FDA Drug Topics: Understanding Generic Narrow Therapeutic Index Drugs

Wenlei Jiang, Ph.D.
Senior Advisor for Innovation and Strategic Outreach

Office of Research and Standards
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration (FDA)

Disclaimer

The views expressed in this presentation are those of the speaker and not necessarily those of the Food and Drug Administration (FDA).

Outline

- Narrow therapeutic index (NTI) drugs and their characteristics
- FDA bioequivalence (BE) and quality standards for NTI drugs
- Global bioequivalence standards for NTI drugs
- FDA post-market research on generic NTI drugs

Learning Objectives

- Recognize general characteristics of NTI drugs
- Describe FDA's approach and criteria to evaluate the bioequivalence of generic NTI drugs
- Discuss examples of FDA's approved generic NTI drugs demonstrating therapeutic equivalence to brand counterparts in patient populations
- List opportunities to facilitate global generic NTI drug development and increase generic NTI substitution

Narrow Therapeutic Index Drugs

- Narrow therapeutic index (NTI) drugs are drugs where small differences in dose or blood concentration may lead to serious therapeutic failures and/or adverse drug reactions that are life-threatening or result in persistent or significant disability or incapacity.

Novel Bioequivalence Approach for Narrow Therapeutic Index Drugs

LX Yu[1], W Jiang[1], X Zhang[1], R Lionberger[1], F Makhlouf[1], DJ Schuirmann[1], L Muldowney[1], M-L Chen[1], B Davit[1,2], D Conner[1] and J Woodcock[1]

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 97 NUMBER 3 | MARCH 2015

General Characteristics

Little separation between therapeutic and toxic doses (or associated blood/plasma concentrations)

Sub-therapeutic concentration may lead to serious therapeutic failure

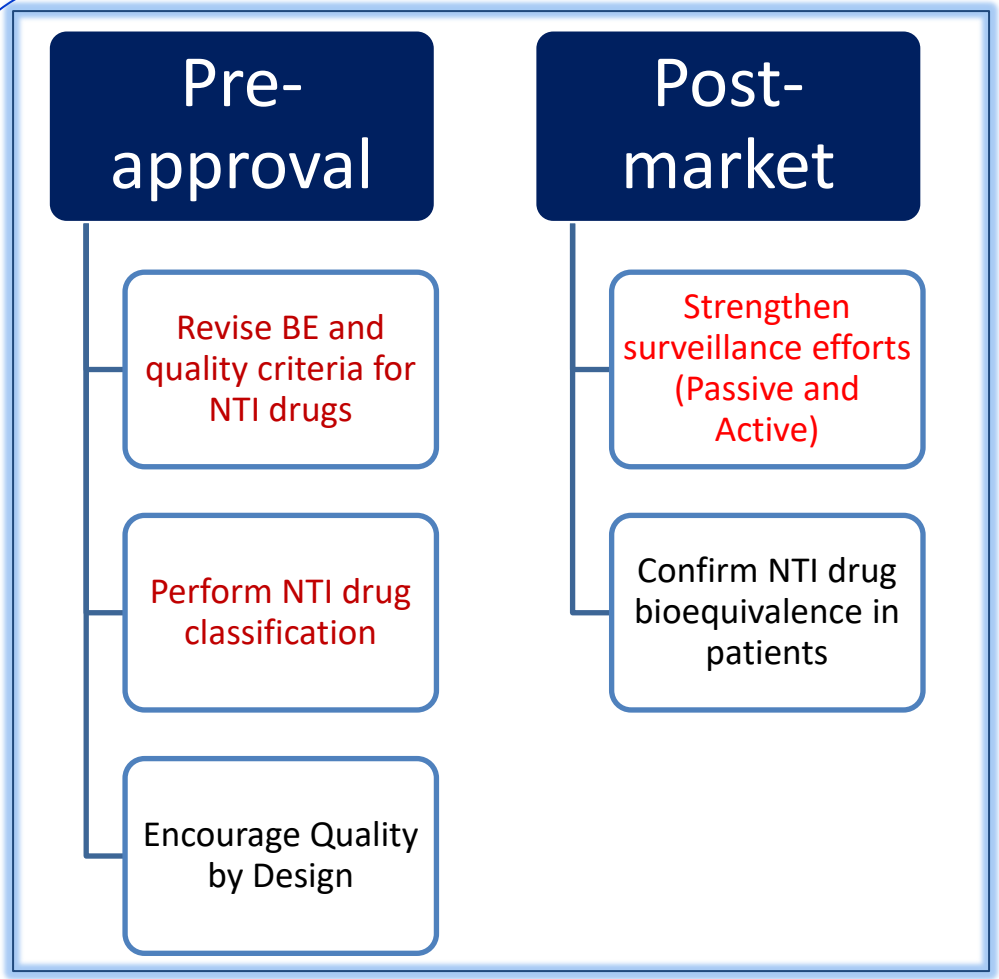
Drugs are subject to therapeutic drug monitoring (TDM) based on pharmacokinetic (PK) or pharmacodynamic (PD) measures

Drugs possess low-to-moderate (i.e., no more than 30%) within-subject variability

In clinical practice, doses are often adjusted in very small increments (less than 20%)

LX Yu, W Jiang, X Zhang, R Lionberger, F Makhlouf, DJ Schuirmann, L Muldowney, M-L Chen, B Davit, D Conner and J Woodcock. Novel Bioequivalence Approach for Narrow Therapeutic Index Drugs. Clinical Pharmacology & Therapeutics 2015

