FDA Q&A: Generic Versions of Narrow Therapeutic Index Drugs *National Survey of Pharmacists'*

Substitution Beliefs and Practices

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Narrow Therapeutic Index (NTI) drugs are drugs for which small differences in dose or blood concentration may lead to serious therapeutic failures or adverse drug reactions. Generic NTI drugs are approved by the

FDA as therapeutically equivalent to the reference drug; that is, they are expected to have equal effect and no difference when substituted for the brand name product. Since small changes in bioavailability of NTI drugs can alter clinical outcomes, FDA recommends tighter quality and bioequivalence (BE) limits to ensure the safety and efficacy of generic NTI drugs.

However, confusion still exists among some healthcare providers and patients over whether generic NTI drugs are safe and effective. As a result, FDA has funded research studies on generic NTI drug substitution.

In the following Q&A, Dr. Wenlei Jiang, Senior Science Advisor in the Office of Research and Standards within the FDA Office of Generic Drugs, discusses the findings of a study that surveyed pharmacists to identify their perceptions of generic NTI drugs. The study, *A National Survey of Pharmacists' Substitution Beliefs and Practices about Generic NTI Drugs*, was led by researchers at Brigham and Women's Hospital and the FDA. It was published in *Clinical Pharmacology & Therapeutics* in November 2017, and it is part of a larger body of research of patient and pharmacist survey studies.

Dr. Jiang has been leading regulatory research in complex drug products, NTI drugs, and modified release products in support of review standards development, and to ensure the post-market safety and efficacy of these drug products. Prior to joining FDA, Dr. Jiang worked for Novartis Pharmaceutical Corporation in formulation development. She received her PhD in Pharmaceutics and Pharmaceutical Chemistry from the Ohio State University.

***GF*: Let's lay the groundwork first: What are Narrow Therapeutic Index drugs and why are they important?**

WJ: NTI drugs are drugs for which small differences in dose or blood concentration may lead to serious therapeutic failures or adverse drug reactions. They are used in therapeutic areas with patients that are quite vulnerable–for example, in transplant patients and epilepsy patients.

Examples of NTI drugs that most people will be familiar with are the anticoagulant warfarin, which we know as the brand drug Coumadin®; and the synthetic hormone levothyroxine, which we know as the brand drug Synthroid®.

Q: Generally speaking, what do generic drug firms need to do to ensure their product is therapeutically equivalent to the brand name version?

A: For generic drug approval, a proposed generic drug must be pharmaceutically equivalent and bioequivalent to its corresponding brand name drug. Approved generic drugs are expected to be clinically substitutable for the brand name drug when given to patients under the conditions specified in labeling.

Pharmaceutical equivalence generally means that the generic drug must contain the same active pharmaceutical ingredient (API) in the same concentration, dosage form, and route of administration as the brand name drug. They must also meet the identical compendial or other applicable quality standards. In some cases, the generic drug can contain different inactive ingredients from the brand name drug.

Q: What role do the inactive ingredients play in the drug?

A: Inactive ingredients are also called excipients. They serve as binders, fillers, dyes, or preservatives that can allow the active ingredient to be delivered in a more convenient dosage form and help it exert its pharmacological action in the body.

FDA requires that there be adequate evidence to demonstrate that excipients in a proposed generic drug product do not impact its quality, safety, or efficacy.

Drug quality testing includes drug assay, disintegration time for tablets, drug dissolution, and others. In simple terms, the drug assay describes how much API the drug tablet contains. A tablet disintegration test measures how fast a tablet breaks up into small granules, and a dissolution test measures how much drug is solubilized in the media.

Q: What else must generic drug firms do to ensure their product is therapeutically equivalent to the brand name version?
A: Among other things, they must ensure bioequivalence (BE). This means that the generic drug has the same rate and extent of absorption as the reference product (the brand name drug). In general, generic applicants conduct BE studies to determine whether the brand and generic formulation behave similarly in the body.

For these studies, healthy volunteers are preferred over patients because we want to focus on the formulation comparison while keeping other variables to a minimum.

In addition, FDA also conducts regular inspections of manufacturing plants around the world ensuring compliance with the agency's regulations on good manufacturing practices.

