078

Survey of Bioequivalence Data of Abbreviated New Drug Applications of Narrow Therapeutic Index Drug Products

Krista Anim Anno[1], Mirette Mina[1], Zhen Zhang[2], Lei Zhang[1], and Wenlei Jiang[1,a]

[1]Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland 20993
[2]Office of Bioequivalence, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland 20993
• [a] Corresponding author: wenlei.jiang@fda.hhs.gov

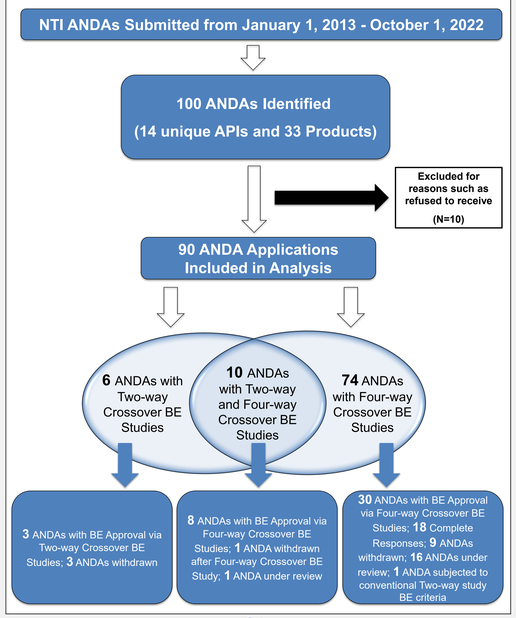
Background

- The U.S. FDA refers to NTI drugs as drug products where minor differences in dose or blood concentration may lead to serious therapeutic failures and adverse drug reactions that are life-threatening or result in significant disability.[1]
- Health professionals have voiced concern pertaining to the BE of a generic NTI drug compared to its RLD using conventional bioequivalence limits of 80.00-125.00%.
- In 2012, FDA tightened both quality and BE standards for NTI drugs, i.e., recommending 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 (2012 NTI BE criteria).[1] In addition, the potency assay limits are tightened to 95.00-105.00% from conventional 90.00-110.00%.
- FDA recommends fully replicated study design, reference scaled BE limits, and variability comparison for BE demonstration of NTI drugs, while most other agencies recommend conventional two-way crossover studies but directly tighten BE limits to 90.00-111.0%.

Objectives

The objective of this study is to survey BE and quality data of ANDAs of NTI drug products submitted and/or approved by the FDA after 2013 in an effort to identify the impact of FDA's innovative BE approach (2012 NTI BE criteria) on generic NTI approval. The results will help support the future international harmonization on NTI BE standards to support ICH M13 development.[2]

Methods



www.fda.gov

Results

Table 1. NTI Drug Products and their Respective PSGs by U.S. FDA [3]

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

Figure 1. Four-way Crossover BE Study Distribution

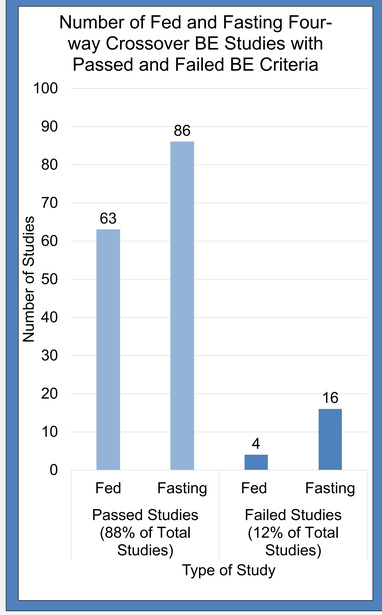


Table 2. BE Criteria Failure Distribution Among Solid Oral IR and ER Products

Type of Study Failure	IR Studies (90 total)	ER Studies (79 total)
Studies failed reference scaled limits only	15	3
Studies failed variability comparison only	0	1
Studies failed both variability and reference scaled limits	0	1
Studies failed either reference or variability comparison	**15 (16.7%)**	**5 (6.3%)**

Figure 2. BE Criteria Failure Distribution

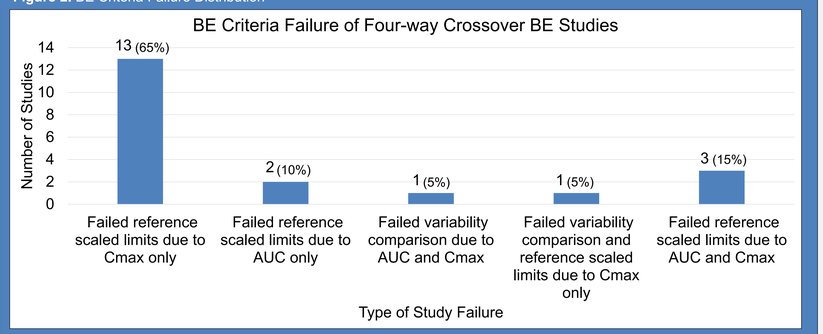


Figure 3. Distribution of Average sWRs for Cmax Among Various Narrow Therapeutic Index Drug Products with Four-way Crossover BE Studies

