

Opinion

Generics Substitution,
Bioequivalence Standards,
and International Oversight:
Complex Issues Facing
the FDA

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The regulations for assessing the quality of generic drugs and their bioequivalence to innovator products are outdated and need to be substantially modernized. There are multiple reasons why these changes are needed, including: (i) the regulations remain largely unchanged since the passage of the Hatch–Waxman Act in 1984; (ii) medication therapies have become substantially more complex over the three decades since the passage of the Act; (iii) a switch from an innovator drug to a generic drug, or switching from one generic to another, is not a benign process – there is substantial clinical professional judgment involved and in some instances these decisions should be better informed; and (iv) pharmaceutical ingredients for finished products, whether innovator or generic, are from multiple sources of supply, adding variability in their production, and which may not be accounted for in specification tolerances. When these elements are viewed together, they clearly suggest that more transparency of responsible manufacturers in product labels and updated standards for bioequivalence are required.

Bioequivalence of Generic Drugs

The passage of the Drug Price Competition and Patent Term Restoration Act (Pub. L. 98-417, known hereafter as the Hatch–Waxman Act) in 1984 made it easier for producers of generic drugs to enter the US pharmaceutical market. Grabowski and Vernon [1] document the resulting increase in generic utilization: generic dispensing (as a share of the total) in the early 1980s averaged 10% but increased to 40% in the mid-1990s. Berndt and Aitken [2] show that between 1999 and 2004 the share grew from 49.7% to 74.5%.

While generic drug utilization has clearly increased following the Hatch–Waxman Act, suggesting that accessibility and affordability of drugs have improved consumer welfare, there are also areas of concern. Bioequivalence standards require only that the generic drug shows bioequivalence with the innovator drug in normal and healthy subjects, and not in the target patient population. As we report, switching to an approved generic has resulted in severe problems for some patients.

Trends

The FDA does not conduct independent analyses when evaluating bioequivalence ratings.

Generic drugs that lose their AB bioequivalence rating are allowed to remain on the market for patient use.

Current labeling laws do not require disclosure of which company manufactures a product or the country of origin.

Greater transparency on quality, bioequivalence, and product sourcing would enable physicians to provide better guidance to their patients.

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Furthermore, the risks associated with switching between different generic products are even less well understood: in principle it is possible for two generic drugs to both be equivalent to the innovator but not to each other. The Code of Federal Regulations defines medications as Narrow Therapeutic Ratio medications when there is less than a twofold difference between minimum toxic and minimum effective concentrations or less than a twofold difference in the median lethal dose and the median effective dose (<https://www.law.cornell.edu/cfr/text/21/320.33>). A drug with a narrow therapeutic ratio is usually discarded for research purposes if the benefits are not large enough or if there are alternatives to treat the target clinical situation [3]. In these cases, even small variations in the concentrations of these drugs can result in an inefficient therapeutic response or toxicity. Generic substitution within these drug classes has to be done with caution.

Earlier this year, Wenlei Jiang, Acting Deputy Director of the Office of Research and Standards in the Office of Generic Drugs at the US FDA pointed out that the agency continues to update its bioequivalence guidance for narrow therapeutic index drugs such as warfarin, tacrolimus, phenytoin, levothyroxine, and carbamazepine (<http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM453697.pdf>). This would suggest that the FDA recognizes the need for different bioequivalent standards for narrow therapeutic index drugs.

A related issue is that consumers often cannot always access the same generic drug. The significant problem of drug shortages also means that pharmacies frequently cannot purchase the same generic products [4]. Finally, the rising share of drugs imported from overseas markets raises issues of oversight.

The problems facing the FDA, and the consequences for consumers, are complex. This opinion article aims to provide a summary of the major issues going forward and highlights potential areas of concern and improvement.

Bioequivalence Standard

The Code of Federal Regulations CFR 320.23 (http://www.ecfr.gov/cgi-bin/text-idx?SID=7583d6a05bcb7876c9e4260085745180&mc=true&node=pt21.5.320&rgn=div5#se21.5.320_123) states 'drug products will be considered bioequivalent drug products if they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the active moiety under similar experimental conditions, either single dose or multiple dose'. The FDA defines bioequivalence as 'the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study' (<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=320.1>). Bioavailability for a given formulation provides an estimate of 'the relative fraction of the orally administered dose that is absorbed into the systemic circulation'. In other words, bioavailability is a measure of how much drug (specifically, its active or relevant ingredient) is circulating in a patient (i.e., is 'available to' or 'absorbed by' the patient) at certain points in time after the drug is taken.

