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# Drug Inequality: Allowable Variations and Illegal Underperformance in Off-Patent Drugs

by

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## *Summary*

Generic drugs are allowed to vary from the originator drug in the amount of active pharmaceutical ingredient (API) likely to be absorbed by a typical patient. We contend that this allowable variation range is too wide to guarantee the same therapeutic effect (bioequivalence) in all drugs and that some generics have been approved without having met even these requirements. Greater availability of generics and increased substitution between them is exacerbating the problem of non-bioequivalence and in principle requires increased monitoring of drug levels in patients, which mitigates price savings. However, drug levels are rarely monitored, leading to unknown but likely significant clinical problems. We present case studies to support these assertions. We urge the FDA to make bioequivalence data on all generic drugs available to physicians, pharmacists and patients, a policy it currently discourages. These interested parties can then be more aware of the variation in bioavailable API content in generic drugs and to take account of possible physiological and adverse effects. We also urge the FDA to require that generics be dispensed with identification of the manufacturer or distributor – a policy which currently exists only in certain states. Ultimately we suggest FDA narrow the allowable range of bioequivalence, at least for specific drug types where small differences in API availability and or speed of delivery can cause critical effects in patients. Given manufacturing problems, notably in India, attention to stated bioavailability and actual variation in patient response is warranted; and likely to identify far more problems than just those based on bioavailability concerns. We present numerous examples of Indian companies cutting corners in production, which risks the lives of patients globally, and even in US. Additionally, the apparent segmentation of the market by some Indian producers must be discouraged by US agencies, not just FDA. FDA must also increase vigilance of pharmaceuticals in the US market, as even surprise plant inspections cannot prevent all problems with non-bioequivalent and even substandard products. Last, we discuss the failings of the current oversight process as it relates to the current regulatory planning at FDA for new, off-patent biological drugs.

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## 1. INTRODUCTION

Over the past three decades, increased access to off-patent or generic pharmaceuticals has provided great benefit and lowered healthcare costs<sup>8</sup>.

The downside, however, has been increased incidences of reduced quality, and the health risks posed. Although problems with products made in the U.S.A. do occur, the driver of most quality risk is the importation of drugs or ingredients in those drugs from emerging nations with non-existent private feedbacks that limit poor quality<sup>9</sup>. These are also usually the markets that are unregulated or under-regulated by domestic governmental authorities. In theory, all products, domestic or imported, must comply with certain manufacturing standards called “current good manufacturing process (cGMP).” In practice, this expectation is based on the honor system. When lapses are detected, it is due to (infrequent) routine testing of products before they enter the market for quality, or more frequently, after substandard products have already caused adverse effects in patients. Long term effects of substandard and adulterated medicines are hard to quantify. A reduced dosage than that prescribed when using substandard drugs may manifest as a symptom much later, and in many cases may be difficult to separate from the natural progression of the disease. Many, perhaps most, are never formally detected or, if suspected by researchers, healthcare providers, patients or others, are never formally addressed by relevant government authorities. Some lapses are true accidents, others are due to negligence, including gross negligence. But some are malicious, they are deliberate and fraudulent attempts to pass off inferior quality products in order to save money and increase profit.

Regulators’ power to check these problems are limited to inspections of manufacturing plants, and assessments of products on the market. While inspections are unannounced in the U.S., in other countries (notably India and China where many products destined for the US originate), they must be conducted with the cooperation and facilitation of national regulators<sup>10</sup> and sometimes even the approval of those inspected, which of course, limits their value (especially when regulators connive with those being inspected, as has been the case in India<sup>11</sup>). Even where there is political will, widespread inspections of final products are expensive and rarely undertaken. What’s more, when problems are identified, resolution can take many years, stretching capabilities of the FDA and other regulators involved. Prosecution of firms headquartered overseas is notoriously difficult given 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.

Furthermore, physicians and patients are given little information of problems and have few choices with any information they do receive. One can demand an innovator product, but one cannot usually demand a specific generic, even if one generic (produced by a company with numerous production lapses) is thought inferior. In fact, in many states generics are dispensed without identification of the manufacturer or distributor, putting the consumer at a great

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<sup>8</sup> Cook et al (2010), Generic Utilization Rates, Real Pharmaceutical Prices, and research and development expenses, NBER Working Paper 15723, February

<sup>9</sup> Roger Bate (2013) Cheap Indian Generic Drugs: Not Such Good Value After All?, Health Policy Outlook, AEI, February

<sup>10</sup> PTI. (January 11, 2015). India wants its officials during FDA inspections at drug units. *The Live Mint*. Retrieved from <http://www.livemint.com/Industry/99oie9vfXwmU9DzDtiQ2JI/India-wants-its-officials-during-FDA-inspections-at-drug-uni.html>

<sup>11</sup> (May 8, 2012). Fifty-ninth report on the functioning of the Central Drugs Standard Control Organisation (CDSCO). *Parliament of India Rajya Sabha*. Retrieved from <http://164.100.47.5/newcommittee/reports/EnglishCommittees/Committee%20on%20Health%20and%20Family%20Welfare/59.pdf>

disadvantage. All drugs can be made useless or even lethal by major production mistakes or intended fraud, but for some drugs even small errors can lead to health concerns for patients. Additionally, the labeling laws in the US do not require the manufacturer or country of origin to be listed on the label. Rather, suppliers can choose to simply list the distributor. Many suppliers choose to have contract manufacturers prepare products that they simply label with their brand. The labeling laws currently make it impossible for clinicians to know where a product was made, or by which company. Even though FDA publishes results of inspections in the form of 483 reports and warning letters, these reports are heavily redacted and manufacturers consider the list of drugs prepared at a factory to be proprietary information that may not be publicly disclosed.

Some drugs have a very narrow dosage range between a drug being therapeutic and a drug becoming ineffective or even toxic. These drugs are known as having a “narrow therapeutic index” or are called “critical dose drugs.” In these cases, variations in the active pharmaceutical ingredient (API) and other ingredients can have a dramatic and erratic effect on its absorption into the bloodstream. 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, often releasing the drug earlier than desired.

These problems are with so-called small molecule drugs – the types that can be synthesized in basic laboratories. Yet such problems are inherent and likely to be even worse in next-generation biologic drugs, whose copies, known as biosimilars, are materially different from the originator medicine. These biosimilars will only exacerbate regulatory problems as these medicines gain wider acceptance and use. We discuss biologic drugs later.

The problems facing the FDA, foreign regulators, companies (domestic and foreign) and patients are complex. Here, we attempt an assessment that highlights the most salient problems, groups them into common threads, and suggest policies that might remedy each of them.

This paper is the product of an expert group meeting convened on 4<sup>th</sup> June 2014 in Washington, D.C., of scientists, physicians, economists, lawyers, pharmaceutical practitioners and former regulators. The group includes the two people most responsible for alerting us to the risks of generic Wellbutrin, a widely used anti-depressant, and the products manufactured by Indian generic firm Ranbaxy.

N.B. After we began this project the FDA announced that it was establishing an office on pharmaceutical quality (OPQ). As FDA says: “OPQ will combine non-enforcement-related drug quality work into one super-office, creating one quality voice and improving our oversight of quality throughout the lifecycle of a drug product.”<sup>12</sup> It is far too early to assess whether this office will improve matters, but perhaps its establishment is a tacit acknowledgement that the situation till now has been unacceptable.

## 11. DEFINING THE STANDARD: BIOEQUIVALENCE

Since the passage of the Patent Term Restoration Act in 1984, more commonly known as the Hatch-Waxman Act, far more generic drugs have been approved by the US Food and Drug Administration (FDA) than earlier<sup>13</sup>. The Act allows generic drugs, once certified as therapeutically equivalent to a branded drug, to be substituted when filling prescriptions for the branded drug.

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<sup>12</sup> <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm418347.htm>

<sup>13</sup> Cook et al (2010), Generic Utilization Rates, Real Pharmaceutical Prices, and research and development expenses, NBER Working Paper 15723, February

With the growing proliferation of generic drugs, current U.S. pharmacy practice is to replenish stocks with the lowest cost generic available and to automatically substitute generics for repeat prescriptions without giving notification – either to the patient or to the prescribing physician.

This practice is based on the assumption that the products being substituted are bioequivalent. Bioequivalence is certified when the bioavailability of two drugs is nearly identical or in an acceptable range of similarity.

Yet provisions in the Hatch Waxman Act limited the FDA from asking for anything more than bioavailability studies when drug companies submit ANDAs – abbreviated new drug applications.<sup>14</sup> Some critics have argued that this provision reduced 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. The scale for determining the similarity of bioavailability is so broad that quite dissimilar drugs may appear equivalent by a comparison based on one criterion.<sup>15 16</sup>

So what is bioavailability? 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. Specifically, 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.*<sup>17</sup>

## II.A. Lapses in Bioequivalence (approval mistakes and unacceptable variability): Is the Bioequivalence Standard Safe for Patients?

