The AAPS Journal (2025) 27:42
https://doi.org/10.1208/s12248-025-01020-1

RESEARCH ARTICLE

Analysis on the Impact of U.S. FDA's Narrow Therapeutic Index Bioequivalence Criteria on Generic Drug Applications

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Received: 30 August 2024 / Accepted: 7 January 2025 / Published online: 12 February 2025

Abstract

Since 2012, the U.S. Food and Drug Administration (FDA) has developed classification criteria of narrow therapeutic index (NTI) drug products and tightened bioequivalence (BE) standards for these products by recommending a fully replicated, two-sequence, two-treatment, four-period crossover study design where BE is based on passing both scaled average BE criterion and within-subject variability comparison criterion, as well as the average BE criterion of 80.00%-125.00%. Currently, the BE study design and criteria for NTI drugs are somewhat different across regulatory agencies. The objective of this study is to 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. Thirty-three NTI drug products from 100 ANDAs were identified with 93 ANDAs included in analysis. Eighty-seven ANDAs had four-way crossover studies, with 69 and 106 fed and fasting BE studies, respectively. For all NTI drugs, the range of average S_{WR} for C_{max}, AUC_t, and AUC_{inf} was between 0.05 and 0.27. Of the 20 studies that failed BE, 90%, 5%, and 5% failed reference scaled criteria only, variability comparison criteria only, and both, respectively. Further communication of this work with global regulatory agencies and the scientific community will help better understand current FDA NTI BE criteria and review experiences. These efforts will support the development of harmonized BE criteria for NTI drugs, in turn improving patient access to generic NTI drugs.

Keywords bioequivalence · four-way crossover · harmonization · narrow therapeutic index · within-subject variability

Abbreviations

ANDA	Abbreviated New Drug Application
API	Active Pharmaceutical Ingredient
BE	Bioequivalence
CI	Confidence Interval
DR	Delayed Release
EMA	European Medicines Agency
ER	Extended Release
FDA	U.S. Food and Drug Administration
ICH	Internal Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IR	Immediate Release
NDA	New Drug Application
NTI	Narrow Therapeutic Index
PD	Pharmacodynamic
PK	Pharmacokinetic
PMDA	Pharmaceuticals and Medical Devices Agency
PSGs	Product-specific Guidances
RLD	Reference Listed Drug
RS	Reference Standard
S_{WR}	Estimate of Within-subject Standard Deviation of Reference
S_{WT}	Estimate of Within-subject Standard Deviation of Test

Part of the manuscript findings was presented at American College of Clinical Pharmacology (ACCP) 2023 Annual Meeting at Bellevue, Washington in September 2023.

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σWR Within-subject Standard Deviation of Reference
σWT Within-subject Standard Deviation of Test
USP United States Pharmacopoeia
TDM Therapeutic Drug Monitoring
WSV Within-subject Variability

Introduction

The U.S. Food and Drug Administration (FDA) describes narrow therapeutic index (NTI) drugs as drug products where minor differences in dose or blood concentration may lead to serious therapeutic failures and/or adverse drug reactions that are life-threatening or result in significant disability (1). Nomenclature and drug product classification for this category of products that warrant stricter assessment criteria varies among regulatory agencies, as Health Canada uses the term critical-dose drugs, European Medicines Agency (EMA) utilizes both critical-dose drug and NTI drug terms, and Pharmaceuticals and Medical Devices Agency (PMDA) of Japan uses the term narrow therapeutic range drug (2). Furthermore, health professionals have voiced concerns pertaining to the bioequivalence (BE) of a generic NTI drug compared to its reference listed drug (RLD) using conventional BE limits of 80.00–125.00% (3). In 2012, the FDA developed NTI classification criteria and tightened BE standards for NTI drugs.

NTI drugs generally exhibit small separation between sub- and supra- therapeutic dose/concentrations, increasing the risk for serious therapeutic failure or adverse events (2). The narrow window for therapeutic concentrations often results in dose adjustments in small increments, often less than 20%, and in clinical practice they are commonly subjected to therapeutic monitoring based on pharmacokinetic (PK) or pharmacodynamic (PD) parameters. Additionally, they commonly possess low-to-moderate within-subject variability (WSV), e.g., less than 30%. WSV refers to the variability observed when the same subject has a variable drug PK response with the same drug product from time to time (4). WSV can be described by within-subject variance or within-subject standard deviation (σ_{WR}: within-subject standard deviation for reference drug; σ_{WT}: within-subject standard deviation for test drug). Although the classification of NTI products varies among regulatory agencies, above are the general characteristics in which FDA has outlined that NTI drugs generally exhibit and have used them for NTI classification (2). In addition, the FDA recommended a fully replicated, two-sequence, two-treatment, four-period crossover study design for generic NTI drugs where BE is based on passing both scaled average BE criterion and average BE limits, as well as within-subject variability comparison criterion (FDA 2012 NTI BE criteria) for both AUC and C_{max} (5).

Specifically, when σ_{WR} equals 0.10, the reference BE limits for NTI drugs are set at 90.00–111.11%. If σ_{WR} is less or greater than 0.10, then the reference-scaled BE limits are narrower or wider than 90.00–111.11%, respectively. These limits expand as the variability increases. However, since it is considered not desirable clinically to have these limits exceed 80.00–125.00%, FDA recommends that all BE studies on NTI drugs must pass both the reference-scaled limits and the unscaled average bioequivalence limits of 80.00–125.00%. In addition, $\sigma_{WT/}\ \sigma_{WR}$ are declared equivalent when the upper limit of the 90% confidence interval for the test/reference $\sigma_{WT/}\ \sigma_{WR}$ is less than or equal to 2.5 (6).

The BE study design and criteria for NTI drugs are different across regulatory agencies. Currently, although the National Medical Products Administration in China recommends a similar reference scaled BE approach as the FDA for NTI drugs, most other regulatory agencies differ in BE approach and criteria from FDA's recommendations (7). For example, Health Canada and EMA use direct tightening of the BE limits to 90.0–112.0% and 90.00–111.11% for AUC, respectively. Additionally, EMA only directly tightens C_{max} to 90.00–111.11% when C_{max} is of particular importance for safety, efficacy, or drug level monitoring. Japan's PMDA guideline keeps BE limits of 80–125% for both AUC and C_{max} (2).