The parameters used to establish bioavailability include the area under the plasma concentration–time curve (AUC) and the maximal plasma concentration (C_{\max}). Average bioequivalence is established if the 90% confidence interval of the ratio of geometric mean responses of the two formulations is 0.8–1.25. Although the FDA states clearly that the 'rate' of drug absorption is a critical factor in establishing bioequivalence, the agency has historically ignored the time to maximal concentration (T_{\max}) metric and other points on the bioequivalence curve. Providing the

C_{\max} data are within tolerable limits, little consideration is given to hourly differences between innovator and generic products, especially with long-acting formulations. In the next section, we provide an overview of several documented cases of problems with the average bioequivalence standard and generic substitution.

Switching From Innovator to Generic Products

Switching from innovator to generic products can be complex and require clinical judgment to avoid harm to the patient. We begin by first documenting several cases in which a switch between the innovator and generic drug has caused adverse effects.

Levothyroxine

Research published in 2008 by the Endocrine Society found that the amount of active ingredient delivered to the patient varied among different versions, although they purportedly contained the same dose (<https://www.endocrine.org/~media/endosociety/Files/Advocacy%20and%20Outreach/Position%20Statements/All/LT4PositionStatementwithmembercommentsheader.pdf>). The Endocrine Society notes that, in 2007, 160 adverse events were reported to the FDA relating to switching the source of levothyroxine. In most of these cases (85%) the substitution was made by a pharmacist without the knowledge of the prescribing physician. Between 1987 and 1994, 58 adverse drug reaction reports for levothyroxine were received by the FDA, all of which were related to either subpotency or superpotency. These reports led the FDA to require levothyroxine to be FDA approved. Before this time, levothyroxine products were marketed without FDA approval under a 'grandfather' status. The American Thyroid Association published a study in 2012 that found that one generic levothyroxine product was not bioequivalent to Synthroid, the innovator product, in children with congenital hypothyroidism [5].

Similar problems with levothyroxine sodium tablets are discussed in a paper by the Medicines and Healthcare Products Regulatory Agency (MHRA), the drug regulator in the UK. In 2011, the MHRA received several reports from health-care professionals regarding Teva's levothyroxine tablets. An investigation of Teva in 2012 led to a suspension of this product from the market (https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/420997/CHM_Review_for_MHRA_website_Levothyroxine_sodium_FINAL_04_Jan_2013.pdf). The MHRA received additional reports about inconsistent levothyroxine tablets, even between different batches of the same product. When reviewing adverse drug reaction reports on levothyroxine generics, the MHRA found that 19% of the reports describe a lack of efficacy in controlling thyroid-stimulating hormone (TSH) levels. Three percent reported adverse reactions after switching from an innovator drug to a generic drug.

Epilepsy/Seizure Drugs

A study by the Strong Epilepsy Center at the University of Rochester shows that two-thirds of reporting physicians said that a patient experienced a breakthrough seizure when switched from an innovator product to a generic antiepileptic drug (<http://www.managedcaremag.com/archives/0803/0803.epilepsy.html>). Another paper by Burkhardt *et al.* [6] documents how seizures increased in eight adult patients after they were switched to generic phenytoin.

Post-transplantation Immunosuppressants

Unlike other drugs, post-transplantation medications have many more possible complications and interactions. For example, SangCya oral solution, a generic cyclosporine-modified product, was taken off the market because it was not bioequivalent when taken in apple juice; this was problematic because apple juice was a popular vehicle for the oral solution for children (<http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm175741.htm>).

Wellbutrin XL

In 2007, patients complained after taking the 300 mg dose of an extended-release version of the popular antidepressant Wellbutrin XL 300 [bupropion hydrochloride extended release 300 mg, marketed at the time by GlaxoSmithKline (GSK) and manufactured by Biovail Corporation] and had recently switched to the generic equivalent, Budeprion XL 300, made by USA-based Impax Pharmaceuticals and marketed by the Israeli generic company Teva (<http://www.peoplespharmacy.com/2007/04/23/side-effects-of/>). Once patients were switched to the generic formulation, they started experiencing 'headaches, anxiety, depression and sleeplessness'. People who had never been suicidal were suddenly reporting suicidal thoughts (<http://abcnews.go.com/Health/fda-finds-generic-antidepressant-original/story?id=17399399>). On investigation, while the active ingredient in the generic Budeprion XL 300 mg and in the innovator Wellbutrin XL 300 products was identical, crucially the rate at which it was released in dissolution testing differed substantially (Figure 1). The generic showed a mean plasma concentration curve that is unlike a once-per-day formula and more like an immediate-release formula (https://www.consumerlab.com/reviews/Wellbutrin_vs_Generic_Bupropion/Wellbutrin/).

