Deep Dive into Generic Drug Applications to Seek Data-Driven Harmonization of Bioequivalence Criteria for Narrow Therapeutic Index Drugs

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Regulatory Agencies' and Paixão's Proposed NTI BE Criteria

Regulatory Agency/ Proposed Criteria	Study Design	BE Limits for AUC	BE Limits for C_{max}	Variability Comparison
European Medicines Agency (EMA)*	2-way crossover	ABE limits of 90.00-111.11% (AUC_t)	ABE limits of 80.00-125.00% (or 90.00-111.11% if C_{max} is important for safety, efficacy, or drug level monitoring)	Not applied
Health Canada	2-way crossover	ABE limits of 90.0-112.0% (AUC_t)	ABE limits of 80.0-125.0%	Not applied
[Japan] Pharmaceuticals and Medical Devices Agency (PMDA)**	2-way crossover	ABE limits of 0.80-1.25 (80-125%) (AUC_t)	Same as BE Limits for AUC	Not applied
U.S. Food and Drug Administration*** (FDA), 2012 Implemented	4-way fully replicated crossover	RS limits and ABE limits of 80.00-125.00% (AUC_t and AUC_i)	Same as BE limits for AUC	Applied
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	Same as current EMA	Not applied
Paixão's proposed criterion 2	3-way partially replicated crossover	Criteria 1 + Apply T/R GMR constraint within 90.00-111.11%	Same as current EMA	Not applied

*Association of Southeast Asian Nations (ASEAN), [Australia] Therapeutic Goods Administration (TGA), [New Zealand] Medicines and Medical Devices Safety Authority (MEDSAFE), and South African Health Products Regulatory Authority (SAHPRA) utilize EMA's BE guidelines

** Applicants are strongly encouraged to use the face-to-face consultancy service of PMDA to discuss their intended BE approach.

***China National Medical Products Administration (NMPA) has the same recommendation as FDA.

Note: Variability comparison criterion: the upper limit of the 90% confidence interval of the ratio of the within-subject standard deviation of the test to reference product is less than or equal to 2.5 (upper sWT/sWR 90% CI $\leq$ 2.5). Both AUC and C_{max} are assessed when this criterion is applied.

Key Questions to Address for Harmonization

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

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

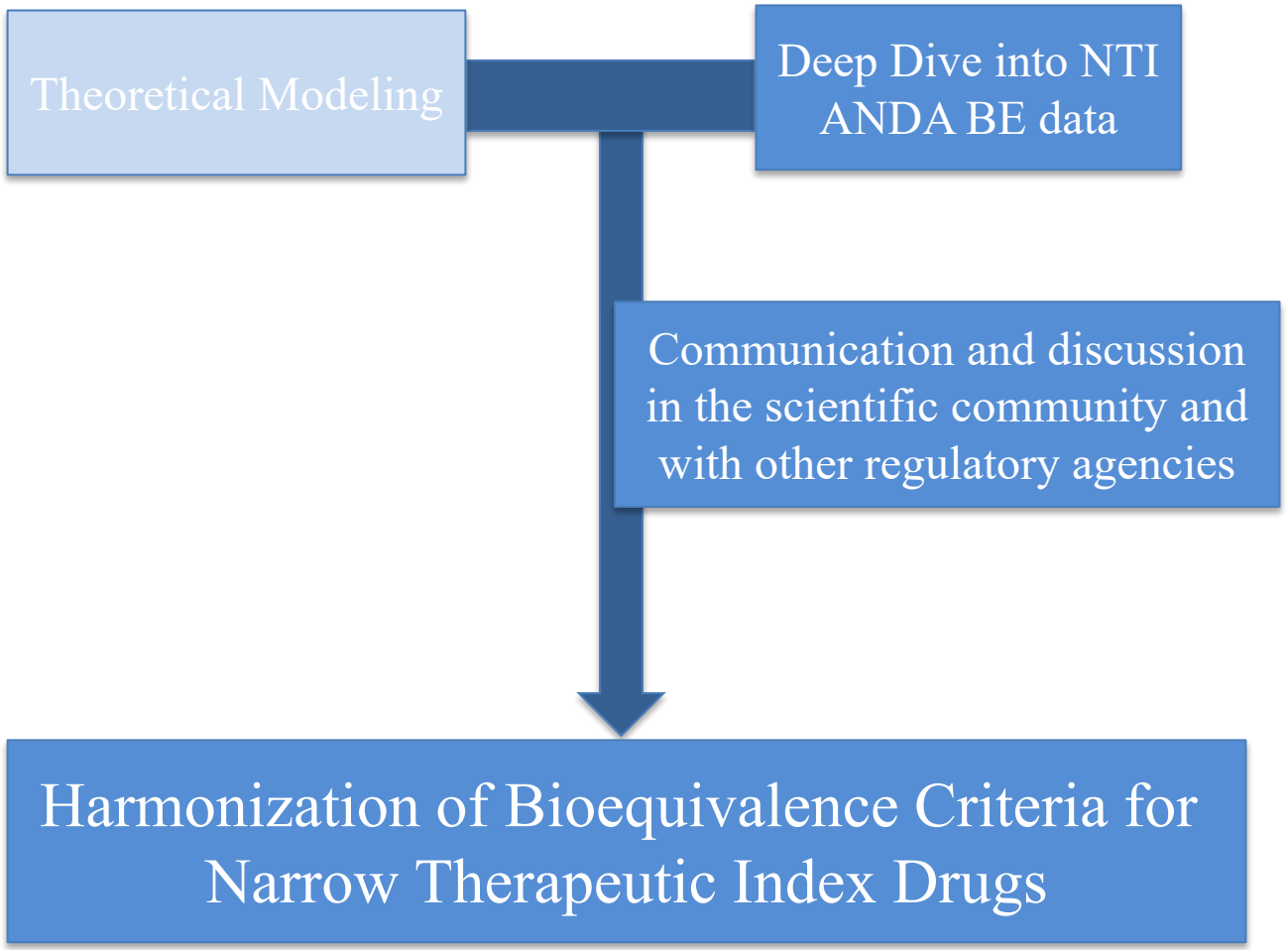
3. Is variability comparison necessary?

