

Brand Versus Generic Drugs: Should We Be Cautious?

John A. Goldman ¹

1. St. Joseph's Hospital

✉ **Corresponding author:** John A. Goldman, jointdoc@mindspring.com
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Abstract

When prescribing a generic drug, there should be confidence the patient would see the same results as a patient taking the brand-name drug. Current Federal Drug Administration (FDA) protocol allows generic drugs to be marketed after having met the criteria for bioequivalence to brand-name drugs, but should that classification be equated with therapeutic equivalence as done by the FDA? Such is the concern of physicians each time they note "generic substitution acceptable" rather than "brand necessary".

Categories: Internal Medicine

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Introduction And Background

When prescribing a generic drug, there should be confidence the patient would see the same results as a patient taking the brand-name drug. Current Federal Drug Administration (FDA) protocol allows generic drugs to be marketed after having met the criteria for bioequivalence to brand-name drugs, but should that classification be equated with therapeutic equivalence as done by the FDA? Such is the concern of physicians each time they note "generic substitution acceptable" rather than "brand necessary".

Review

Brand drugs are labeled AA but generics are labeled AB by the FDA

The generics are the main copies of pharmaceutical products no longer protected by patent [1]. The FDA labels brand drugs, which they also call Single Source drugs, as "AA" and generics, which they call Multi-Source drugs, allowed on the market as "AB"; however, this simplification has a lot of variations as noted in the 1160 page, 2009, 29th edition of the FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations." It is known as the "Orange Book", because at one time was a large orange book, hence the name, but it is now available on the FDA website [1].

Generic drugs, to be bioequivalent, must have the same amount of active ingredient but not other components of the brand drug

The generic drug product must have "data demonstrating that the drug product is bioequivalent to the pioneer (innovator = AKA Brand Product) drug product" [1]. "Bioavailability refers to the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug product and becomes available at the site of drug action." The AB drug may differ in shape, scoring configuration, release mechanisms, packaging, what are referred to as excipients (including colors, flavors, preservative), expiration time, and even to a degree, labeling" [1].

FDA standard comparison is crossover study to show pharmaceutical sameness

There is no longer a FDA requirement that the generic drug needs to be tested in patients: just 24 – 36 adult volunteers! Patient testing was abandoned in 1984 [2]. The basis is that the active ingredient is in the generic and the active ingredient has already been proven in the studies that brought the innovator drug to market. While New Drug Applications (NDA) to the FDA require patient testing, generic drugs are considered under Abbreviated New Drug Applications (ANDA) and no patient testing is required. The active ingredient is tested using PK measurements that are performed and include area under the plasma concentration-time curve (AUC) and the maximum or peak drug concentrations (Cmax). If there is a difference of greater than 20% for each of the tests, then this is determined to be significant and thus undesirable [1]. This is expressed as a limit of each of these two tests of 80% and by convention that all of the data is expressed as a ratio of the average response (AUC and Cmax) and the limit for the second statistical test is 125% (reciprocal of 80%). Thus, a generic has to be within a 46% guideline of 80% to + 125% of the branded product. This is to protect against approval of products that are not bioequivalent. The two one-sided tests at the 0.05 level of significance ensures that there is no more than a 5% chance that a generic product that is not truly equivalent to the reference will be approved" [1].

The FDA feels that bioequivalent products and therapeutically equivalent products can be substituted for each other without any adjustment in dose. ANDA drugs brought to market are compared to the innovator drug, but one generic is not compared to another generic. Figure 1 suggests a possible concern when one compares two different generic drugs. Outcomes of these bioequivalent studies are not always clearly available in the generic package inserts.