It was recognized early on in drug development that even innovator (another term for “branded”) products were never perfectly identical to each other. Trying to make sure every product delivered exactly the same amount of active ingredient was very costly and thought not necessary. Whether a product delivers 98.3 percent of active ingredient prescribed as compared to the innovator product, or 101.8 percent is almost never a matter for concern (partly given variations in humans) and hence it is pragmatic to allow minor variations. However, the Hatch-Waxman Act allows a much wider range of variation than that. It allows between 80 percent and 125 percent of the concentration of the drugs in blood plasma over time of tested patients as

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<sup>14</sup> Mossinghoff, G. J. (1999). Overview of the Hatch-Waxman Act and its impact on the drug development process. *Food and Drug Law Journal*, 54, 187.

<sup>15</sup> Mossinghoff, G. J. (1999). Overview of the Hatch-Waxman Act and its impact on the drug development process. *Food and Drug Law Journal*, 54, 187.

<sup>16</sup> Testing procedures for off-patent drugs which are made to mimic biologic drugs (grown from proteins) known as ‘biosimilar’ are in their infancy. Forceful arguments have been made that, because biosimilars can never be an exact copy of the innovator biologic, full Phase III clinical trials be carried out for each biosimilar and for each disease it is intended to treat.

<sup>17</sup> (April 1, 2014). CFR - Code of Federal Regulations Title 21, Volume 5. *U.S. Food and Drug Administration*. Retrieved from <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=320.1>

compared with the innovator for it to be deemed bioequivalent and hence be approved and receive a registration for use in the U.S.<sup>18 19</sup>).

There are broadly two potential problems with this, even assuming no production errors. The first is that such a range might be too broad for some drugs for some conditions, such as post-transplant immunosuppression, where minor variations in a drug might lead to organ rejection. In other words *any* generic product approved under such range might not work properly in patients with such conditions. We discuss such an example shortly.

The second is that with substitution from one generic to another (the current pharmacy practice), two generic drugs that are deemed bioequivalent to the innovator product may not be bioequivalent *to each other*, which might cause additional problems. For instance, a patient might be doing well on a generic drug that delivers more API than the branded product, but would experience clinical failure if switched to a different generic that delivers less API. An additional problem, of course, is if manufacturers fail to sustain approved standards of production, so that the products taken would not be considered bioequivalent. We address these problems later.

There are well-documented cases in which a switch between the innovator and generic drug has caused adverse effects.<sup>20</sup> However, we have found no formal studies of bioequivalence *between* generic drugs, not even for drugs with narrow therapeutic indices, though credible evidence of disparity and ensuing harm has been available to the FDA for many years. The agency is now funding a variety of research projects at U.S. institutions to assess substitution among generics and related problems<sup>21 22</sup>.

Physicians are aware of these risks, especially in the case of critical-dose drugs, and may undertake extra laboratory tests to monitor how the drugs are performing in the patient. This is a

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<sup>18</sup> Technically the FDA demands that 90% Confidence Intervals of the relative mean  $C_{max}$ ,  $AUC_{(0-t)}$  and  $AUC_{(0-\infty)}$  of the generic under evaluation to reference/innovator formulation, should be within 80% to 125%.

<sup>19</sup> Several commentators, including Klintmalm [Klintmalm, G. B. (2011). Immunosuppression, generic drugs and the FDA. *American Journal of Transplantation*, 11(9), 1765-1766.] have criticized testing procedures for allowing such wide variation in API from different generic formulations; however, Latran in response [Latran, M. (2012). Response to Klintmalm on the use of generic immunosuppression. *American Journal of Transplantation*, 12(3), 791-791.] points out that 90% CI of AUC and  $C_{max}$  must also fall within 80% and 125%, moreover, that this information is available from the manufacturer.

<sup>20</sup> Henderson, J. D., & Esham, R. H. (January, 2001). Generic substitution: issues for problematic drugs. *Southern Medical Journal*, 94(1), 16-21.

<sup>21</sup> See the following:

FY 2013 awarded GDUFA regulatory research contracts and grants. Retrieved from <http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM386955.pdf>

(April 2, 2013). Grant for study on Bioequivalence of Generic Bupropion. *Department of Health and Human Services*. Retrieved from <http://grants.nih.gov/grants/guide/rfa-files/RFA-FD-13-021.html>

FY 2014 GDUFA regulatory research priorities. Retrieved from <http://www.fda.gov/Drugs/NewsEvents/ucm367997.htm>

(February 13, 2015). Open grant: Pharmacometric Modeling and Simulation for Long Acting Injectable Products (U01). *Center for Drug Evaluation and Research (CDER)*. Retrieved from <http://grants.nih.gov/grants/guide/rfa-files/RFA-FD-15-008.html>

<sup>22</sup> We note that the bioequivalence studies currently under way are funded from registration fees levied on generic drug producers and paid to FDA, and as such, the results of those studies will be public knowledge; we hope to be allowed to interrogate the findings.

critical problem to mitigate in transplant patients who are taking immunosuppressants to minimise the risk of rejection of the grafted organ.

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,<sup>23</sup> this average masked some astonishing 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."<sup>24</sup>

The costs of extra vigilance are significant – blood tests, laboratory time, clinic visits, physician's time – and can easily outweigh any saving in the purchase price of the drug. Moreover, since standard practice requires re-stocking at lowest-cost and automatic substitution, these tests must be repeated after every prescription, since patients could be provided a different generic each time the prescription is filled.<sup>25</sup>

One might hope that the FDA would recognize the need for narrower bioequivalence ranges for certain drugs. Indeed, the agency's guidelines state that applicants for bioequivalence certification "consider additional testing and/or controls to ensure the quality of drug products containing narrow therapeutic range drugs." These additional measures are mere suggestions, however, and the FDA neither enforces testing nor provides parameters for tests that should be performed.<sup>26</sup> Rumors are circulating that FDA is considering tightening BE standards for narrow therapeutic drugs.

## II.B. Switching Between Generics: Evidence Of The Risks

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)<sup>27</sup>. We searched for evidence proving bioequivalence *between* generic versions of these drugs (as opposed to data comparing the generic to the branded product), and only in the case of levothyroxine could any statistically relevant results be found. Doctors often advise that patients who are tolerating one specific generic drug stay on that same generic or the

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<sup>23</sup> Momper, J. D., Ridenour, T. A., Schonder, K. S., Shapiro, R., Humar, A., & Venkataramanan, R. (2011). The impact of conversion from prograf to generic tacrolimus in liver and kidney transplant recipients with stable graft function. *American Journal of Transplantation*, 11(9), 1861-1867.

<sup>24</sup> Klintmalm, G. B. (2011). Immunosuppression, generic drugs and the FDA. *American Journal of Transplantation*, 11(9), 1765-1766.

<sup>25</sup> Klintmalm, G. B. Editorial. (2011). *Am J Transplant*, 11(9), 1765-1766.

<sup>26</sup> (March 2003). Guidance for industry: Bioavailability and Bioequivalence studies for orally administered drug products- General considerations. *Center for Drug Evaluation and Research (CDER)*. Retrieved from <http://www.fda.gov/downloads/Drugs/Guidances/ucm070124.pdf>

<sup>27</sup> Henderson, J. D., & Esham, R. H. (January, 2001). Generic substitution: issues for problematic drugs. *Southern Medical Journal*, 94(1), 16-21.

same name brand in the case of all four drugs.<sup>28</sup> (This, however, is difficult to do, particularly in states in which the manufacturers or distributors identity is not included with dispensed medication.)

Lacking bioequivalence studies, we then searched the literature for studies of clinical effects of generic–generic switching for these four drugs, but found studies only for levothyroxine.

### 11.B.1. Case Study in Bioequivalence: Levothyroxine

Research published in 2008 by the Endocrine Society<sup>29</sup> was at odds with FDA guidelines on switching between generic versions of levothyroxine as it found that the amount of active ingredient delivered to the patient varied among different versions – even though they purportedly contained the same dosage. 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<sup>30</sup>.

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.<sup>31</sup>

The FDA had requested stability data from manufacturers between July 2003 and June 2005. The data were much more complete than the data submitted with the license application, and showed that there was a trend in potency loss.

According to the FDA’s own data, the shelf life of various generic levothyroxine products varies from as little as 24 hours to as much as 8 months, showing a marked difference in stability.<sup>32</sup> In response, the FDA narrowed the allowable variability from 80–125 percent to 95–105 percent throughout its shelf life as compared with the innovator product. This action is welcome and affects nine manufacturers, but the FDA’s statement that it had observed stability and potency problems in certain levothyroxine sodium products as long ago as 1997, makes one think that FDA may arrive at the right solution, but takes a very long time to do so.<sup>33</sup>

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<sup>28</sup> Henderson, J. D., & Esham, R. H. (January, 2001). Generic substitution: issues for problematic drugs. *Southern Medical Journal*, 94(1), 16-21.