Q: What work is the FDA doing to ensure that generic NTI drugs remain safe and effective?
A: For generic NTI drugs, FDA applies tighter limits for both quality assay and bioequivalence than for generic non-NTI drugs. For example, for the quality assay, the limit for a generic NTI drug is tightened to 95 to 105 percent. In contrast, the limit for generic non-NTI drugs is 90 to 110 percent. For bioequivalence, the limit of NTI drugs is equal to or tighter than 80 to 125 percent. For generic non-NTI drugs and non-highly variable drugs, the limit is always 80 to 125 percent.

FDA has strengthened the focused monitoring of approved generic drugs and communication with health care providers about generic NTI drugs. This study is part of those efforts.

Q: What questions did this study address?

A: The study addressed how pharmacists perceive generic NTI drug safety and efficacy; how frequently they perform generic NTI substitution for the brand drug; and finally, what factors predict the pharmacists' behavior.

Q: Why was the study designed around pharmacists?

A: Despite pharmacists' centrality to the prescription marketplace, large and rigorous national surveys of pharmacists are rarely performed. Because pharmacists are responsible for dispensing prescriptions, we predicted that it would be very enlightening to learn about their experiences dispensing generic NTI drugs. We were also interested in learning about inquiries they received from patients, and the strategies they used to address the inquiries.

A separate paper, *A Survey of Patients' Perceptions of Pill Appearance and Responses to Changes in Appearance for Four Chronic Disease Medications*, was published in the *Journal of General Internal Medicine* this past March.

Q: How did you select the pharmacists for the survey?

A: The Harvard research group, including Dr. Ameet Sarpatwari from the Program on Regulation, Therapeutics, and Law (PORTAL), division of Pharmacoeconomics in the Department of Medicine at Brigham and Women's Hospital and Harvard Medical School, partnered with Nielsen, a media company with a survey research arm, to select the pharmacists. They randomly selected more than 2,000 licensed pharmacists practicing in independent, franchise, and chain settings across all 50 states from over 100,000 pharmacists master files.

Q: Can you share an example of one question that was part of the survey?

A: Here is an example of one question: *When you receive a prescription, first time or a refill for a brand-name narrow therapeutic index drug that permits substitution, and the patient does not request brand-only, how often do you fill the prescription with a generic?*

Q: Can we talk about the findings of the survey?

A: This national survey of pharmacists revealed widespread confidence in the safety and efficacy of generic NTI drugs. There was some skepticism about generic NTI drugs, which was more pronounced among pharmacists in non-chain settings, and among female pharmacists. Generic substitution of initial NTI prescriptions was more common among pharmacists in chain settings, female pharmacists, younger pharmacists, pharmacy owners, and chief pharmacists.

Q: Didn't you say that female pharmacists were more skeptical?

A: That is correct. However, this is the study result we observed. Sometimes thoughts and actions may not be consistent.

Q: Did anything surprise you?

A: One of the most striking differences among pharmacists' responses was the frequency with which they reported performing generic NTI substitution of initial and refill prescriptions. Whereas 82 percent of pharmacists reported almost always substituting initial prescriptions with a generic, only 60 percent reported substituting a generic for refills of the brand-name version. This may reflect a hesitancy to intervene when a patient was thought to be well-controlled on the brand-drug, or they want to minimize possible confusion over a change in pill appearance when switching products.

Q: What did you learn that you didn't know before?

A: We learned that pharmacists have a high level of confidence in the safety and efficacy of generic NTI drugs and they frequently substitute generic NTI drugs for the brand drug.

There are associations between pharmacists who reported substitution of the initial prescription for brand-name NTI drugs and their number of years in practice and the practice setting. Pharmacists in practice longer (per year odds ratio (OR) =1.04; 95% confidence interval (CI) =1.02-1.06), were more likely not to perform generic substitution for an initial NTI prescription. They also associate the substitution of the initial prescription for the brand-name NTI drugs with affirmative patient consent and NTI-specific substitution state requirements. For example, pharmacists working in the non-chain

setting tend to not substitute an initial prescription for a brand-name NTI drug.

Q: Interesting. What is a possible reason for this?

A: The survey found that skepticism was more pronounced among pharmacists in non-chain settings. One supposition, though not a survey result, could be that in non-chain pharmacies pharmacists may not have the most up-to-date information and/or education about generic drugs.

Generic substitution was similarly more common in States that did not require affirmative patient consent for substitution and in States without NTI carve-out legislation.