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

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

6. Capping BE limits at the lower sWR range?

7. Apply alpha adjustment?

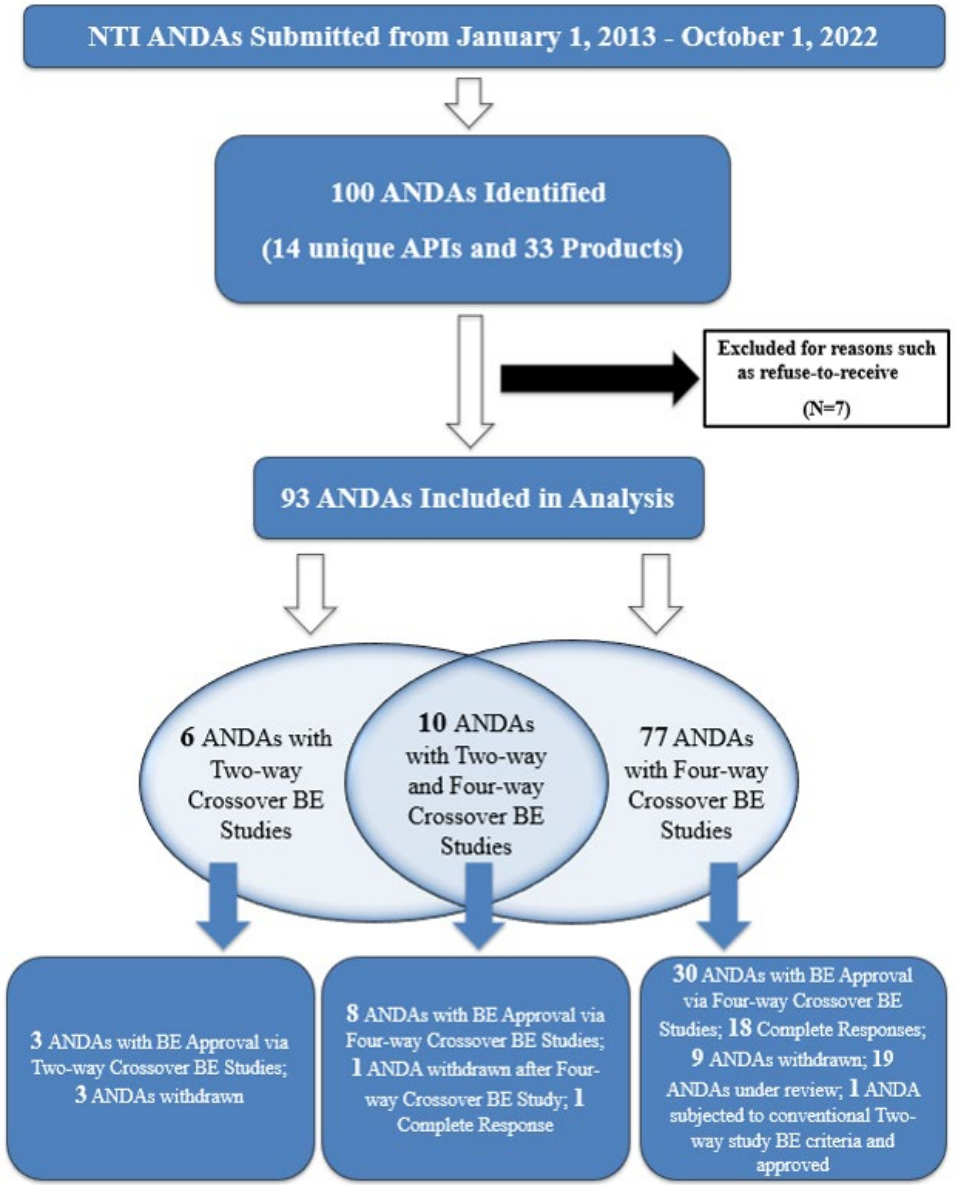


Objectives

- Survey pharmacokinetic BE data of abbreviated new drug applications (ANDAs) of NTI drugs submitted to the FDA with initial submission dates between January 1, 2013 and October 1, 2022 to identify the impact of FDA's current BE approach on generic NTI approval.
- Subject the BE data of abbreviated new drug applications (ANDAs) of NTI drug products received by the FDA to NTI BE criteria from different regulatory agencies, literature proposed and modified criteria, to compare the passing rate
- Understand the strengths and limitations of each criterion, seeking data-driven harmonization of NTI BE criteria

