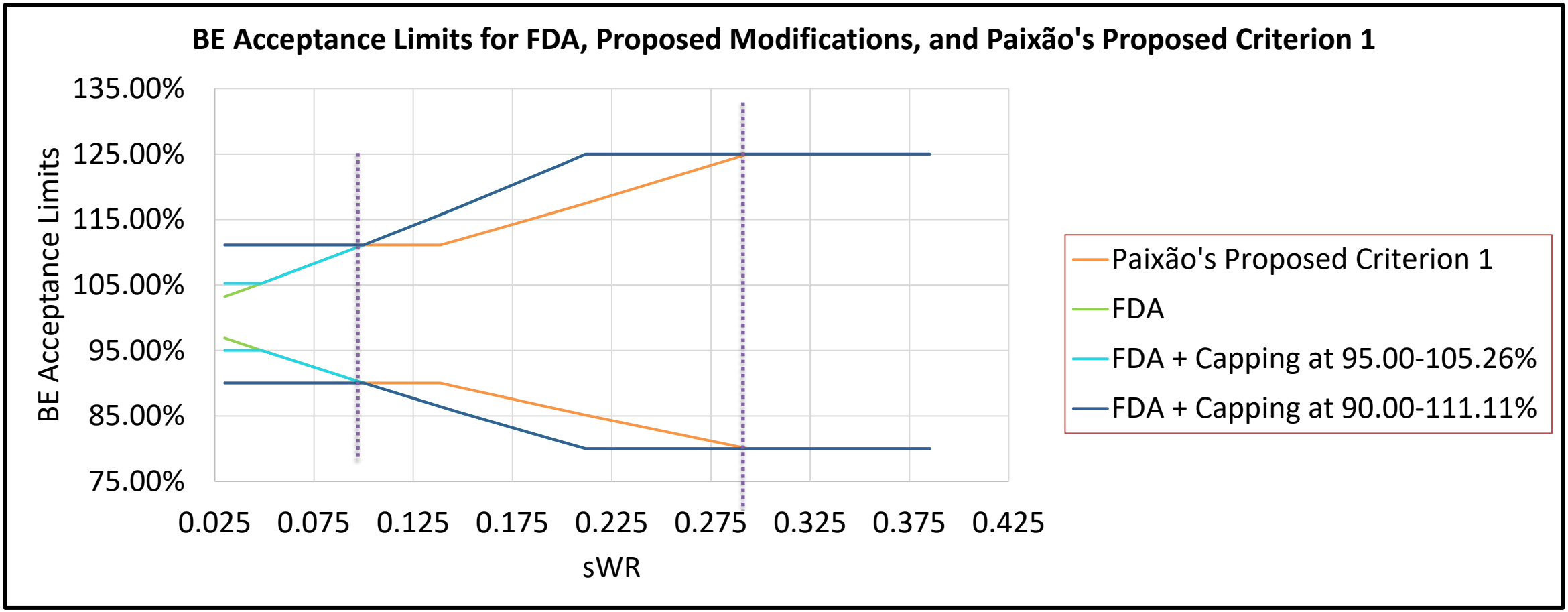
Distribution of Average sWRs for Cmax for NTI Products



Distribution of Average sWRs for AUC for NTI Products



Capping BE Limits at Lower sWR & Regulatory Constant



Paixão's proposed criterion 1	3-way partially replicated crossover	Reference scaled limits and capping at 90.00-111.11% if sWR $\leq$ 0.1386 (13.93% CV) and capping at 80.00-125.00% if sWR > 0.29356 (30% CV); Reference scaled limits only if 0.1386 < sWR $\leq$ 0.29356

