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

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Background

- The **U.S. Food and Drug Administration (FDA)** recommends a fully replicated, 4-way crossover bioequivalence (BE) study for generic narrow therapeutic index (NTI) drugs where BE is based on reference scaled and unscaled average BE (RSABE) limits, as well as test and reference within-subject variability comparison (sWT vs. sWR) of pharmacokinetic (PK) parameters. [1]
- Most other regulatory agencies have different BE approaches and criteria for NTI drugs.
- **International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)** serves to ensure safe, effective, and high-quality drugs worldwide through global harmonization of guidelines for drug development. With a three-series BE guideline in progress, M13C is indicated to harmonize data analysis and BE assessment for NTI drugs. [2]
- This research is a continuation of NTI abbreviated new drug applications (ANDA) BE data assessed to analyze the impact of FDA's BE criteria on generic NTI approval. [3]

Objectives

- Subject the BE data of ANDAs of NTI drug products received by FDA to NTI BE criteria from different regulatory agencies, previously proposed and newly modified criteria, to compare the passing rate
- Understand the strengths and limitations of each criterion, seeking data-driven harmonization of NTI BE criteria

Methods

- Collect information from NTI ANDAs submitted from January 1, 2013 to October 1, 2022
  - **90** ANDAs included in analysis
- Compile NTI BE criteria from different regulatory agencies and literature reported (Table 2)
  - 5 regulatory agencies, 2 literature proposed, and 11 newly proposed ("Modified FDA")
- Modify current FDA NTI criteria including:
  - With vs. without variability comparison
    - 4-way fully replicated vs. 3-way partially replicated crossover study design
  - Capping the reference scaled limits at the lower end of sWR ranges
    - Capping at 94.87-105.41% if sWR $\leq$ 0.05 vs. capping at 90.00-111.11% if sWR $\leq$ 0.10
  - Apply reference scaled approach to AUC only vs. both AUC and C_{max}
- Subject BE data of **86** ANDAs with **175** four-way crossover studies to **18** different NTI BE criteria
- Analyze test-to-reference (T/R) and reference-to reference (R1/R2) passing rates
- Plot the number of passed and failed PK parameters when applying different BE criteria against R1/R2 GMR at different sWR ranges

Summary and Conclusions

- sWR for the same API vary among IR and ER products (generally higher for ER products) (Table 1)
- ANDA applicants tend to have conservative estimation of sample size (generally more subjects)
- When the NTI ANDA 4-way crossover study data subjected to different BE criteria, the passing rate percentage (ranked low to high) are: **EMA < Health Canada < U.S. FDA/[China] NMPA < Paixão's proposal 2 < Paixão's proposal 1 < most Modified FDA criteria < [Japan] PMDA** (Table 2)
- When compared different BE criteria, EMA's and Health Canada's limits may be too stringent for products with medium within-subject variability (e.g., sWR > 0.10)
- Reference scaled approach is necessary

Reference Scaled BE Approach	Strengths	Limitations
Current FDA criteria	Overall, quite reasonable. Failed studies with GMR largely off 1.	Maybe too stringent when sWR $\leq$ 0.05. R vs. R had 50% passing rate.
Paixão's proposal 1 [4]	Overall, quite reasonable. R vs. R had > 90% passing rate across all sWR ranges.	Maybe a little too relaxed when sWR $\leq$ 0.05 as studies with GMR largely off 1 can still pass the criteria.
Paixão's proposal 2 (with GMR constraint (cGMR) within 90.00-111.11%) [5]	Overall, quite reasonable. R vs. R had > 90% passing rate across all sWR ranges.	May be too stringent when sWR > 0.20. R vs. R decreased from 93.64% (no cGMR) to 92.73%.
Modified FDA criteria with capping BE limits (e.g., proposed criteria 1&2, 4&5)	Slightly increasing passing rate of studies with sWR $\leq$ 0.05.	Maybe a little too relaxed if capping at 90.00-111.11% as studies with GMR largely off 1 can still pass the criteria. 94.87-105.41% capping limits do not have much of an impact or difference from FDA's current criteria.
Modified FDA criteria applying reference scaled limits on AUC and only on C_{max} if clinically relevant (e.g., proposed criteria 3-5)	Aligned with current EMA and Health Canada thinking (focusing only on AUC), significantly increases the passing rate.	Need to determine whether C_{max} is of significance to safety and efficacy.
Modified FDA criteria by removing variability comparison (e.g., proposed criteria 6-11)	Significantly reduce study duration, thus increasing subject compliance and decreasing study cost.	May pass studies with significant difference in within-subject variability.
Proposed options: (1) Apply capping at the lower end; (2) Adjust the regulatory constant; (3) Apply risk-based variability comparison, e.g., apply variability comparison for modified-release products, not IR products; (4) Apply tighter limits only to AUC; (5) Point estimate constraint		
Other option: Conduct a specially designed 3-way crossover study with the capability of performing variability comparison of test and RLD (under evaluation by FDA)		

