FDA Drug Topics: Understanding Generic Narrow Therapeutic Index Drugs

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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 Yu¹, W Jiang¹, X Zhang¹, R Lionberger¹, F Makhlouf¹, DJ Schuirmann¹, L Muldowney¹, M-L Chen¹, B Davit¹,², D Conner¹ and J Woodcock¹

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General Characteristics

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

- Sub-therapeutic concentration may lead to serious therapeutic failure

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

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

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

FDA Efforts to Ensure Generic NTI Drug Safety and Efficacy

**Pre-approval**
- Revise BE and quality criteria for NTI drugs
- Perform NTI drug classification
- Encourage Quality by Design

**Post-market**
- Strengthen surveillance efforts (Passive and Active)
- Confirm NTI drug bioequivalence in patients

Perception about Generic NTI Drugs

Today’s focus
Streamline NTI Classification
FDA NTI Classification Data Sources and Approach

- Drug product labeling
- New drug application (NDA) and abbreviated new drug application (ANDA)
- Literature data
- Clinical practice data
- PK-PD modeling

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

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 $C_{\text{max}}$ and $\text{AUC}_{0-t}$ from single-dose two-way crossover BE studies

<table>
<thead>
<tr>
<th>Drug products</th>
<th># of BE Studies</th>
<th>$\text{AUC}_{0-t}$</th>
<th>$C_{\text{max}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>Range</td>
</tr>
<tr>
<td>Warfarin</td>
<td>29</td>
<td>5.7</td>
<td>3.3, 11.0</td>
</tr>
<tr>
<td>Lithium carbonate</td>
<td>16</td>
<td>7.8</td>
<td>4.5, 14.0</td>
</tr>
<tr>
<td>Digoxin</td>
<td>5</td>
<td>21.7</td>
<td>13.1, 32.2</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>12</td>
<td>9.2</td>
<td>4.1, 18.6</td>
</tr>
<tr>
<td>Theophylline</td>
<td>3</td>
<td>17.9</td>
<td>12.8, 24.2</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>6</td>
<td>21.9</td>
<td>16.8, 26.6</td>
</tr>
</tbody>
</table>

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

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

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

**Note:**
- Yes: Indicates that the drug is subject to TDM within the subject variability range.
- No: Indicates that the drug is not subject to TDM within the subject variability range.
- ND: Not determined.
- TDM: Therapeutic Drug Monitoring.
- NTI?: Indicates whether the drug is known to be a Not-to-Increase (NTI) drug. Yes means the drug is an NTI drug, and No means it is not an NTI drug.
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.
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

ANNUAL SAVINGS FROM GENERICS ($BILLIONS)

Generics Account for 18.1% of Total Medicine Spending

BRAND AND GENERIC SHARE OF TOTAL MEDICINE SPENDING (%)

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)

<table>
<thead>
<tr>
<th>NDA</th>
<th>ANDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Chemistry</td>
<td>1. Chemistry</td>
</tr>
<tr>
<td>3. Testing</td>
<td>3. Testing</td>
</tr>
<tr>
<td>4. Labeling</td>
<td>4. Labeling</td>
</tr>
<tr>
<td>5. Inspection</td>
<td>5. Inspection</td>
</tr>
<tr>
<td>7. Clinical Studies</td>
<td></td>
</tr>
<tr>
<td>8. Bioavailability</td>
<td></td>
</tr>
</tbody>
</table>
**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%

C<sub>max</sub> - time of maximum concentration

No better
No worse

AUC - area under the curve

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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

<table>
<thead>
<tr>
<th>Types of Drugs</th>
<th>Study Design</th>
<th>Sequence</th>
<th>BE criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-NTI, Non HVD drugs</td>
<td>Single-dose 2-way crossover</td>
<td>T, R</td>
<td>Yes, CI 80.00-125.00%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R, T</td>
<td>No</td>
</tr>
<tr>
<td>HVD drugs</td>
<td>Single-dose, partially replicated, 3-way crossover</td>
<td>T, R, R</td>
<td>Yes, CI scaled, point estimate constraint</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R, R, T</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Single-dose, fully replicated 4-way crossover</td>
<td>T, R, T, R</td>
<td>Yes</td>
</tr>
</tbody>
</table>
|                         |                                                  | R, T, R, T        | 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