Methods

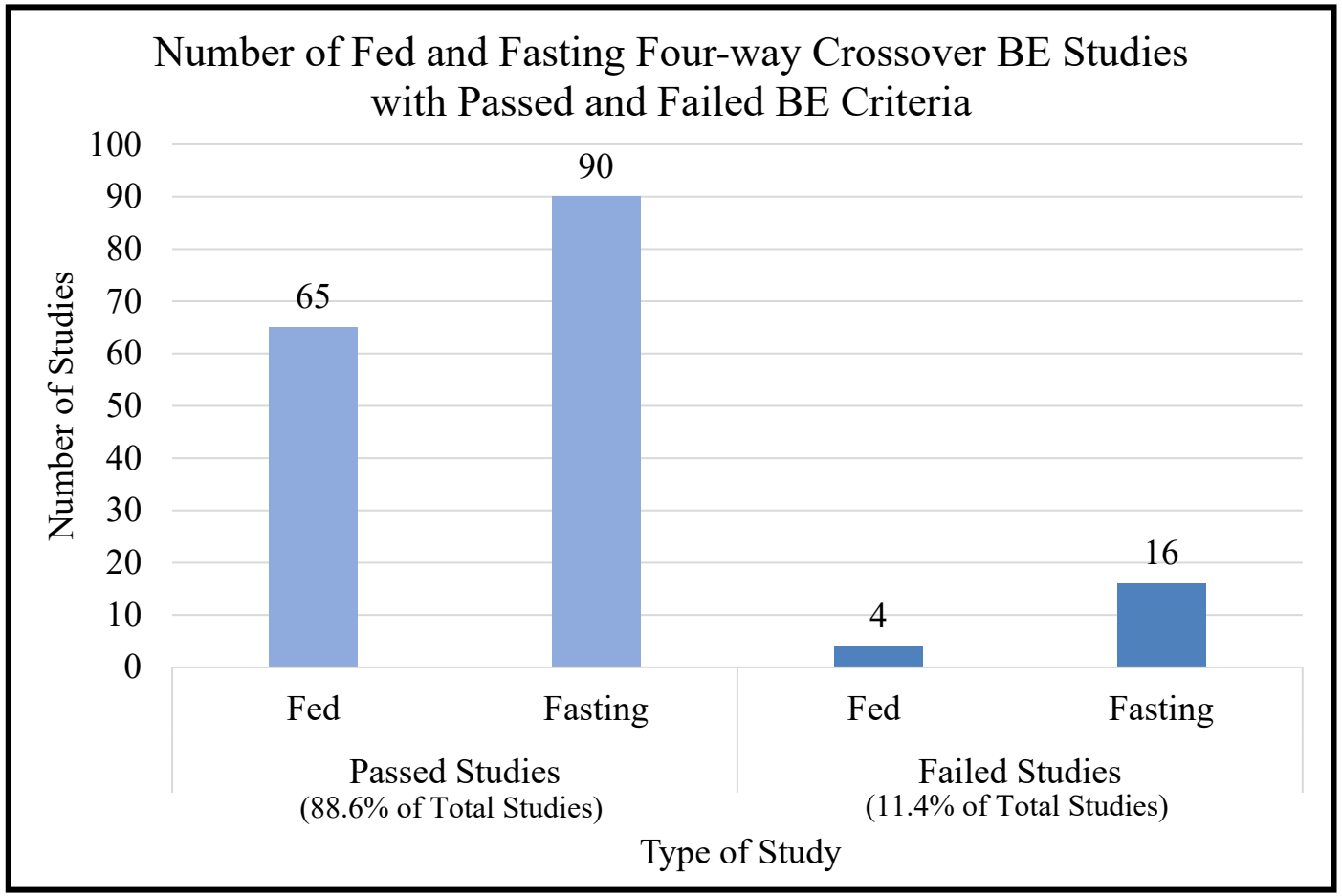
Survey pharmacokinetic BE data of ANDAs of NTI drugs submitted to the FDA to identify the impact of FDA's current BE approach on generic NTI approval.



1. Analyze the relationship of NTI application approval basis with PSG publication or revision date
2. Compare EMA and FDA's designation on NTI drugs and published PSGs
3. Analyze distribution of passed and failed four-way crossover BE studies
4. Investigate reasons for failure
5. Understand the within-subject variability (sWR) of different NTI drug products and sample size estimation in submitted ANDAs
6. Subject the BE data of abbreviated new drug applications (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

Four-way Crossover BE Study Distribution

- There are 33 product-specific guidances for NTI drug products recommending four-way crossover studies with 2012 NTI BE criteria.
- Three NTI ANDAs were approved in or after 2013, via conventional two-way crossover studies and BE criteria, prior to their PSG updates.
- 175 four-way crossover BE studies were submitted (155 passed and 20 failed).

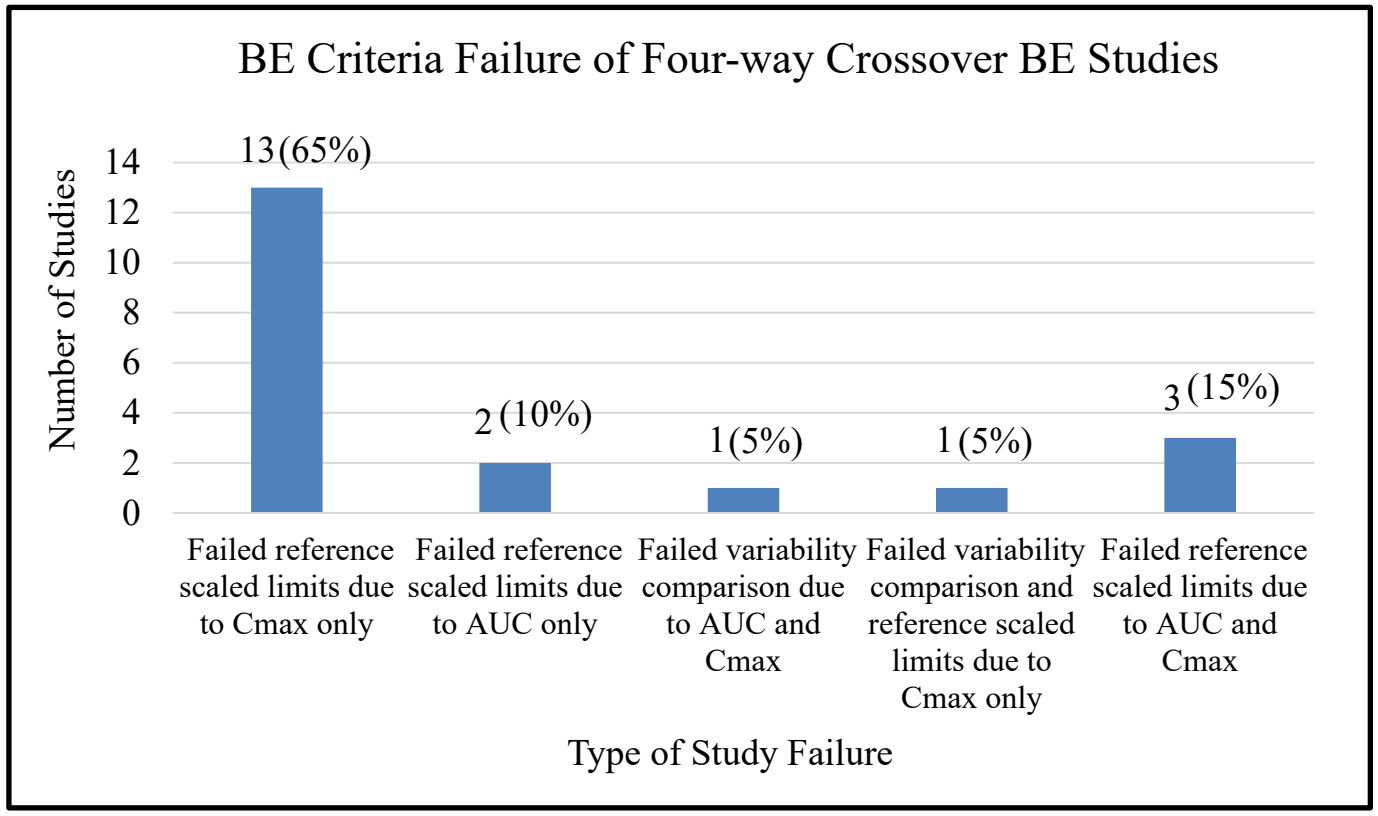


Among the failed fed studies, two IR products failed both fasting and fed while two ER products failed the fed study only.