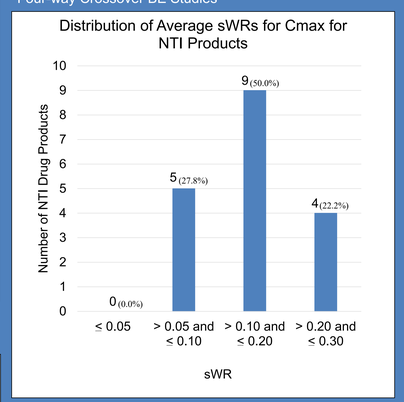


Figure 4. Distribution of Average sWRs for AUC Among Various Narrow Therapeutic Index Drug Products with Four-way Crossover BE Studies

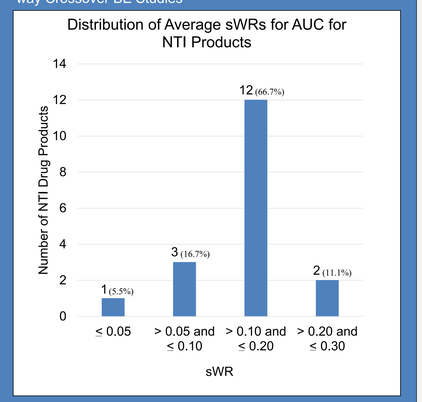


Figure 5. Proportion of sWRs per PK Parameter among Four-way Crossover Passed BE Studies

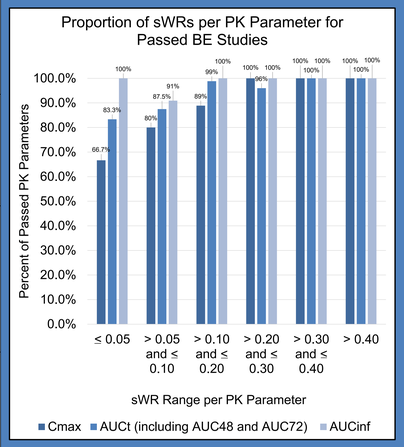
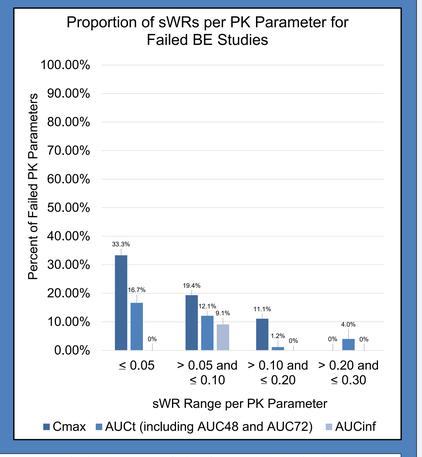


Figure 6. Proportion of sWRs per PK Parameter among Four-way Crossover Failed BE Studies



Abbreviations: United States (U.S.); Food and Drug Administration (FDA); Narrow Therapeutic Index (NTI); Bioequivalence (BE); Reference Listed Drug (RLD); Abbreviated New Drug Applications (ANDAs); International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH); Active Pharmaceutical Ingredients (APIs); Product-Specific Guidances (PSGs); Reference Standard (RS); Immediate Release (IR); Extended Release (ER); Delayed Release (DR); Pharmacokinetic (PK); Center for Drug Evaluation and Research (CDER)

Summary

- Since 2012, FDA has published and updated 29 PSGs for NTI drug products to recommend four-way crossover BE studies and 2012 NTI BE criteria. All recommend fasting and fed BE studies, except levothyroxine (BE studies under fasting conditions only).
- Three NTI ANDAs were approved in or after 2013, via conventional two-way crossover studies and BE criteria, prior to their PSG updates.
- Over 150 four-way crossover BE studies were submitted. Approximately, 88% passed 2012 NTI BE criteria.
- Of the studies that failed BE criteria, approximately 65% failed reference scaled limits due to Cmax only. Approximately 5% of BE studies failed due to failing variability comparison criteria only. IR and ER products failed 2012 NTI BE criteria at 16.7% and 6.3%, respectively.
- For all NTI drug products, the range of average sWR for Cmax and AUC was between 0.05 and 0.28, mostly within 0.10 and 0.20, consistent with the NTI attribute (having low to moderate within-subject variability).
- For the same API with distinctly different dosage forms, differences in average sWRs were observed.
- Among failed BE studies, there is a higher percentage of failed PK parameters when the PK parameters have a lower sWR.

Conclusions

- This work helps the Agency better understand the impact of FDA NTI BE criteria on the approval of generic NTIs submitted to FDA.
- Further exchange of this work with global regulatory agencies and scientific community will clarify the strengths and limitations of different BE approaches and criteria for NTI drugs and promote the development of harmonized BE approaches and criteria for NTI drugs, in turn improving patients access to generic NTI drugs.

Acknowledgements & Disclaimer

This project was supported in part by an appointment of 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. Special thanks to CDER NTI working group for their review and input on this project.

The contents in this poster reflect the views of the authors and should not be construed to represent U.S. FDA's views or policies.

References

1. Yu LX, Jiang W, Zhang X, et al. Novel bioequivalence approach for narrow therapeutic index drugs. Clin Pharmacol Ther. 2015; 97(3):286-91.
2. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: https://www.ich.org/
3. U.S. FDA PSG Database: https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development