AMERICAN ENTERPRISE INSTITUTE

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

Roger Bate
American Enterprise Institute

Aparna Mathur
American Enterprise Institute

Harry M. Lever
Cleveland Clinic

Dinesh Thakur
Medassure Global Compliance Corporation

Joe Graedon
PeoplesPharmacy.com

Tod Cooperman
ConsumerLab.com and PharmacyChecker.com

Preston Mason
Brigham and Women's Hospital and Harvard Medical School

Erin R. Fox
University of Utah Health Care Drug Information Service

AEI Economic Policy Studies Working Paper 2015-05
May 4, 2015

ABSTRACT

The rules underlying the assessment of quality of generic drugs, and their bioequivalence to brand name 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 imply that two bioequivalent products are not identical to each other. Providing evidence from medications to treat epilepsy, depression and other serious conditions this paper shows that switching from an innovator brand to a generic may result in adverse consequences for patients. Moreover, the clinical impacts of shifting from one generic to another generic are also unknown. In a self-conducted survey, we provide original data to show that in only 10% of pharmacies surveyed over four consecutive months was the same generic (atorvastatin) available. Hence consumers often have less choice with respect to the generics they buy from brick and mortar pharmacies and we need more information to understand whether this type of enforced generic switching is advisable. Additionally, generic and brand name drugs source more ingredients and even final products from outside the U.S. especially India and China, countries with 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, US patients are still prescribed their products. In this paper, we document these complex issues facing the FDA and conclude that transparency as well as updating of bioequivalence standards may be important to overcome some of these challenges. Further, transparency in labelling where products are sourced from could be a first step towards improving patient safety.

Corresponding author: Aparna Mathur, American Enterprise Institute, 1150 17th Street NW, Washington D.C. 20036. Email: amathur@aei.org Phone: 202-828-6026

This paper has benefited tremendously from an expert group meeting convened on June 4, 2014 in Washington, D.C., of scientists, physicians, economists, lawyers, pharmaceutical practitioners and former regulators. Roger Bate received limited travel funds from the International Policy Network.

1. Introduction

The passage of the Hatch-Waxman Act in 1984 made it easier for producers of generic drugs to enter the U.S. pharmaceutical market. Before 1984, generics producers were required to demonstrate the safety and effectiveness of their products by putting them through clinical trials. The time and expense involved in doing this were a significant disincentive for generics manufacturers. According to Mossinghoff (1999), prior to Hatch-Waxman, more than 150 products existed in the market which had neither patent protection nor generic entry. Hatch-Waxman eliminated the requirement for separate clinical trials for generic manufacturers. However, generics manufacturers were required to demonstrate "bioequivalence" with branded products by showing that the active ingredient in their product diffused into the human bloodstream in a manner similar to the branded product. The Act also helped innovator products by extending the life of pharmaceutical patents which had lost time on their "patent clocks" waiting for FDA approval (Grabowski 2007).

Grabowski and Vernon (1996) document the increase in generic utilization following the passage of Hatch-Waxman in 1984. They find that generic dispensing in the early 1980s averaged 10 percent, but increased to 40 percent in the mid-1990s. Berndt and Aitken (2010) show that since then generic prescription shares have been increasing dramatically. Between 1999 and 2004, the share grew from 49.7 percent to 74.5 percent. This rapid generic entry is associated with correspondingly rapid declines in generics prices. Rizzo and Zeckhauser (2005) further document that this decline in prices of generics is associated with a decline in the average price of brand name drugs. Recently, the prices of some generic drugs have increased dramatically resulting in a House Committee on Oversight and Government Reform investigation.[1]

While generic drug utilization has clearly increased following Hatch-Waxman suggesting that accessibility and affordability of drugs have improved consumer welfare, there are also areas of concern. Generic drugs may suffer from poor quality or may not be as beneficial for patients as the innovator. Meredith (2003) suggests that substitution of generic drugs for brand-name products is of great concern to healthcare providers, principally because the development of generic products no longer requires extensive trials in patients. In addition, bioequivalence

[1] http://democrats.oversight.house.gov/news/press-releases/cummings-and-sanders-investigate-staggering-price-increases-for-generic-drugs

standards only require the generic drug to show bioequivalence with the brand-name drug in normal and healthy subjects, and not in the target patient population. The lack of transparency in drug labeling makes it difficult to determine the source of any medication. US labeling laws only require that drug products list the supplier name. Further complicating the situation is the practice of contract drug manufacturing, where a company may manufacture a product for another supplier or even multiple suppliers. Many drug labels carry language such as "manufactured for x company" but do not disclose which company actually manufactured the product or where the ingredients came from. For instance, Marathon sells Isuprel injections. However, the labeling on the package says "manufactured for Marathon" rather than "manufactured by" which contractor.[2] Similarly, Greenstone's combination amlodipine/atorvastatin says "Distributed by Greenstone, Made in Germany" but does not say who made the product.[3] Clinicians may also have difficulty navigating which products are rated as bioequivalent. Authorized generics are typically not included in any FDA listings as these products are usually the brand name product sold as a generic or licensed by the brand name manufacturer. There is no need to rate these products as bioequivalent because they are actually the identical product to the brand.