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Possible variance in bioequivalence observed in brand-name versus two generic drugs

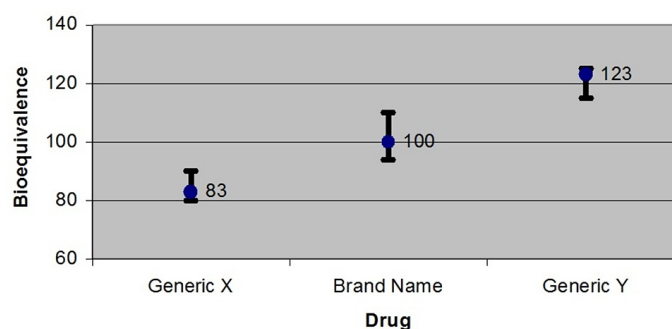


FIGURE 1: Possible variance in bioequivalence observed in brand-name versus two generic drugs

This figure illustrates how significantly different two generic drugs – both classified by the FDA as bioequivalent to the brand-name drug – can be while falling within the FDA's specified range for bioequivalence. If two drugs are so different while still considered bioequivalent, this should raise concern about whether they should be considered therapeutically equivalent? The data collected at the FDA compares generic substitution of generic X or generic Y versus Brand Name but does not compare Generic X versus Generic Y. Clinically physicians are often substituting Generic X for Generic Y and have no scientific data to compare these two.(3) [reprinted by permission American College of Rheumatology]

Narrow therapeutic range (NTI) drugs

NTI drug products are subject to therapeutic drug concentration or pharmacodynamic monitoring. Such examples are: Digoxin, Lithium, Phenytoin and Warfarin. But the traditional bioequivalence limit of 80 to 125% has been unchanged for these products, although recently changed for levothyroxine [2,4].

The last FDA requirement for patient studies to be performed before generic drugs were approved for marketing was before 1978

The present generic drug approval began over the past 30 years. In 1970, the FDA approved a new ANDA process for review and approval of all generic products approved between 1938 through 1962. For drugs approved after 1962, generic drug manufacturers were required to submit safety and efficacy studies and these were required until 1978. After 1978, manufacturers were required to cite published studies on safety and efficacy but not submit studies. Since the former safety and efficacy studies were expensive to perform and the latter published data were difficult to find, in 1984 (early in the Acquired Immunodeficiency [AIDS] epidemic) the beginnings of the generic drug program, the Hatch-Waxman Amendments of the Federal Food, Drug, and Cosmetic Act, were passed [2]. This created the generic drug industry as we know it today [2]. The Drug Price Competition and Patent Term Restoration Act focused on accelerating the ANDA process and gave the FDA statutory authority to approve generic drugs approved after 1962 as safe and effective. Unlike the New Drug Application (NDA) process where new drugs are required to submit safety and efficacy data, ANDA was revised and did not require preclinical and safety data. This was decided because the data regarding the efficacy and safety of the active ingredient had already been documented for the original NDA of the innovator drug [2]. Thus, the process of pharmaceutical equivalence and bioequivalence was developed, and the generic drug was presumed to be therapeutically equivalent.

Office of generic drugs surveys

The Office of Generic Drugs conducted and reported two surveys to quantify the differences between generic and brand name products, one in 1987 and the other in 1997. These studies included a total of 351 bioequivalence tests [5-6].

This is out of 12,910 products as of March 2009. The number of approved NDA and ANDA products is: Single Source or Brand 2,449; Multisource or Generic 10,372. Out of the 10,372 multi-source drugs, 10,216 were therapeutically equivalent, 156 were not therapeutically equivalent, and there were 89 exceptions [7].

Orange books states physician responsibility

The Orange Book states that professional care and judgment should be exercised in using the list, but that "FDA evaluation of therapeutic equivalence in no way relieves practitioners of their professional responsibilities in prescribing and dispensing such products with due care and with appropriate information to individual patients. In those circumstances where the characteristics of a specific product, other than its active ingredient, are important in the therapy of a particular patient, the physician's specification of that product is appropriate" [1]. Thus, it is a physician's responsibility to prescribe a drug that the FDA says is bioequivalent whether or not he or she is convinced it is therapeutically equivalent.

In October 2002, the *Medical Letter* published an article discussing the FDA's generic drug approval criteria [8]. It was presented as an information article without discussing any specific medication. When inquiring whether such information about specific generic medications will be discussed, the *Medical Letter* reply was it will be when there is evidence-based medicine to discuss this topic (personal communication). We should ask if this information is not available, why isn't it? There is a recent *Medical Letter* regarding generic bupropion XL, generic for Wellbutrin XL, changing led to worsening side-effects and relapse of previously controlled depressive symptoms. *Medical Letter* suggested a double blind clinical trial and pharmacokinetic studies [9].