FDA vs Paixao Regulatory Constant

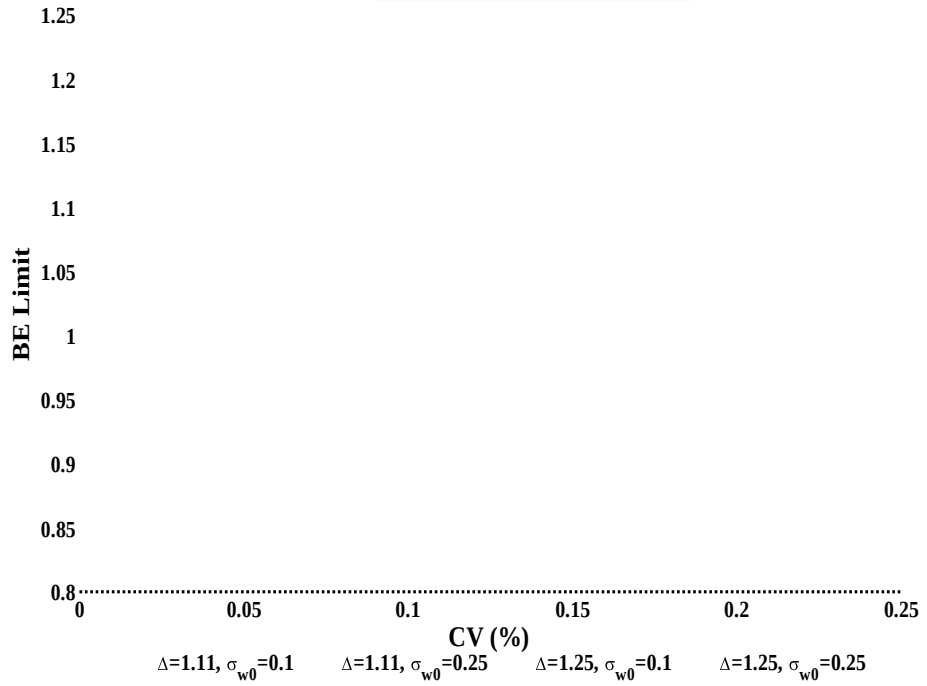
Current FDA:

- $k = \frac{ln(1.11111)}{\sigma_0=0.1} =$ 1.05361;

Paixao:

- $k = \frac{ln(1.25)}{\sigma_0=0.294} = 0.76$

Simulation



Red: $\Delta = 1.11$, $\sigma_{W0} = 0.10$; Blue: $\Delta = 1.11$, $\sigma_{W0} = 0.25$; Magenta; $\Delta = 1.25$, $\sigma_{W0} = 0.10$; and Black: $\Delta = 1.25$, $\sigma_{W0} = 0.25$. Note: 1.11 = 1/0.9.

- Δ=1.11 and σ_{W0}=0.10 were selected for further analysis because at σ_{W0}=0.10 (i.e., a common value to define small WSV), the implied BE limits coincide with other major health regulatory standards for NTI drugs.

ANDA Analysis

Majority of NTI drug products (>80%) have average sWR less than 0.21, supporting the use of FDA regulatory constant

CV_{WR}	Reference Scaled BE limits
5	94.87 - 105.41
10	90.02 - 111.08
15	85.35 - 117.02
20	81.17 - 123.20
>21.42	80.00 - 125.00

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Capping BE limits at 90.00-111.11% vs 95.00-105.00% + Apply Point Estimate Constraints + Regulatory Constant

ANDA Analysis + Simulation

Exploratory Analysis of Passing Rates of PK Parameters for Reference vs. Reference Products from Four-way Crossover Study Data

Method:

1. Generate R vs. R from a fully replicated design by removing test products
2. Create 200 randomized datasets by randomizing RR to TR or RT within each sequence of the fully replicated design.
3. Conduct SAS analysis using above PK datasets with and without alpha adjustment

R vs R passing rate should be close to 100%.