As we document in the study, switching to an approved generic has resulted in severe problems for some patients. We study the case of Levothyroxine, Epilepsy/Seizure drugs, post-transplant immunosuppressants and Wellbutrin. In each of these cases, while the generic drugs were considered bioequivalent, the switch from an innovator drug led to adverse reactions, suggesting that there is either something lacking in the current bioequivalent standards established by the FDA, or manufacturers are not following Current Good Manufacturing Practices (cGMP).

Furthermore, the risks associated with switching *between* different generics products are even less well understood – in principle it is quite possible for two generic drugs to both be equivalent to the innovator but not to each other. Some drugs have a very narrow dosage range between a drug being therapeutic and becoming ineffective or even toxic. These drugs are known as having a "narrow therapeutic index" or are called "critical dose drugs." A drug with a narrow therapeutic index is usually discarded for research purposes if the benefits are not large enough or if there are alternatives to treat the target clinical situation (Paveliu et al. 2011). In these cases,

[2] http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=abf5e543-36e8-416e-b053-483ddbf4e568
[3] Ibid.

even small variations in 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. Other problems may exist with more complicated medicines, such as extended release formulations. These products exhibit a time delay in the release of the medication, but often, the generic versions of the extended release mechanism lead to different absorption patterns, releasing the drug earlier than desired.[4] Such problems may be even worse in next-generation biologic drugs, whose copies, known as biosimilars, are materially different from the originator medicine.[5]

A related issue is that consumers often don't have the choice to continue with the same generic drug. In our own sampling, we assessed the availability of atorvastatin (generic Lipitor) that could be bought with prescriptions in three states Virginia, Maryland and Pennsylvania and in Washington, DC. In October 2014 we undertook one-off sampling from 121 bricks and mortar pharmacies, 22 in Virginia, 23 in Maryland, 6 in Washington D.C. and 70 in Pennsylvania. The location of production was not always stated on samples shown to us by the pharmacist because manufacturers are not required to include this information on the label, although some suppliers choose to do so. The ownership of the companies making the product was identifiable. We found that 46 (38%) of the samples were from Indian owned companies. Another 12 (10%) were from Canadian companies, 17 (14%) were from Switzerland, 33 (28%) from the U.S., and 13 (10%) from Ireland. We repeated sampling in 20 Pennsylvania pharmacies in subsequent months (November, December and January) and found that in six of the pharmacies, (30%), patients received a different generic each month and in only two pharmacies (10%) was the same generic offered for four months in a row. Anecdotally, from conversations with pharmacists, changes in availability were primarily due to turnover of stock, presumably some pharmacies are just busier, filling more prescriptions every month. The significant problem of drug shortages also means pharmacies frequently cannot purchase the same generic products.[6] Switching between generics could be a problem for sensitive patients, since it might undermine their cholesterol control, possibly leading to significant heart problems later in life.

---

[4] http://www.fda.gov/Drugs/DrugSafety/ucm422568.htm

[5] The FDA has not yet determined how interchangeability will be determined. Biosimilars must have clinical trials as part of their approval process unlike small molecules. The complex nature of biologic production means there are small differences between batches of brand name biologic products. For more, see http://www.ncbi.nlm.nih.gov/pubmed/18020619

[6] http://www.ncbi.nlm.nih.gov/pubmed/24582195

Finally, the rising share of drugs imported from overseas markets raises issues of oversight. The FDA regulates the quality of pharmaceuticals under the "Current Good Manufacturing Practice (CGMP)" standard.[7] FDA regulators inspect manufacturing plants and if a company is not complying with CGMP regulations, any drug it makes will be considered "adulterated". While inspections are unannounced in the U.S., in other countries (such as India and China) they must be conducted with the cooperation and facilitation of national regulators, which limits their value.[8] Problems obtaining visas also inhibit inspections. Seven years ago FDA planned to increase the number of inspectors in China to 26. The current number is 3 full time and 2 temporary due to China's slow system of granting work permits. There are no consequences for Chinese firms that are inspected less frequently than US firms.[9] In this study, we document the case of the Indian firm, Ranbaxy, which provided fraudulent data to the FDA in order to get its generics approved. Moreover widespread inspections of final products are expensive and rarely undertaken. Further, when problems are identified, resolution can take many years, stretching capabilities of the FDA and other regulators involved. Prosecution of firms headquartered overseas is difficult given that the international treaties and access to on-the-ground evidence is very difficult. During that time, the FDA does not usually suspend public sales of the potentially dangerous drugs under investigation.