<sup>29</sup> (June 2008). Bioequivalence of Sodium Levothyroxine. *The Endocrine Society*. Retrieved from <https://www.endocrine.org/~media/endosociety/Files/Advocacy%20and%20Outreach/Position%20Statements/All/LT4PositionStatementwithmembercommentsheader.pdf>

<sup>30</sup> (June 2008). Bioequivalence of Sodium Levothyroxine. *The Endocrine Society*.

<sup>31</sup> Carswell, J.M., Gordon, J.H., Popovsky, E., Hale, A., & Brown R.S. (December 21, 2012). Generic and branded Levothyroxine preparations are not bioequivalent in children with Congenital Hypothyroidism. *Clinical Thyroidology*, 25(2), 31-32.

<sup>32</sup> (October 3, 2007). Questions and answers on Levothyroxine Sodium products. *U.S. Food and Drug Administration*. Retrieved from <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm161266.htm>

<sup>33</sup> (October 3, 2007). Questions and answers on Levothyroxine Sodium products. *U.S. Food and Drug Administration*. Retrieved from <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm161266.htm>



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 an unexpected increase in 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.<sup>34</sup> 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.<sup>35</sup>

## II.B.2. Case Study in Bioequivalence: Musical chairs in generic cholesterol control

One of the complaints made by patients and physicians in US is the change in generics made by pharmacists apparently based on little more than what happens to be in stock this week. This is allowable because of the belief that all FDA-approved generics of the same medicine and same dose are interchangeable. Yet the medical literature has established non-bioequivalence between innovator and generic, and anecdotal evidence suggesting non-bioequivalence between different generics of the same medicine. To see both where the medicines we use come from and how often they are changed we decided to investigate 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. It was likely that numerous manufacturers would be eager to make it and ironically the Indian company with the worst production record, Ranbaxy, was granted initial generic exclusivity by FDA.

In an attempt to evaluate the variability in statins supplied to patients, we<sup>36</sup> assessed the availability of generic atorvastatin that could be bought with prescriptions in three states Virginia, Maryland and Pennsylvania and in Washington, DC. We sampled from between October 2014 and January 2015. One-off sampling was undertaken from 121 bricks and mortar pharmacies (22 VA, 23 MD, 6 WDC and 70 PA). 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%) from Canadian, 17 (14%) from Swiss, 33 (28%) from US, 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 (7<sup>th</sup>, 8<sup>th</sup> or 9<sup>th</sup>) of every month – October, November, December and January). While the product range remained the same, most of the pharmacies would not provide the same generics each time in order to fill a prescription.

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<sup>34</sup> (January 07, 2013). Levothyroxine Tablet products: A review of clinical & quality considerations. *Medicines and Healthcare Products Regulatory Agency*. Retrieved from <http://webarchive.nationalarchives.gov.uk/20141205150130/http://www.mhra.gov.uk/home/groups/pl-p/documents/drugsafetymessage/con222566.pdf>

<sup>35</sup> (January 07, 2013). Levothyroxine Tablet products: A review of clinical & quality considerations. *Medicines and Healthcare Products Regulatory Agency*. Retrieved from <http://webarchive.nationalarchives.gov.uk/20141205150130/http://www.mhra.gov.uk/home/groups/pl-p/documents/drugsafetymessage/con222566.pdf>

<sup>36</sup> In this instance “we” is 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.

In six of the pharmacies (30%), patients would receive a different generic each month and in only two pharmacies (10%) was the same generic the one 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.

Consumer choice does not exist for generic medicines. Having different products on the market is usually beneficial; choice and competition are nearly always good. But choice does not lie with the patient or his physician but the pharmacist, his supplier, an insurance company or governmental entity. Consumers cannot apply selective pressure as they would buying a car or a soda, and quality may not be the highest priority of those making the choice on behalf of the patient.

If the patient (or his physician) is very persistent and is prepared to ask around he can probably find the same generic each time to refill his prescription, but this requires effort – effort that FDA does not think is worthwhile. All the other players in the distribution chain have developed systems based on interchangeability and hence there are no vested interests pushing consumer choice as a priority. After all, in only 10% of the pharmacies sampled was the same generic offered at subsequent visits. For the most sensitive patients constant change of product could be undermining 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 US market, we could purchase dozens of additional products online, from licensed pharmacies in numerous countries, with an extraordinary range of prices; from \$0.21 for generics (per pill) to \$4.97 for brand name Lipitor (per pill).

If a patient bought online, where there is this far greater selection of products, it is quite possible for them to take a different generic every month for many years, with potentially dangerous consequences. Of course the advantage of the online market could be that consumers can repeatedly choose a specific generic, perhaps one they know they tolerate well. In this way selective pressure could drive demand for better products. We know of no studies that have actually identified this for medicines.

### II.B.3. Case Study in Bioequivalence: Epilepsy/Seizure

In the past, FDA has told doctors that generic anti-seizure medicines are equivalent to the innovator drug.<sup>37</sup> FDA's approval process has come into question because of a lack of bioequivalence testing on patients with epilepsy. "Doses used in studies may not yield relevant ranges in serum concentration, and bioequivalence does not guarantee that a generic will produce the same therapeutic effect or result in the same adverse effects as the branded drugs" noted Harvard neurologist Steven Schachter who is also a member of the board of directors of the Epilepsy Foundation.<sup>38</sup> In other words, bioequivalence testing does not give the full story because bioequivalence studies tend to be carried out in scenarios that are not often clinically relevant – typically, a single dose is given to young, healthy, male volunteers, whereas patients tend to be elderly and have other illnesses or conditions requiring medication. Schachter also

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<sup>37</sup> Sipkoff, Martin. (March 2008). The Epilepsy battle in the war between brands and generics. *Managed Care*. Retrieved from <http://www.managedcaremag.com/archives/0803/0803.epilepsy.html>

<sup>38</sup> Sipkoff, Martin. (March 2008). The Epilepsy battle in the war between brands and generics. *Managed Care*. Retrieved from <http://www.managedcaremag.com/archives/0803/0803.epilepsy.html>

points to a study by the Strong Epilepsy Center at the University of Rochester, where two-thirds of reporting physicians said that a patient experienced a breakthrough seizure when switched from brand-name to generic AED (anti-epileptic drug).<sup>39</sup>

The American Epilepsy Society and the Epilepsy Foundation are currently working on a study of generic epilepsy medications. The goal of their research is to see if the complaints about the side effects or loss of seizure control are founded scientifically seeing as “no one knows if these complaints are truly because of problems with the generic drug.”<sup>40</sup> At this point, the study is still looking for participants. This research is going to look at how patients with epilepsy respond to various generics as well as the brand product.<sup>41</sup>

#### II.B.4. Case Study in Bioequivalence: Post-transplant immunosuppressants

Patients and doctors have also voiced concerns about generic immunosuppressants; mainly, the concerns regarding the lack of testing of the generic on transplant patients, the lack of labeling of generics and the variability of the generic. Many doctors and pharmacists say that the allowable variation of 80%-125% of the concentration of deliverable API is far too wide for immunosuppressants that have a narrow therapeutic index.<sup>42</sup> Unlike many other drugs, post-transplant medications have more possible complications and interactions. For example, SandCya 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.

Like the case of anti-epilepsy drugs, patients are switched from brand name to generic drugs without their consent or knowledge. Several papers by members of transplant communities comment that the biggest problem in generic immunosuppressants is that patients can be switched at any point. They suggested better labeling to help patients spot changes in manufacturer. They also recommend that there should be consistency in state regulations for pharmacists to notify their patients and the physician prior the changes in medication.<sup>43</sup> This recommendation has been made by the Journal of Transplantation, and other journals.<sup>44</sup>

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<sup>39</sup> Sipkoff, Martin. (March 2008). The Epilepsy battle in the war between brands and generics. *Managed Care*. Retrieved from <http://www.managedcaremag.com/archives/0803/0803.epilepsy.html>

<sup>40</sup> Privitera, Michael., University of Cincinnati. (October 13, 2014). Equivalence among Antiepileptic drug generic and brand products in people with Epilepsy: Single-dose 6-period replicate design (EQUIGEN single-dose study). *Clinicaltrials.gov*. <https://clinicaltrials.gov/ct2/show/NCT01733394>

<sup>41</sup> Privitera, Michael., University of Cincinnati. (October 13, 2014). Equivalence among Antiepileptic drug generic and brand products in people with Epilepsy: Single-dose 6-period replicate design (EQUIGEN single-dose study). *Clinicaltrials.gov*. <https://clinicaltrials.gov/ct2/show/NCT01733394>

<sup>42</sup> Singh, A. K., & Narsipur, S. S. (2011). Cyclosporine: a commentary on brand versus generic formulation exchange. *Journal of Transplantation*, 2011.