Harmonization of BE criteria for NTI drugs among regulatory agencies is of great interest because inconsistencies among NTI classification and BE criteria globally can result in increased drug development time, decreased cost effectiveness, and potentially hinder access to generic NTI drugs in particular regions (8). To support efficient generic drug development, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) recently adopted the first guideline, ICH M13A, in a series of guidelines that describes the scientific and technical aspects of study design and data analysis to support BE assessment for immediate release (IR) solid oral dosage forms (9). The third guideline in the series, ICH M13C, is outlined to include data analysis and BE assessment for drugs with narrow therapeutic index (8, 10). However, reaching consensus on NTI classification is not included in the scope of ICH M13C.

To support ICH M13C development, we surveyed BE data of abbreviated new drug applications (ANDAs) of NTI drug products initially submitted between January 2013 and October 2022 to the FDA with a focus on submissions with fully replicated BE studies. Since 2009, FDA requires ANDA applicants to submit all BE studies, both passing and non-passing, for evaluation (11). We analyzed PK parameter variability among NTI drug products, examined the distribution of passed and failed four-way crossover BE studies in different dosage forms and fasting/fed study conditions, as well as investigated reasons for failure of BE criteria. This

study aids in clarifying the impact of 2012 FDA NTI classification and BE criteria for NTI drugs on generic approval and supports the identification of paths to potential harmonization of NTI BE standards, in turn, improving generic NTI drug product access globally.

Materials and Methods

A list of drug products classified as NTI by FDA was identified by scanning through FDA product-specific guidelines (PSGs), as this is currently the best source for identifying NTI drug products based on BE study recommendations (12). The year of PSG publication or revision to recommend a four-way crossover BE study was collected. In addition, EMA's PSGs for NTI and critical dose drug products that were published between January 2009 to April 2023 were collected via EMA's product-specific bioequivalence guidance website (13). An FDA internal review database was utilized to collect information on ANDAs for NTI drug products with initial submission dates on or after January 2013 to October 2022. ANDAs were excluded for data collection for reasons such as the application being either withdrawn before the BE assessment was completed, refuse-to-receive, and others (14). Applications were sorted for whether BE data were deemed adequate based on a two-way crossover BE study or four-way crossover BE study. Individual applications were further examined to determine the number of passed and failed four-way crossover BE studies. Additionally, PK parameters: C_{max}, and AUCs were collected. The point estimate, 90% confidence interval (CI), critical bound, S_{WT} (the estimate of within-subject standard deviation for the test), S_{WR} (the estimate of within-subject standard deviation for the reference), S_{WT}/S_{WR} ratio, and upper S_{WT}/S_{WR} 90% CI were collected for each PK parameter. NTI variability ranges, distribution of passed and failed four-way crossover BE studies, and reasons for failure to meet FDA 2012 NTI BE criteria were also included in analysis. Additionally, the relationship of application approval basis with PSG publication or revision year were included in the analysis.

Results

FDA NTI ANDAs Approval Basis and Application Status as of October 1, 2022

In total, 100 ANDAs for NTI drug products with initial submission dates from the FDA on or after January 2013 to October 2022 were identified (Fig. 1). Collectively, they comprised of 14 unique active pharmaceutical ingredients (APIs) and 33 drug products. Seven ANDAs were excluded due to the applications being withdrawn before the BE assessment was completed, refused-to-receive, the BE review was completed after October 1, 2022, or for other reasons. Overall, this resulted in 93 ANDAs being included in our analysis. Of the 93 ANDAs, 6 ANDAs had two-way crossover BE studies only, 10 ANDAs conducted both two-way and four-way crossover BE studies, and 77 ANDAs had four-way crossover BE studies only. Of the 6 ANDAs with solely two-way crossover BE studies conducted, 3 ANDAs had BE studies deemed adequate based on two-way crossover studies prior to their respective PSGs being updated and 3 ANDAs were withdrawn prior to approval. Among the 10 ANDAs with both two-way and four-way crossover BE studies conducted, 8 of the ANDAs were approved based on four-way crossover BE study data, 1 ANDA was withdrawn after a four-way crossover BE study was conducted, and 1 ANDA received a complete response. From the 77 ANDAs with four-way crossover BE studies only, 30 ANDAs were approved, 18 received complete responses, 9 ANDAs were withdrawn, 19 ANDAs are under review, and 1 ANDA was subjected to conventional average BE limits of 80.00–125.00%, as the PSG was updated to recommend four-way BE study criteria only after the ANDA was approved.

FDA and EMA PSG Availability for NTI Drug Products

There are 33 FDA PSGs for NTI drug products (14 unique APIs) recommending four-way crossover BE studies with 2012 FDA NTI BE criteria (Table I) between 2012 and 2023. All 33 PSGs recommend fasting and fed BE studies, except levothyroxine sodium whose recommended BE study is under fasting conditions only. Currently, NTI drugs are considered "high-risk". In addition, patients may not strictly follow the labeling instructions. Thus, for these "high-risk" products, in most cases FDA recommends both fasting and fed BE studies for NTI IR drug products regardless of if labeling recommends taking with food or not. For ER products, FDA recommends fasting and fed BE studies due to concerns of dose dumping under the fed conditions. Cyclosporine IR capsule, lithium extended release (ER) tablet, phenytoin sodium ER capsule, and theophylline ER tablet have two unique PSGs for drug products that have different RLD and/or reference standard (RS) numbers but share the same API and dosage form with either different strengths and/or formulations.

EMA has six product-specific bioequivalence guidances for NTI drug products and critical dose drugs, which include: acenocoumarol tablets, colchicine tablets, everolimus tablets and dispersible tablets, levothyroxine sodium tablets, sirolimus coated tablets, and tacrolimus granules for oral suspension. Ciclosporin is also considered as an NTI drug by EMA although no PSGs was published for this drug (15). Among