FDA Efforts to Ensure Generic NTI Drug Safety and Efficacy



Perception about Generic NTI Drugs

Today's focus

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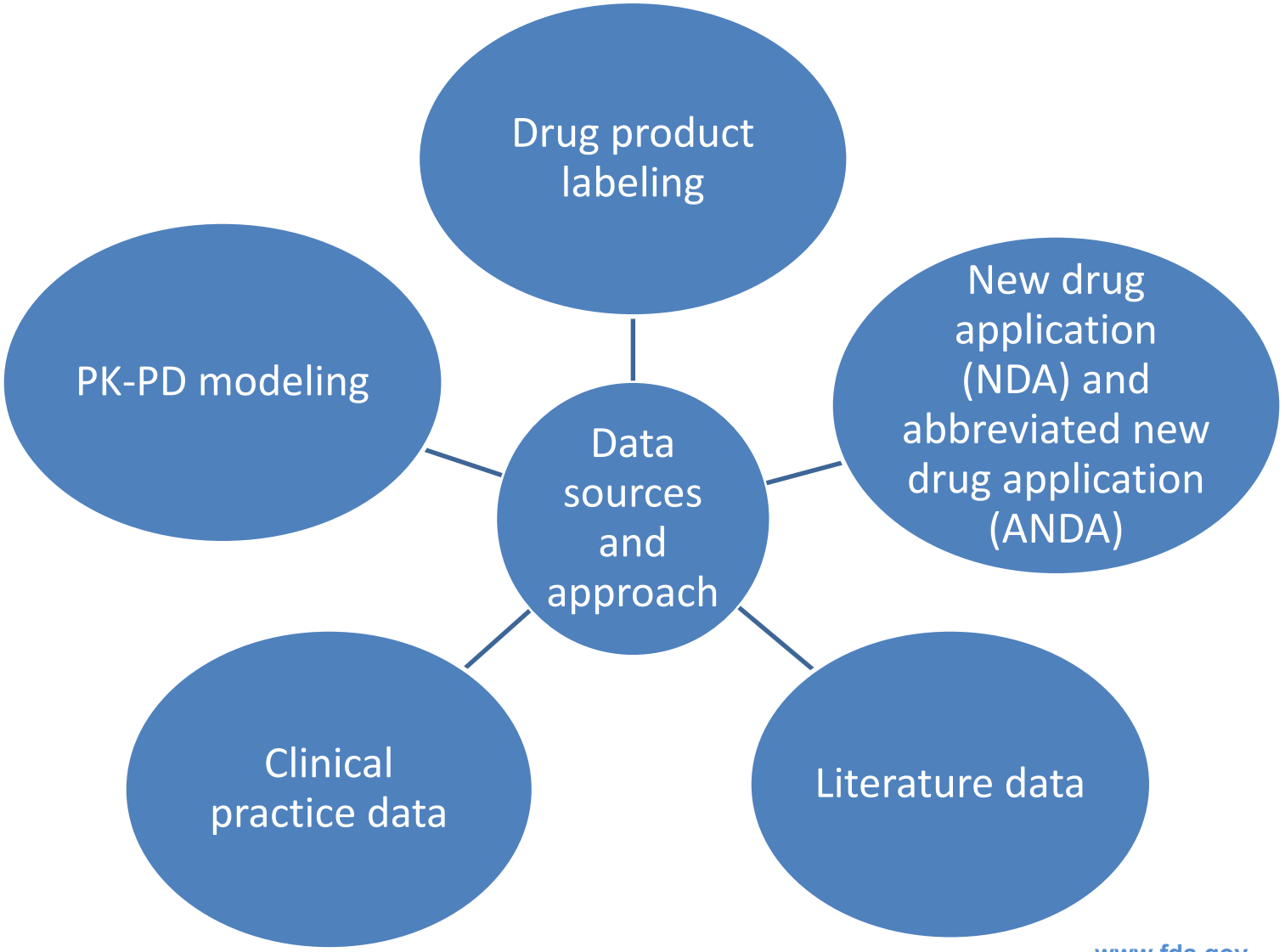
Streamline NTI Classification

FDA NTI Classification Data Sources and Approach



PK-PD: Pharmacokinetic-Pharmacodynamic

NTI Classification (1): Sub or super concentrations cause serious therapeutic failure and adverse events?

- Serious therapeutic failure

  Epilepsy, immunosuppression, heart failure, anticoagulation…..

- Serious adverse events

  Dose-dependent drug substance related adverse events

NTI Classification (2): Determine if little separation between toxic and therapeutic doses (conc.)?

- Determined based on population level PK/PD and/or exposure/dose response data
- Estimated based on therapeutic window

Drugs	Therapeutic range	Plasma concentration associated with serious toxicity	Estimated toxic/ effective concentration ratio
Phenytoin (http://www.clinicalpharmacology-ip.com/Forms/drugoptions.aspx?cpnum=484&n=Phenytoin)[a]	10–20 mcg/ml	>40 mcg/ml	2.7

- Inferred from individual level data

TDM and small dose adjustment can be a hint of steep exposure-response relationship within individuals, therefore, little separation is anticipated.