<sup>43</sup> Singh, A. K., & Narsipur, S. S. (2011). Cyclosporine: a commentary on brand versus generic formulation exchange. *Journal of Transplantation*, 2011.

<sup>44</sup> See: Alloway, R. R., Isaacs, R., Lake, K., Hoyer, P., First, R., Helderman, H., Bunnapradist, S., Leichtman, A., Bennett, M.W., Tejani, A and Takemoto, S.K. (August 13, 2003). Report of the American Society of Transplantation conference on immunosuppressive drugs and the use of generic immunosuppressants. *American Journal of Transplantation*, 3(10), 1211-1215. and Haug 3rd, M., & Wimberley, S. L. (July, 2000). Problems with the automatic switching of generic cyclosporine oral solution for the innovator product. *American Journal of Health-System Pharmacy: AJHP: official journal of the American Society of Health-System Pharmacists*, 57(14), 1349.

So for at least three categories of medications where the impact of inferior medicines will be obvious, it does indeed appear that there are problems with some generic medications. And this adds further to the evidence to support the notion that perhaps many classes of medications have bioequivalency or even outright quality problems.

#### II.B.5. Case Study in Bioequivalence: Wellbutrin and Concerta generics – products approved without being appropriately tested

##### *Wellbutrin*

In 2007, the syndicated columnists and radio hosts at the People's Pharmacy, received 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.<sup>45</sup>

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."<sup>46</sup>

Within weeks, hundreds of complaints had flooded the People's Pharmacy website describing identical symptoms. Graedon asked the independent health product testing group, ConsumerLab.com, if it would test the drug. 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.<sup>47</sup>

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.<sup>48</sup>

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<sup>45</sup> (April 23, 2007). Side effects of Generic Wellbutrin, [ Q&A]. *The People's Pharmacy*. Retrieved from <http://www.peoplespharmacy.com/2007/04/23/side-effects-of/>

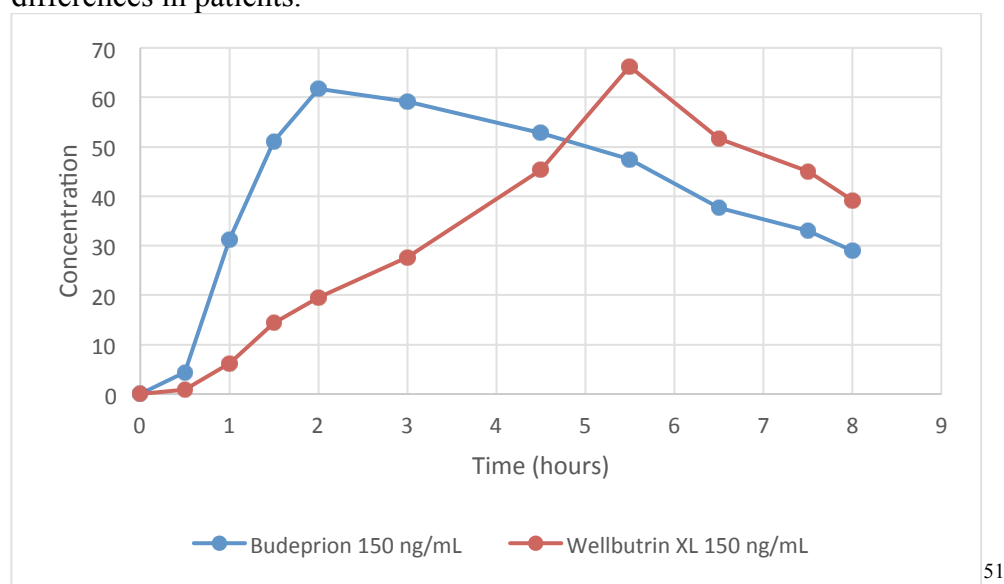
<sup>46</sup> Neporent, Liz. (October 4, 2012). FDA asks for voluntary recall of popular generic antidepressant. *ABC News*. Retrieved from <http://abcnews.go.com/Health/fda-finds-generic-antidepressant-original/story?id=17399399>

<sup>47</sup> (October 12, 2007, Tod Cooperman). Wellbutrin vs. Generic Bupropion. [Drug Test]. *Consumer Lab*. Retrieved from [https://www.consumerlab.com/reviews/Wellbutrin\\_vs\\_Generic\\_Bupropion/Wellbutrin/](https://www.consumerlab.com/reviews/Wellbutrin_vs_Generic_Bupropion/Wellbutrin/)

<sup>48</sup> (October 12, 2007). Wellbutrin vs. Generic Bupropion. [Drug Test]. *Consumer Lab*. Retrieved from [https://www.consumerlab.com/reviews/Wellbutrin\\_vs\\_Generic\\_Bupropion/Wellbutrin/](https://www.consumerlab.com/reviews/Wellbutrin_vs_Generic_Bupropion/Wellbutrin/)

People's Pharmacy took its concerns to the FDA and requested information on the human drug trials that companies are typically required to submit for drug approval. After what Graedon described as "a lot of back and forth," the FDA revealed that the 300 mg product had never undergone bioequivalence testing even though this is typical agency protocol.<sup>49</sup> Instead, their approval was based on tests of a 150 mg version of the drug.

The chart below 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<sup>50</sup>. The area under the curves represent 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.



Although it is well understood that different dosages of drugs frequently do not have the same results and can produce varied side effects, the agency stood by its approval of the 300 mg dose of the generic. However, it asked Teva to *voluntarily* perform its own trials involving people who had reported problems.<sup>52</sup>

Citing difficulty recruiting subjects, the company never performed the tests. Then in 2010, the FDA took the unusual step of conducting 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

<sup>49</sup> (October 10, 2013). Update: Bupropion Hydrochloride extended-release 300 mg Bioequivalence studies. *U. S. Food and Drug Administration*. Retrieved from <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm322161.htm>

<sup>50</sup> 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?

<sup>51</sup> (October 17, 2013). Update: Wellbutrin vs. Generic Bupropion. [Drug Test]. *Consumer Lab*. Retrieved from [https://www.consumerlab.com/reviews/Wellbutrin\\_vs\\_Generic\\_Bupropion/Wellbutrin/](https://www.consumerlab.com/reviews/Wellbutrin_vs_Generic_Bupropion/Wellbutrin/)

<sup>52</sup> Neporent, Liz. (October 4, 2012). FDA asks for voluntary recall of popular generic antidepressant. *ABC News*. Retrieved from <http://abcnews.go.com/Health/fda-finds-generic-antidepressant-original/story?id=17399399>

reach 40%.<sup>53</sup> "This discrepancy in dosage could render the drug less effective in treating depression and could explain the side effects we were hearing about," Graedon said.<sup>54</sup>

When results of the trials became available in 2012, FDA allowed the products to remain approved but reclassified them as not equivalent to Wellbutrin XL 300. However, the FDA sent both Teva and Impax communications asking them to voluntarily withdraw the drug from the market. Both companies complied with the request.<sup>55</sup> It is unclear if any other national markets demanded a withdrawal of these products.

The FDA continued the spin: agency spokesperson Sandy Walsh stressed that this was not a recall, which is typically done when a drug is unsafe. "This is a voluntary market withdrawal by the company for a drug that may not work well for some people. It is one type of generic Wellbutrin XL in the 300mg strength only, made by Teva. This does not impact the other manufacturers or the 150 mg strength pills," Walsh said. There are no solid numbers on how many patients took these inferior medicines.<sup>56</sup>

FDA asked other manufacturers of generic 300 mg dose versions of Wellbutrin to conduct their own studies and submit their data no later than March 2013.<sup>57</sup> Then, on 10 October 2013, the FDA quietly posted an update to its website announcing that another company Watson Pharmaceuticals—had submitted data that "determined that the company's generic bupropion HCl ER 300 mg tablet product is not therapeutically equivalent to Wellbutrin XL 300 mg." "Watson has agreed to voluntarily withdraw this product from the distribution chain," the FDA wrote.

All these withdrawals caused the agency to reevaluate how it conducts bioequivalency testing, and in April 2013, the FDA initiated a contracting process with the stated intent of "understanding the scientific basis causing the failure of the 300 mg tablets," calling it "important for future guidance development and review processes."<sup>58</sup>

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<sup>53</sup> (October 3, 2012). FDA Update: Budeprion XL 300 mg not therapeutically equivalent to Wellbutrin XL 300 mg. *U.S. Food and Drug Administration*. Retrieved from <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm322161.htm> (Woodcock, J., Khan, M., & Yu, L. X. (2012). Withdrawal of generic budeprion for nonbioequivalence. *New England Journal of Medicine*, 367(26), 2463-2465. Retrieved from <http://www.nejm.org/doi/full/10.1056/NEJMp1212969>.)