Distribution of Failed Four-way Crossover Studies

BE Criteria Failure Distribution Among Solid Oral Immediate Release (IR) and Extended Release (ER) Products

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%)**



Reference Within-Subject Variability of Example NTI Drug Products

Active Pharmaceutical Ingredient (API)	NTI Drug Product [Immediate-release (IR) and Extended-release (ER)] (reference listed drug or reference standard #)	sWR for AUC (Ave ± SD)	sWR for C_{max} (Ave ± SD)	No. of Subjects* (Ave ± SD)	T/R Potency Ratio (Ave ± SD)
Carbamazepine	Carbamazepine IR Tablet (016608)	0.11 ± 0.07	0.10 ± 0.04	41 ± 9	1.00 ± 0.02
	Carbamazepine IR Suspension (018927)	0.06 ± 0	0.11 ± 0.03	35 ± 7	1.01 ± 0.03
	Carbamazepine ER Tablet (020234)	0.19 ± 0.06	0.18 ± 0.06	47 ± 16	1.00 ± 0.02
Cyclosporine	Cyclosporine IR Capsule (050715)	0.13 ± 0.02	0.22 ± 0.08	52 ± 12	1.02 ± 0.01
Digoxin	Digoxin IR Tablet (020405)	0.11 ± 0.03	0.23 ± 0.03	55 ± 12	1.02 ± 0.03
Divalproex Sodium	Divalproex Sodium DR Pellet Capsule (019680)	0.06 ± 0.01	0.06 ± 0.03	30 ± 6	1.02 ± 0.03
	Divalproex Sodium ER Tablet (021168)	0.23 ± 0.09	0.19 ± 0.06	43 ± 8	1.01 ± 0.01
Everolimus	Everolimus IR Tablet (021560)	0.15 ± 0.03	0.18 ± 0.04	46 ± 19	0.99 ± 0.02
Levothyroxine Sodium	Levothyroxine Sodium IR Tablet (021116; 021210; 021301; 021342; 021402)	0.16 ± 0.06	0.14 ± 0.05	61 ± 36	1.01 ± 0.02
Phenytoin Sodium	Phenytoin Sodium ER Capsule (084349)	0.15 ± 0.08	0.14 ± 0.06	41 ± 16	1.00 ± 0.02
Sirolimus	Sirolimus IR Tablet (021110)	0.17 ± 0.03	0.17 ± 0.06	40 ± 7	1.01 ± 0.01
Tacrolimus	Tacrolimus ER Capsule (204096)	0.17 ± 0.04	0.21 ± 0.04	43 ± 8	0.97 ± 0.03
	Tacrolimus IR Capsule (050708)	0.17 ± 0.03	0.21 ± 0.04	43 ± 13	1.00 ± 0.03
Theophylline	Theophylline ER Tablet (090430; 086998; 085328)	0.11 ± 0.03	0.11 ± 0.03	32 ± 7	1.00 ± 0.01

- Average sWR≤0.1: 23.5%
  0.1<sWR≤0.21: 58.8-64.7%
  sWR>0.21: 11.8-17.6%
- Different dosage forms of the same API have different average sWR.
- sWR of the same reference drug product does vary among different studies.
- Average T/R potency ratio close to 1
- Sample size estimation tend to be conservative

*Number of subjects included in PK analysis

Note: The average and standard deviation values were obtained from at least four studies and two batches. The specific numbers were removed to not disclose any proprietary information.

Subject NTI ANDAs with Four-way Crossover Study Data to Different BE Criteria

- 86 NTI ANDAs with four-way fully replicated crossover studies (n=175) submitted to the FDA were subjected to a total of 22 BE criteria (5 regulatory agencies, 2 literature proposed, and 15 modified criteria) to determine the passing rate

- Modifications were made to current Paixao and FDA's criteria (15 proposed criteria)

1. Apply Piaxao's criteria 1 and 2 to both AUC and Cmax

Combination of the following modifications:

1. Remove variability comparison
2. Cap the reference scaled limits at the lower end of sWR ranges Capping at 95.00-105.26% if sWR $\leq$ 0.048684 vs. capping at 90.00-111.11% if sWR $\leq$ 0.10 (W/ and W/O Alpha Adjustment)
3. Apply reference scaled ABE to AUC only
4. Apply point estimate constraint (PEC) within 90.00-111.11% to both AUC and Cmax

Passing Rates of Four-way Crossover Studies Based on Different Agency Criteria

Passing rates: EMA < Health Canada < U.S. FDA/[China] NMPA < [Japan] PMDA

Current EMA criterion is the most stringent!

Regulatory Agency	Passing Rate (% of Studies Passed)
European Medicines Agency (EMA)	78.29%
Health Canada	80.00%
[Japan] Pharmaceuticals and Medical Devices Agency (PMDA)	99.43%
U.S Food and Drug Administration (FDA)	88.57%

Passing Rates of PK Parameters for Test vs. Reference Products Based on Different Agency Criteria

- Current FDA criterion is more stringent at lower sWR range while EMA/Health Canada criteria fail more studies at moderate sWR range.

BE Criteria	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%

Note #1: Passing rate is calculated as the percentage of PK parameters passing BE criteria over the total number of PK parameters.