NTI Classification (3): Estimate Within-Subject Variability

- Estimated via root mean square error (RMSE) values of the bioequivalence parameters C_{max} and AUC_{0-t} from single-dose two-way crossover BE studies

		AUC0-t		C_{max}	
Drug products	# of BE Studies	Mean	Range	Mean	Range
Warfarin	29	5.7	3.3, 11.0	12.7	7.7, 20.1
Lithium carbonate	16	7.8	4.5, 14.0	13.5	6.4, 24.4
Digoxin	5	21.7	13.1, 32.2	21.0	14.3, 26.1
Phenytoin	12	9.2	4.1, 18.6	14.9	7.4, 20.0
Theophylline	3	17.9	12.8, 24.2	18.2	11.8, 25.8
Tacrolimus	6	21.9	16.8, 26.6	19.0	15.0, 24.4

NTI drugs generally have small to medium within-subject variability, e.g., < 30%.

LX Yu, W Jiang, X Zhang, R Lionberger, F Makhlouf, DJ Schuirmann, L Muldowney, M-L Chen, B Davit, D Conner and J Woodcock. Novel Bioequivalence Approach for Narrow Therapeutic Index Drugs. Clinical Pharmacology & Therapeutics 2015

NTI Classification (4): Evaluate the need for Therapeutic Drug Monitoring (TDM)

- Monitoring purpose
- Routine or occasionally
- In special population

NTI Classification (5): Evaluate dose adjustment pattern

- Multiple dose strengths available for the product

- Actual clinical practice data show small increment or decrement with patients

  - Dose adjustment when therapeutic failure or adverse events occurred

  - Drug-drug interaction data

  - Food effect

Determination of NTI Drugs

Drug product	Estimated toxic/ effective ratio	Sub-therapeutic concentrations lead to therapeutic failure	TDM	Within-subject variability (AUC)	Small dose adjustment	NTI?
Carbamazepine	2.5	Yes	Yes	12.6%	Possible	Yes
Lamotrigine	10	Yes	Not routinely	10%	Possible	No
Levetiracetam	ND	Yes	No	27.7%	Possible	No
Phenytoin	2.7	Yes	Yes	10.6%	Possible	Yes
Topiramate	ND	Yes	No	8.5%	Possible	No
Valproic Acid	2-2.7	Yes	Yes	12.0%	Possible	Yes
Tacrolimus	~2	Yes	Yes	21.9%	Possible	Yes

FDA NTI Working Group

1. Develop a science- and risk-based regulatory approach to identify NTI drugs based on the relevant information from new drug development programs and elsewhere

2. Establish a consistent process to resolve key NTI-related scientific and regulatory issues in a transparent and collaborative manner

3. Create (or develop) a consistent process for monitoring and re-evaluating NTI drugs in the early post-marketing stage to support timely availability of product-specific guidance (PSG) recommendations for generic drug development

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Update FDA Bioequivalence and Quality Standards for NTI Drugs

Generic Drugs

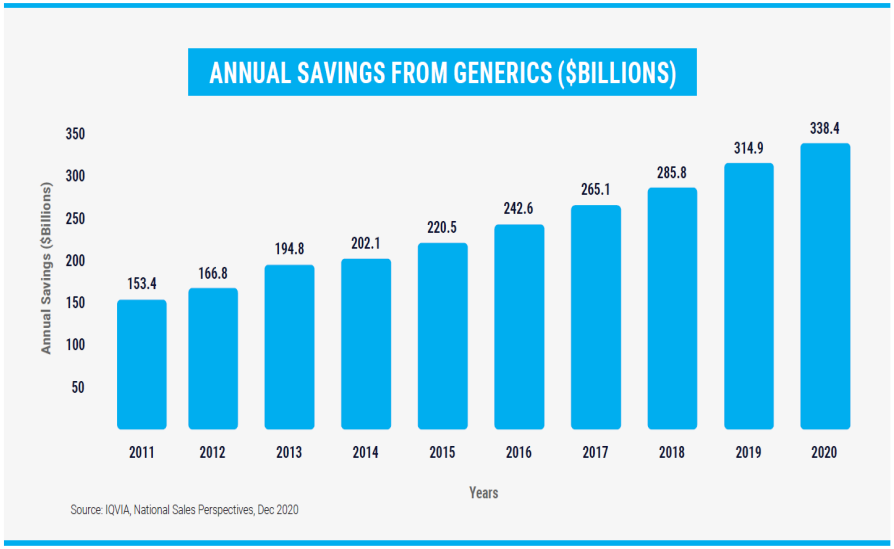
- Generic drugs are “copies” of their respective reference listed drugs (RLDs)

- Generally, this means same active ingredient(s), dosage form, strength, route of administration, conditions of use, and labeling (with certain limited exceptions). Must also demonstrate bioequivalence and ensure product’s identity, strength, quality, and purity.