<sup>54</sup> (October 12, 2007). Wellbutrin vs. Generic Bupropion. [Drug Test]. *Consumer Lab*. Retrieved from [https://www.consumerlab.com/reviews/Wellbutrin\\_vs\\_Generic\\_Bupropion/Wellbutrin/](https://www.consumerlab.com/reviews/Wellbutrin_vs_Generic_Bupropion/Wellbutrin/)

<sup>55</sup> (October 10, 2013). Update: Bupropion Hydrochloride extended-release 300 mg Bioequivalence studies. *U. S. Food and Drug Administration*. Retrieved from <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm322161.htm>

<sup>56</sup> Neporent, Liz. (October 4, 2012). FDA asks for voluntary recall of popular generic antidepressant. *ABC News*. Retrieved from <http://abcnews.go.com/Health/fda-finds-generic-antidepressant-original/story?id=17399399>

<sup>57</sup> (October 10, 2013). Update: Bupropion Hydrochloride extended-release 300 mg Bioequivalence studies. *U. S. Food and Drug Administration*. Retrieved from <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm322161.htm>

<sup>58</sup> Park, Marcia O. (April 12, 2013). Pharmacokinetic study of Bupropion Hydrochloride products with different release patterns. *U.S. Food and Drug Administration*. Retrieved from <https://www.fda.gov/index?s=opportunity&mode=form&id=6f384372223e3789eaa621998987ad5b&tab=core&view=0>

\*THE RAPS ARTICLE SITE THE MARCIA PAPER, BUT INCASE YOU WANTED TO CITE THE RAPS ARTICLE.\*

That study has not yet been completed, but it is already running into a notable problem. The FDA can only study the drug if it can get its hands on it, which has become significantly harder because Teva and Watson's generic drugs have been pulled off the market and their manufacturing operations have ceased.<sup>59</sup> If the FDA cannot obtain the out-of-production drug, it will be more difficult for the FDA to understand what went wrong.

### *Concerta*

More recently, on November 13, 2014, the U.S. FDA expressed concerns about whether two approved generic versions of Concerta tablets (methylphenidate hydrochloride extended-release tablets), used to treat attention-deficit hyperactivity disorder in adults and children, are therapeutically equivalent to the brand-name drug. The two approved generic versions of [Concerta](#) in question are manufactured by Mallinckrodt Pharmaceuticals and Kudco Ireland Ltd.

An analysis of adverse event reports, an internal FDA re-examination of previously submitted data, and FDA laboratory tests of products manufactured by Mallinckrodt and Kudco have raised concerns that the products may not produce the same therapeutic benefits for some patients as the brand-name product, Concerta, manufactured by Janssen Pharmaceuticals, Inc. (Janssen also manufactures an authorized Concerta generic, which is marketed by Actavis under a licensing agreement and is identical to Janssen's Concerta. FDA included the [authorized generic](#) in its analysis and found it to be bioequivalent to, and substitutable for, Concerta.) Apart from the Mallinckrodt, Kudco, and Actavis products, there are no other generics for Concerta.

Methylphenidate hydrochloride extended-release products approved as generics for Concerta are intended to release the drug in the body over a period of 10 to 12 hours. This should allow for a single-dose product that is consistent with the effect of a three times per day dose of immediate-release methylphenidate hydrochloride.

In some individuals, the Mallinckrodt and Kudco products may deliver drug in the body at a slower rate during the 7- to 12-hour range. The diminished release rate may result in patients not having the desired effect.

As a result, the FDA has changed the therapeutic equivalence (TE) rating for the Mallinckrodt and Kudco products from AB to BX. This means the Mallinckrodt and Kudco products are still approved and can be prescribed, but are no longer recommended as automatically substitutable at the pharmacy (or by a pharmacist) for Concerta<sup>60</sup>.

### III. LAPSES IN BIOEQUIVALENCE: GROSS NEGLIGENCE, FRAUD AND CORRUPTION

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Gaffney, Alexander. (April 15, 2013). Non-withdrawn Antidepressant's Bioequivalency problems raises unanswered issues, FDA says. *Regulatory Focus*. Retrieved from <http://www.raps.org/regulatoryDetail.aspx?id=8374>

<sup>59</sup> Gaffney, Alexander. (August 13, 2013). A generic conundrum: How do you study a drug that has been withdrawn from the market? *Regulatory Focus*. Retrieved from <http://www.raps.org/focus-online/news/news-article-view/article/3927>

<sup>60</sup> <http://www.fda.gov/Drugs/DrugSafety/ucm422568.htm>

Up to this point, we have examined problems with lapses in bioequivalence for generic drugs, created, as far as we can tell by a regulatory process that is weak, slow or otherwise inadequate, and a statutory standard that is likely too low. In some instances unintentional production accidents (or possibly negligence) by generic manufacturers may have led to some of the problems, but if so these flaws were not identified by FDA or other interested parties. However, that is only one path to substandard medicines. The other path is outright, deliberate fraud, corrupt practices and gross even criminal negligence. And there are plenty of examples of this type of fraud. In the U.S., where the FDA and other regulatory agencies have the judicial support of the tort system and the criminal code, fraud is more rare, though still possible, as documented in a case study below. The epidemic of fraud, however, is primarily found in foreign manufacturers where the FDA and U.S. law enforcement jurisdictional claims are tenuous.

#### *CASE STUDY: The Ranbaxy Fraud*

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 US) discovered a widespread system of fabricated data and data manipulation undertaken across myriad products and manufacturing plants in order to win contracts from agencies and buyers, including the U.S. Government and the United Nations. Several dozen 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<sup>61</sup> had to be removed from sale in US.

What the team, including co-author of this paper Dinesh Thakur, found would lead Ranbaxy into a multiyear regulatory battle with the FDA and into the crosshairs of a Justice Department investigation that, nearly nine years later, was finally resolved.<sup>62</sup>

Ranbaxy's corporate culture encouraged management to dictate the results it wanted and for those beneath to bend the process to achieve it. Thakur described how Ranbaxy deliberately took its greatest liberties in markets where regulation was weakest and the risk of discovery was lowest.<sup>63</sup>

This was a case of outright fraud, in which the company knowingly sold substandard drugs around the world -- including in the U.S. -- while working to deceive regulators. Millions of people worldwide ingested medicine of dubious quality from Ranbaxy.

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

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<sup>61</sup> (May, 2013). Ranbaxy sells the following generic medications in the United States. *Fortune Magazine*. Retrieved from <http://fortunedotcom.files.wordpress.com/2013/05/ranbaxy-products.pdf>

<sup>62</sup> Eban, Katherine. (May 15, 2013). Dirty medicine. *Fortune Magazine*. Retrieved from <http://fortune.com/2013/05/15/dirty-medicine/>

<sup>63</sup> (2013). Ranbaxy writ petition. *Supreme Court of India*. Retrieved from <http://www.scribd.com/doc/160520772/149915683-Ranbaxy-Writ-Petition>



pay \$500 million in fines, forfeitures, and penalties -- the most ever levied against a generic-drug company. Notably, no current or former Ranbaxy executives were charged with crimes.<sup>64</sup>

*Rampant Fraud in the Indian Generic Industry – Ranbaxy was the tip of the iceberg*

Following the Ranbaxy scandal, the FDA and the UK's MHRA have identified similar behavior 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 alone, at least twelve pharmaceutical companies with facilities in India have been banned from shipping products to America.<sup>65</sup> A far from exhaustive list of regulatory findings by both regulators is below:

- In June 2010, an intravenous antibiotic manufactured by Claris Lifesciences Limited in India, with three manufacturing plants in Ahmedabad,<sup>66</sup> 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.<sup>67</sup>
- Sun Pharma, an Indian manufacturer with plants in Dadra, Jammu, Sikkim, Silvassa and Haloj,<sup>68</sup> 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.<sup>69</sup>
- Zydus Cadila, based in Ameddabad, Baddi, Sikkim and Goa,<sup>70</sup> and Aurobindo, based in Hyderabad and Haryana,<sup>71</sup> both falsely reported that no microbiological contaminants existed in its quality testing.<sup>72 73</sup> These tests are done to ensure that employees do not contaminate the product. The detection of microbial contamination during multiple FDA

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<sup>64</sup>\*Here is the citation to the actual court decision\*

(May 13, 2013). Generic drug manufacturer Ranbaxy pleads guilty and agrees to pay \$500 million to resolve false claims allegations, cGMP violations and false statements to the FDA. *The U.S. Department of Justice*. Retrieved from <http://www.justice.gov/opa/pr/2013/May/13-civ-542.html>

Eban, Katherine. (May 13, 2013). Maker of generic Lipitor pleads guilty to selling 'Adulterated drugs'. *Fortune Magazine*. Retrieved from <http://fortune.com/2013/05/13/maker-of-generic-lipitor-pleads-guilty-to-selling-adulterated-drugs/>

<sup>65</sup> Edney, Anna and Gokhale, Ketaki. (December 3, 2014). Drug batch tainted? Just hit delete and ship it to the U.S. *Bloomberg Business*. Retrieved from <http://www.bloomberg.com/news/2014-12-03/indian-labs-deleted-test-results-for-u-s-drugs-documents-show.html>