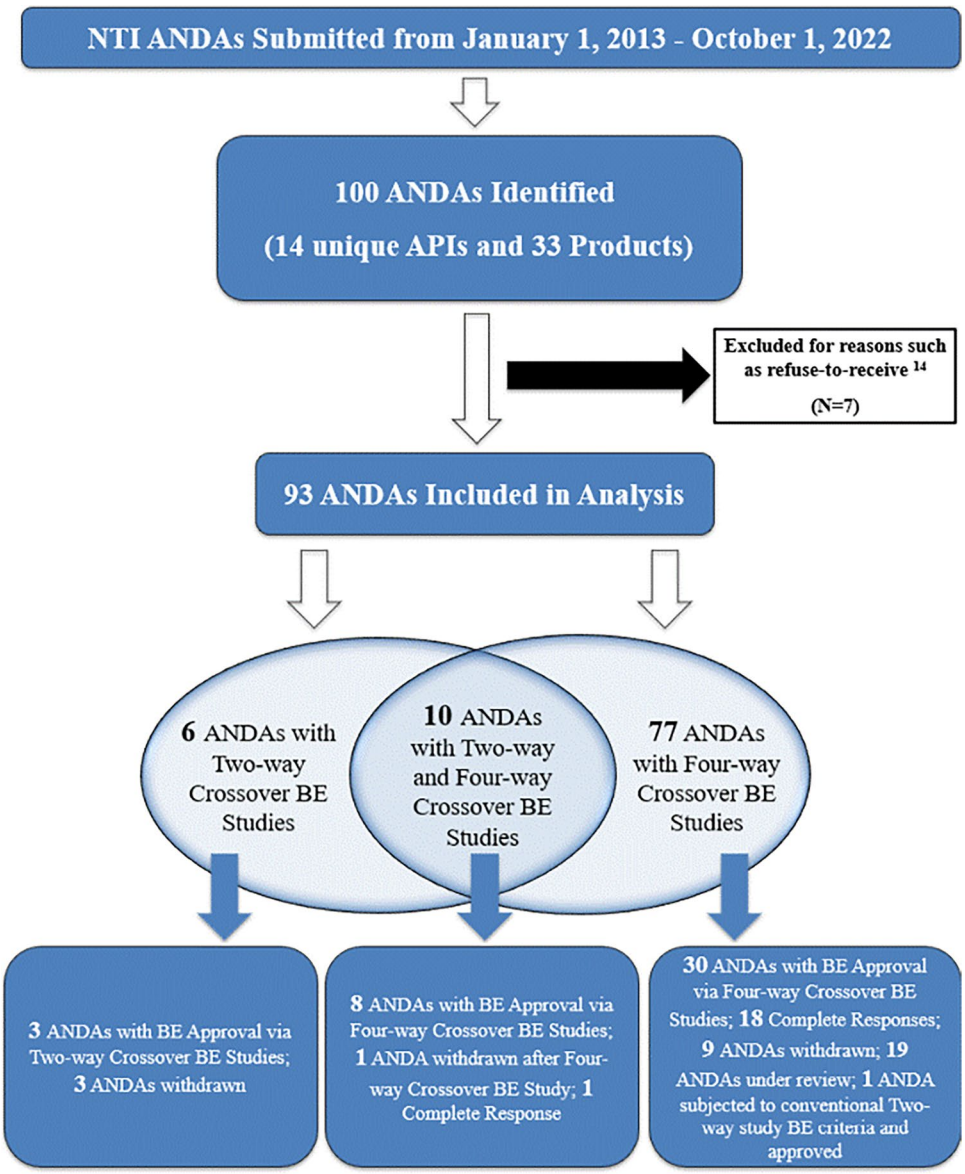

Fig. 1 Abbreviated new drug applications bioequivalence data collection for narrow therapeutic index drug products (2013–2022)

the six available product-specific bioequivalence guidances, they all recommend BE limits 90.00–111.11% for AUC, and standard BE limits of 80.00–125.00% for C_{max}. Furthermore, FDA does not classify colchicine as an NTI product, and recommends conventional two-way crossover studies for BE demonstration of colchicine 0.6 mg oral tablet and oral capsule, respectively. For the remaining five products, FDA does consider them as NTI drugs and recommends 2012 NTI BE criteria for BE assessment. It is of note that EMA's PSGs for acenocoumarol, colchicine, and tacrolimus recommend a fasting single-dose, two-way crossover study, while FDA's PSG recommends both fasting and fed single-dose, four-way fully replicated crossover studies. EMA's PSGs are consistent with EMA's current *Guideline on the Investigation of Bioequivalence*, as it states in general a BE study should be conducted under fasting conditions only (16).

Analysis of Four-way Crossover BE Studies

Average S_{WR} of Different Narrow Therapeutic Index Drug Products

WSV for the reference drug is an important parameter as the BE limits of NTI drugs are scaled based upon the WSV of PK parameters, as a lower WSV results in tighter BE limits with current FDA NTI BE criteria (4). In a fully replicated crossover BE study, S_{WR} and S_{WT} can be obtained. Thus, S_{WR} and S_{WT} are compared to determine whether they differ significantly. In a partially replicated crossover study with reference drug given twice and test drug given once, only S_{WR} is obtained, therefore, no variability comparison of test and reference products can be performed with this type of study design.

Table I Narrow Therapeutic Index Drug Products and Product-specific Guidance Availability

API	NTI Drug Product	PSG (RLD and/or RS)	PSG Publication or Revision Year to Include 4-way Crossover Study
Carbamazepine	Carbamazepine IR Tablet	Carbamazepine IR Tablet (016608)	2015
	Carbamazepine IR Suspension	Carbamazepine IR Suspension (018927)	2015
	Carbamazepine ER Tablet	Carbamazepine ER Tablet (020234)	2015
	Carbamazepine ER Capsule	Carbamazepine ER Capsule (020712; 021710)	2015
	Carbamazepine IR Chewable Tablet	Carbamazepine IR Chewable Tablet (018281)	2022
Cyclosporine	Cyclosporine IR Capsule	Cyclosporine IR Capsule (050625)	2016
	Cyclosporine IR Capsule	Cyclosporine IR Capsule (050715)	2016
Digoxin	Digoxin IR Tablet	Digoxin IR Tablet (020405)	2017
Divalproex Sodium	Divalproex Sodium DR Tablet	Divalproex Sodium DR Tablet (018723)	2016
	Divalproex Sodium DR Pellet Capsule	Divalproex Sodium DR Pellet Capsule (019680)	2016
	Divalproex Sodium ER Tablet	Divalproex Sodium ER Tablet (021168)	2016
Everolimus	Everolimus IR Tablet	Everolimus Tablet (021560)	2016
Levothyroxine Sodium	Levothyroxine Sodium IR Tablet	Levothyroxine Sodium IR Tablet (021116; 021210; 021301; 021342; 021402)	2014
	Levothyroxine Sodium IR Capsule	Levothyroxine Sodium IR Capsule (021924)	2018
Liothyronine Sodium	Liothyronine Sodium IR Tablet	Liothyronine Sodium IR Tablet (010379)	2021
Lithium	Lithium ER Tablet	Lithium ER Tablet (076691)	2023
	Lithium ER Tablet	Lithium ER Tablet (018027)	2023
	Lithium IR Tablet	Lithium IR Tablet (018558)	2023
	Lithium IR Capsule	Lithium IR Capsule (017812)	2023
Phenytoin / Phenytoin Sodium	Phenytoin IR Chewable Tablet	Phenytoin IR Chewable Tablet (084427)	2017
	Phenytoin IR Suspension	Phenytoin IR Suspension (008762)	2017
	Phenytoin Sodium ER Capsule	Phenytoin ER Capsule (040298)	2014
	Phenytoin Sodium ER Capsule	Phenytoin ER Capsule (084349)	2014
Sirolimus	Sirolimus IR Tablet	Sirolimus IR Tablet (021110)	2015
Tacrolimus	Tacrolimus ER Tablet	Tacrolimus ER Tablet (206406)	2016
	Tacrolimus ER Capsule	Tacrolimus ER Capsule (204096)	2014
	Tacrolimus IR Capsule	Tacrolimus IR Capsule (050708)	2012
	Tacrolimus IR For Suspension	Tacrolimus IR For Suspension (210115)	2020
Theophylline	Theophylline ER Tablet	Theophylline ER Tablet (090430; 086998; 085328)	2022
	Theophylline ER Tablet	Theophylline ER Tablet 600 mg (040560)	2020
	Theophylline ER Capsule	Theophylline ER Capsule (081034)	2020
Valproic Acid	Valproic Acid IR Capsule	Valproic Acid IR Capsule (018081)	2017
Warfarin Sodium	Warfarin Sodium IR Tablet	Warfarin Sodium IR Tablet (009218)	2012