Generic Drugs

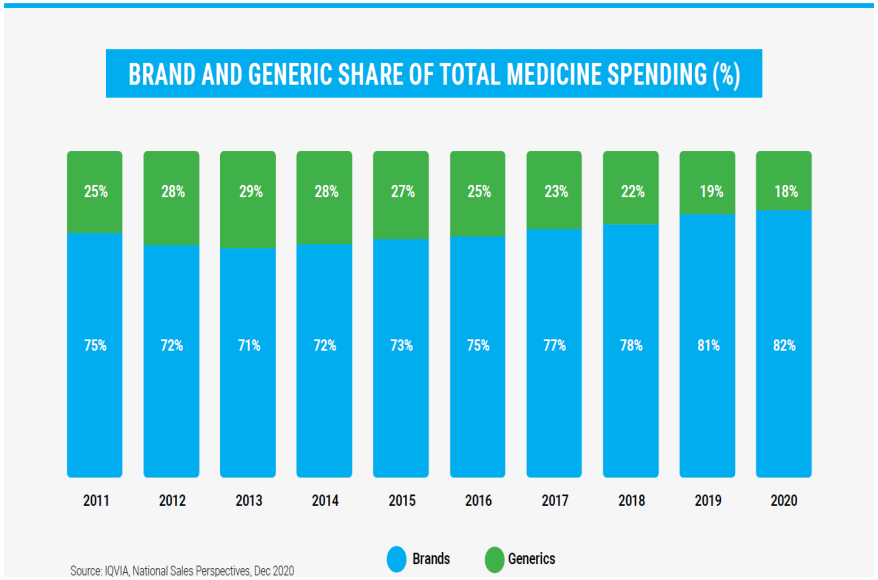
Savings from Generics and Biosimilars Totaled $338 Billion in 2020

GENERIC AND BIOSIMILAR SAVINGS INCREASED BY $23.5 BILLION FROM 2019 TO 2020



Generics Account for 18.1% of Total Medicine Spending

GENERICS MAKE UP 90% OF ALL PRESCRIPTIONS



[Report: 2021 U.S. Generic and Biosimilar Medicines Savings Report | Association for Accessible Medicines (accessiblemeds.org)]

New Drug Application (NDA) vs. Abbreviated New Drug Application (ANDA)

NDA

1. Chemistry
2. Manufacturing
3. Testing
4. Labeling
5. Inspection
6. Animal Studies
7. Clinical Studies
8. Bioavailability