Implied BE limits on Geometric Mean (T/R) Ratios

<table>
<thead>
<tr>
<th>CV&lt;sub&gt;WR&lt;/sub&gt;</th>
<th>Reference Scaled BE limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>94.87 - 105.41</td>
</tr>
<tr>
<td>10</td>
<td>90.02 - 111.08</td>
</tr>
<tr>
<td>15</td>
<td>85.35 - 117.02</td>
</tr>
<tr>
<td>20</td>
<td>81.17 - 123.20</td>
</tr>
<tr>
<td>&gt;21.42</td>
<td>80.00 - 125.00</td>
</tr>
</tbody>
</table>

Warfarin Sodium Product Specific Guidance.
## Tighter Assay Limits for NTI Drugs

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Assumption</th>
<th>Assay Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-NTI</td>
<td>20% variation in pharmacokinetics (PK) won't lead to clinically relevant difference</td>
<td>90.0-110.0%</td>
</tr>
<tr>
<td>NTI</td>
<td>10% or lower variation in PK won't lead to clinically relevant difference</td>
<td>95.0-105.0%</td>
</tr>
</tbody>
</table>

Global Bioequivalence Standards for NTI Drugs and Further Opportunities
## Global Variations in NTI Descriptions

<table>
<thead>
<tr>
<th>Regulatory Agencies</th>
<th>Term Used</th>
<th>Regulatory Descriptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Canada</td>
<td>Critical dose drugs</td>
<td>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.</td>
</tr>
<tr>
<td>Europe Medicines Agency (EMA)</td>
<td>Narrow therapeutic index drugs</td>
<td>No definition</td>
</tr>
<tr>
<td>U.S. Food and Drug Administration (FDA)</td>
<td>Narrow therapeutic index drugs</td>
<td>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.</td>
</tr>
<tr>
<td>Japan Pharmaceutical and Food Safety Bureau (MHLW/PMDA)</td>
<td>Narrow therapeutic range drugs</td>
<td>No definition</td>
</tr>
<tr>
<td>South Africa Medicine Control Council</td>
<td>Narrow therapeutic range drugs having steep dose response curve</td>
<td>No definition</td>
</tr>
</tbody>
</table>


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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, levothyroxine, and etc.

- **MHLW/PMDA**: Aprindine, Carbamazepine, Clindamycin, Clonazepam, Clonidine, Cyclosporine, Digitoxin, Digoxin, Disopyramide, Ethinyl Estradiol, Ethosuximide, Guanethidine, Isoprenaline, Lithium, Methotrexate, Phenobarbital, Phenytoin, Prazosin, Primidone, Procaainamide, Quinidine, Sulfonylurea antidiabetic drugs compounds, Tacrolimus, Theophylline compounds, Valproic Acid, Warfarin, Zonisamid, Glybuzole
## BE Criteria for NTI Drugs

<table>
<thead>
<tr>
<th>Regulatory Agencies</th>
<th>Bioequivalence Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC</td>
</tr>
<tr>
<td>Health Canada</td>
<td>90.0% -112.0%</td>
</tr>
<tr>
<td>EMA</td>
<td>90.00-111.11%</td>
</tr>
<tr>
<td></td>
<td>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</td>
</tr>
<tr>
<td>South Africa Medicine Control Council</td>
<td>80.0-125.0%</td>
</tr>
<tr>
<td>MHLW/PMDA</td>
<td>80.0-125.0%</td>
</tr>
<tr>
<td>U.S. FDA</td>
<td>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.</td>
</tr>
</tbody>
</table>


[www.fda.gov](http://www.fda.gov)
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

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

Post-market Research and Perceptions of Generic NTI Drugs
Comparative Effectiveness of Generic vs Brand-name Levothyroxine

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


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.
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)
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

• 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)
Acknowledgement

CDER Narrow Therapeutic Index Drug Bioequivalence Standards Working Group

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FDA Office of Generic Drugs and Office of Chief Scientist contract to Brigham and Women’s Hospital Research Team (HHSF223201310232C)

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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
Thank you!

Questions?