Among the 18 NTI drug products with four-way crossover BE studies submitted between January 2013 to October 2022, the average S_{WR} of C_{max} and AUC (AUC_t and AUC_{inf}) per NTI product was calculated. Approximately 0.0%, 22.2%, 50.0%, and 27.8% of these products had average S_{WR} for C_{max} less than or equal to 0.05, 0.05–0.10, 0.10–0.20,

and 0.20–0.30, respectively (Fig. 2). For AUC, approximately 5.6%, 22.2%, 61.1%, and 11.1% of these products had S_{WR} less than or equal to 0.05, 0.05–0.10, 0.10–0.20, and 0.20–0.30, respectively (Fig. 2). Overall, for both C_{max} and AUC, the majority of average S_{WR} fell within 0.10–0.20, at 50.0% and 61.1%, respectively. In addition, more drug products had an average S_{WR} less than or equal to 0.05 for AUC than C_{max}, at 5.6% versus 0.0%, respectively. The distribution range of average S_{WR} for AUC was slightly broader than C_{max}, as there was one drug product with an average S_{WR} for AUC at 0.27 compared to 0.24 for C_{max}.

Of 14 NTI drug products with at least 4 BE studies submitted (Table III), the average S_{WR} for AUC was between 0.06 and 0.23 and the average S_{WR} for C_{max} was between 0.10 and 0.23. For carbamazepine IR tablet, IR suspension, and ER tablet, the average S_{WR} (standard deviation) for AUC was 0.11 (0.07), 0.06 (0), 0.19 (0.06) and average S_{WR} (standard deviation) for C_{max} was 0.10 (0.04), 0.11 (0.03), 0.18 (0.06), respectively (Table III). Divalproex sodium delayed release (DR) pellet capsule and ER tablet had an average S_{WR} (standard deviation) for AUC of 0.06 (0.01) and 0.23 (0.09); and average S_{WR} (standard deviation) for C_{max} of 0.06 (0.03) and 0.19 (0.06), respectively (Table III). Overall, for most NTI drug products, the average S_{WR} was below 0.21.

For products with labeling recommending taking drug on empty stomach, e.g., tacrolimus ER tablets and ER capsules, both fasting and fed BE studies were conducted. Slightly lower average S_{WR} was observed with fed BE study than fasting BE study. For tacrolimus ER tablets and ER capsules, the presence of a meal affects the absorption of tacrolimus; the rate and extent of absorption is greatest under fasting conditions. For this reason, the labeling states that "Take once daily on empty stomach at the same time of the day, preferably in the morning.". For products with labeling recommending drug to be taken with food, e.g., carbamazepine IR and ER tablets, both fasting and fed BE studies were conducted. There is also lower average S_{WR} with fed BE studies than fasting BE studies.

Distribution of Passed and Failed Four-way Crossover Bioequivalence Studies

There were 175 four-way crossover BE studies submitted (Fig. 3). In total, 89% of the BE studies passed 2012 FDA NTI BE criteria and 11% failed the criteria. Of the passed

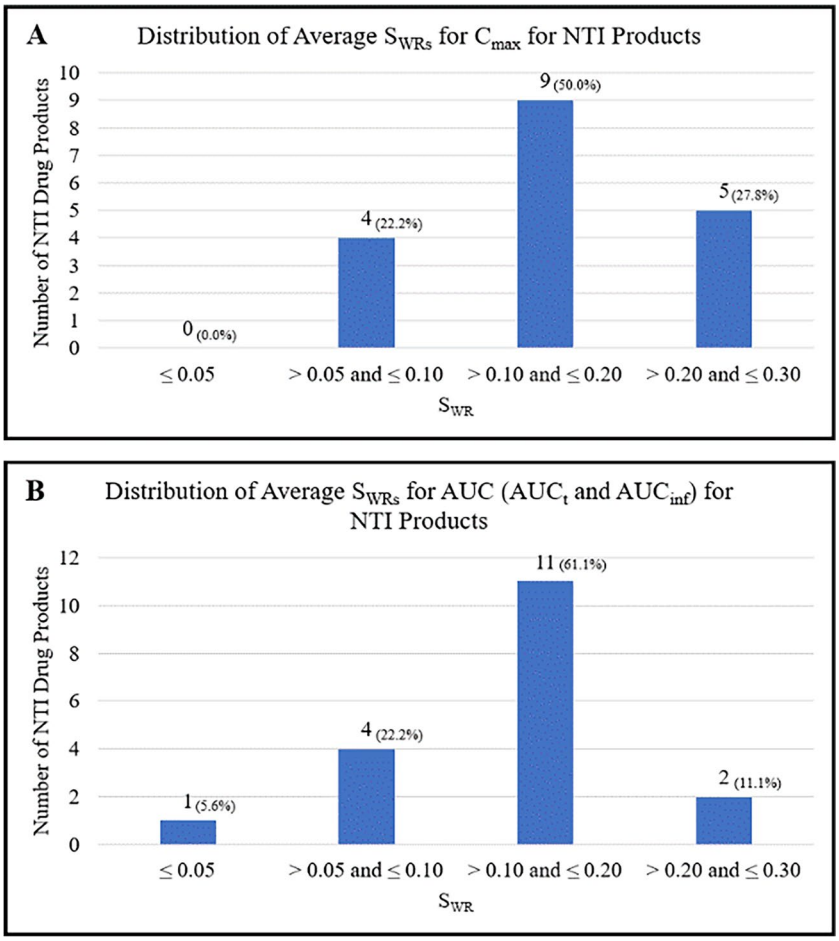

Fig. 2 Distribution of average S_{WR} of various narrow therapeutic index drug products with four-way crossover bioequivalence studies