<sup>66</sup> "Company Overview" website. *Claris Lifesciences*. Retrieved from <http://www.clarislifesciences.com/global/Claris-Lifesciences-Company-Overview.html>

<sup>67</sup> Shetty, Uday. (July 24, 2013). Can data from Indian companies be trusted? *Drug Relations*. Retrieved from <http://www.drugregulations.org/2013/07/can-data-from-indian-companies-be.html>

<sup>68</sup> "Manufacturing Locations" website. *Sun Pharma*. Retrieved from <http://www.sunpharma.com/manufacturing>

<sup>69</sup> Shetty, Uday. (July 24, 2013). Can data from Indian companies be trusted? *Drug Relations*. Retrieved from <http://www.drugregulations.org/2013/07/can-data-from-indian-companies-be.html>

<sup>70</sup> "Manufacturing" website. *Zydus Cadila*. Retrieved from <http://www.zyduscadila.com/manufacturing.html>

<sup>71</sup> "Our Operations" website. *Aurobindo*. Retrieved from <http://www.aurobindo.com/about-us/our-operations/indian>

<sup>72</sup> Shetty, Uday. (July 24, 2013). Can data from Indian companies be trusted? *Drug Relations*. Retrieved from <http://www.drugregulations.org/2013/07/can-data-from-indian-companies-be.html>

<sup>73</sup> (May 20, 2011). Inspections, Compliance, Enforcement, and Criminal Investigations: Aurobindo Pharma Limited 5/20/11. *U.S. Food and Drug Administration*. Retrieved from <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm256861.htm>

inspections questions the validity of the data generated by these Indian firms.<sup>74</sup>

- RPG Life Sciences, with its main facilities in Navi Mumbai and Ankleshwar,<sup>75</sup> selectively reported test results, publicizing successful tests and deleted all initial data that might have been unfavorable.<sup>76</sup>
- Fresenius Kabi, a global health care company, in a similar fashion as RPG, ignored results that were undesirable.<sup>77</sup>
- In 2011, Sun Pharmaceutical Industries deleted more than 5,300 failed chromatography test results according to FDA documents recently obtained by Bloomberg News<sup>78</sup>. 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,<sup>79</sup> 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.<sup>80</sup>

All of these companies are large and highly visible members of India’s pharmaceutical industry. There are a number of 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 which don’t often make news because of their small size.

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 (CHMP) looked at over 1,000 pharmaceutical forms and strengths of medicines studied at GVK

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<sup>74</sup> Shetty, Uday. (July 24, 2013). Can data from Indian companies be trusted? *Drug Relations*. Retrieved from <http://www.drugregulations.org/2013/07/can-data-from-indian-companies-be.html>

<sup>75</sup> “Manufacturing Facilities” website. *RPG Life Sciences*. Retrieved from [http://www.rpplifesciences.com/about\\_manufacture.jsp](http://www.rpplifesciences.com/about_manufacture.jsp)

<sup>76</sup> Shetty, Uday. (July 24, 2013). Can data from Indian companies be trusted? *Drug Relations*. Retrieved from <http://www.drugregulations.org/2013/07/can-data-from-indian-companies-be.html>

<sup>77</sup> Shetty, Uday. (July 24, 2013). Can data from Indian companies be trusted? *Drug Relations*. Retrieved from <http://www.drugregulations.org/2013/07/can-data-from-indian-companies-be.html>

<sup>78</sup> Edney, Anna and Gokhale, Ketaki. (December 3, 2014). Drug batch tainted? Just hit delete and ship it to the U.S. *Bloomberg Business*. Retrieved from <http://www.bloomberg.com/news/2014-12-03/indian-labs-deleted-test-results-for-u-s-drugs-documents-show.html>

<sup>79</sup> “Our Facilities” website. *Wockhardt*. Retrieved from <http://www.wockhardt-knowhow.com/ourfacilities.html>

<sup>80</sup> Shetty, Uday. (July 24, 2013). Can data from Indian companies be trusted? *Drug Relations*. Retrieved from <http://www.drugregulations.org/2013/07/can-data-from-indian-companies-be.html>

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. To quote the agency's official statement: "Their systematic nature, the extended period of time during which they took place and the number of members of staff involved cast doubt on the integrity of the way trials were performed at the site generally and on the reliability of data generated at that site".<sup>81</sup>

Unfortunately, this is not unique. In 2003, investigation into the fraudulent practices at Ranbaxy began with an inspection of bioequivalence studies conducted for Ranbaxy at another CRO named Vimta Laboratories. Dinesh Thakur found a similar pattern of extensive data fabrication of clinical records, ECGs and other supporting documentation for clinical supplies based on which several anti-viral drugs were approved for patient use.

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.

#### IV. IMPACT ON U.S. PATIENTS

##### IV.A. Imported Drugs from Fraudulent Foreign Manufacturers

Evidence of poor quality drugs entering the US market is not hard to find – 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 typically are the penultimate step (before their products are banned from import into the US) and are issued during investigations which may have been going on for several years – from inspection, recommendations, responses and so on.

While the FDA does engage in these efforts to maintain quality, the official agency response to well-founded and documented concerns from two co-authors to this paper has been disappointing.

Dr. Harry Lever, a senior cardiologist at the Cleveland Clinic, started reporting problems with a blood pressure medicine (motoprolol succinate) to FDA in 2012. FDA eventually responded two year later that his concerns were unfounded.<sup>82</sup>, but within three months more than 20,000 bottles of the suspect product were recalled by the manufacturer.

Additionally, Dr. Preston Mason, a cardiological scientist at Harvard Medical School, who assesses medicine quality from around the world, found that 30 different and mostly Indian-made versions of the most popular drug in the world, atorvastatin (generic Lipitor), contained

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<sup>81</sup> Brennan, Zachary. (September 26, 2014). EMA opens investigation into India's GVK Bio over ECG falsifications. *Outsourcing-Pharma.com*. Retrieved from <http://www.outsourcing-pharma.com/Clinical-Development/EMA-opens-investigation-into-India-s-GVK-Bio-over-ECG-falsifications>

<sup>82</sup> Bate, Roger. (April 7, 2014). FDA suppresses concerns about Indian generics. *Real Clear Policy*. Retrieved from [http://www.realclearpolicy.com/blog/2014/04/07/fda\\_suppresses\\_concerns\\_about\\_indian\\_generics\\_902.html](http://www.realclearpolicy.com/blog/2014/04/07/fda_suppresses_concerns_about_indian_generics_902.html)

significant impurities that would undermine of efficacy of the product<sup>83</sup>. Despite presenting detailed findings to both FDA and Congress, Dr. Mason and his findings were dismissed.

#### IV.B. U.S. Patient Impact: Fraudulent Domestic Manufacturers

In 1989, three FDA employees pleaded guilty to accepting thousands of dollars in bribes from US drug manufacturers to approve new generic drugs based on false data.<sup>84,85</sup>

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 in order to establish product efficacy.<sup>86</sup> Deficiencies were found in 12 American plants.<sup>87</sup>

These failings were not publicly admitted by the FDA. Instead, the scandal was exposed by another generic drug manufacturer, Mylan Laboratories Inc. of Pittsburgh. Frustrated by delays in its own applications to the FDA, the company hired private detectives who discovered the bribes from other drug companies. After the Hatch-Waxman Act of 1984, which enabled rapid approval of generics, it is possible the FDA became overwhelmed. Moreover, when the bribery scandal broke, the FDA didn't have an inspector general to oversee the approval process.<sup>88</sup>

Representative John D. Dingell (D., Mich.), the head of the House Energy and Commerce Investigations subcommittee at the time, labelled the FDA and the generic-drug industry "the most pervasively corrupt" industry he had ever scrutinized.<sup>89</sup>

Oversight and practices at FDA have undoubtedly improved in the past 25 years, and we include this sordid passage in FDA history simply to demonstrate that not all problems with drugs emanate from Asia and particularly India. The most positive reaction to these FDA problems was improved practices, but has transparency improved?

## V. POLICY CONSIDERATIONS AND RECOMMENDATIONS

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<sup>83</sup> Mason, R.P., Jacob, R.F. & Gerard, S.A. (2013). Atorvastatin generics obtained from multiple sources worldwide contain a methylated impurity that reduces their HMG-CoA reductase inhibitory effects. *Journal of Clinical Lipidology*. 7(3), 287.