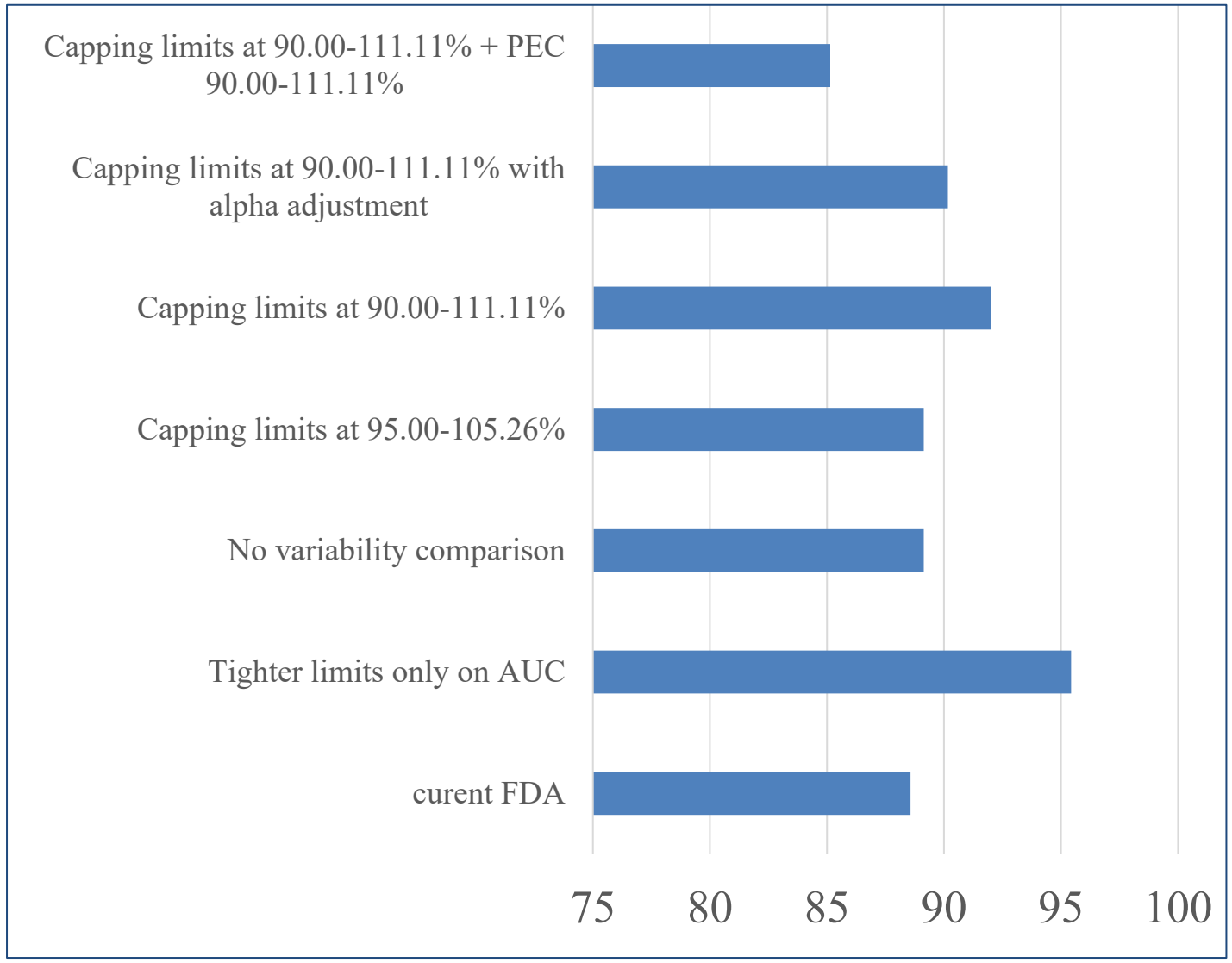
Passing Rates of Studies Based on Paixão's Proposed Criteria and Further Modifications

- Similar study passing rate when applying Paixao's proposed criteria 1, 2, and current FDA criterion
- When applying Paixao's proposed criterion 1 & 2 on both AUC and Cmax, passing rates dropped more than 10%.

Proposed Criteria	BE Limits for AUC*	BE Limits for C_{max}	Passing Rate (% of Studies Passed)	
			AUC_t, AUC_i, and C_{max}	AUC_t and C_{max}
Paixão's proposed criterion 1	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	ABE limits of 80.00-125.00% (Apply reference scaled limits to C_{max} only if clinically relevant)	89.71%	90.86%
Paixão's proposed criterion 2	Same as above +Apply T/R GMR constraint within 90.00-111.11%	Same as above	88.00%	89.71%
Paixão's proposed criterion 1A (proposed modification)	Same as Paixao proposed criterion 1	Same as BE limits for AUC	78.29%	79.43%
Paixão's proposed criterion 2A (proposed modification)	Same as Paixao proposed criterion 2	Same as BE limits for AUC	77.14%	78.29%

Without alpha adjustment

Passing Rates of Studies Based on Proposed Modifications to FDA NTI BE Criteria



Passing Rates of PK Parameters (AUC_t and C_{max}) for Test vs. Reference Products from 4-way Crossover Study Data

- Capping at 95.00-105.26% increases the passing rate: 66.67% to 83.33% with studies sWR≤ 0.05
- Capping at 90.00-111.11% increases the passing rate: 66.67% to 83.33% with studies sWR≤ 0.05, 84.62% to 92.31% with studies sWR>0.05 and ≤ 0.10
- When applying Paixao proposed criteria 1 and 2, above 90% passing rates across all sWR ranges
- When applying Paixao proposed criteria 1 and 2 to both AUC and Cmax, significant drop in passing rates for studies with sWR>0.10 (14%, 6%)
- Applying PEC 90.00-111.11% to FDA modified criteria significantly decreased the passing rate (~10%) for studies with sWR>0.20