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

II. Bioequivalence Standard

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.[10] Bioavailability for a given formulation provides an estimate of "the relative fraction of the orally administered

[7] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm169105.htm
[8] http://www.livemint.com/Industry/99oie9vfXwmU9DzDtiQ2JI/India-wants-its-officials-during-FDA-inspections-at-drug-uni.html
[9] http://www.fiercepharmaasia.com/story/smoke-and-mirrors-visas-increase-us-fda-inspectors-china-wsj-says/2015-04-14
[10] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=320.1

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 percent confidence interval of the ratio of geometric mean response of the two formulations is 0.8 to 1.25. Although the FDA states quite clearly that "rate" of drug absorption is a critical factor in establishing bioequivalence, the agency has historically ignored the T_{max} (time to maximal concentration) metric and other points on the bioequivalence curve. As long as the C_{max} data is within tolerable limits, little consideration is given to hourly differences between brand and generic products, especially when it comes to long-acting formulations.

As discussed in Meredith (2003), a generic copy of a reference drug must contain identical amounts of the same active ingredient in the same dose formulation and route of administration, as well as meet standards for strength, purity, quality and identity.

Meredith (2003) outlines several concerns with the use of the FDA bioequivalence standards. First, the use of a single regulatory limit for all drugs is of concern, particularly for drugs with a narrow therapeutic index, such as digoxin and carbamazepine. Second, since the development of a generic requires only demonstration of its bioequivalence with the brand name drug in a small sample (two dozen or fewer) normal and healthy subjects, it is not clear that it would work equally well for the target patient population. The validity of the current bioequivalence criteria depends upon the existence of a clear relationship between drug concentration and therapeutic efficacy and tolerability. However, evidence in this regard is lacking. A related third concern is the substitutability of generic drugs across individuals. The issue here is that with substitution from one generic to another, two generic drugs that are deemed bioequivalent to the innovator product may not be bioequivalent to each other. For instance, a patient might be doing well on a generic drug that delivers more active ingredient than the branded product, but would experience clinical failure if switched to a different generic that delivers less of the active ingredient. Hence patient-related factors that affect the pharmacokinetic properties of a drug may result in differences between branded and generic formulations that are not detected in a normal, healthy population.

In general, while problems exist with the average bioequivalence standard, the FDA continues to rely on it as the main criterion for approving generics. Provisions in the Hatch Waxman Act limit the FDA from asking for anything more than bioavailability studies when drug companies submit abbreviated new drug applications (ANDAs) (Mossinghoff 1999). Some critics have argued that this provision reduces the information available to the FDA since it can only measure the similarity of generics and the brand-name products through a comparison of certain aspects of bioavailability (Mossinghoff 1999).

In the next section, we provide an overview of several documented cases of problems with the average bioequivalence standard and generic substitution.

III. Switching From Branded to Generics Products

We begin by first documenting several cases in which a switch between the innovator and generic drug has caused adverse effects. Evidence from the literature as early as 2001 pointed to substitution problems with narrow therapeutic index generic versions of digoxin (used for various heart conditions), levothyroxine (used for thyroid deficiency), warfarin (an anticoagulant used to prevent thrombosis and thromboembolism) and albuterol (used to treat asthma and chronic obstructive pulmonary disease COPD) (Henderson and Esham 2001).

Levothyroxine

Research published in 2008 by the Endocrine Society found that the amount of active ingredient delivered to the patient varied among different versions – even though they purportedly contained the same dosage.[11] In 2007, 160 adverse events were reported relating to switching the source of levothyroxine. In most of these cases (85%) substitution was made by a pharmacist without the knowledge of the prescribing physician.[12] Between 1987 and 1994, a total of 58 adverse drug reaction reports with Levothyroxine were received by the FDA, all of which were either related to subpotency or superpotency. These reports led FDA to require levothyroxine to be FDA-approved. Prior to 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

[11] https://www.endocrine.org/~/media/endosociety/Files/Advocacy%20and%20Outreach/Position%20Statements/All/LT4PositionStatementwithmembercommentsheader.pdf
[12] Ibid.

bioequivalent to Synthroid, the innovator product, in children with congenital hypothyroidism (Carswell et al. 2012).