<sup>84</sup> Andrews, Edmund L. (August 13, 1989). A scandal raises serious questions at the F.D.A. *New York Times*. Retrieved from <http://www.nytimes.com/1989/08/13/business/a-scandal-raises-serious-questions-at-the-fda.html>

<sup>85</sup> Shaw, Donna. (January 17, 1991). Lawmaker assails FDA for not uncovering Generic-drug scandal. *The Inquirer*. Retrieved from [http://articles.philly.com/1991-01-17/business/25820052\\_1\\_generic-drugs-generic-drug-fda-employees](http://articles.philly.com/1991-01-17/business/25820052_1_generic-drugs-generic-drug-fda-employees)

<sup>86</sup> Goodman, C., Painton, P., & Thompson, D. (August 28, 1989). A prescription for scandal payoffs and faked lab results taint the Generic-drug industry. *Time Magazine*. Retrieved from <http://content.time.com/time/magazine/article/0,9171,958423,00.html>

<sup>87</sup> Leary, Warren E. (September 12, 1989). F.D.A details problems at drug makers. *Special to the New York Times*. Retrieved from <http://www.nytimes.com/1989/09/12/business/fda-details-problems-at-drug-makers.html>

<sup>88</sup> (October 2, 1989).The generic drug scandal. *The New York Times*. Retrieved from <http://www.nytimes.com/1989/10/02/opinion/the-generic-drug-scandal.html>

<sup>89</sup> Shaw, Donna.( January 17, 1991). Lawmaker assails FDA for not uncovering Generic-drug scandal. *The Inquirer*. Retrieved from [http://articles.philly.com/1991-01-17/business/25820052\\_1\\_generic-drugs-generic-drug-fda-employees](http://articles.philly.com/1991-01-17/business/25820052_1_generic-drugs-generic-drug-fda-employees)

## V.A. Consideration 1: Ensuring Bioequivalence in a Globalized Generics Industry

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. This expansion in responsibility requires a fundamental change in the agency's approach to enforcing regulation given the differences in managerial and cultural methods followed by overseas manufacturers. This will be, at best, an iterative learning process<sup>90</sup>.

It also demands an increase in the frequency and extent of pharmacovigilance (and especially market surveillance)<sup>91</sup>. 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. If we are primarily to rely on the regulator to ensure medicine quality, then the FDA still does not conduct nearly enough market surveillance relative to the enormous volume of products entering the U.S. from these sources. The problems discussed in this paper become acute in a world where FDA's active surveillance systems are limited and its passive surveillance systems suffer from widespread misattribution of adverse events.

Ultimately, we will only be able to trust the FDA's bioequivalence assessment process if we are allowed to see the bioequivalence (BE) curves and the absorption data – particularly of most slow-release (once-a-day) formulations based on which it accords approval to market these formulations to generic manufacturers. This is the aim of legislation promoted by Amy Paulin, State Congresswoman for Scarsdale, (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<sup>92</sup>.

Without BE data we are left thinking that there may be hundreds of other Budeprion XL 300-like generic formulations on the market. If the BE curves and the absorption data are indeed "identical" to the brand name products, then such concerns will melt away. This is why it is imperative that the FDA release BE data for hundreds of generic drug approvals so that physicians, pharmacists, researchers, and buyers at pharmacy chains can see for themselves how the FDA determines bioequivalence. Otherwise, the process remains mysterious and opaque.

While transparency will not in the short run improve consistency in manufacturing, if BE curves are shown to vary over time, it will probably drive change in manufacturing standards. For example, currently manufacturers can change the suppliers of ingredients (active and excipients) without being required to undertake new BE studies, if they stipulated they would buy from a wide list of suppliers in their ANDA. But differing supplies of the same ingredients may produce different BE results.

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<sup>90</sup> 2014 Annual report on inspections of establishments. *U.S. Food and Drug Administration*. Retrieved from <http://www.fda.gov/downloads/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticAct/FDCA/SignificantAmendmentstotheFDCA/FDASIA/UCM384063.pdf>

<sup>91</sup> For a detailed assessment for the importance of pharmacovigilance see Laufer, M., Pugatch, M., & Torstensson, D. (December 2, 2014). Developing a culture of Pharmacovigilance: Towards International best practices. *Pugatch Consilium*. Retrieved from <http://www.pugatch-consilium.com/reports/Developing%20a%20Pharmacovigilance%20Culture.pdf>

<sup>92</sup> One can view the Bill on the Assembly website ( [assembly.state.ny.us](http://assembly.state.ny.us) ), by typing the bill number A.145 on the "Bill Search" area.

## *Recommendations*

1-A: FDA to immediately publish all bioequivalence data, starting with narrow therapeutic and time release medicines, and eventually all medicines. Increase focus on signal detection from individual case reports (ICSRs) and mandate reporting of adverse events for drug products sold worldwide immaterial of their US market authorization status.

1-B: FDA to require that dispensed generic drugs have their manufacturer or distributor identified.

1-C: Increase transparency for the patients, providers, investors and the public by posting detailed metrics and compliance data from Establish Inspection Reports, Form 483s, Warning Letters and other OAI actions on the OpenFDA Dashboard.

1-D: Allow generic manufacturers with good bioequivalence data and records of production to advertise such data in product promotions to doctors and patients, thus effectively segmenting the generic market based on a key measure of quality.

1-E: NIH should support a study into the long term effects of mandatory generic substitution given the problem articulated in our paper. We know of no federally funded study that is looking at this problem. Given how much our healthcare system relies on generic drugs, don't we owe it to ourselves to understand the long term economic impact of what our decisions are in the short term?

## V.B. Consideration 2: Protecting the Public During Investigations

As Fortune magazine said of the saga, “what occurred inside Ranbaxy and how the FDA responded to it raises serious questions about whether our government can effectively safeguard a drug supply that last year was 84% generic, according to the IMS Institute for Healthcare Informatics, much of that manufactured in distant places. More than 80% of active pharmaceutical ingredients for all U.S. drugs now come from overseas, as do 40% of finished pills and capsules. As the Ranbaxy story makes vividly clear, generic-drug makers intent on breaking the rules -- especially those operating abroad -- can easily do so.”<sup>93</sup>

This raises many questions for us – mainly regarding whether the FDA acted appropriately and in a timely fashion in its dealings with Ranbaxy. (It should be noted that despite our criticisms, no other national regulatory agency has acted with such vigor against Ranbaxy).

Firstly, should the FDA have acted faster? It received information in August 2005 and didn't prevent Ranbaxy from exporting products to the US until three years later.<sup>94 95</sup> In fact, it

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<sup>93</sup> Eban, Katherine. (May 13, 2013). Maker of generic Lipitor pleads guilty to selling ‘Adulterated drugs’. *Fortune Magazine*. Retrieved from <http://fortune.com/2013/05/13/maker-of-generic-lipitor-pleads-guilty-to-selling-adulterated-drugs/>

<sup>94</sup> Reinberg, Steven. (September 16, 2008). FDA bars generic drugs from Indian company. *Health Day*. Retrieved from <http://consumer.healthday.com/public-health-information-30/food-and-drug-administration-news-315/fda-bars-generic-drugs-from-indian-company-619453.html>

continued to provide approval for the firm's ANDAs including for some blockbuster products like simvastatin, despite an ongoing investigation alleging fraud.

Also, it allowed Ranbaxy to become the only supplier of atorvastatin in the market in 2011, many years after it knew of dubious practices by the company, only to force a massive recall of this drug six months after launch for manufacturing deficiencies.<sup>96</sup> Should the agency have restricted Ranbaxy's ability to win generic exclusivity and also limited its exports sooner?

More importantly, the agency advised patients to continue taking their medications while implementing its Application Integrity Policy against Ranbaxy, which banned approximately 30 products manufactured in India from entering the US market. This begs the question: what, if any, clinical data does the FDA have when it implements such punitive actions as import alerts? Are adverse event data from generic drugs enough to make a determination of the quality and therapeutic benefit of these drugs? Does the agency have good clinical data required during the application approval process to make informed decisions on therapeutic effectiveness such as Certificates of Analyses?

The reaction at the agency appears to have been to conduct more inspections and, since the resolution of the Ranbaxy case nearly two years ago, it has documented similar data integrity issues at other large Indian generic manufacturers, namely Wockhardt and Sun Pharma, both of which supply a substantial portfolio of generic drugs to the US market.<sup>97</sup>

Our concern is slightly different – that is, that FDA did not actively engage in significant pharmacovigilance (and particularly market surveillance)<sup>98</sup>. Given that so many new producers entered the market, making cost-cutting vital for profitability, if no one was actively looking at what was produced then no one would spot problems of non-bioequivalence or simply poor quality products (western generic producers certainly do not have much incentive to do so since they currently cannot differentiate their products based on quality in marketing material). Critical to improvements in assessing the problems with medicines will be an increase in pharmacovigilance. The EMA may point the way forward here. For example its withdrawal of benfluorex, a diabetes treatment, is one of the first examples of expanded PV leading to a product withdrawal<sup>99</sup>.