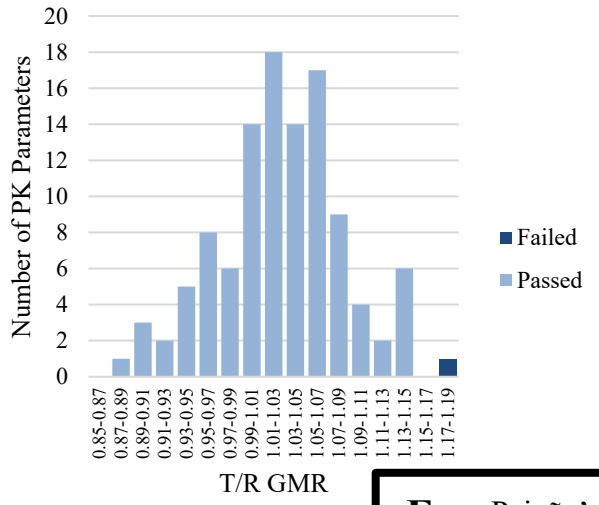
	PK Parameters (AUC_t and C_{max}) [N=352 without alpha adjustment]			
	sWR ≤ 0.05	sWR > 0.05 and ≤ 0.10	sWR > 0.10 and ≤ 0.20	sWR > 0.20
BE Criteria	N=6	N=65	N=200	N=81
RSABE + capping at 95.00-105.26% if sWR ≤ 0.048684	83.33%	84.62%	94.00%	98.77%
RSABE + capping at 95.00-105.26% if sWR ≤ 0.048684 + PEC [0.9000, 1.1111]	83.33%	84.62%	91.50%	88.89%
RSABE + capping at 90.00-111.11% if sWR ≤ 0.10	83.33%	92.31%	94.00%	98.77%
RSABE + capping at 90.00-111.11% if sWR ≤ 0.10 + PEC [0.9000, 1.1111]	83.33%	92.31%	91.50%	88.89%
Paixão's proposed criterion 1	100.00%	96.92%	94.50%	96.30%
Paixão's proposed criterion 2	100.00%	96.92%	94.50%	93.83%
Paixão's proposed criterion 1A (proposed modification)	100.00%	95.38%	80.50%	90.12%
Paixão's proposed criterion 2A (proposed modification)	100.00%	95.38%	80.50%	86.42%

NTI ANDA BE Data Evaluated Against Different BE Criteria: Investigate Passed and Failed PK Parameters in Relationship to T/R GMR

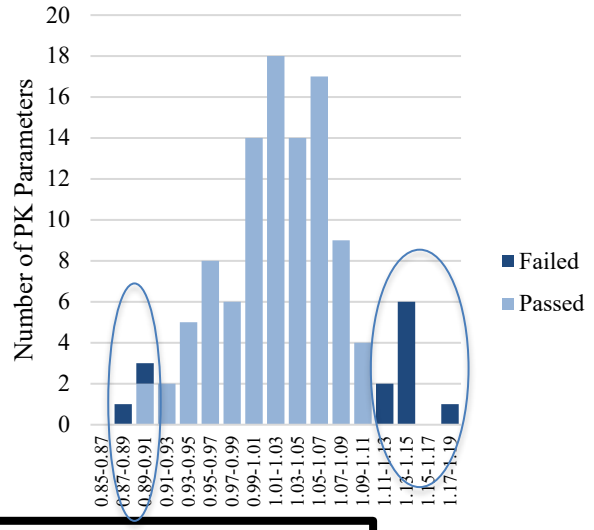
- When sWR $\leq$ 0.05 for surveyed studies, T/R GMR very close to 1 (0.95-1.03).
- Overall, studies with GMR far from 1 failed current FDA, modified FDA criteria, and Paixao criteria.
- Applying PEC 90.00-111.11% has no impact on studies with sWR$\leq$ 0.10 but significantly decreased the passing rate of studies with sWR > 0.20 (failed the GMR outside 90-111.11%).

T/R GMR Distribution for PK Parameters with sWR > 0.20 for FDA, Proposed Modifications, and Paixão's Proposed Criteria

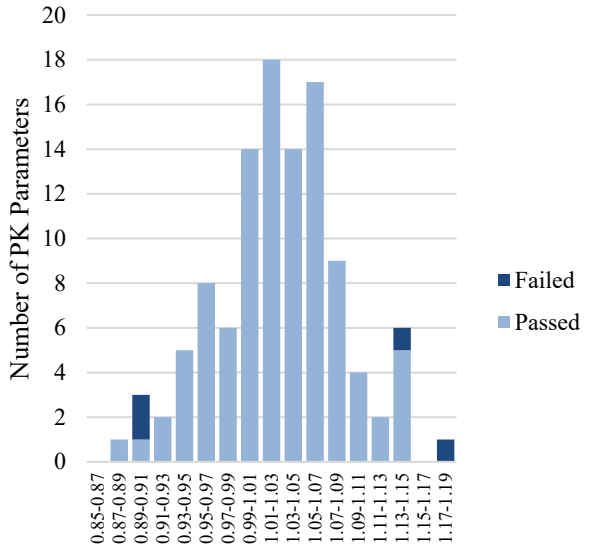
A FDA, FDA + Capping at 95.00-105.26% if sWR ≤ 0.048684, & FDA + Capping at 90.00-111.11% if sWR ≤ 0.10



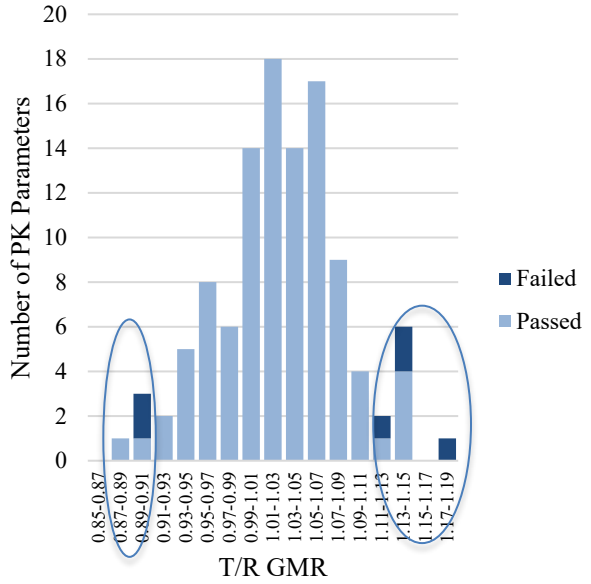
B FDA + Capping at 90.00-111.11% if sWR ≤ 0.10 + PEC