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, MHRA received several reports from healthcare professionals regarding Teva's levothyroxine tablets. An investigation of Teva in 2012 led to a suspension of this product from the market.[13] Separate from this set of complaints, MHRA received reports about inconsistent levothyroxine tablets, even between different batches of the same product. When reviewing adverse drug reaction reports on levothyroxine generics, MHRA found that 19 percent of the reports describe a lack of efficacy in controlling TSH levels. Three percent reported adverse reactions after being switched from a brand name drug to a generic.[14]

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 brand-name to generic AED (anti-epileptic drug).[15] Another paper by Burkhardt et al. (2004) documents how seizures increased in eight adult patients after they were switched to generic phenytoin.

Post-transplant Immunosuppressants

Unlike other drugs, post-transplant 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.[16]

One study of post-transplant patients who had been given a generic alternative, showed that, while average amounts of drug in the patients' blood reduced by 15.9 percent and 11.9 percent respectively, compared with the branded version, this average masked some astonishing

[13] http://webarchive.nationalarchives.gov.uk/20141205150130/http://www.mhra.gov.uk/home/groups/pl-p/documents/drugsafetymessage/con222566.pdf
[14] Ibid.
[15] http://www.managedcaremag.com/archives/0803/0803.epilepsy.html
[16] http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm175741.htm

variations in individual patients. Some experienced decreases of 50 percent, while others showed increases of 50 percent, findings which prompted one medical journal editor to claim that conversion to a generic alternative offered "no savings, while exposing patients to dangers of acute and chronic rejection or an increase in toxic side-effects."

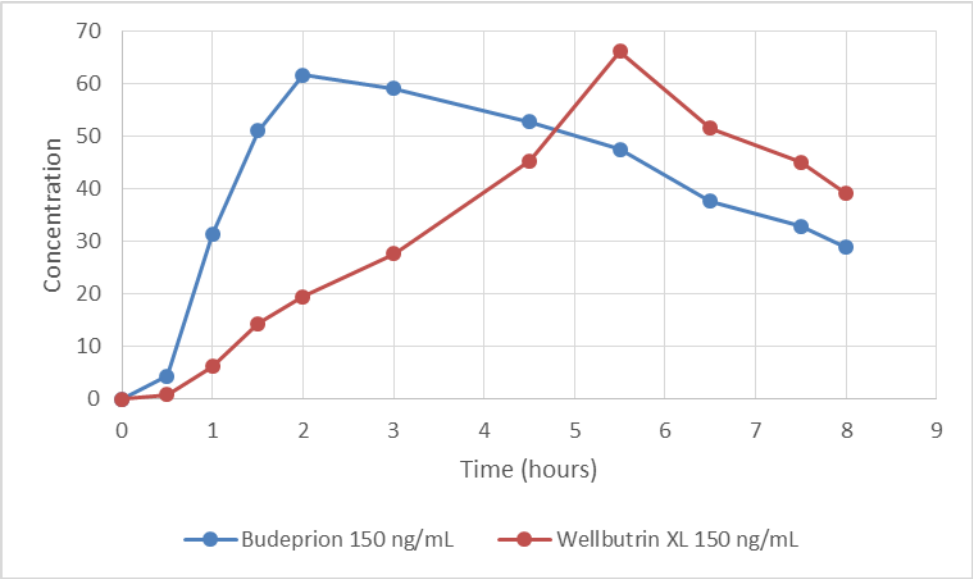
Wellbutrin

In 2007, there were complaints from patients who had been taking the 300 mg dose of an extended-release version of the popular antidepressant, Wellbutrin XL 300, and had recently switched to the generic equivalent, Budeprion XL 300, made by US-based Impax Pharmaceuticals and marketed by the Israeli generic company Teva.[17] Once patients were switched to the generic formulation, they started experiencing "headaches, anxiety, depression and sleeplessness," People's Pharmacy cofounder, Joe Graedon said. "People who had never been suicidal were all of a sudden reporting suicidal thoughts."[18] On investigation, ConsumerLab.com found that while the active ingredient in the generic Budeprion XL 300 mg and brand-name Wellbutrin XL 300 mg products was identical, crucially, the rate at which it was released in dissolution testing differed substantially. "In the first two hours of a dissolution test, Budeprion released 34 percent of the drug, while Wellbutrin released 8 percent. At four hours, the Teva product released nearly half of its ingredient, while original Wellbutrin released 25 percent. The generic did not act like a once-a-day formula but more like an immediate release formula," said Dr. Tod Cooperman of ConsumerLab.com which undertook the analysis.[19]

The problems arose because, while the patent on the drug itself had expired, making it available in generic form, the time-release mechanism used in the original had not. The original pill has a membrane formulation which releases the drug over time; the generic disintegrates in its entirety like a traditional tablet.[20] Most health professionals are unaware that the way in which a drug formulation releases the active pharmaceutical ingredient may differ substantially from the brand to the generic because of different patent protections

[17] http://www.peoplespharmacy.com/2007/04/23/side-effects-of/
[18] http://abcnews.go.com/Health/fda-finds-generic-antidepressant-original/story?id=17399399
[19] https://www.consumerlab.com/reviews/Wellbutrin_vs_Generic_Bupropion/Wellbutrin/
[20] Ibid.