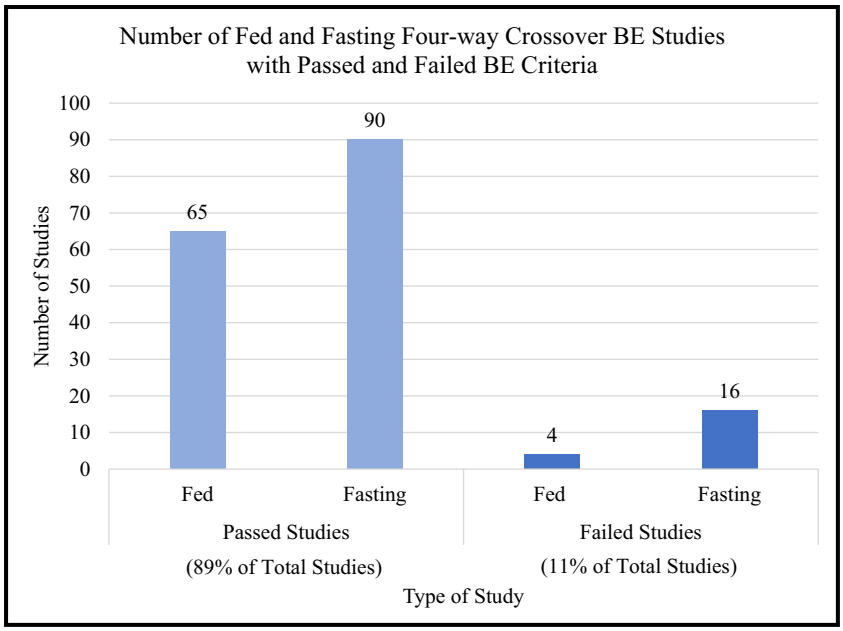

Fig. 3 Distribution of passed and failed fasting and fed four-way crossover bioequivalence studies

studies, 65 were fed and 90 were fasting BE studies. Among the studies that failed NTI BE criteria, 4 were fed and 16 were fasting BE studies. Of the four failed fed BE studies, two failed fed BE studies had corresponding failed fasting BE studies, both of which are IR products. Two failed fed BE studies had corresponding passing fasting BE studies, both of which are ER products. Additionally, among the failed fed studies, three studies failed due to reference scaled limits and one study failed due to variability comparison, as the test product had much higher variability than the reference product. Overall, based on all failed fasting and fed BE studies, the majority have lower within-subject variability under fed conditions.

As shown in Table II, 20 studies failed 2012 FDA NTI BE criteria, with 15 (16.7% of IR products) of the failed studies being for IR NTI drug products and 5 (5.9% of the ER products) being for ER NTI drug products (Table II). For the IR products which failed the NTI BE criteria, they only failed the reference scaled criterion, not variability comparison. Namely, 11, 2, and 2 BE studies failed reference scaled criterion for C_{max} only, for AUC only, and for both C_{max} and AUC, respectively. For the failed BE studies with ER products, 2, 1, 1, and 1 failed the reference scaled criterion for C_{max} only, failed reference scaled criterion for AUC and C_{max}, failed variability comparison for AUC and C_{max}, and failed variability comparison and reference scaled criterion for C_{max} only, respectively. Overall, about 90% of study failures are related to C_{max}; 90% of study failures are related to failed reference scaled criterion. Only ER products failed variability comparison.

S_{WR} Ranges for Passed and Failed Four-way Crossover BE Studies

The ranges of S_{WR} among failed and passed four-way crossover BE studies were analyzed. The range of S_{WR} for AUC $_t$ among failed four-way crossover BE studies exhibited a mean and median of 0.12 and 0.08, respectively (Fig. 4). Meanwhile, for passed four-way crossover BE studies, a slightly higher mean and median of S_{WR} for AUC_t were

Table II Distribution of Bioequivalence Study Failures Among Solid Oral Immediate Release (IR) and Extended Release (ER) Narrow Therapeutic Index Drug Products

Type of Study Failure	IR Studies (90 total)	ER Studies (85 total)
Failed reference scaled criterion due to C_{max} only	11	2
Failed reference scaled criterion due to AUC only	2	0
Failed reference scaled criterion due to AUC and C_{max}	2	1
Failed variability comparison due to AUC and C_{max}	0	1
Failed variability comparison and reference scaled criterion due to C_{max} only	0	1
Studies failed either reference scaled criterion or variability comparison	**15 (16.7%)**	**5 (5.9%)**