There are other studies that show differences between generic and brand. Space limits full discussion, but there are been studies of generics: Warfarin with for requiring retesting INRs in patients, antiarrhythmics with loss of rhythm control and some deaths, transplantation medication ineffective, and generic Fosamax regarding disintegration, dissolution, bioavailability, esophageal adhesiveness, bioavailability clinical efficiency and safety profiles.

How do pharmacists view the quality of generic drugs?

Pharmacists have concern regarding generic NTI drugs and the FDA criteria regarding generic drugs and therapeutic conversion. Pharmacists' views are affected by the generic drug scandal that occurred in the Midwest in 1988 [10-11]. In the late 1980's, Mylan Laboratories was concerned that the generic competitor for its product, Maxzide®, and Smith Kline and French's, Dyazide®, had been given a waiver from the standards that had been imposed on Mylan. This was a complaint against the FDA and went to a congressional hearing led by Representative John Dingell (D-Mich.), Chairman of the House Oversight and Investigations Subcommittee. During this investigation, it was found that the generic drug company, Vitarine Pharmaceuticals, Springfield Gardens, NY, had inserted Dyazide® into its Vitarine generic capsules for its bioequivalence testing and Par Pharmaceuticals, Spring Valley, NY had bribed the FDA reviewers. During these hearings, 11 generic firms were investigated, at least 26 drugs were recalled, and suspensions were issued for 141 other drugs. Approvals of 28 of these drugs were proposed to be revoked due to "untrue statements."

Federal Trade Commission (FTC)

The FTC reviewed the topic of Pharmacy Benefit Managers (PBMs): Ownership of Mail Order Pharmacies. Congress requested that in response to the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) that the FTC undertake a "Conflict of Interest Study" to examine "differences in payment amounts for pharmacy services provided to enrollees in group health plans that utilize pharmacy benefit managers" [12]. Congress wanted to be certain the plans were maximizing competition and to compare the differences in costs incurred by such enrollees and plans for prescription drugs dispensed.

The FTC found that the profits were higher with generic drugs compared to brand drugs, even when they got payments (rebates based on volume-based payments of discounts) from the pharmaceutical manufacturers for brand drugs to be included on their formulary. The PBMs sought to increase generic substitution at both mail and retail. This study gives us a lot of insight into the range of issues regarding generic drugs and the pharmacy and pharmaceutical industries.

Canadian-based pharmacies

Brand name pharmaceuticals may be substantially less expensive when purchased from Canadian-based internet pharmacies compared to US chain pharmacies [13]. Americans can save about 24% of the price of their prescription drugs. When it comes to generic drugs, U.S. internet pharmacies offer lower prices than their Canadian counterparts [13]. FDA studies have shown that generic drug costs are less in the United States than Canada [14]. There is concern at the FDA about imported drugs. The FDA points out that these may not be drugs that have FDA approval and may not have even originated in Canada [15]. There are internet sites that can compare prices at Canadian and other pharmacies, such as pharmacychecker.com [16].

The case of Levothyroxine – a case for and against generic drug efficacy

The case of concern over generics that sparked a FDA action was levothyroxine. The FDA received reports of wide deviations in stability and potency that raised concerns about the quality of the products used in clinical practice. In 1997, FDA declared that oral levothyroxine sodium drug products were considered new drugs and would be required to obtain marketing approval under new drug applications (NDA). Seven levothyroxine products were developed and approved using the NDA criteria. The "Equivalence of Levothyroxine Sodium Products: Joint Public Meeting" was co-sponsored with the American Thyroid Association, The Endocrine Society, and the American Association of Clinical Endocrinologists, Monday May 23, 2005 [17]. This meeting about levothyroxine and is germane to the dilemma of other generic products.

Narrowing the goalposts

The concern was that levothyroxine sodium has a narrow therapeutic range drug (NTI) and that the current bioequivalence standards were based on T-4. The goal was to take everyone to the next step in precise thyroxine dosing: more stringent standards for bioequivalent testing (narrowing the goalposts [(the – 20% + 25% standard is the goalpost) or not], the use of TSH as a pharmacodynamic measure which was not being done, stricter regulation and label warnings regarding the switching between formulations, requirement for re-titration which was said to be widely ignored, and finally to amass data for each of these preceding steps.