R vs R Passing Rate Range Simulation Results (200 Simulations)

BE Criteria	PK Parameters (AUC_t, AUC_i, and C_{max}) [N=463]			
	sWR ≤ 0.05 % Passed	sWR > 0.05 and ≤ 0.10 % Passed	sWR > 0.10 and ≤ 0.20 % Passed	sWR > 0.20 % Passed
	N=1	N=(83-93)	N=(260-276)	N=(103-113)
RSABE	0.00%	89.01-100.00%	95.49-100.00%	87.27-100.00%
RSABE + capping at 95.00-105.26% if sWR ≤ 0.048684	0.00%	89.01-100.00%	95.49-100.00%	87.27-100.00%
RSABE + capping at 90.00-111.11% if sWR ≤ 0.10	0.00-100.00%	94.38-100.00%	95.49-100.00%	87.27-100.00%
RSABE + capping at 90.00-111.11% if sWR ≤ 0.10 + PEC [0.9000, 1.1111]	0.00-100.00%	94.38-100.00%	95.49-100.00%	84.82-100.00%
Paixão's proposed criterion 1A (both AUC and Cmax)	0.00-100.00%	94.38-100.00%	83.33-96.97%	80.73-100.00%

- Capping BE limits at 90.00-111.11% is more reasonable than capping at 95.00-105.25%.
- Hypothetical R vs R GMR (sWR>0.20) can range from 0.77 to 1.34. Applying Point Estimate Constraint (PEC) 0.9000-1.1111 slightly decrease the study power when sWR >0.20 and may not be necessary.
- Paixão's regulatory constant may generate criteria too stringent when sWR > 0.10.

Alpha Adjustment

Simulation*

	FDA Threshold sWR=0.1 w/ alpha=0.0338	Paixao Threshold sWR=0.13 w/ alpha=0.042
Type 1 Error Rate Control	**Good**	**Good**
Power	**About the Same**	**About the Same**

With alpha adjustment, Type I error was controlled.