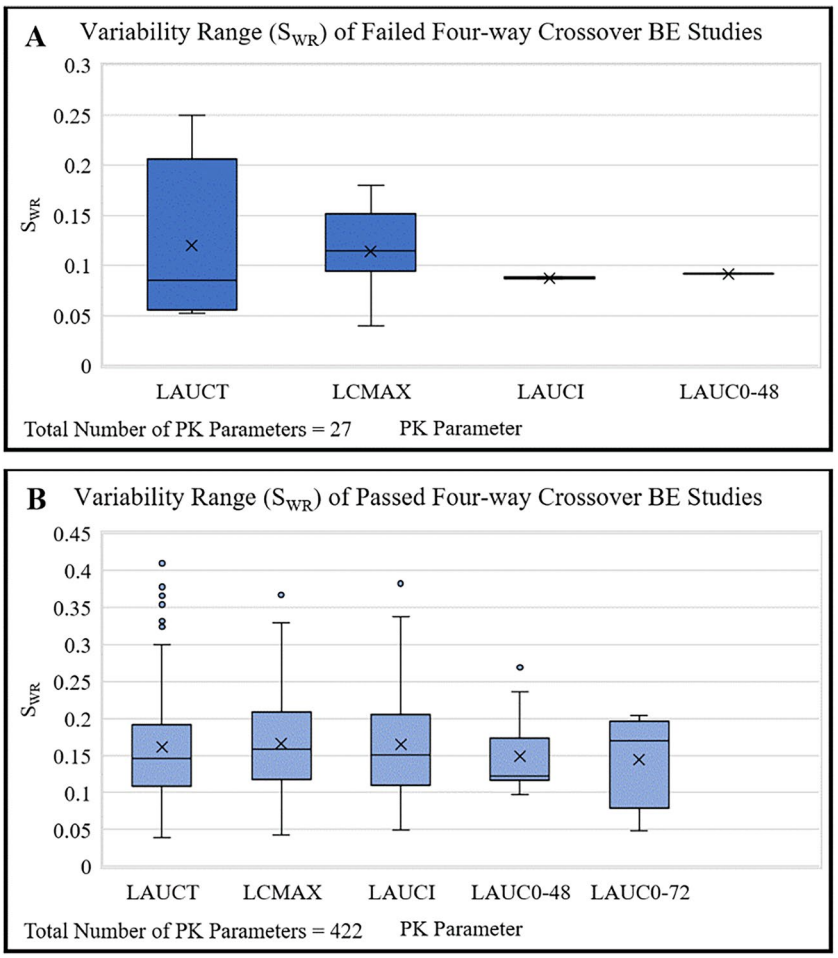

Fig. 4 S_{WR} of failed and passed four-way crossover bioequivalence studies

observed at 0.16 and 0.15, respectively. For C_{max}, failed BE studies demonstrated a slightly lower mean S_{WR} than passed studies, i.e., 0.11 vs 0.17. Likewise, for both AUC_{inf} and AUC_{0-48} a lower mean and median for S_{WR} were observed among failed four-way crossover BE studies compared to passed four-way crossover BE studies. Additionally, among passed four-way crossover BE studies, several S_{WR} at the higher end were observed, e.g., S_{WR} for AUC_t was 0.41 in one ANDA for divalproex sodium ER tablet. However, among 11 studies submitted for divalproex sodium ER tablet, the average S_{WR} for AUC for this drug product is 0.23. The applications that have a $S_{WR} \geq 0.2142$ are subject to BE limits of 80.00–125.00%.

We further analyzed the proportion of S_{WR} among passed BE studies for C_{max}, AUC_t, and AUC_{inf}. For C_{max}, there was 33.3%, 78.6%, 88.0%, 100.0%, 100.0%, and 100.0% passing rate for the S_{WR} ranges of less than or equal to 0.05, between 0.05–0.10, 0.10–0.20, 0.20–0.30, 0.30–0.40, and greater than 0.40, respectively (Fig. 5). For AUC_t, the passing rate was 100%, 73.0%, 91.0%, 96.8%, 100.0%, and 100.0% in the above ranges, respectively (Fig. 5). For AUC_{inf}, passing rates were 100.0% for all S_{WR} ranges except the passing rate was 75.0% and 96.8% when S_{WR} is in the range of 0.05–0.10 and 0.10–0.20, respectively (Fig. 5). Overall, there was a higher failure rate (66.7%) for C_{max} but not AUC when the S_{WR} is less than or equal to 0.05. When S_{WR} is between 0.05 and 0.10, approximately 75% of all PK parameters passed the NTI BE criteria (Fig. 5).

Discussion

Since the introduction of the 2012 NTI BE criteria, the FDA published or revised PSGs for NTI drugs with the updated recommendation of four-way crossover study design and 2012 NTI BE criteria. A limited number of ANDAs (3) were approved based on the two-way crossover study design and conventional BE limits of 80.00–125.00%, as their PSGs were not yet revised to include the updated approach during the ANDA assessment. If a PSG had been published or revised to include the four-way crossover BE studies during the ANDA assessment, the ANDA applicants were requested to resubmit a BE study with a four-way crossover study design. Some ANDA applicants decided to withdraw

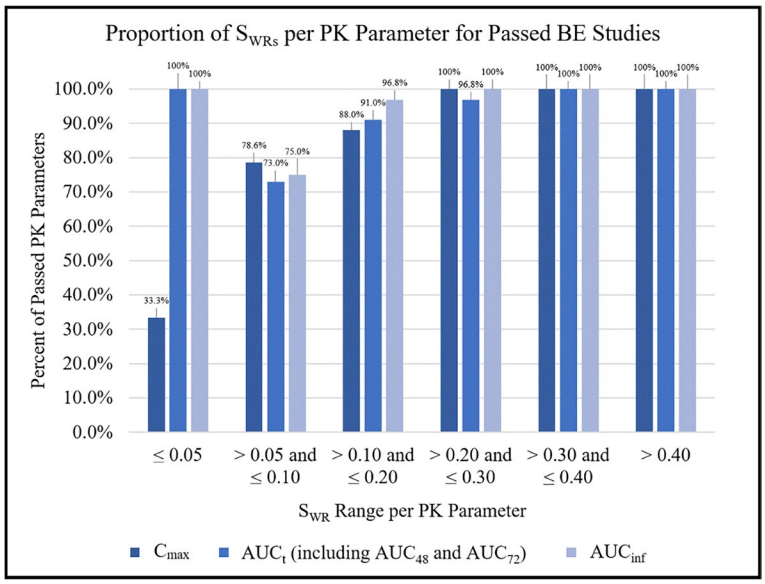

Fig. 5 Proportion of S_{WR} per pharmacokinetic parameter for passed bioequivalence studies

Table III NTI Drug Products and Respective S_{wR} (Within-subject Variability of RLD and/or RS) in Four-way Crossover Fully Replicated BE Studies Submitted to FDA

API	NTI Drug Product (RLD and/or RS)	S_{WR} for AUC (AUC_t and AUC_i) (Ave ± SD)*	S_{WR} for C_{max} (Ave ± SD)*
Carbamazepine	Carbamazepine IR Tablet (016608)	0.11 ± 0.07	0.10 ± 0.04
	Carbamazepine IR Suspension (018927)	0.06 ± 0	0.11 ± 0.03
	Carbamazepine ER Tablet (020234)	0.19 ± 0.06	0.18 ± 0.06
Cyclosporine	Cyclosporine IR Capsule (050715)	0.13 ± 0.02	0.22 ± 0.08
Digoxin	Digoxin IR Tablet (020405)	0.11 ± 0.03	0.23 ± 0.03
Divalproex Sodium	Divalproex Sodium DR Pellet Capsule (019680)	0.06 ± 0.01	0.06 ± 0.03
	Divalproex Sodium ER Tablet (021168)	0.23 ± 0.09	0.19 ± 0.06
Everolimus	Everolimus IR Tablet (021560)	0.15 ± 0.03	0.18 ± 0.04
Levothyroxine Sodium	Levothyroxine Sodium IR Tablet (021116; 021210; 021301; 021342; 021402)	0.16 ± 0.06	0.14 ± 0.05
Phenytoin Sodium	Phenytoin Sodium ER Capsule (084349)	0.15 ± 0.08	0.14 ± 0.06
Sirolimus	Sirolimus IR Tablet (021110)	0.17 ± 0.03	0.17 ± 0.06
Tacrolimus	Tacrolimus ER Capsule (204096)	0.17 ± 0.04	0.21 ± 0.04
	Tacrolimus IR Capsule (050708)	0.17 ± 0.03	0.21 ± 0.04
Theophylline	Theophylline ER Tablet (090430; 086998; 085328)	0.11 ± 0.03	0.11 ± 0.03