The problems arose because, while the patent on the drug itself had expired, making it available in generic form, the patent for the time-release mechanism used in the original had not expired. The original pill has a membrane formulation that releases the drug over time; the generic disintegrates in its entirety like a traditional tablet (https://www.consumerlab.com/reviews/Wellbutrin_vs_Generic_Bupropion/Wellbutrin/). Many health professionals are probably unaware of this difference.

Figure 1 shows the results of bioequivalence tests of the two drugs by measuring their concentration over time for the 150 mg doses of Budeprion and Wellbutrin XL. These are the data that were used to approve the bioequivalence of the 300 mg dose (<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm153270.htm>). It is important to note that the Wellbutrin data were provided by Teva, not by GSK, the marketer of Wellbutrin. The AUCs represent the concentrations of the drugs in blood plasma, which are similar, but the peak concentrations and the rates of absorption are different, potentially leading to clinical differences in patients. Despite the significant difference in absorption rates between the 150 mg formulations, the FDA still considers these two products bioequivalent.

In 2010, the FDA conducted its own independent trial of 24 subjects. It found that the maximum concentration of Budeprion XL 300 in the blood plasma reached only 75% of the amount that

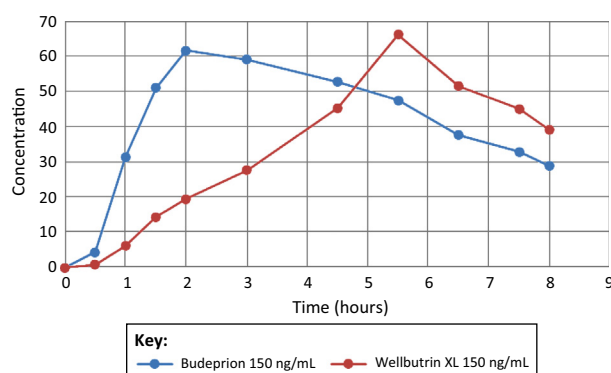


Figure 1. Mean Plasma Concentration of Bupropion (Budeprion XL and Wellbutrin XL) as a Function of Time.

The areas under the curves represent the concentrations of the drugs in blood plasma, which are similar, but the peak concentrations and the rates of absorption are different, potentially leading to clinical differences in patients. Despite the significant difference in absorption rate between the 150-mg formulations, the FDA still considers these two products bioequivalent. Source: FDA (2012) *Review of Therapeutic Equivalence Generic Bupropion XL 300 mg and Wellbutrin XL 300 mg*. Published online October 3, 2012 (<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm153270.htm>).

Wellbutrin XL 300 released and, in some volunteers, the level never reached 40% (<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm322161.htm>) [7].

Concerta®

In November 2014, the FDA changed the ratings for the Mallinckrodt and Kudco generic products from AB to BX. This means that they are still approved and can be prescribed but are no longer recommended as automatically substitutable at the pharmacy (or by a pharmacist) for Concerta® (methylphenidate), a drug for the treatment of attention-deficit hyperactivity disorder (ADHD) (<http://www.fda.gov/Drugs/DrugSafety/ucm422568.htm>).

Switching Between Generic Drugs

Drug substitution is allowed in the USA under substitution laws that were passed in 1984 (<https://www.ftc.gov/sites/default/files/documents/reports/generic-substitution-prescription-drug-prices-economic-effects-state-drug-product-selection-laws/massonsteiner.pdf>). Currently, all states have laws allowing pharmacists some choice in product selection when filling a prescription, unless the physician writes 'dispense as written'. The laws aim to lower costs to consumers through substitution of lower-price generics for higher-price innovator products. Many state laws prohibit generic switches or require physician notification before switching drugs with a narrow therapeutic index (<http://www.uspharmacist.com/content/s/78/c/13854/>). Switching between generic medications may also be of concern. Bioavailability between generics can vary from one generic to another (http://www.analysisgroup.com/uploadedFiles/Publishing/Articles/Generic%20and%20Brand%20Drugs_JME_11.08.pdf), yet the impact on safety and efficacy of that switching has not been adequately studied. This is of concern especially when pharmacies routinely swap one generic for another based on FDA equivalence ratings.