- Through communication and collaboration with other regulatory agencies, these NTI ANDA BE data along with theoretical modeling simulations will be used to support **global harmonization of BE criteria for NTI drugs**

Results

Table 1. Example NTI Drug Products and Respective sWRs (Within-subject Variability of Reference Standard (RS)), Subject Sample Size, Test to Reference Potency Ratios, and Passing Rate in Four-way Crossover Fully Replicated BE Studies Submitted to FDA

Active Pharmaceutical Ingredient (API)	NTI Drug Product [Immediate-release (IR) and Extended-release (ER)] (RS Number)	sWR for AUC (Ave ± SD)	sWR for C_{max} (Ave ± SD)	No. of Subjects* (Ave ± SD)	T/R Potency Ratio (Ave ± SD)	Percentage of Studies Within Each RS that Passed Current FDA BE Criteria
Carbamazepine	Carbamazepine IR Tablet (016608)	0.11 ± 0.07	0.10 ± 0.04	41 ± 9	1.00 ± 0.02	81.82%
	Carbamazepine IR Suspension (018927)	0.06 ± 0	0.11 ± 0.03	35 ± 7	1.01 ± 0.03	50.00%
	Carbamazepine ER Tablet (020234)	0.19 ± 0.06	0.18 ± 0.06	47 ± 16	1.00 ± 0.02	100.00%
Cyclosporine	Cyclosporine IR Capsule (050715)	0.13 ± 0.02	0.22 ± 0.08	52 ± 12	1.02 ± 0.01	100.00%
Digoxin	Digoxin IR Tablet (020405)	0.11 ± 0.03	0.23 ± 0.03	55 ± 12	1.02 ± 0.03	100.00%
Divalproex Sodium	Divalproex Sodium DR Pellet Capsule (019680)	0.06 ± 0.01	0.06 ± 0.03	30 ± 6	1.02 ± 0.03	75.00%
	Divalproex Sodium ER Tablet (021168)	0.23 ± 0.09	0.19 ± 0.06	43 ± 8	1.01 ± 0.01	90.91%
Everolimus	Everolimus IR Tablet (021560)	0.15 ± 0.03	0.18 ± 0.04	46 ± 19	0.99 ± 0.02	100.00%
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	73.37%
Phenytoin Sodium	Phenytoin Sodium ER Capsule (084349)	0.15 ± 0.08	0.14 ± 0.06	41 ± 16	1.00 ± 0.02	87.50%
Sirolimus	Sirolimus IR Tablet (021110)	0.17 ± 0.03	0.17 ± 0.06	40 ± 7	1.01 ± 0.01	66.67%
Tacrolimus	Tacrolimus ER Capsule (204096)	0.17 ± 0.04	0.21 ± 0.04	43 ± 8	0.97 ± 0.03	80.00%
	Tacrolimus IR Capsule (050708)	0.17 ± 0.03	0.21 ± 0.04	43 ± 13	1.00 ± 0.03	93.33%
Theophylline	Theophylline ER Tablet (090430; 086998; 085328)	0.11 ± 0.03	0.11 ± 0.03	32 ± 7	1.00 ± 0.01	100.00%

*Number of subjects included in PK analysis
Note: The average and standard deviation values were obtained from at least 4 studies and 2 batches. The specific numbers were removed to not disclose any proprietary information.

Table 3. Passing Rates for Reference vs. Test Products of PK Parameters Based on sWR from NTI ANDAs with Four-way Fully Replicated Crossover Studies Submitted to FDA

BE Criteria	PK Parameters (AUC_t* and C_{max}) Passing Rate with sWR $\leq$ 0.05 (n=6)	Passing Rate with sWR > 0.05 and $\leq$ 0.10 (n=64)	Passing Rate with sWR > 0.10 and $\leq$ 0.20 (n=200)	Passing Rate with sWR > 0.20 (n=82)
EMA	100.00%	96.88%	92.00%	75.61%
Health Canada	100.00%	96.88%	92.50%	78.05%
[Japan] PMDA	100.00%	100.00%	100.00%	98.78%
Paixão's proposed criterion 1	100.00%	96.88%	94.50%	96.34%
Paixão's proposed criterion 2	100.00%	96.88%	94.50%	93.90%
BE Criteria	**PK Parameters (AUC_t*, AUC_I*, and C_{max})** Passing Rate with sWR $\leq$ 0.05 (n=8)	Passing Rate with sWR > 0.05 and $\leq$ 0.10 (n=88)	Passing Rate with sWR > 0.10 and $\leq$ 0.20 (n=264)	Passing Rate with sWR > 0.20 (n=110)
FDA	75.00%	86.36%	95.45%	99.09%
FDA + capping at 94.87-105.41% if sWR $\leq$ 0.05	87.50%	86.36%	95.45%	99.09%
FDA + capping at 90.00-111.11% if sWR $\leq$ 0.10	87.50%	92.05%	95.45%	99.09%
Paixão's proposed criterion 1	100.00%	96.59%	93.18%	96.36%
Paixão's proposed criterion 2	100.00%	96.59%	93.18%	94.55%