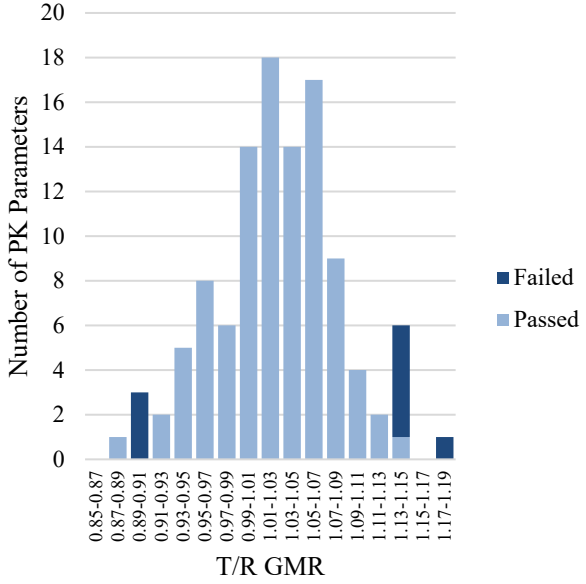
C Paixão's Proposed Criterion 1



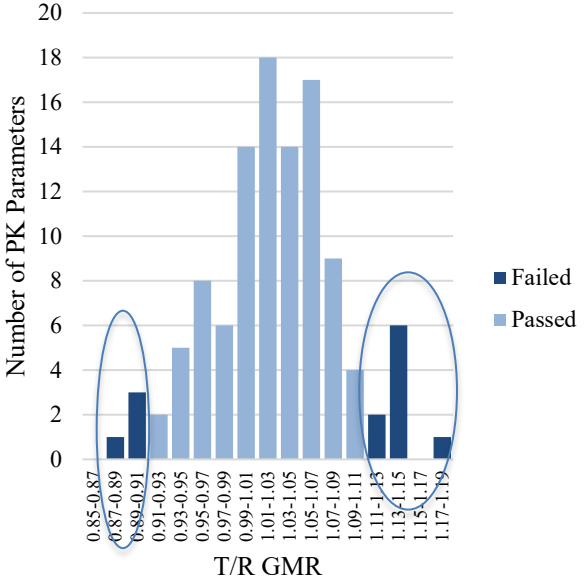
D Paixão's Proposed Criterion 2



E Paixão's Proposed Criterion 1A



F Paixão's Proposed Criterion 2A



n = 110

n = Number of PK parameters (includes AUC_t, AUC_i, and C_{max})

Without alpha adjustment

- With PEC, studies with sWR>0.20 and GMR around 0.89-0.91, 1.11-1.13 failed (both modified FDA criteria & Paixao 2, 2A)

NTI ANDA BE Data Extracted for Exploratory Analysis of Hypothetical Reference vs. Reference Products

Method:

1. Generate R vs. R from a fully replicated design by removing test products
2. Create five 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

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

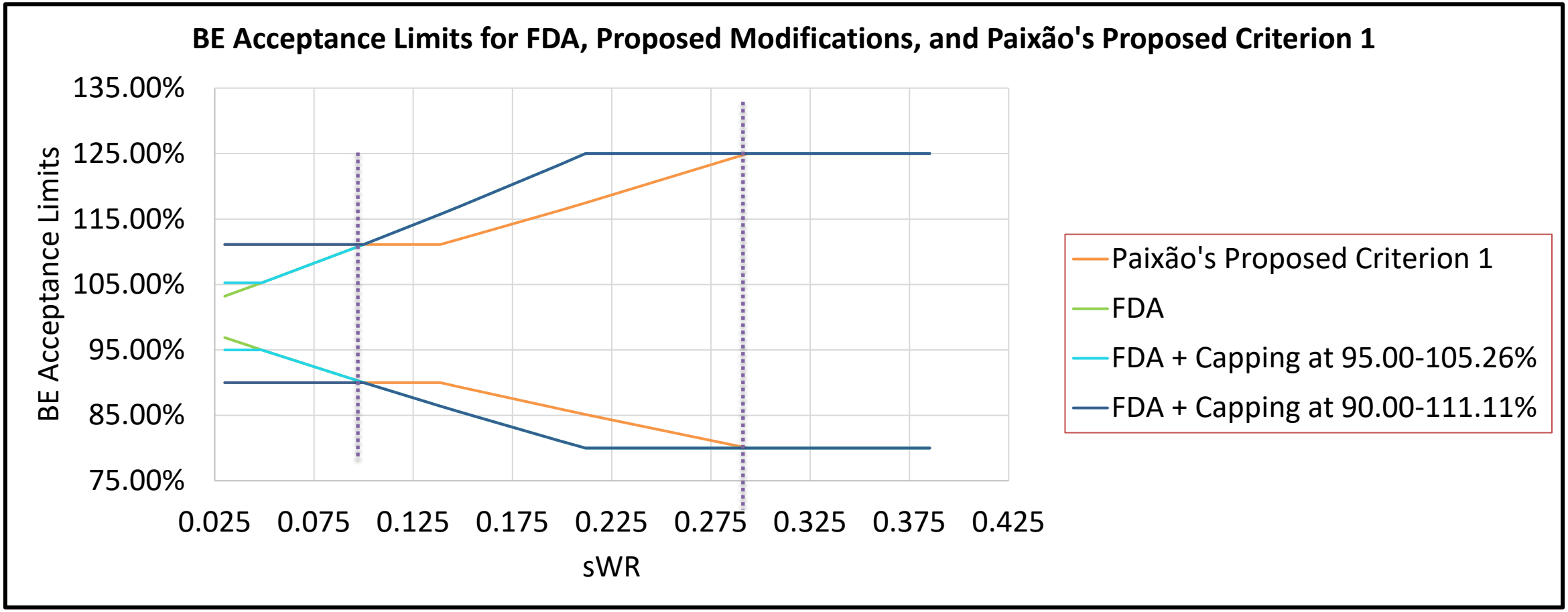
- R vs R passing rates above 80% with all criteria listed in this table.
- However, only with FDA criterion + capping at 90.00-111.11% (when sWR ≤ 0.10), R vs R passing rates are above 90% across all sWR ranges.