The chart below[21] shows the results of bioequivalence tests of the two drugs by measuring concentration of medicine 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.[22] The area under the curves represents the concentration 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 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 percent of the amount Wellbutrin XL 300 released, and, in some volunteers, the level never reach 40%.[23] [24]

Other cases have been documented in Meredith (2003) such as the FDA's recent change in the therapeutic equivalence rating for two approved generic versions of Concerta tablets (methylphenidate hydrochloride extended-release tablets). In November 2014, the FDA changed the ratings for the Mallinckrodt and Kudco generic products from AB to BX. This means they are still approved and can be prescribed, but are no longer recommended as automatically

[21] https://www.consumerlab.com/reviews/Wellbutrin_vs_Generic_Bupropion/Wellbutrin/
[22] It is important to note that the Wellbutrin data was provided by Teva, not by GSK, the maker of Wellbutrin. Was GSK's data any different?
[23] http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm322161.htm
[24] See Woodcock et al. (2012).

substitutable at the pharmacy (or by a pharmacist) for Concerta, an ADHD drug.[25] All of these suggest that a measure of average bioequivalence is not necessarily sufficient to ensure bioequivalence for wide and narrow therapeutic index drugs.

IV. Switching Between Generics Drugs

Drug substitution is allowed in the United States under substitution laws that were passed in 1984.[26] Currently, all states have laws allowing pharmacists some choice in selecting which brand of drug to dispense in filling a prescription that names a specific brand (unless the physician writes "dispense as written." Many state laws prohibit generic switches, or require physician notification prior to switching drugs with a narrow therapeutic index.[27] The purpose of these laws is to allow consumers to pay lower prices and have more choice through substitution of lower price generics for higher price brands. Yet as is evident from the cases documented above, the medical literature has established non-bioequivalence between innovator and generic drugs. Further, switching between generic medications is arguably an even greater area of concern. Bioavailability between generics can vary by 45 percent from one generic to another,[28] yet the impact on safety and efficacy of that switching has not be adequately studied. This is of concern especially when pharmacies routinely swap one generic for another, assuming their equivalence.

To study the issue of generic substitution, we conducted our own analysis of one of the most important medicines used in US –atorvastatin (generic Lipitor).

In 2011, Lipitor was the most valuable drug in the world before it came off patent. The Indian company, Ranbaxy, was granted initial generic exclusivity by FDA, despite a track record of cGMP violations including warning letters in 2002, 2006, 2008, and 2009 and an import ban of 30 products in 2008.[29]

In an attempt to evaluate the variability in statins supplied to patients, we assessed the availability of generic atorvastatin that could be bought with prescriptions in three states

---

[25] http://www.fda.gov/Drugs/DrugSafety/ucm422568.htm
[26] https://www.ftc.gov/sites/default/files/documents/reports/generic-substitution-prescription-drug-prices-economic-effects-state-drug-product-selection-laws/massonsteiner.pdf
[27] http://www.uspharmacist.com/content/s/78/c/13854/
[28] http://www.analysisgroup.com/uploadedFiles/Publishing/Articles/Generic%20and%20Brand%20Drugs_JME_11.08.pdf
[29] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/ucm118411.htm

Virginia, Maryland and Pennsylvania and in Washington, DC.[30] In October 2014 we sampled from 121 bricks and mortar pharmacies, 22 in Virginia, 23 in Maryland, 6 in Washington D.C. and 70 in Pennsylvania. The location of production was not always stated on samples shown to us by the pharmacist, but the ownership of the companies making the product was identifiable. We found that 46 (38%) of the samples were from Indian owned companies. Another 12 (10%) were from Canadian companies, 17 (14%) were from Switzerland, 33 (28%) from the U.S., and 13 (10%) from Ireland.

Twenty of the pharmacies in Pennsylvania were sampled three further times to establish any changes in product availability (a follow up assessment was conducted roughly the same time (on the 7th, 8th or 9th) of every month – November, December and January). While the product range remained the same, most of the pharmacies were not providing the same generics each time in order to fill a prescription. It is not clear why these prescription shortages occur and patients often have to wait weeks to get a new supply of a common drug.[31]

In six of the pharmacies, (30%), patients received a different generic each month and in only two pharmacies (10%) was the same generic offered for four months in a row. Anecdotally, from conversations with pharmacists, changes in availability were primarily due to turnover of stock, presumably some pharmacies are just busier, filling more prescriptions every month. This is an issue since for certain sensitive patients, switching between different generics could undermine their cholesterol control, possibly leading to significant heart problems later in life.