ANDA

1. Chemistry
2. Manufacturing
3. Testing
4. Labeling
5. Inspection
6. Bioequivalence

General Bioequivalence Study Design and Criteria

Study design:
Single dose 2-way crossover

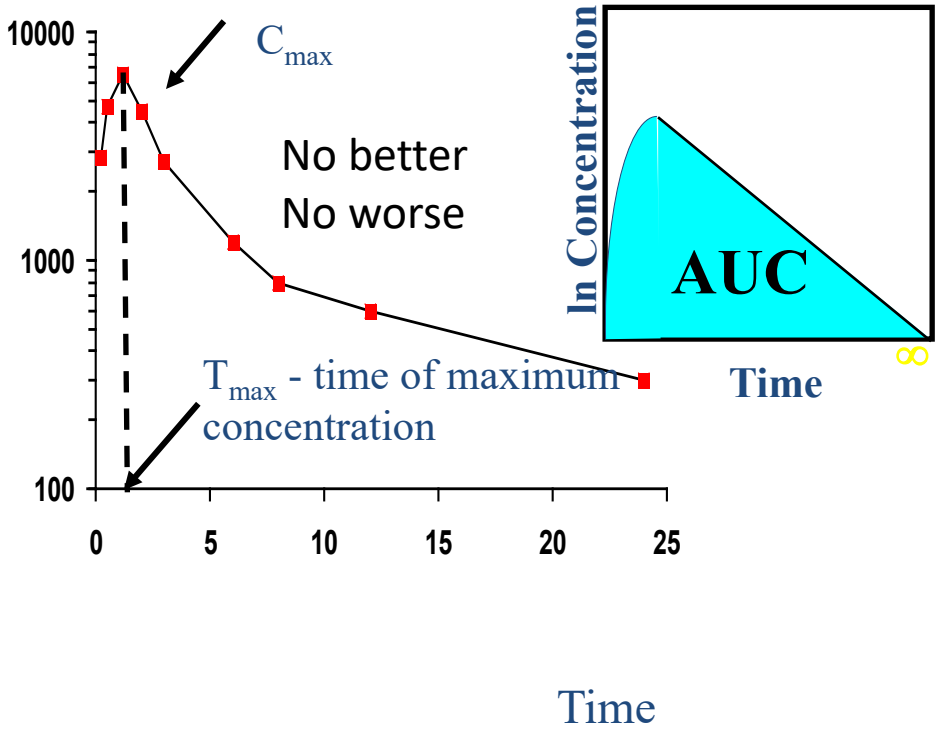
Sequence 1

T – washout period – R

Sequence 2

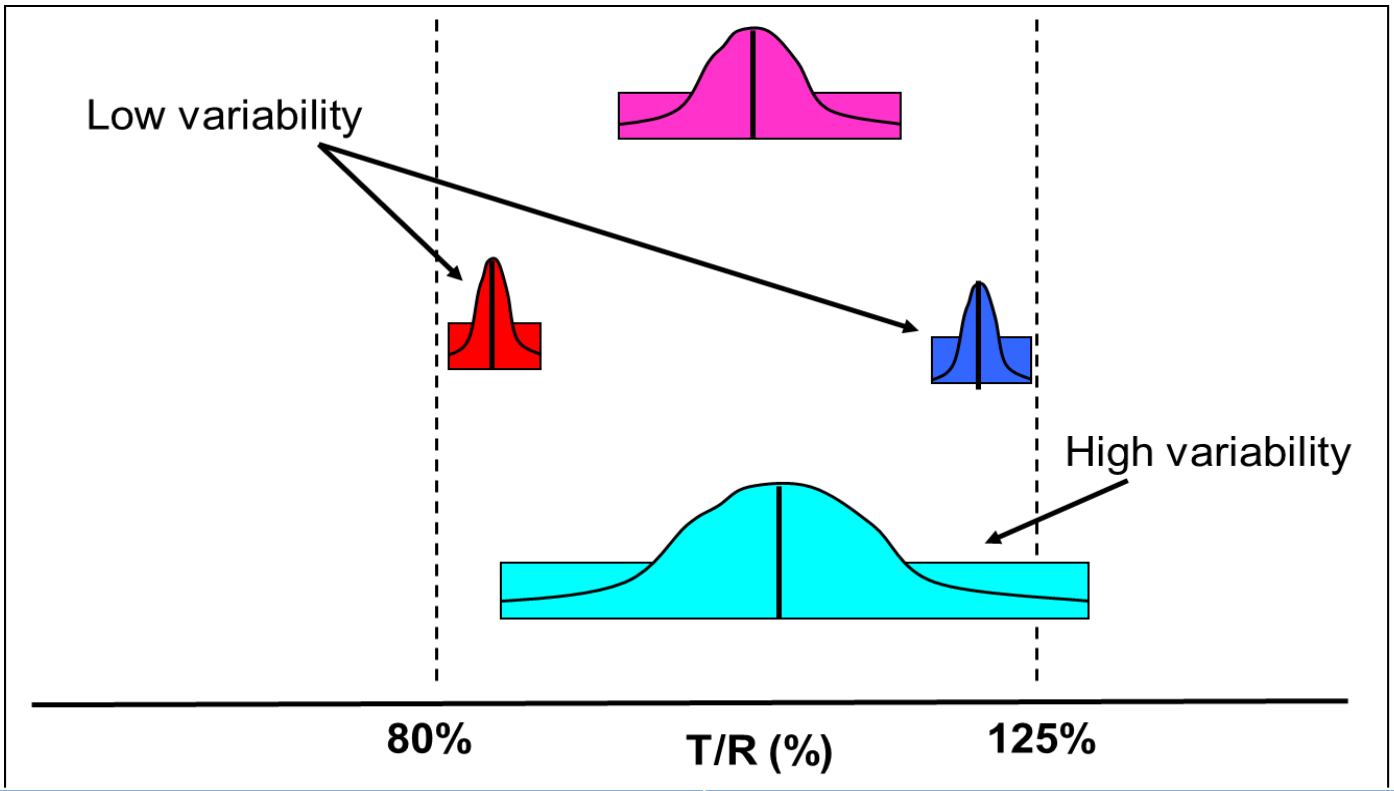
R – washout period – T

- T= Test Drug
- R= Reference Listed Drug (RLD)



90% confidence interval (CI) for the geometric mean ratio of test/reference within 80.00-125.00%

One-Size Bioequivalence Criteria Do Not Fit All Drugs

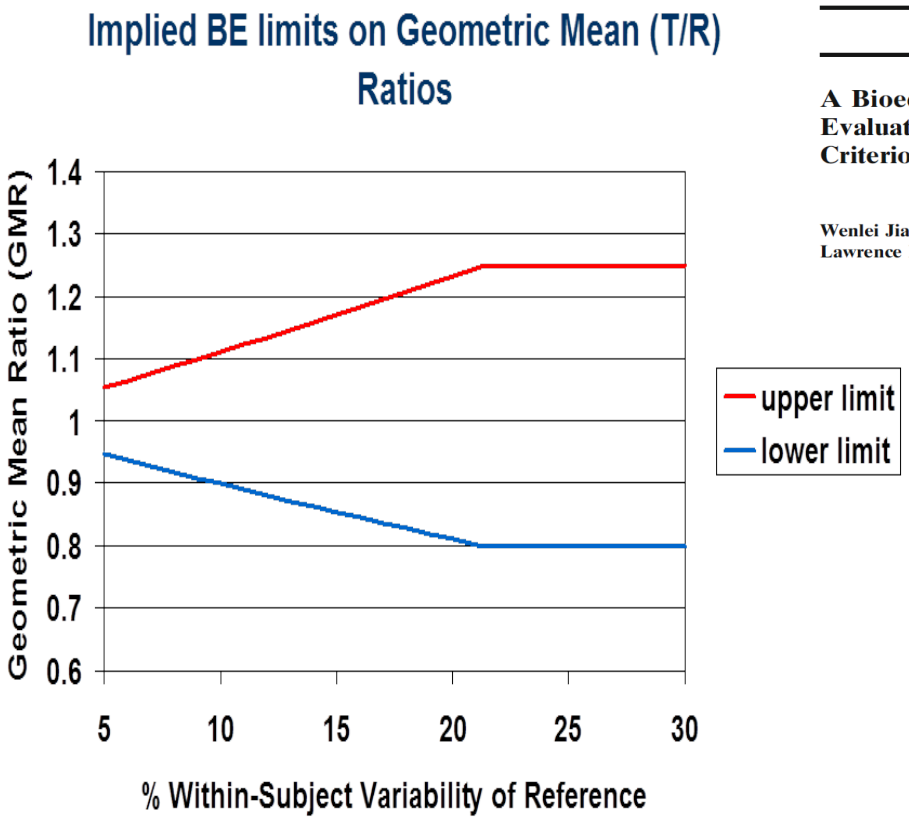


Drugs	Within-subject variability (WSV)
NTI drugs	≤ 30%
Highly variable drugs (HVDs)	> 30%