*RS limits applied according to their respective BE criteria
Note #1: Passing rate is calculated as the percentage of PK parameters passing BE criteria over the total number of PK parameters
Note #2: [China] NMPA applies the same NTI BE criteria as FDA

Table 4. Passing Rates for Reference vs. Reference Products of PK Parameters (AUC_t, AUC_I, and C_{max}) Based on sWR from NTI ANDAs with Four-way Fully Replicated Crossover Studies Submitted to FDA

BE Criteria	Passing Rate with sWR $\leq$ 0.05 (n=6*)	Passing Rate with sWR > 0.05 and $\leq$ 0.10 (n=84*)	Passing Rate with sWR > 0.10 and $\leq$ 0.20 (n=264)	Passing Rate with sWR > 0.20 (n=110)
FDA	50.00%	84.52%	98.11%	93.64%
FDA + capping at 94.87-105.41% if sWR $\leq$ 0.05	50.00%	84.52%	98.11%	93.64%
FDA + capping at 90.00-111.11% if sWR $\leq$ 0.10	100.00%	91.67%	98.11%	93.64%
Paixão's proposed criterion 1	100.00%	92.86%	92.80%	93.64%
Paixão's proposed criterion 2	100.00%	92.86%	92.80%	92.73%

*6 PK parameters (2 PK parameters with sWR $\leq$ 0.05; 4 PK parameters with sWR > 0.05 and $\leq$ 0.10) not included in analysis because no data were submitted by applicant
Note #1: Passing rate is calculated as the percentage of PK parameters passing BE criteria over the total number of PK parameters
Note #2: [China] NMPA applies the same NTI BE criteria as FDA

Table 2. Passing Rates of NTI ANDAs with Four-way Crossover Studies Submitted to FDA Based on Regulatory Agencies' and Proposed Criteria

Regulatory Agency/ Proposed Criteria	Study Design	BE Limits for AUC	BE Limits for C_{max}	Variability Comparison	Passing Rate
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	78.29%
Health Canada	2-way crossover	ABE limits of 90.0-112.0% (AUC_t)	ABE limits of 80.0-125.0%	Not applied	80.00%
[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	99.43%
[China] National Medical Products Administration (NMPA)	4-way fully replicated crossover	RSABE limits of 80.00-125.00% (AUC_t and AUC_I)	Same as BE limits for AUC	Applied	88.57%
FDA	4-way fully replicated crossover	RSABE limits of 80.00-125.00% (AUC_t and AUC_I)	Same as BE limits for AUC	Applied	88.57%
Proposed criterion 1	4-way fully replicated crossover	RSABE limits of 80.00-125.00% and capping at 94.87-105.41% if sWR $\leq$ 0.05 (AUC_t and AUC_I)	Same as BE limits for AUC	Applied	89.14%
Proposed criterion 2	4-way fully replicated crossover	RSABE limits of 80.00-125.00% and capping at 90.00-111.11% if sWR $\leq$ 0.10 (AUC_t and AUC_I)	Same as BE limits for AUC	Applied	92.00%
Proposed criterion 3	4-way fully replicated crossover	RSABE limits of 80.00-125.00% (AUC_t and AUC_I)	ABE limits of 80.00-125.00%	Applied	95.43%
Proposed criterion 4	4-way fully replicated crossover	RSABE limits of 80.00-125.00% and capping at 94.87-105.41% if sWR $\leq$ 0.05 (AUC_t and AUC_I)	ABE limits of 80.00-125.00%	Applied	95.43%
Proposed criterion 5	4-way fully replicated crossover	RSABE limits of 80.00-125.00% and capping at 90.00-111.11% if sWR $\leq$ 0.10 (AUC_t and AUC_I)	ABE limits of 80.00-125.00%	Applied	96.57%
Proposed criterion 6	3-way partially replicated crossover	RSABE limits of 80.00-125.00% (AUC_t and AUC_I)	Same as BE limits for AUC	Not applied	89.14%
Proposed criterion 7	3-way partially replicated crossover	RSABE limits of 80.00-125.00% and capping at 94.87-105.41% if sWR $\leq$ 0.05 (AUC_t and AUC_I)	Same as BE limits for AUC	Not applied	90.29%
Proposed criterion 8	3-way partially replicated crossover	RSABE limits of 80.00-125.00% and capping at 90.00-111.11% if sWR $\leq$ 0.10 (AUC_t and AUC_I)	Same as BE limits for AUC	Not applied	93.14%
Proposed criterion 9	3-way partially replicated crossover	RSABE limits of 80.00-125.00% (AUC_t and AUC_I)	ABE limits of 80.00-125.00%	Not applied	96.57%
Proposed criterion 10	3-way partially replicated crossover	RSABE limits of 80.00-125.00% and capping at 94.87-105.41% if sWR $\leq$ 0.05 (AUC_t and AUC_I)	ABE limits of 80.00-125.00%	Not applied	96.57%
Proposed criterion 11	3-way partially replicated crossover	RSABE limits of 80.00-125.00% and capping at 90.00-111.11% if sWR $\leq$ 0.10 (AUC_t and AUC_I)	ABE limits of 80.00-125.00%	Not applied	97.71%
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	ABE limits of 80.00-125.00% (Apply reference scaled limits to C_{max} only if clinically relevant)	Not applied	89.71% (RS limits applied to AUC_t and AUC_I); 90.86% (RS limits applied to AUC_t only)
Paixão's proposed criterion 2	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; Apply point estimate constraint within 90.00-111.11%	ABE limits of 80.00-125.00% (Apply reference scaled limits to C_{max} only if clinically relevant)	Not applied	88.57% (RS limits applied to AUC_t and AUC_I); 89.71% (RS limits applied to AUC_t only)