Oversight of International Manufacturing of Generics

We have so far examined problems with lapses in bioequivalence for generic drugs. These problems are compounded when many of these generic drugs are bought from overseas markets where the FDA has no jurisdiction. More than 80% of active pharmaceutical ingredients for all drugs in the USA now come from overseas, as do 40% of finished pills and capsules. The FDA's Office of Manufacturing and Product Quality publishes the warning letters that it issues to companies that have failed to comply with current good manufacturing process. In 2014, 18 warning letters were issued; six to companies in China, six to companies in India, and one each to companies in Jordan, Australia, Italy, Germany, and Hong Kong.

In 2004, senior managers at Indian generics manufacturer Ranbaxy (the eighth-largest generic manufacturer and the fastest-growing generics manufacturer in the USA) discovered a widespread system of fabricated data and data manipulation undertaken across myriad products and manufacturing plants in India. Several products sold across the world by Ranbaxy were approved by regulators based on fraudulent data submitted by the company seeking their market authorization. Ultimately, 30 products had to be removed from sale in the USA [8].

Ranbaxy knowingly sold substandard drugs around the world, including in the USA. Dinesh Thakur, the whistleblower, described how Ranbaxy deliberately took its greatest liberties in markets where regulation was weakest and the risk of discovery was lowest. Ranbaxy pled guilty in the USA to seven federal criminal counts of selling adulterated drugs with intent to defraud, failing to report that its drugs did not meet specifications, and making intentionally false statements to the government. Ranbaxy agreed to pay US\$500 million in fines, forfeitures, and penalties (<http://www.justice.gov/opa/pr/2013/May/13-civ-542.html>).

Following the Ranbaxy scandal, the FDA and the MHRA identified similar activities in other Indian companies. Most of the FDA's focus has been on the lack of data integrity or the falsification or doctoring of the results of the tests required to prove the quality or safety of medicines. In the past year, at least 12 pharmaceutical companies with facilities in India have been banned from shipping products to the USA (<http://www.bloomberg.com/news/2014-12-03/indian-labs-deleted-test-results-for-u-s-drugs-documents-show.html>). While many of these cases relate to large firms, there are several import alerts on smaller Indian companies like Amsal Chem, Fleming Laboratories, Kamud Drugs, Konduskar Laboratories, Nivedita Chemicals, Promed Exports, Posh Chemicals, Smruthi Organics, Stericon Pharma, Unique Chemicals, Vignesh Life Science, Wintac, Yag Mag Labs, and Global Calcium.

These types of fraudulent activities in unregulated or under-regulated markets add another layer of complexity to the already difficult problem of the standards with which we measure the therapeutic equivalence of a generic drug to an innovator drug. However, problems exist within the domestic market as well. Growing suspicion of poor manufacturing quality led the FDA to inspect various US manufacturing plants, where it found irregularities in manufacturing and record-keeping at numerous generic drug makers. Companies were substituting other companies' medication for testing to establish product efficacy (<http://content.time.com/time/magazine/article/0,9171,958423,00.html>). Deficiencies were found in 12 American plants (<http://www.nytimes.com/1989/09/12/business/fda-details-problems-at-drug-makers.html>).

Policy Considerations

The FDA has expanded its mandate, from just ensuring the safe and effective manufacture of drugs in the USA to overseeing the manufacturing facilities and quality of products made both domestically and overseas and sold to US patients as a consequence of the FDA Safety & Innovation Act of 2013. This requires an increase in the frequency and extent of pharmacovigilance (and especially market surveillance)[†]. Yet such surveillance is almost nonexistent, presumably because the FDA assumes that its oversight of production facilities (incorrectly) ensures that the products that reach the market are always good.

Perhaps a partial solution is that when products manufactured by foreign companies with a history of quality problems in the past 10 years are being investigated for additional compliance-related problems, the FDA could be allowed increased authority to block the importation of products from such overseas manufacturing locations without waiting for adverse event reports or physical evidence, which is often hard to find in such cases.

Furthermore, increased transparency regarding the bioequivalence data may help offset some of the concerns and enable physicians and consumers to make better choices. For example, this is the aim of legislation promoted by Amy Paulin, State Congresswoman for the 88th New York State Assembly District (D-NY) and her colleagues. They want companies that wish to sell into the lucrative NY market to release their bioequivalency data even if the FDA does not require it. [One can view the Bill on the Assembly website (<http://assembly.state.ny.us>) by typing the bill number, A.145, in the 'Bill Search' area.] Currently, manufacturers can change the suppliers of ingredients (active and excipients) without being required to undertake new bioequivalence studies if they stipulated that they would buy from a wide list of suppliers in their Abbreviated New Drug Application (ANDA). However, differing supplies of the same ingredients may produce different results.