Bioequivalence Study Design Tailored for Different Drug Products

Types of Drugs	Study Design	Sequence	BE criteria	
			Mean comparison	Variability comparison
Non-NTI, Non HVD drugs	Single-dose 2-way crossover	T, R R, T	Yes, CI 80.00-125.00%	No
HVD drugs	Single-dose, partially replicated, 3-way crossover Single-dose, fully replicated 4-way crossover	T, R, R R, R, T T, R, T, R R, T, R, T	Yes, CI scaled, point estimate constraint	No
NTI drugs	Single-dose, fully replicated, 4-way crossover	T, R, T, R R, T, R, T	Yes Must pass both the reference scaled limits and the unscaled average bioequivalence limits of 80.00-125.00%.	Yes The upper limit of the 90% CI of the ratio of the within-subject standard deviation of the test to reference product is less than or equal to 2.5.

Reference Scaled BE Limits for NTI Drugs



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Research Article

A Bioequivalence Approach for Generic Narrow Therapeutic Index Drugs: Evaluation of the Reference-Scaled Approach and Variability Comparison Criterion

Wenlei Jiang,[1] Fairouz Makhlouf,[2] Donald J. Schuirmann,[2] Xinyuan Zhang,[1] Nan Zheng,[1] Dale Conner,[1] Lawrence X. Yu,[3] and Robert Lionberger[1,4]

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

Warfarin Sodium Product Specific Guidance.
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201283.pdf

Tighter Assay Limits for NTI Drugs

Drugs	Assumption	Assay Limits
Non-NTI	20% variation in pharmacokinetics (PK) won't lead to clinically relevant difference	90.0-110.0%
NTI	10% or lower variation in PK won't lead to clinically relevant difference	95.0-105.0%

Wenlei Jiang. Pharmaceutical Quality of NTI Drug Products. 2011 Advisory Committee for Pharmaceutical Sciences and Clinical Pharmacology, Jul 26, 2011
https://wayback.archiveit.org/7993/20170405230007/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM266777.pdf

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Global Bioequivalence Standards for NTI Drugs and Further Opportunities

Global Variations in NTI Descriptions

Regulatory Agencies	Term Used	Regulatory Descriptions
Health Canada	Critical dose drugs	Drugs where comparatively small differences in dose or concentration lead to dose- and concentration-dependent, serious therapeutic failures and/or serious adverse drug reactions which may be persistent, irreversible, slowly reversible, or life threatening, which could result in inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, or death.
Europe Medicines Agency (EMA)	Narrow therapeutic index drugs	No definition
U.S. Food and Drug Administration (FDA)	Narrow therapeutic index drugs	Drugs where small differences in dose or blood concentration may lead to serious therapeutic failures and/or adverse drug reactions that are life-threatening or result in persistent or significant disability or incapacity.
Japan Pharmaceutical and Food Safety Bureau (MHLW/PMDA)	Narrow therapeutic range drugs	No definition
South Africa Medicine Control Council	Narrow therapeutic range drugs having steep dose response curve	No definition

W Jiang and LX Yu. Bioequivalence for narrow therapeutic index drugs. In L.X. Yu and B.V. Li (eds.), FDA Bioequivalence Standards, 2014 AAPS Advances in the Pharmaceutical Sciences Series, Springer Science New York 2014

Examples of NTI or Critical Dose Drugs

Health Canada	Digoxin, flecainide, lithium, phenytoin, sirolimus, tacrolimus, cyclosporine, theophylline, and warfarin
EMA	Tacrolimus, sirolimus, cyclosporine
FDA	Warfarin, tacrolimus, sirolimus, phenytoin, carbamazepine, levothyroxyine, and etc.
MHLW/ PMDA	Aprindine, Carbamazepine, Clindamycin, Clonazepam, Clonidine, Cyclosporine, Digitoxin, Digoxin, Disopyramide, Ethinyl Estradiol, Ethosuximide, Guanethidine, Isoprenaline, Lithium, Methotrexate, Phenobarbital, Phenytoin, Prazosin, Primidone, Procainamide, Quinidine, Sulfonylurea antidiabetic drugs compounds, Tacrolimus, Theophylline compounds, Valproic Acid, Warfarin, Zonisamide, Glybuzole

BE Criteria for NTI Drugs

Regulatory Agencies	Bioequivalence Criteria	
	AUC	Cmax
Health Canada	90.0% -112.0%	80.0-125.0%
EMA	90.00-111.11%	80.00-125.00% Where Cmax is of particular importance for safety, efficacy or drug level monitoring, the 90.00-111.11% acceptance interval should also be applied to Cmax
South Africa Medicine Control Council	80.0-125.0%	80.0-125.0%
MHLW/PMDA	80.0-125.0%	80.0-125.0%
U.S. FDA	Must pass both the reference scaled limits and the unscaled average bioequivalence limits of 80.00-125.00%. In addition, 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.	