### *Recommendations*

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<sup>95</sup> (September 16, 2008). FDA issues warning letters to Ranbaxy Laboratories Ltd., and an import alert for drugs from two Ranbaxy plants in India. *U.S. Food and Drug Administration*. Retrieved from <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116949.htm>

<sup>96</sup> Eban, Katherine. (May 6, 2011). The war over Lipitor- Full version. *Fortune Magazine*. Retrieved from [http://archive.fortune.com/2011/05/03/news/companies/lipitor\\_ranbaxy\\_full\\_version.fortune/index.htm](http://archive.fortune.com/2011/05/03/news/companies/lipitor_ranbaxy_full_version.fortune/index.htm)

<sup>97</sup> D'Monte, Leslie and Unnikrishnan, C.H. (May 23, 2014). US FDA to expand scrutiny into Sun Pharma. *The Live Mint*. Retrieved from <http://www.livemint.com/Companies/74iss1oOUkSyerCyqplStK/US-FDA-to-expand-scrutiny-into-Sun-Pharma-data.html>

<sup>98</sup> "Pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem." *World Health Organization*. Retrieved from [http://www.who.int/medicines/areas/quality\\_safety/safety\\_efficacy/pharmvigi/en/](http://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/)

<sup>99</sup> Benfluorex. *European Medicines Agency*. Retrieved from [http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Benfluorex/human\\_referral\\_000220.jsp&mid=WC0b01ac05805c516f](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Benfluorex/human_referral_000220.jsp&mid=WC0b01ac05805c516f)

2-A: 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 should have increased authority to block the importation of products from such overseas manufacturing locations without waiting for physiological evidence, which is hard to find in such cases. The agency should also pursue the “Park Doctrine” and hold willful wrongdoers whose fraudulent behavior results in substandard and adulterated drugs criminally liable in the US justice system.

2-B: Increased market surveillance. The FDA undertakes very few random samples of medicines from US pharmacies and clinics. It should increase this, perhaps targeting narrow therapeutic index medicines and Indian manufacturers to begin with, to see how variable final products quality actually is.

### V.C. Consideration 3: Old Methods and New Technologies – Can bioequivalence keep up?

As science gallops ahead of a plodding regulatory and statutory framework, policy makers face many challenges. First we will consider the case of the advance of compounding as an example of scientific frontiers that are on the margins of the regulatory framework and the problems that arose. Then we will consider the next frontier – “generics” in the context of biological drugs.

#### *Compounding*

Compounding is the tailoring of drugs for the unique treatment of each patient. Whilst it can be hugely beneficial for patients where generic formulations are not suitable, it also introduces new opportunities for fraud.

In 2012, the worst outbreak of fungal meningitis in US history, which killed 64 and sickened more than 750, was traced by the FDA to the New England Compounding Center, which had shipped a tainted steroid to 20 states. FDA Commissioner, Margaret Hamburg, successfully argued for new legislation as the magnitude and complexity of compounding, which tailors drugs to certain needs, had “outpaced the patchwork of state laws that differ in prescription requirement and quality control rules” and several compounders refused to allow FDA inspectors to see their records<sup>100</sup>.

Congress passed the Drug Quality and Security Act in 2013 as an amendment to the Federal Food, Drug and Cosmetic Act, setting exacting requirements for manufacturing and reporting by companies and for supervision by FDA. However, enrolment under the Act is voluntary: the hope is that purchasers will favor producers which submit to regulation<sup>101</sup>.

#### *Biologics: The Coming Wave*

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<sup>100</sup> Palmer, Eric. (March 26, 2013). Third compounder in week recalls products. *FiercePharma Manufacturing*. Retrieved from <http://www.fiercepharmamanufacturing.com/story/third-compounder-week-recalls-products/2013-03-26>

<sup>101</sup> Keenan, Joseph. (December 4, 2014). Plan filed to set aside \$135M for NECC fungal meningitis victims. *FiercePharma Manufacturing*. Retrieved from <http://www.fiercepharmamanufacturing.com/story/plan-filed-set-aside-135m-necc-fungal-meningitis-victims/2014-12-04>



All of the problems we have raised in this paper will be exacerbated by next-generation biologic drugs, which are rapidly gaining in circulation among patients. 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. They are more expensive to create – and arguably far more difficult to regulate.

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 production of identical or nearly identical generic copies.<sup>102</sup> This is why copies of biologics are called biosimilars, because they cannot be identical “generic biologics”. Bioequivalence as we have defined it for chemical drugs simply cannot function in the same way as a regulatory yardstick.

This is especially problematic in light of the global manufacturing projections. 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 production lines, commanding as much as 70 percent of the global market – currently valued at \$20 billion – over the next few years.<sup>103</sup>

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. Yet none of the India or Chinese based manufacturers have conducted a pivotal clinical study for a new molecule outside of India/China. Their ability to properly plan and conduct clinical studies to demonstrate therapeutic equivalence and provide reproducible results which can be replicated in the western world is yet to be established.

It is beyond the scope of this paper to discuss the details of FDA regulation of these products, but we remain highly skeptical that imported biosimilars from India and China will be consistently therapeutically similar to innovator biologics.

### *Recommendations*

*3-A:* The main recommendation for compounding pharmacies is an extension of recommendation 1, which is market surveillance, random sampling of products made in compounding pharmacies to be alerted to possible problems

*3-B:* One of the key criteria to allow importation of biosimilars from countries like India and China is confidence in the characterization of the large molecule. NIH should fund the

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<sup>102</sup> For a more detailed discussion of the differences between chemical and biologic drugs, see here: <http://www.bio.org/articles/how-do-drugs-and-biologics-differ>

<sup>103</sup> BS Reporter. (October 27, 2014). India, China to command 70% of \$20-bn global biosimilars market. *Business Standard*. Retrieved from [http://www.business-standard.com/article/companies/india-china-to-command-70-of-20-billion-global-biosimilars-market-114102700655\\_1.html](http://www.business-standard.com/article/companies/india-china-to-command-70-of-20-billion-global-biosimilars-market-114102700655_1.html)

development of characterization kits (e.g., Endotoxin assay kits for small molecules) which can help importers quickly assess the purity, conformation of the protein and its activity before a batch can be allowed to enter the US market.

#### V.D. Consideration 4: Racism and market segmentation – what role can the U.S. play?

There is increasing evidence that some manufacturers segment the market, exporting inferior medicines to markets where oversight is likely to be poor.

##### *Empirical evidence of substandard Indian products sold in Africa*

Over the past seven years some of the authors of this paper have conducted random procurement surveys and tests of thousands of medicines from Africa; most recently TB medicines and antibiotics. From within this sample we look at a subset of 1470 samples of antibiotics and tuberculosis medicines that were ostensibly “made in India”, as per the labeling on the package.<sup>104</sup> We focused on these drugs because broad-spectrum antibiotics and specialized tuberculosis medicines in solid oral form are among the most commonly used in all developing countries.

We found that 10.9 percent of samples failed basic quality tests. Within these, both antibiotics and TB drugs had more substandard than falsified products, suggesting that poor drug quality might be a result of negligence rather than outright crime. Moreover, drugs purchased from Africa were more likely to fail quality tests than the same type of drugs in the Indian domestic or non-Africa groups.

Our sample of “Indian-made” medicines reveals two patterns: first, drug quality among drugs purchased inside African countries is inferior compared with those purchased inside India or middle-income countries. Second, the biggest driver of this quality difference is substandard drugs that contain insufficient API and are not registered in the African market where they were bought.

Our findings support what has been known anecdotally for years: that some Indian drug companies segment the global medicine market into portions and supply them with different quality medicines. India is by no means the only large exporter of drugs. Further research into the drug quality of Chinese and other export countries would be useful to understand how widespread the problem may be.

Whether the U.S. never bought drugs for non-Americans, the fact that it is regulating these foreign manufacturers for import into the U.S. market while knowing that these manufacturers segment the market and target lower quality products to other markets arguably makes the U.S. complicit. One can make the case that the U.S. should use its market power to force these manufacturers out of this market segmentation behavior as a condition of participating in the U.S. market.

Second, as US is one of the largest purchasers of many drugs in Africa, Asia and Latin America, through its bilateral aid programs and the funding of multilateral aid programs, it must

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<sup>104</sup> Bate, R., Jin, G. Z., Mathur, A., & Attaran, A. (September, 2014). Poor quality drugs and global trade: A pilot study (No. w20469). *National Bureau of Economic Research*. Retrieved from <http://www.nber.org/papers/w20469>

ensure it only ever procures high quality medicine – in line with medicines prescribed for US patients. Yet there are many examples of substandard medicines in these geographic areas. How sure are we that US taxpayer support is only of good quality medicine?

*Recommendations*

4-A: Condition U.S. market access for foreign manufacturers on proof that there is no market segmentation going on delivering lower quality drugs to other markets, namely, browner, poorer markets.

4-B: Condition procurement of medicines by U.S. taxpayer dollars through State, USAID, HHS, DoD bilateral programs as well as multilateral contributions to WHO, UNICEF, UNDP, UNFPA, Global Fund, World Bank and others, on the documentation of quality of those medicines.