However, there does exist an online market for atorvastatin. In addition to the six products available in the domestic U.S. market, we could purchase dozens of additional products online, from licensed pharmacies in numerous countries, with an extraordinary range of prices (and perhaps quality); from $0.21 for generics (per pill) to $4.97 for brand name Lipitor (per pill).

Without sufficient information about the risks associated with switching, a patient could potentially take a different generic every month for many years, with dangerous consequences. Of course one possible advantage of the online market, or mail order market, could be that repeat consumers could always choose the same specific generic, perhaps one they know they tolerate well.

---

[30] In this instance "we" refers to several authors, but not all authors of this paper. Bate and Mooney were responsible for the assessment, with assistance of a prescription from Harry Lever.

[31] http://www.healthline.com/health-news/shortages-of-prescription-drugs-reported-072114#1

VI. Oversight of International Manufacturing of Generics

Up to this point, we have 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 is unable to exert adequate pressure to enforce quality standards. More than 80% of active pharmaceutical ingredients for all U.S. drugs 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 China, six to India and one each to Jordan, Australia, Italy, Germany and Hong Kong. These warning letters are issued during investigations which may have been going on for several years – from inspection, recommendations, responses and so on. Even though FDA publishes the warning letters, the exact drugs involved are frequently redacted, and because the labeling laws do not require disclosure of manufacturer, it is impossible to know the true source of medications.

In 2004, a couple of senior managers at Indian generics manufacturer Ranbaxy (the eighth largest generic manufacturer and the fastest growing generics manufacturer in the U.S) 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 US.[32]

This was a case of outright fraud, in which the company knowingly sold substandard drugs around the world, including in the U.S.[33] On May 13, 2013, Ranbaxy pleaded guilty in US to seven federal criminal counts of selling adulterated drugs with intent to defraud, failing to report that its drugs didn't meet specifications, and making intentionally false statements to the government. Ranbaxy agreed to pay $500 million in fines, forfeitures, and penalties.[34] [35]

---

[32] http://fortunedotcom.files.wordpress.com/2013/05/ranbaxy-products.pdf

[33] 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.

[34] http://www.justice.gov/opa/pr/2013/May/13-civ-542.html

[35] http://fortune.com/2013/05/13/maker-of-generic-lipitor-pleads-guilty-to-selling-adulterated-drugs/

Following the Ranbaxy scandal, the FDA and the UK's MHRA have identified similar activities in other Indian companies. Most of the agency's focus has been on the lack of data integrity, that is, falsifying or doctoring the results of tests required to prove quality or safety of medicines. In the past year, at least twelve pharmaceutical companies with facilities in India have been banned from shipping products to America.[36] Some of these cases are documented below.

- In June 2010, an intravenous antibiotic manufactured by Claris Lifesciences Limited in India, with three manufacturing plants in Ahmedabad,[37] was discovered to be non-sterile and to contain floating white particles, identified in at least one case as mold. Three of the manufacturer's products were recalled and in November 2010, the FDA placed Claris Lifesciences under import alert, preventing its products from entering the United States.[38]

- Sun Pharma, an Indian manufacturer with plants in Dadra, Jammu, Sikkim, Silvassa and Haloj,[39] was found in November 2010 to have failed to disclose information in a timely fashion about problems with its distributed batches of promethazine hydrochloride, an antihistamine often used as an antiemetic.[40]

- Zydus Cadila, based in Amdedabad, Baddi, Sikkim and Goa,[41] and Aurobindo, based in Hyderabad and Haryana,[42] both falsely reported that no microbiological contaminants existed in its quality testing.[43] [44] These tests are done to ensure that employees do not contaminate the product. The detection of microbial contamination during multiple FDA inspections questions the validity of the data generated by these Indian firms.[45]

- RPG Life Sciences, with its main facilities in Navi Mumbai and Ankleshwar,[46] selectively reported test results, publicizing successful tests and deleted all initial data

[36] http://www.bloomberg.com/news/2014-12-03/indian-labs-deleted-test-results-for-u-s-drugs-documents-show.html
[37] http://www.clarislifesciences.com/global/Claris-Lifesciences-Company-Overview.html
[38] http://www.drugregulations.org/2013/07/can-data-from-indian-companies-be.html
[39] http://www.sunpharma.com/manufacturing
[40] http://www.drugregulations.org/2013/07/can-data-from-indian-companies-be.html
[41] http://www.zyduscadila.com/manufacturing.html
[42] http://www.aurobindo.com/about-us/our-operations/indian
[43] http://www.drugregulations.org/2013/07/can-data-from-indian-companies-be.html
[44] http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm256861.htm
[45] http://www.drugregulations.org/2013/07/can-data-from-indian-companies-be.html
[46] http://www.rpglifesciences.com/about_manufacture.jsp

that might have been unfavorable.[47]