W. Jiang. Bioequivalence Approach for Narrow Therapeutic Index (NTI) Drugs. Antiepileptic drug and device trials XIII, May 13-15, 2015

Further Opportunities for Harmonization of Standards for Generic Drugs

- Develop a series of International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on standards for demonstrating equivalence (e.g., bioequivalence) for non-complex dosage forms

- Develop a series of ICH guidelines on standards for demonstrating equivalence (e.g., bioequivalence) for more complex dosage forms or products

https://admin.ich.org/sites/default/files/2019-04/ICH_ReflectionPaper_GenericDrugs_Final_2019_0130.pdf

Further Opportunities for Harmonization of Standards for Generic Drugs

M13: Bioequivalence for Immediate-Release Solid Oral Dosage Forms

- General considerations and principles on BE study design
- Data analysis
- Biowaiver for additional strengths
- Advanced BE study design considerations
- Data analysis and BE assessment for highly variable drugs and drugs with a narrow therapeutic index

https://admin.ich.org/sites/default/files/2019-04/ICH_ReflectionPaper_GenericDrugs_Final_2019_0130.pdf

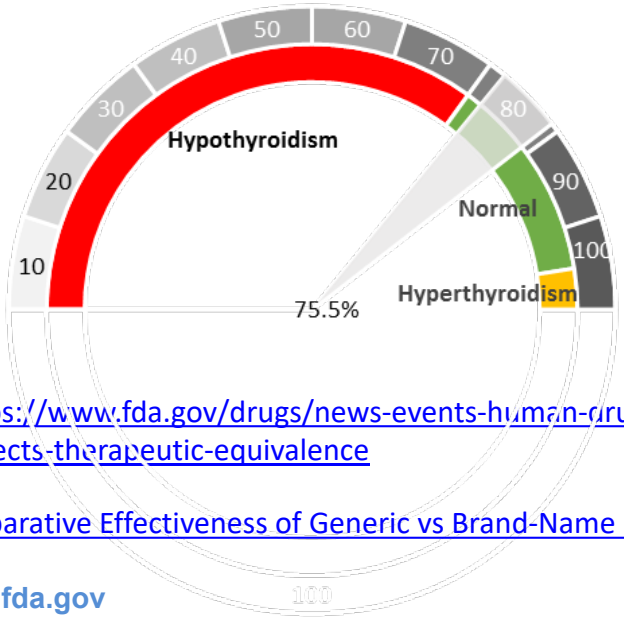
Post-market Research and Perceptions of Generic NTI Drugs

Comparative Effectiveness of Generic vs Brand-name Levothyroxyine

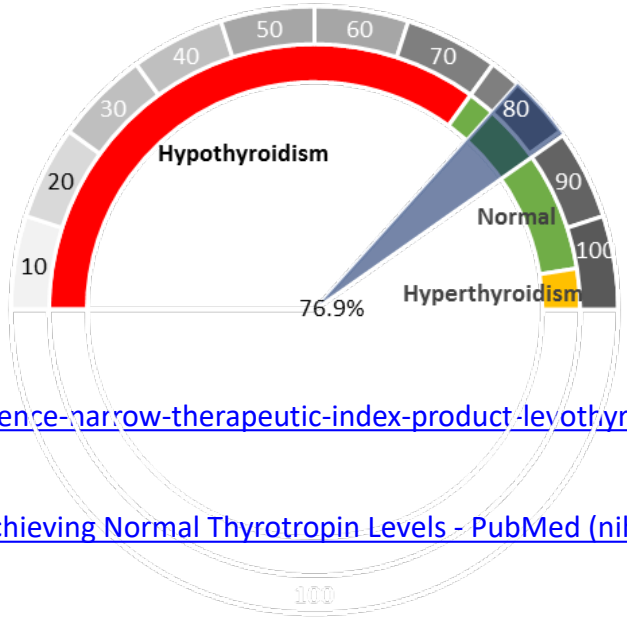
Objective: To compare the effectiveness of generic vs brand levothyroxine in achieving and maintaining normal thyrotropin levels among new users.

Findings: In a cohort study of 17,598 patients from a national administrative claims database, a similar proportion of generic vs brand-name levothyroxine users achieved target thyrotropin levels.

A. Generic Levothyroxine



B. Brand-Name Levothyroxine



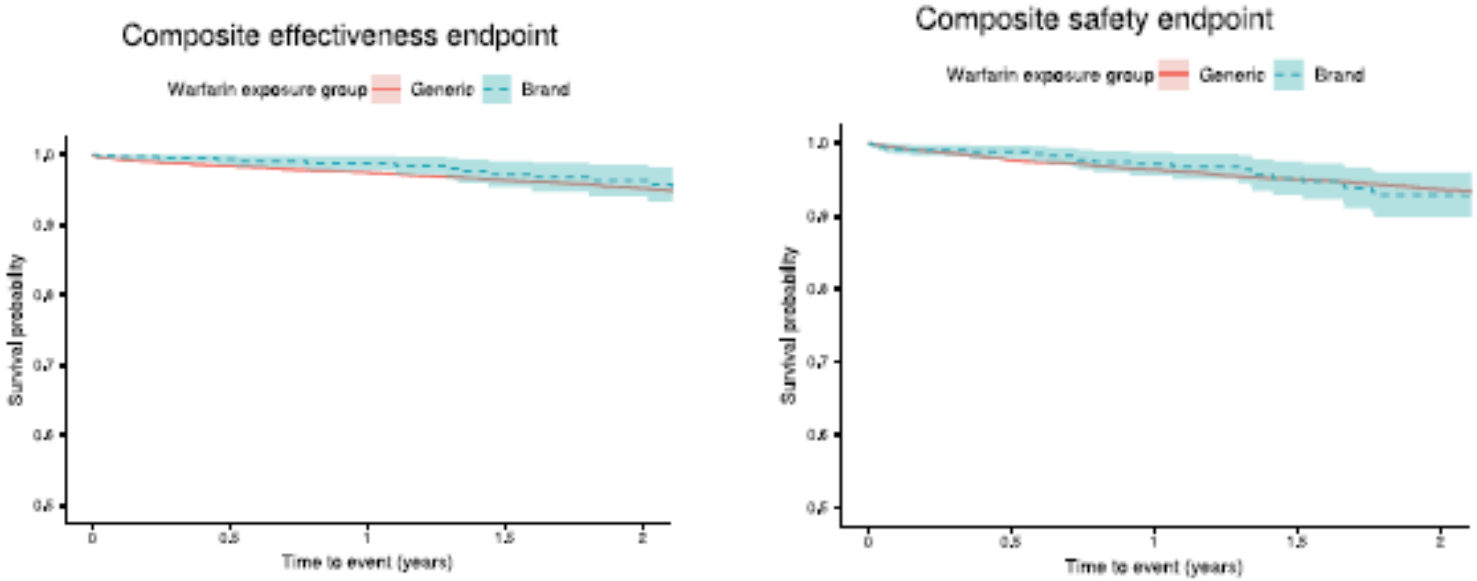
- https://www.fda.gov/drugs/news-events-human-drugs/real-world-evidence-narrow-therapeutic-index-product-levothyroxine-reflects-therapeutic-equivalence