There was concern that current bioequivalence standards are inadequate, and in every case of levothyroxine products, one of the 95 percent confidence limits exceeds the 9 percent narrow therapeutic index goal. Since dosing can be changed in small jumps (i.e., 125 micrograms verses 137 micrograms), the guideline of a 9% FDA mandate is difficult (remember -20% to +25% goalposts) perfection.

This pill does not look the same

There is complete confusion in the marketplace where every time the patient walks into the pharmacy since they may walk out with a different-shaped or colored pill, generating more phone calls and both physician and patient concern and confusion. (17 pp. 209-210) There is a spectrum of differences among the levothyroxine AB products (for example, ranging from 12.5 percent difference in bioavailability down to around 3 percent difference in bioavailability) and there may be differences amongst the generic substitutables. In testing, the generics are compared to the reference drugs but not to each other, but in the marketplace patients are getting different generics with different prescriptions. There is no data on the comparability of going from one generic levothyroxine to another levothyroxine (Remember Figure 1).

On October 3, 2007, the FDA announced that it "has issued letters to all NDA and ANDA holders requiring that they change the specifications for their products so that all levothyroxine sodium products approved for use in humans will meet a 95% to 105% potency specification throughout their labeled shelf-lives" [18]. They also include a "Table of Approved Levothyroxine Sodium Oral Formulations" [19].

Suggested remedy

Physicians are required to take the risk and responsibility of prescribing the generic drugs, yet given no easy access to information about the generic efficacy that has been tested in non-patients before the generic comes to market. There is responsibility of assuming it is therapeutically similar to the brand drug, even though it does not have all of the exact components of the innovator drugs. We need a solution that is safe and effective for our patients and gives us enough information to scientifically support these regulations. We want data to show that pharmaceutical sameness is clinical sameness.

Some suggestions might include:

- 1) Require all generic drug prescriptions to indicate on the product the name of the drug, the dosage and the manufacturer.
- 2) Have all generic drugs package insert given to the patients, indicating the manufacturer, the country of origin, factory of origin, and clearly diagram the results of the FDA bioequivalence testing.
- 3) Have easy access of the generic package inserts for physicians.
- 4) Better still, have all generic drugs tested in the patients they are indicated for--like the requirement before 1978.
- 5) Consider requiring narrow therapeutic index for all drugs.
- 6) Have a registry for all patients to have an option to call when the generic drug does not do as well as the brand name drug they were on before.

Conclusions

We want certainty that, when we give patients generic drugs, we want both pharmaceutical and clinical sameness of the generic compared to the brand. There are reported differences in bioavailability, efficacy, and pharmacodynamics (even within the same lot numbers) despite the FDA guidelines. Whenever there is a change in their medications, patients need to be monitored whether it is Warfarin or levothyroxine which have a narrow therapeutic range or any medication in view of the potential variations when medications are changed. The levothyroxine meeting is the 'Poster Child' for the concerns clinicians have of generic medications, and the ensuing dialogue from this meeting should cause all of us to reflect on this issue when our patients have to change to generic medications because of the requirements of their insurance coverage and cost of medications.

The scientific scrutiny of our medications can only help our patients and help us help our patients. In the future, we are going to see generics for biotech drugs [20]. These may or may not be called AB generics but are presently called Biosimilars or "follow-on protein products" (FOPPs). Already the generic pharmaceutical companies have noted their concern for expediency for FOPPs [21, 22]. The FDA has begun to study the generic FOPPs [23]. CDE (Center for Drug Evaluation and Research) and not CBER (Center for Biologics Evaluation and Research) regulates the therapeutic biologic drugs we use. CBER regulates vaccines, gene therapy products, tissue products, blood products, etc. [24]. The FDA has developed FDA issues draft guidance on biosimilar product development [25]. We need to carefully follow the regulatory structure for these follow-ons. We must be ready for the future, but we need to carefully assess the present immediately.

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** John A. Goldman declare(s) from Pfizer. Speaker. John A. Goldman declare(s) an alternate financial activity from Amgen. Speaker. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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