Range of passing rates for **5** randomized datasets

BE Criteria	PK Parameters (AUC_t, AUC_i, and C_{max}) [N=463]			
	sWR ≤ 0.05 (n=4-5)*	sWR > 0.05 and ≤ 0.10 (n=82-84)*	sWR > 0.10 and ≤ 0.20 (n=264-268)	sWR > 0.20 (n=109-112)*
FDA (RSABE)	80.00-100.00%	93.90-98.81%	97.01-99.62%	90.99-95.41%
RSABE + capping at 95.00-105.25% if sWR ≤ 0.048684	80.00-100.00%	93.90-98.81%	97.01-99.62%	90.99-95.41%
RSABE + capping at 90.00-111.11% if sWR ≤ 0.10	100.00%	96.34-98.81%	97.01-99.62%	90.99-95.41%
RSABE + capping at 90.00-111.11% if sWR ≤ 0.10 + PEC [0.9000, 1.1111]	100.00%	96.34-98.81%	96.64-99.62%	89.09-93.64%
Paixão's proposed criterion 1	100.00%	96.34-98.81%	91.42-95.51%	87.39-93.75%
Paixão's proposed criterion 2	100.00%	96.34-98.81%	91.42-95.51%	87.39-93.75%
Paixão's proposed criterion 1A (proposed modification by ORS)	100.00%	96.34-97.81%	86.57-91.01%	85.59-92.73%
Paixão's proposed criterion 2A (proposed modification by ORS)	100.00%	96.34-98.81%	86.57-91.01%	85.59-91.82%

Sequence randomization; without alpha adjustment

Comparison of Paixao and FDA Criteria with Capping Limits



Considerations for Harmonization Priority & Supportive Data

Priority	Harmonization options	Y/N	Supportive Data		
			FDA Simulation	FDA ANDA Analysis	Other Agencies' practice
1	Use Reference-scaled approach to tighten BE limits?		2012 Simulation*: Direct tightening BE limits to 90-111.11% not ideal, low power of passing (unreasonably stringent) at medium sWR. (e.g., when the RLD is compared to itself or an identical generic product (i.e., GMR=1, σWR= σWT), the passing rate with BE limits of 90.00-111.11% is lower than 30% when σWR= 0.25. 2024 Simulation: Power of EMA criteria is very low and sample size is very large when σWR is high.	Consistent with simulation: lowest passing rate with current EMA criterion failing most studies at moderate sWR	EMA and Health Canada currently use direct tightening of BE limits. EMA potentially adopts reference-scaled approach (Paixao proposed approach) PMDA generally does not apply tighter BE limits based on the published guidelines.
2	Tighter limits applied to AUC, only on Cmax if it is of clinical significance to safety and efficacy?		N/A	Majority of ANDAs failed reference scaled BE limits due to Cmax. If removing tighter limits on Cmax, significant increases in ANDA passing rates	Only applying tighter limits to Cmax when it is of clinical significance is current EMA practice.

* A Bioequivalence Approach for Generic Narrow Therapeutic Index Drugs: Evaluation of the Reference-Scaled Approach and Variability Comparison Criterion. AAPS J. 2015 Jul; 17(4): 891–901. Wenlei Jiang, Fairouz Makhlouf, Donald J. Schuirmann, Xinyuan Zhang, Nan Zheng, Dale Conner, Lawrence X. Yu, and Robert Lionberger

Considerations for Harmonization Priority & Supportive Data

Priority	Harmonization options	Y/N	Supportive Data		
			FDA Simulation	FDA ANDA Analysis	Other Agencies' practice
3	Is variability comparison necessary for IR or ER products?		2012 simulation*: variability comparison can provide additional assurance of therapeutic equivalence. Tighter reference scaled ABE limits alone cannot ensure T and R have comparable WSV. 2024 simulations: Specially designed 3-way crossover study can support variability comparison	❑ 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 WSV. WSV of the same reference drug product does vary among different studies. ❑ Some IR formulation design can still be complex	No other agency recommends variability comparison
4	Is point estimate constraint 90.00-111.11% necessary?		2012 simulation*: additional PECs demonstrated a σWR-dependent effect on the study power. The higher the σWR, the more power decreasing was observed with tighter PECs. In the case of moderate σWR (e.g., between 0.2 and 0.3), additional PEC will enforce test and reference product BE limits to be closer with each other. 2024 simulation: More power reduction as GMR deviates more from 1 (e.g., GMR<0.9 or >1.1), especially when sWR is moderate (0.2-0.3).	❑ PEC does restrict passing of studies with GMR largely off 1. ❑ Maybe a little stringent when sWR > 0.2. T/R or R/R passing rate < 90%. ❑ Hypothetical R vs R GMR can range from 0.87 to 1.14	Paixao criterion 2 added PEC 90.00-111.11%.

Considerations for Harmonization Priority & Supportive Data

Priority	Harmonization options	Y/N	Supportive Data		
			FDA Simulation	FDA ANDA Analysis	Other Agencies' practice
5	Which regulatory constant is more appropriate? *Current FDA*: $k = \frac{ln(1.11111)}{\sigma_0=0.1} =$ 1.05361; or Paixao: $k = \frac{ln(1.25)}{\sigma_0=0.294} = 0.76$		2012 simulation* Δ=1.11 and σW0=0.10 were selected because at σW0=0.10 (i.e., a common value to define small WSV), the implied BE limits 90.00-111.11% coincide with other major health regulatory standards for NTI drugs.	Majority of NTI drug products (>80%) have average sWR less than 0.21, supporting the use of FDA regulatory constant	Paixao (potential EMA approach) utilizes 2) $k = \frac{ln(1.25)}{\sigma_0=0.294} = 0.76$
6	Is it necessary to cap BE limit to 95.00-105.26% when sWR≤ 0.048684 or to 90.00-111.11% when sWR≤0.10?		2024 simulation demonstrates that extremely large sample size needed for BE studies with products having very low sWR, suggesting the need of capping limits	❑ Very few studies have sWR less than 0.05 (total 8 PK parameters); The lowest sWR observed is ~ 0.04 ❑ Capping BE limits at 90.00-111.11% maybe a little too relaxed as studies with GMR deviating from 1 (e.g., 0.93, 1.09) when sWR > 0.05 and < 0.10 can still pass the criteria.	Paixao's criteria have the capping limits 90.00-111.11 %.
7	Alpha adjustment		2024 simulation suggests alpha adjustment can effectively control Type I error	With alpha adjustment, the passing rates slightly decreased	Paixao also added alpha adjustment in his new proposal

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 except applicants provide justifications 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 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% seems reasonable.
- Alpha adjustment is necessary to control 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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