Comparative Effectiveness of Generic vs Brand-Name Levothyroxine in Achieving Normal Thyrotropin Levels - PubMed (nih.gov)

Comparative Outcomes of Treatment Initiation with Brand vs Generic Warfarin in Older Patients

Objective: Evaluate whether outcomes are comparable between generic warfarin products and brand warfarin in patients ≥65 years old.

Findings: In an observational cohort study of 33,645 patients 65 years or older who initiated warfarin, no differences were observed in outcomes, including stroke or venous thromboembolism, major bleeding, and all-cause mortality, between generic vs. brand warfarin.



[Comparative Outcomes of Treatment Initiation With Brand vs. Generic Warfarin in Older Patients - PubMed (nih.gov)]

Pharmacists' Perceptions of Generic NTI Drugs

- Of 710 respondents (33% response rate), 87% perceived generic NTI drugs as effective as their brand-name versions and 94% as safe.
- Whereas 82% almost always performed generic NTI substitution for initial prescriptions, only 60% did for refills.
- Pharmacists in non-chain settings, in pharmacy practice longer, in states with affirmative patient consent laws, and in states with NTI-specific substitution requirements were more likely not to substitute initial prescriptions.
- Education of non-chain and veteran pharmacists and elimination of affirmative patient consent and NTI-specific substitution requirements could increase generic NTI substitution.

Generic Versions of Narrow Therapeutic Index Drugs: A National Survey of Pharmacists' Substitution Beliefs and Practices - PubMed (nih.gov)
https://globalforum.diaglobal.org/issue/july-2019/fda-qa-generic-versions-of-narrow-therapeutic-index-drugs-national-survey-of-pharmacists-substitution-beliefs-and-practices/

Conclusions

FDA is committed to ensure generic NTI drug safety and efficacy and has undertaken efforts to enhance public confidence on generic NTI drugs

- FDA developed novel BE approach and criteria for NTI drugs
  - Fully replicated study design
  - Scaled based on within-subject variability of the RLD
  - Variability comparison
- FDA established process to classify NTI drugs and tightened both quality and bioequivalence standards for NTI drugs
- Real-world evidence reflects the therapeutic equivalence of generic NTI drug products
- Education of non-chain and veteran pharmacists and elimination of affirmative patient consent and NTI-specific substitution requirements could increase generic NTI substitution

Further harmonization of NTI drug classification and bioequivalence approaches are needed among global regulatory agencies

References

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- https://globalforum.diaglobal.org/issue/july-2019/fda-qa-generic-versions-of-narrow-therapeutic-index-drugs-national-survey-of-pharmacists-substitution-beliefs-and-practices/
- Generic Versions of Narrow Therapeutic Index Drugs: A National Survey of Pharmacists' Substitution Beliefs and Practices - PubMed (nih.gov)
- Comparative Outcomes of Treatment Initiation With Brand vs. Generic Warfarin in Older Patients - PubMed (nih.gov)

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Fairouz Makhlouf

Lawrence Yu

Lei Zhang

Robert Lionberger

Challenge Questions

1. Which of the following is not a narrow therapeutic index (NTI) drug?

A) Phenytoin

B) Topiramate

C) Warfarin

D) Tacrolimus

2. Which of the following statements are true about FDA's approach for NTI drugs? Select all that apply

A) Reference scaling of bioequivalence limits
B) Bioequivalence limits will exceed 80.00-125.00%
C) Variability comparison
D) Scaling of Cmax only
E) Both A&C

3. Which of the following statements are true? Select all that apply

A) NTI drugs generally have low to medium within subject variability

B) For NTI drugs, sub-therapeutic concentration may lead to serious therapeutic failure

C) All anti-epileptic drugs (AED) are NTI drugs

D) FDA applies the same bioequivalence limits for all drug products

E) Both A and B

4. Pharmacists in non-chain settings, in pharmacy practice longer, in states with affirmative patient consent laws, and in states with NTI-specific substitution requirements were more likely not to substitute initial prescriptions

A) True

B) False

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Thank you!

Questions?