- Fresenius Kabi, a global health care company, in a similar fashion as RPG, ignored results that were undesirable.[48]

- In 2011, Sun Pharmaceutical Industries deleted more than 5,300 failed chromatography test results according to FDA documents recently obtained by Bloomberg News.[49] FDA inspectors concluded, "Our review found that analysts regularly delete undesirable chromatographic results, and products are retested without initiating an investigation as required."

- Wockhardt, which has its biggest plant in Baddi, Himachal Pradesh,[50] a large exporter of medications to US, including the recently withdrawn heart medication metoprolol, repeatedly delayed, denied and then limited an inspection by the FDA in 2013. Products that failed to meet the in-process visual inspection were reported by Wockhardt employees as having met all specifications. Sample preparation data were also destroyed, making calculations and analysis impossible. In addition, the inspection documented over 40 instances of incomplete training records for three staff members. In each case, the trainee and trainer names were left blank on the questionnaires, but were pre-filled with the answers.[51]

While the above 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.

On 23 January 2015, the European Medicines Agency recommended suspension of several medicines for which authorization for sale in the EU was primarily based on bioequivalence studies conducted at a contract research organization (CRO) based in Hyderabad, India named GVK Biosciences. The EMA's Committee for Medicinal Products for Human Use

[47] http://www.drugregulations.org/2013/07/can-data-from-indian-companies-be.html
[48] Ibid.
[49] http://www.bloomberg.com/news/2014-12-03/indian-labs-deleted-test-results-for-u-s-drugs-documents-show.html
[50] http://www.wockhardt-knowhow.com/ourfacilities.html
[51] http://www.drugregulations.org/2013/07/can-data-from-indian-companies-be.html

(CHMP) looked at over 1,000 pharmaceutical forms and strengths of medicines studied at GVK Biosciences. For 300 of them, it established that sufficient supporting data from other sources were available; but for the other 700, the agency's inspection found data manipulations of electrocardiograms (ECGs) during the conduct of bioequivalence studies that have appeared to have taken place over a period of at least five years.[52]

These type of fraudulent activities in unregulated or under-regulated markets add another layer of complexity to an already difficult problem of the standards with which we measure a generic drug's therapeutic equivalence 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 U.S. manufacturing plants, where it found irregularities in manufacturing and record-keeping at numerous generic drug makers. Companies were substituting other companies' medication for testing in order to establish product efficacy.[53] Deficiencies were found in 12 American plants.[54]

VII. Policy Considerations

The FDA has expanded its mandate, from just ensuring the safe and effective manufacture of drugs in the United States, to overseeing the manufacturing facilities and quality of products made both domestically and overseas and sold to the US patient as a consequence of the FDA Safety & Innovation Act of 2013.

To effectively do this would require an increase in the frequency and extent of pharmacovigilance (and especially market surveillance).[55] Yet such surveillance is almost non-existent. Perhaps a partial solution is that when products manufactured by foreign companies with a history in the last 10 years of quality problems are being investigated for additional compliance related problems, the FDA could be allowed increased authority to block the

---

[52] http://www.outsourcing-pharma.com/Clinical-Development/EMA-opens-investigation-into-India-s-GVK-Bio-over-ECG-falsifications

[53] http://content.time.com/time/magazine/article/0,9171,958423,00.html

[54] http://www.nytimes.com/1989/09/12/business/fda-details-problems-at-drug-makers.html

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

importation of products from such overseas manufacturing locations without waiting for physiological evidence, which is often hard to find in such cases.

In addition, the FDA could undertake more random sampling of medicines from US pharmacies and clinics, perhaps targeting narrow therapeutic index medicines and manufacturers with poor track records.

Further, more transparency regarding the bioequivalence data may help offset some of the concerns and enable physicians and consumers to make better choices.[56] Currently manufacturers can change the suppliers of ingredients (active and excipients) without being required to undertake new bioequivalence studies, if they stipulated they would buy from a wide list of suppliers in their ANDA. However, differing supplies of the same ingredients may produce different results.

Transparency in medication labeling would assist physicians and patients. Perhaps drug labels could include the manufacturer as well as the country of origin because some companies have multiple manufacturing sites that span the globe.