[†]Pharmacovigilance is the name given to the mechanisms and tests that together map and ensure the safety of a medicine throughout its lifespan from test tube to patient. For a detailed assessment of the importance of pharmacovigilance, see the 2014 report from Laufer *et al.* at <http://www.pugatch-consilium.com/reports/Developing%20a%20Pharmacovigilance%20Culture.pdf>.

Transparency in medication labeling would assist physicians and patients and may help purchasers reward manufacturers who invest in quality. Woodcock and Wosinska argue that because quality is not transparent, manufacturers have little incentive to make quality production a priority [9]. Labels could be required to include the manufacturing entity [the license holder responsible to the FDA for Current Good Manufacturing Practice (CGMP) compliance] for clinicians to link public quality-oversight reports to the manufacturing entity.

Finally, to better understand the risks of switching between generic products, a federally funded study into the long-term effects of mandatory generic substitution is worth consideration.

These challenges are likely to become even more daunting in the future. All of the problems we have raised here may be exacerbated by next-generation biologic drugs now reaching the market. This new class of medicines represents the future of treatments for many diseases and conditions. Unlike pharmaceutical medicines, which are manufactured through chemical synthesis, biologic drugs are created within a living organism, such as an animal or plant cell. By definition, they are not carbon copies of one another and therefore do not lend themselves to the production of identical or nearly identical generic copies (<http://www.ncbi.nlm.nih.gov/pubmed/25220442>).

This is why copies of biologics are called biosimilars or interchangeable biologics, because they cannot be identical to 'generic biologics'. Therefore, bioequivalence standards will have to be revised accordingly. Roughly US\$80 billion worth of biologics will lose patent protection in 2015. Establishing therapeutic equivalence in the case of biosimilars presents a challenging problem. India and China are poised to take over much of those productions lines, commanding as much as 70% of the global market – currently valued at US\$20 billion – over the next few years (http://www.business-standard.com/article/companies/india-china-to-command-70-of-20-billion-global-biosimilars-market-114102700655_1.html).

Concluding Remarks

The rules underlying the assessment of the quality of generic drugs, and their bioequivalence to innovator products, have not changed significantly since the passage of the Hatch–Waxman Act in 1984. Yet the products on the market are significantly more complicated today, which may result in two allegedly bioequivalent products not being interchangeable. Providing evidence from medications to treat epilepsy, depression, and other serious conditions we show that switching from an innovator drug to a generic may result in adverse consequences for patients. Moreover, the clinical impacts of shifting from one generic to another generic are unknown. We need more information to understand whether this type of generic switching is advisable (see Outstanding Questions). The FDA should start by making public the bioequivalence information it routinely requires from all generic manufacturers. Physicians could then assess whether two allegedly bioequivalent products are indeed similar enough for their patients. Further, the FDA should assess how prevalent is generic switching; in principle, it could occur every time a prescription is renewed. For those product areas where switching is most likely to be problematic, the FDA could provide guidance to discourage routine switching.

Additionally, generic and innovator drugs source more ingredients and even final products from outside the USA, especially from countries such as India and China that have poor regulatory oversight. This would impact quality in US markets. The most notable failure in this regard was with the Indian firm Ranbaxy. Even after repeated failures to ensure quality at Ranbaxy and other Indian firms, and weak oversight in China, USA patients are still prescribed their products. These are complex issues facing the FDA and a step toward transparency as well as updating of bioequivalence standards may be important to overcome some of these challenges. However, since some manufacturers selling into the USA appear to cheat on

Outstanding Questions

Should products that lose their AB bioequivalence rating be allowed to remain on the market?

Should manufacturers with track records of not following good manufacturing practices receive additional approvals?

Should labeling laws be changed to allow transparency regarding the country of origin and manufacturer of medicines?

quality control, the FDA simply overseeing production plants is not enough oversight. Routine surveillance of products sold on the market must be expanded from the current very low level. Further, transparency in labeling where products are sourced from could be important in improving patient safety.

Greater openness from the FDA about the problems with interchangeability with generics would also assist physicians and patients appreciate the challenges of switching between innovator biologics and biosimilars (and eventually between biosimilars). In short, the FDA does an important job in keeping patients safe from substandard and otherwise problematic medicines in the USA. However, it makes mistakes and is not omniscient, and greater transparency on quality, bioequivalence, and product sourcing would enable physicians to provide better guidance to their patients.

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