*Wanjie Sun, 6th GBHI Presentation

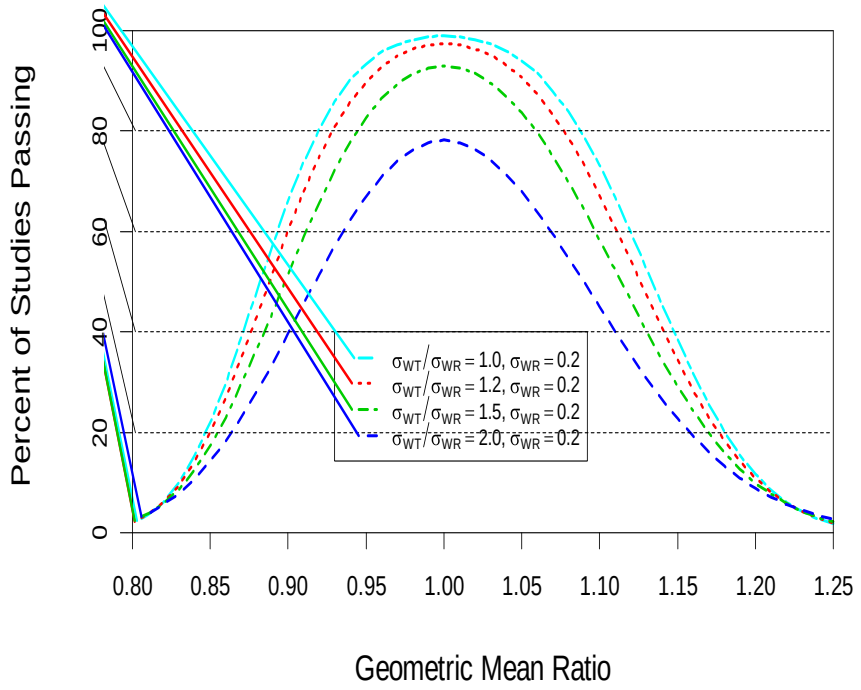
ANDA Analysis

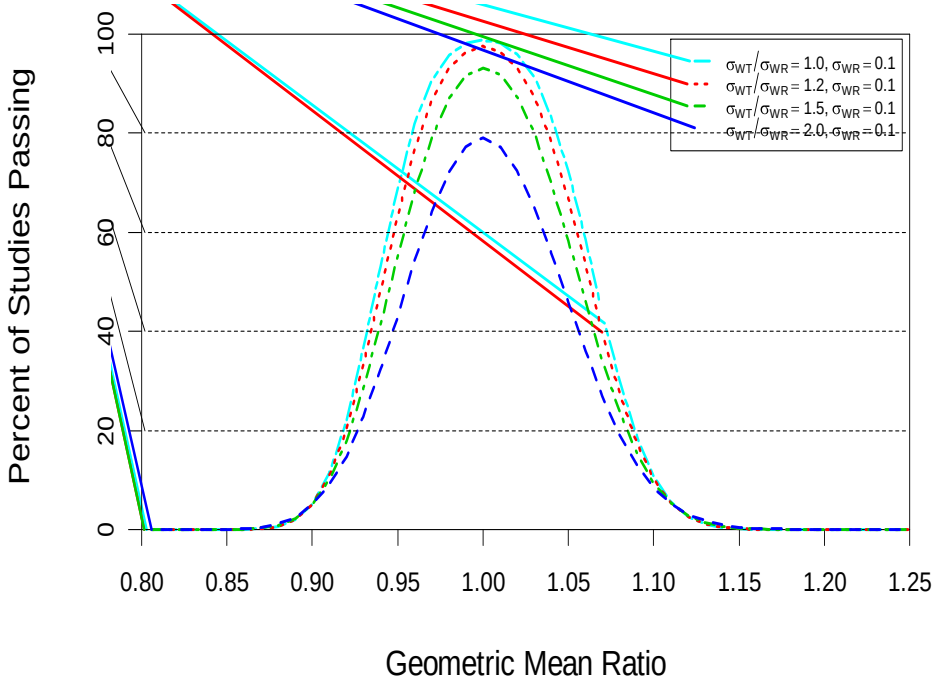
BE criteria	Passing rate %
RSABE	88.57
RSABE + Capping at 90.00-111.11% if sWR≤0.10	92
RSABE + Capping at 90.00-111.11% if sWR≤0.10 with alpha adjustment	90.17

When applying alpha adjustment,
the ANDA passing rates slightly decreased

Variability Comparison Necessary

Simulation





- Reference scaled BE limit alone is insufficient to fail BE studies with large differences (two-fold differences) in reference and test σWR when the GMR is close to 1. Therefore, variability comparison is necessary.

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Variability Comparison Necessary

ANDA Analysis

Type of Study Failure	IR Studies (90 total)	ER Studies (85 total)
Studies failed reference scaled limits only	15	3
Studies failed variability comparison only	0	1
Studies failed both variability comparison and reference scaled limits	0	1
Studies failed either reference or variability comparison in each product category	**15 (16.7%)**	**5 (5.9%)**

- No surveyed immediate release (IR) product ANDA failed variability comparison. A small number of ER product ANDA failed variability comparison. After reformulation, passed variability comparison criteria.
- Different IR or ER formulations do have different sWR. sWR of the same reference drug product does vary among different studies.
- Some IR formulation designs can still be complex, e.g., solid dispersion, nanosuspension, and others.

3-way Fully Replicated Crossover Study

Simulation

A **Three**-Period **Fully** Replicated Study Design

Sequence 1: T R T

Sequence 2: R T R

- Three-period fully replicated design permits variability comparison but requires **more subjects** and a **shorter study duration** than a four-period fully replicated design