*The average and standard deviation values were obtained from at least 4 bioequivalence (BE) studies and 2 batches. The specific numbers of BE studies were not reported in this table to avoid disclosure of any proprietary information

the applications, while others submitted additional four-way crossover BE studies for evaluation. In one ANDA, the applicant submitted four-way crossover BE studies prior to PSG updates. However, the ANDA applicant still analyzed the data based on average BE criteria of 80.00–125.00% limits, deemed acceptable by FDA. In general, if an ANDA has previously been approved based on a two-way crossover study design and later a PSG is published updating the recommendation to a four-way crossover study design, FDA does not require the ANDA applicant to submit a new study implementing the new recommended study design unless FDA believes that not following the new BE recommendations would result in a change in the safety or effectiveness of the drug product or there is post-marketing data suggesting safety or efficacy concerns on products approved based on previous BE recommendation (17, 18).

FDA determines the NTI status based on overall drug product properties, not on the API itself. For example, everolimus and tacrolimus, do not have 2012 NTI BE criteria recommended in PSGs for all available dosage forms of

these APIs. Per the Orange Book, there are three everolimus new drug applications (NDAs) approved by FDA indicated as RLDs and/or RSs. Two of the NDAs, available as everolimus oral tablet and everolimus oral tablet for suspension, are collectively available in strengths varying from 2 to 10 mg and indicated for the treatment of various oncologic conditions. These products are not considered NTI drugs as they are often given at a maximum tolerable dose for maximum response in chemotherapy, which allows for a higher tolerance of adverse events. Therefore, the PSGs for these two products recommend single-dose, two-treatment, two-period crossover in vivo BE studies. The other NDA for everolimus oral tablet is available in the strengths of 0.25 mg, 0.5 mg, 0.75 mg, and 1 mg, and is indicated for the prophylaxis of organ rejection in adult patients at low-to-moderate immunologic risk receiving a kidney transplant (19). For everolimus 1 mg strengths and below, which are utilized as an immunosuppressant, the FDA has classified them as NTI drug products (19). For this indication, everolimus is subjected to routine therapeutic drug monitoring (TDM) using steady state trough concentration (C_{min}). There is a narrow therapeutic concentration range recommended in the product labeling, i.e., between 3 and 8 ng/ml. Consequently, the PSG for everolimus 1 mg tablet recommends single-dose, four-way, fully replicated crossover in vivo BE studies under both fasting and fed conditions. Tacrolimus has six NDAs indicated as RLDs and/or RSs, per Orange Book. Tacrolimus oral capsule and oral ER capsule are both available in EQ 0.5 mg base, EQ 1 mg base, and EQ 5 mg base. Tacrolimus oral ER tablet is available in EQ 0.7 mg base, EQ 1 mg base, and EQ 4 mg base. Additionally, there is a tacrolimus injectable injection EQ 5 mg base, topical ointment in 0.03% and 0.1%, and oral for suspension available in EQ 0.2 mg base/packet and EQ 1 mg base/packet. All NDAs are indicated as immunosuppressants, except tacrolimus topical ointment, which is indicated for moderate to severe atopic dermatitis (16). There are PSGs specific to each NDA, except for tacrolimus injectable injection. Tacrolimus oral capsule, oral ER capsule, oral ER tablet, and oral for suspension are recognized as NTI drugs by FDA and therefore their PSGs each recommend single-dose, four-way fully replicated crossover in vivo BE studies. However, topical ointments (0.03% and 0.1%) are not currently recognized as NTI. Overall, as demonstrated by everolimus and tacrolimus, FDA determines NTI status based on specific drug product information, not on the API itself.

FDA continues evaluating, publishing, and revising PSGs for NTI drug products. FDA has an internal working group to determine NTI status of products and ensure consistent PSG recommendations. More recently, the NTI drug working group at the FDA published a paper on FDA's experience and process in the evaluation of candidate NTI drugs (20). Upon comparing NTI PSGs published by the EMA and FDA, there is a much higher number of products determined as NTI by FDA than EMA. Additionally, not all NTI classification aligns between these two agencies. For example, colchicine oral tablet or capsule is approved for treatment of gout, familial Mediterranean fever, and for the prevention of cardiovascular events by both FDA and EMA (19, 21, 22). EMA has a published PSG for colchicine 0.5 mg and 1 mg oral tablet, indicating the product as an NTI drug. FDA has PSGs for the 0.6 mg colchicine oral tablet and capsule, and neither PSG recognizes colchicine as an NTI drug. Overall, there is inconsistency in NTI classification among agencies. Reaching scientific consensus on NTI classification among regulatory agencies, is another important task besides the global harmonization of NTI BE criteria. A comprehensive NTI list agreed by all agencies may be overly challenging. At least global regulators should agree on general methodology to classify NTI drugs, e.g., whether NTI is drug substance specific or drug product specific, which data should be collected for NTI classification.

After 2012, the majority of BE studies (over 90%) submitted to FDA for NTI drug products are four-way crossover BE studies. FDA has gathered a significant amount of data regarding within-subject variability of NTI drugs. For both C_{max} and AUC, the majority of average S_{WR} of NTI drug products fell within 0.10–0.20, consistent with one of the NTI characteristics, i.e., NTI has low to moderate within-subject variability. Most NTI drug products had an average S_{WR} for AUC and C_{max} below 0.21. In addition, some ER products had a relatively higher S_{WR} than IR or DR products (Table III). For example, carbamazepine IR suspension had an average S_{WR} for AUC of 0.06, whereas carbamazepine ER tablet had an average S_{WR} for AUC of 0.19 (Table III). The same trend was observed with divalproex sodium DR pellet capsule and ER tablet, as the average S_{WR} for C_{max} was 0.06 (for DR pellet) versus 0.19 (for ER tablet), respectively (Table III). Overall, the difference in S_{WR} among different dosage forms is notable and can be explained by their unique formulation characteristics.