Several states are known to enact “carve-out” to their drug product selection laws that imposed unique requirements for generic NTI substitution. For example, North Carolina required affirmative physician and patient consent prior to generic substitution for refill prescriptions of NTI drugs. Connecticut, Idaho, and Illinois made generic substitution of anti-epileptic drugs more difficult by adding requirements of physician and patient notification, or affirmative physician consent. Some anti-epileptic drugs, such as carbamazepine, phenytoin, and valproic acid, are NTI products. The likelihood of pharmacists in these states substituting an initial prescription for an NTI drug was significantly lower.

Q: What is the main message from the study that you would like to share?

A: The main message we want to communicate is that pharmacists are very influential and can help educate patients about drugs–particularly about generic NTI drugs. They can reassure patients that generic drugs, including generic NTI drugs, are equally as safe and effective and of the same quality as the brand name drug.

Q: Beside this study, what other research on NTI drugs has FDA funded?

A: In 2012, FDA funded a pharmacokinetics study to compare a brand immunosuppressant product and two different approved generic immunosuppressant products in stable kidney and liver transplant patients.

In this study, we evaluated the product bioequivalence in stable transplant patients because we wanted to address long-time concerns of patients and physicians that bioequivalence studies in healthy subjects may not predict product bioequivalence in patients.

In this study, tacrolimus, a narrow therapeutic index drug, was used as a model drug to test bioequivalence in transplant patients because it is a commonly prescribed immunosuppressant.

The study results demonstrated that the brand and two generic drug products were bioequivalent to each other in stable transplant patients when applying the “tighter” bioequivalence limits used for NTI that we discussed earlier. In addition, the two generic tacrolimus products from different manufacturers also demonstrated bioequivalence to each other in stable transplant patients.

Q: What was the impact of this study?
A: This study was published in *PLOS Medicine*, a journal of the Public Library of Science, and shared with transplant physicians and surgeons at the American Transplant Society Annual Meeting. At the time, it was highlighted as a practice-changing study because some physicians may have changed their negative perceptions about generic immunosuppressants.

Q: What is on the horizon at FDA for research on NTI?
A: Broad implementation of tighter quality and BE limits for NTI drugs relies on consistent classification of NTI drugs. In some cases, there are difficulties or lack of data in characterizing the therapeutic index of drugs. Additionally, well-controlled pharmacokinetics studies to evaluate the *within-subject* variability are rarely available.

At the pre-market stage, FDA research has been focusing on methods and criteria for classifying NTI drugs. We have a working group at the FDA that helps with the consistent classification of NTI drugs.

At the post-market stage, FDA is developing active and passive surveillance methods to monitor and ensure generic NTI drug safety and

efficacy. We use the FDA Adverse Event Report System (or FAERS) and Sentinel for these surveillance activities.

Q: How can we learn more about FDA's Regulatory Science Research initiatives on generic drugs?

A: If you want to know more about FDA research on NTI drugs and other research priorities, you can search *GDUFA regulatory science* at FDA.gov.

Q: *Bottle of Lies*, a book published in 2019, has received a great deal of media coverage and is premised on the fact that almost 90 percent of our pharmaceutical market is comprised of generics, the majority of which are manufactured outside the US. The author argues that some generic drugs manufactured in foreign plants may not be as safe or effective as their brand-named counterparts due to these plants not meeting FDA requirements. Can FDA reassure the American public on this matter?

A: Yes, we can. Protecting patients is the highest priority of the FDA, and Americans can be confident in the quality of the products the FDA approves. Our standards require that brand-name and generic medications have the same intended use and perform the same way in the human body, and we take multiple steps to ensure that generics are just as safe and effective as their brand-name counterparts.

Whether a drug is made in the US or overseas, manufacturers must undergo the same, rigorous application process, and the information must be fully reviewed by our highly-trained scientific staff. The FDA inspects brand-name and generic manufacturing facilities around the world that manufacture product for the U.S. market to confirm they meet FDA's manufacturing requirements.

The FDA's global inspection efforts focus on higher risk facilities to prevent, uncover, and combat data integrity issues and manufacturing problems. Using a risk-based site selection surveillance inspection model, we prioritize domestic and foreign inspections based on

multiple factors carefully selected to appropriately target our resources. Over the past several years, we have conducted unannounced inspections at foreign manufacturing facilities–a critical approach when we have information from a whistleblower or when the FDA is investigating a drug safety issue. We also monitor reports from industry, patients, and healthcare providers to identify, and to resolve potential quality problems.

If you have questions about NTI or generic drug product development, contact: GenericDrugs@fda.hhs.gov

FDA Division of Drug Information Webinar (Continuing Education): *Building Confidence in Generic Therapeutic Index (NTI) Drugs*

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