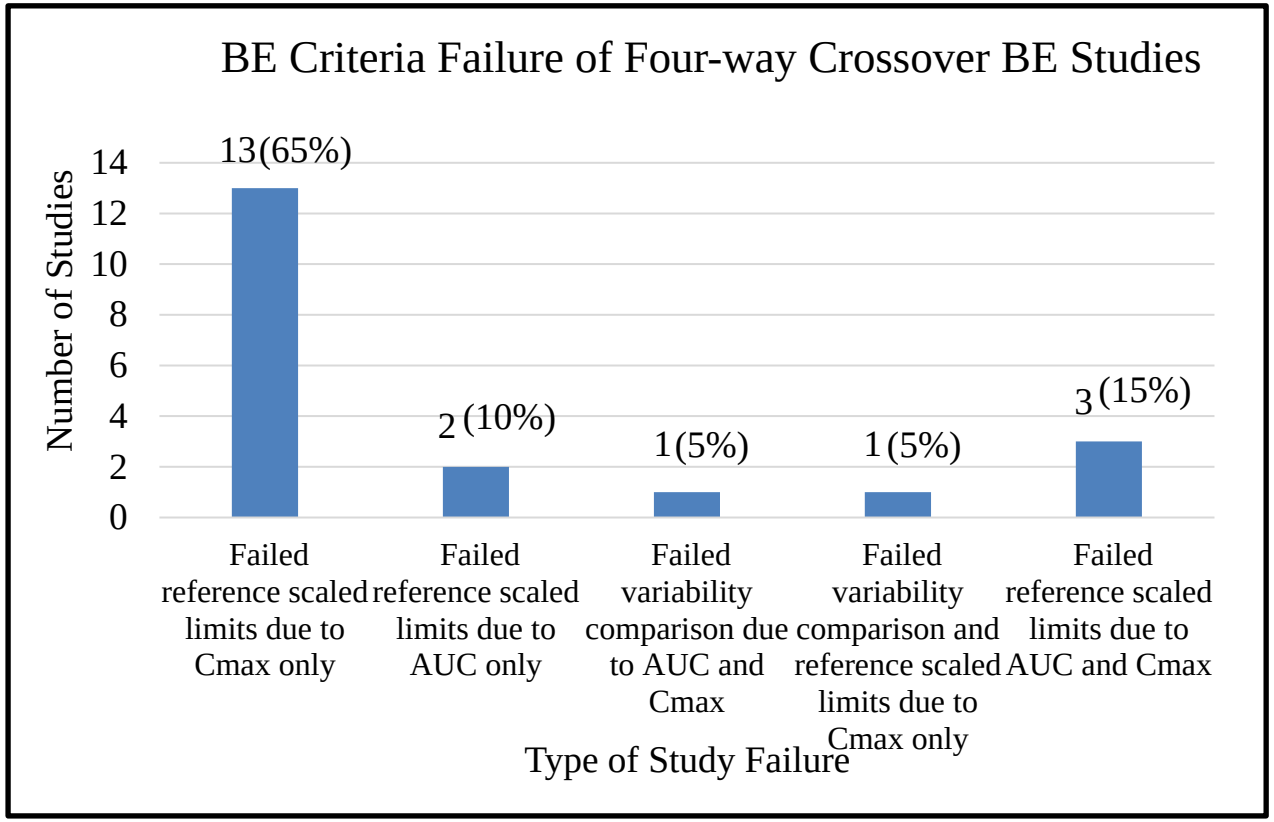
σ_{WR}	Sample size*	
	4-way	3-way
0.05	>1000	>1000
0.075	68	110
0.1	34	52
0.15	20	34
0.2	18	28
0.25	18	28
0.3	22	34

*Wanjie Sun, 6th GBHI Presentation

Tighter Limits Applied to both AUC and Cmax?

ANDA Analysis

- Tighter limits should be applied to both AUC and Cmax unless an applicant provides justification that Cmax is not important for safety, efficacy, or drug level monitoring.



Majority of ANDAs failed reference scaled BE limits due to Cmax.

Summary

Based on simulation and ANDA analysis:

- Reference scaled approach is preferred to tighten NTI BE limits. Tighter limits should be applied to both AUC and Cmax unless an applicant provides justification that Cmax is not important for safety, efficacy, or drug level monitoring.
- Variability comparison is generally considered necessary to prevent significantly higher test variability than that of the reference. Either fully-replicated four-way crossover study or three-way crossover study can be utilized to obtain test and reference variability.
- Current FDA regulatory constant and capping BE limits at 90.00-111.11% seem reasonable.
- Alpha adjustment can control for Type I error.
- PEC (90.00-111.11%) may not be necessary.

Further communication and discussion in the scientific community and with other regulatory agencies to reach scientific consensus

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Thank you!