Based on recently published ICH M13A guideline, in studies with multiple comparator products, bioequivalence decisions will be made independently about a test product relative to a single comparator product within a single jurisdiction. If reference scaled approach for NTI drugs is adopted by global regulatory agencies and S_{WR} needs to be calculated, the S_{WR} will be calculated for individual comparator product separately in studies with multiple comparator products. The type I error rate in the study having multiple comparator product should remain similar to that of the study having one single comparator product. In addition, with the fully replicated study design, for the first time, the within-subject variability of test and reference standard can be compared. In a partially replicated crossover study with reference drug given twice and test drug given once, only

S_{WR} is obtained, therefore, no variability comparison of test and reference products can be performed with this type of study design. Of failed studies, no IR but only ER products failed the variability comparison (Table II). Overall, this is plausible as ER products are known to have a greater degree of complexity in their formulations and manufacturing process compared to IR products, thus may introduce more product variability. There have been debates whether the variability comparison is necessary for NTI products. Previous simulation work by Jiang, et al. suggested that variability comparison would provide additional assurance of BE for NTI drugs. Jayachandran and Benet, et al. also demonstrated the value of additional variability comparison with warfarin tablets (an IR product) (23, 24). In a recent publication, Lechat et al. also conducted simulation and concluded that switchability between reference and generic NTI drugs can only be achieved if the within-subject variance of generic is less than or equal to that of the reference or if the distribution of the generic/generic individual exposure ratios is included within the therapeutic margins of the reference drug (25). In another publication, Endrenyi, et al. commented that the variability comparison information is interesting but not more important and essential for comparing formulations of NTI drugs than any other drugs (26). Paixão, et al. recently proposed to conduct a three-way partially replicated crossover BE study, i.e., administering reference drug twice and test drug once, and scale BE limits based on reference within-subject variability. The reference scaled criterion for AUC is capped at 90.00–111.11% when $S_{WR} \leq 0.1386$ or at 80.00–125% when $S_{WR} > 0.29356$, and/or apply additional point estimate constraints and adjustment of the one-sided significance level α (15, 27, 28). In their proposal, no variability comparison will be performed for any NTI drug products. A three-way crossover BE study may involve shorter study duration and less subject dropouts, thus decreasing development time and costs. While this is one plausible proposal for global NTI BE criteria harmonization, further analysis of various BE criteria proposals as well as further discussion among the global regulatory agencies on the need of variability comparison are needed, e.g., applying variability comparison criteria based on formulation risks or using an innovative 3-way fully replicated design for variability comparison.

If variability comparison is necessary, another consideration is whether the current FDA variability comparison criteria differentiates clinical difference vs. statistical difference. For example, a S_{WR} of 0.08 and S_{WT} of 0.22, is considered statistically different, and may be clinically different. In another case, a S_{WR} of 0.04 and S_{WT} of 0.10 is statistically different and would fail the variability comparison. However, is this difference clinically acceptable as both variabilities are very small? Should we apply different variability comparison criteria in different variability ranges? All these questions need further discussion among regulatory scientists to reach global consensus.

It was observed that most study failures were due to failed reference scaled criterion with C_{max} only (Table II). Out of 20 failed studies, 11 studies for IR products and 2 studies for ER products failed reference scaled criterion due to C_{max} only (Table II). FDA currently applies tighter reference scaled criterion to both AUC and C_{max} as FDA considers that both AUC and C_{max} are of importance to NTI drug safety and efficacy, i.e., sub- and supra- therapeutic dose and/or concentrations of NTI drugs increases the risk for serious therapeutic failure or adverse events. Paixão's proposal only applies reference scaled criterion to AUC, while conventional BE limits of 80.00–125.00% are applied to C_{max} unless deemed clinically relevant in which reference scaled criterion would be applied (27). Additionally, EMA only tightens C_{max} to 90.00–111.11% when C_{max} is of particular importance for safety, efficacy, or drug level monitoring. Based on EMA PSGs, for acenocoumarol tablets, colchicine tablets, everolimus tablets and dispersible tablets, levothyroxine sodium tablets, sirolimus coated tablets, and tacrolimus granules for oral suspension, EMA may not consider C_{max} of these products of particular importance for safety, efficacy, or drug level monitoring. Necessity of tighter limits on C_{max} warrants further discussion among global regulatory agencies.

For individual PK parameters, when S_{WR} is > 0.20, almost 100% of PK parameters passed 2012 NTI BE criteria (Fig. 5). For an NTI drug with $S_{WR} > 0.2142$, the BE limits are capped within 80–125%. For example, if the $S_{WR} = 0.31$, the BE limits for an NTI drug will still be 80.00–125.00%. Usually, for a highly variable drug with $S_{WR} = 0.31$, the BE limits will be wider than 80.00–125.00%. Thus, tighter criteria are still applied to NTI drugs in the high S_{WR} region. When S_{WR} is ≤ 0.20, there is a trend for lower passing rate at lower S_{WR} for C_{max}, but not with AUC_t and AUC_{inf} when $S_{WR} \leq 0.05$ (Fig. 5). Paixão, et al. previously proposed capping the BE limits at 90.00–111.11% when S_{WR} is ≤ 0.1386. In warfarin data analysis, Benet, et al. concluded that there is little concern the low WSV of warfarin will cause a warfarin formulation to fail the United States Pharmacopeia (USP) content labeling variance of ±5% (24). Further work on the option of capping the BE limits at 90–111% or 95–105% when S_{WR} is low (e.g., < 0.1) should be explored.

Conclusion

This work helps the agency better understand the impact of FDA's NTI classification and BE criteria on the approval of generic NTI drugs. It clarifies the range of within-subject variability for PK parameters of NTI drugs and delineates specific reasons for studies which failed 2012 NTI BE

criteria, e.g., failed mostly reference scaled criterion for C_{max}. Future work will include subjecting these ANDA BE data to other regulatory agencies' NTI BE standards and other proposed NTI BE criteria (e.g., Paixão's and others). Additionally, communication of this work with global regulatory agencies and the scientific community will support the development of harmonized BE approaches and criteria for NTI drugs, in turn improving patients access to generic NTI drugs.

Acknowledgements This project was supported in part by an appointment of Drs. Krista Anim Anno and Mirette Mina to the Research Participation Program at the U.S. Food and Drug Administration administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the U.S. Department of Energy and the U.S. Food and Drug Administration.

Part of the manuscript findings was presented at American College of Clinical Pharmacology (ACCP) 2023 Annual Meeting at Bellevue, Washington in September 2023.

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Funding This project was supported in part by an appointment of Drs. Krista Anim Anno and Mirette Mina to the Research Participation Program at the U.S. Food and Drug Administration administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the U.S. Department of Energy and the U.S. Food and Drug Administration.

Declarations

Conflict of Interest The authors declared no competing interests for this work. This manuscript reflects the views of the authors and should not be construed to represent FDA's views or policies.

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