Finally, in order 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 in this paper may be exacerbated by next-generation biologic drugs, now reaching the market. This new class of medicines represents the future of treatments and cures for lung and heart diseases, cancer, arthritis, diabetes and many other costly 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 don't lend themselves to the

[56] This is the aim of legislation promoted by Amy Paulin, State Congresswoman for the 88th New York State Assembly District (Scarsdale, Eastchester, Tuckahoe, Bronxville, Pelham, Pelham Manor, and parts of New Rochelle and White Plains), (D-NY) and her colleagues. They want companies that wish to sell into the lucrative NY market to release their BE data even if FDA doesn't require it. One can view the Bill on the Assembly website, assembly.state.ny.us, by typing the bill number A.145 in the "Bill Search" area.

production of identical or nearly identical generic copies.[57] 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 $80 billion worth of biologics will lose patent protection in 2015. And according to a recent estimate by Omics Group, which publishes scientific journals, India and China are poised to take over much of those productions lines, commanding as much as 70 percent of the global market – currently valued at $20 billion – over the next few years.[58]

In light of this inherent variability and the diverse and complex analytical methods required to identify the molecules, it is not realistic to replicate an innovator molecule exactly. The ability to properly express protein (upstream fermentation), purify the drug substance (downstream purification), and manufacture a drug product (stable formulation & delivery) each present a unique hurdle. Establishing therapeutic equivalence in the case of biosimilars presents a challenging problem.

VIII. Conclusion

To conclude, the rules underlying the assessment of quality of generic drugs, and their bioequivalence to brand name 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 imply that two bioequivalent products are not identical to each other. Providing evidence from medications to treat epilepsy, depression and other serious conditions this paper shows that switching from an innovator brand to a generic may result in adverse consequences for patients. Moreover, the clinical impacts of shifting from one generic to another generic are also unknown. In a self-conducted survey, we provide original data to show that in only 10% of pharmacies surveyed over four consecutive months was the same generic available. Hence consumers often have less choice with respect to the generics they buy from brick and mortar pharmacies and we need more information to understand whether this type of enforced generic switching is advisable.

---

[57] For a more detailed discussion of the differences between chemical and biologic drugs, see http://www.bio.org/articles/how-do-drugs-and-biologics-differ

[58] http://www.business-standard.com/article/companies/india-china-to-command-70-of-20-billion-global-biosimilars-market-114102700655_1.html

Additionally, generic and brand name drugs source more ingredients and even final products from outside the U.S. especially from countries like India and China which 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, U.S. patients are still prescribed their products. These are complex issues facing the FDA and a step towards transparency as well as updating of bioequivalence standards may be important to overcome some of these challenges. Further, transparency in labelling where products are sourced from could be important in improving patient safety.

References

Berndt, E., Aitken, M., 2010. Brand loyalty, generic entry, and price competition in pharmaceuticals in the quarter century after the 1984 Hatch-Waxman legislation. NBER Working Paper No. 16431.

Burkhardt, R., Leppik, I., Blesi, K., Scott, S., Gapany, R., Cloyd, J., 2004. Lower phenytoin serum levels in persons switched from brand to generic phenytoin. Neurology 63(8), 1494-1496.

Carswell, J., Gordon, J., Popovsky, E., Hale, A., Brown R., 2012. Generic and branded Levothyroxine preparations are not bioequivalent in children with Congenital Hypothyroidism. Clinical Thyroidology 25(2), 31-32.

Grabowski, H., 2007. Competition between generic and branded drugs. In Pharmaceutical Innovation: Incentives, Competition, and Cost-Benefit Analysis in International Perspective, Sloan, F., Hsieh, C. (eds.), Cambridge University Press: Cambridge, MA.

Grabowski, H., Vernon, J., 1996. Longer patents for increased generic competition: The Waxman Hatch Act after one decade. Pharmacoeconomics 10, 110–123.

Henderson, J., Esham, R., 2001. Generic substitution: issues for problematic drugs. Southern Medical Journal 94(1), 16-21.

Meredith, P., 2003. Bioequivalence and other unresolved issues in generic drug substitution. Clinical Therapeutics 25(11), 2875-2890.

Mossinghoff, G., 1999. Overview of Hatch-Waxman act and its impact on the drug development process. Food and Drug Law Journal 54(2), 187-194.

Paveliu, M., Bengea, S., Paveliu, F., 2011. Generic substitution issues: brand-generic substitution, generic-generic substitution, and generic substitution of narrow therapeutic index (NTI)/critical dose drugs. Maedica 6(1), 52-58.

Rizzo, J., Zeckhauser, R., 2005. Generic scrip share and the price of brand-name drugs: the role of consumer choice. NBER Working Paper No. 11431.

Woodcock, J., Khan, M., Yu, L., 2012. Withdrawal of generic budeprion for nonbioequivalence. New England Journal of Medicine 367(26), 2463-2465.