Note: Variability comparison is defined as 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.

Figure 1. R1/R2 GMR Distribution for PK Parameters for FDA, Modified, and Paixão's Proposed Criteria

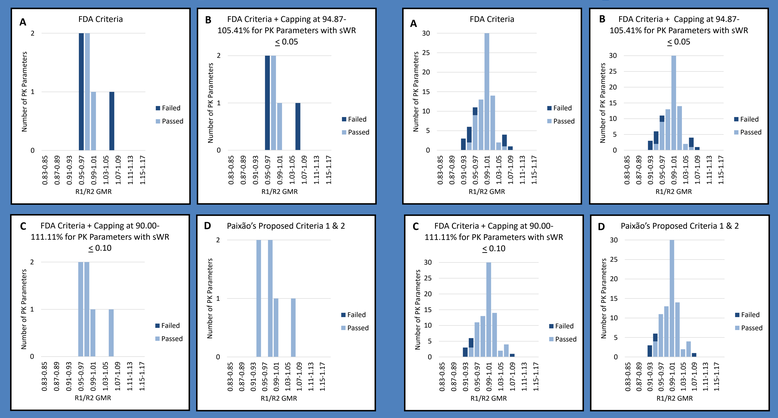


Figure 1 Continued. R1/R2 GMR Distribution for PK Parameters for FDA, Modified, and Paixão's Proposed Criteria

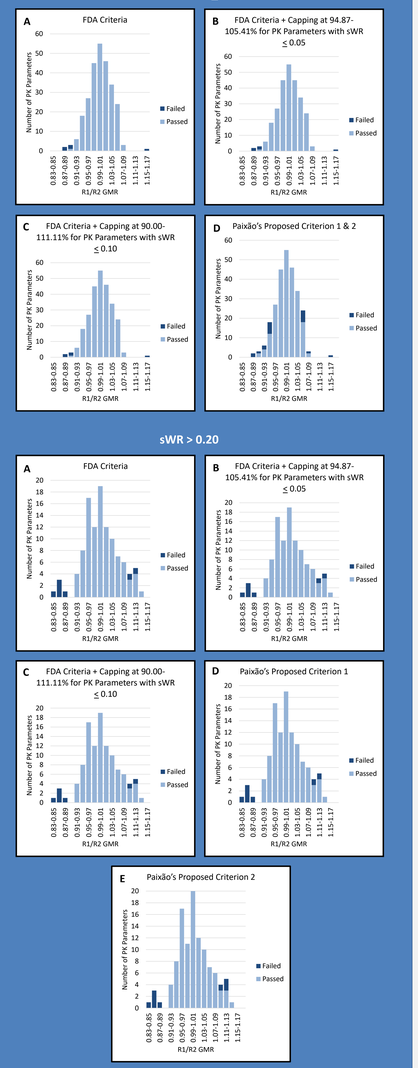
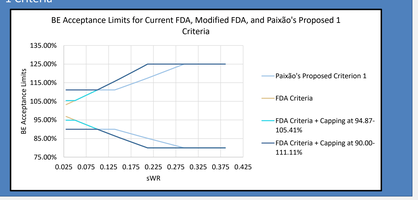


Figure 2. BE Acceptance Limits for FDA, Modified, and Paixão's Proposed 1 Criteria



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Disclaimer

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