

ENSURING SAFETY & EFFICACY: FDA'S GENERIC DRUG APPROVALS AND THE CHALLENGE OF BIOEQUIVALENCE

by

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Generic pharmaceutical products command a deeply significant and growing presence in American medical care and governmental health care policies. According to reports from IMS Health, generic drugs account for 69% of all prescriptions written in the United States. The administration of President George W. Bush consistently pursued policies which sped approval of generic drugs and advanced their deployment in government health programs like Medicare and Medicaid. Generic drugs are also a centerpiece of President Barack Obama's plan to reduce what he calls "the exploding cost of health care in America." Such an objective relies on patients' and physicians' continued confidence that generics are as safe and effective as the original "branded" drugs.

Even though polls reflect increases in consumer preference for generics,¹ Janet Woodcock, Director of the Food & Drug Administration's (FDA) Center for Drug Evaluation and Research, warned an audience of generic drug manufacturers that there is a "rising tide of skepticism" about the equivalence of generic and branded drugs.² The safety and efficacy of generic versions of drugs to treat conditions such as epilepsy, depression, acute pain, and deadly gastrointestinal infections have increasingly been called into question, as has FDA's commitment to sound science and transparency in generic approval. These developments, along with mounting political pressure to swiftly approve generics, necessitate closer examination of FDA's approval of generic drugs and, in particular, how FDA's Office of Generic Drug's determines *bioequivalence*.

ANDA & Bioequivalence Background. The Drug Price Competition and Patent Restoration Act of 1984, better known as the "Hatch-Waxman Act," relieved generic manufacturers of the need to conduct lengthy and expensive clinical trials. Instead, such producers could file an Abbreviated New Drug Application (ANDA) based upon an already approved or "reference listed" drug. The ANDA applicant must demonstrate that its product is bioequivalent to the listed drug. Hatch-Waxman specifically defines bioequivalence, and FDA regulations further define it as "the absence of significant difference in the rate and extent to which the active ingredient . . . becomes available at the site of drug action when administered at the same . . . dose under similar conditions in an appropriately designed study." 21 C.F.R. § 320.1(e).

¹The Harris Poll, Press Release, Jan. 26, 2009 at http://www.harrisinteractive.com/harris_poll/pubs/Harris_Poll_2009_01_26.pdf.

²James G. Dickenson, *Woodcock Cites Generic Skepticism as Priority*, MED. MARKETING & MEDIA, Jan. 1, 2009, at <http://www.allbusiness.com/pharmaceuticals-biotechnology/pharmaceutical/11761063-1.html>.

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The statute also granted FDA discretion on the method used to determine bioequivalence, which is normally either “in vitro” — testing a drug’s dissolution in a laboratory — or “in vivo,” where studies are conducted in the human body. 21 U.S.C. § 355(j)(6)(A)(i)(III). The *in vivo* clinical testing is traditionally done on 24-36 *healthy* adult volunteers. Generally, the rate and extent of a generic drug’s absorption rate into the blood are measured. Generics can be up to 20% below or 25% above the reference drug’s absorption for FDA to deem the generic drug bioequivalent, and thus, in the agency’s opinion, *therapeutically* equivalent.³

Does Bioequivalence Equal Therapeutic Equivalence? The “rising tide of skepticism” about which FDA’s Ms. Woodcock spoke is largely centered on that question. Some concerns arise from patients’ and doctors’ adverse experiences with approved generic drugs, while others have been vigorously voiced by manufacturers who are concerned that FDA is not applying the correct bioequivalence standards when evaluating generic copies of their branded drugs.

Epilepsy Medications. For an increasing number of people suffering from epilepsy, switching from a branded to a generic medicine which is “*more or less the same* may not be close enough.”⁴ Epilepsy is an especially challenging condition to treat, with the choice of medication often meaning the difference between the extremes of full control or seizures.

A growing body of case studies, doctor surveys, and patient accounts reflect a strong belief in the medical community that the risk of “breakthrough” seizures or toxic side effects increase when switching patients from branded antiepileptic drugs (AEDs) to generics. An American Academy of Neurology study found that nearly half of the surveyed physicians had patients who lost seizure control due to substituting a generic AED. M.J. Berg, MD, et al., *Generic substitution in the treatment of epilepsy*, NEUROLOGY, 71:525-530 (2008). The authors concluded that FDA bioequivalence testing “may not be adequate for AEDs and suggests that more clinical evidence is needed.” An Epilepsy Foundation report, which includes poignant narratives from epileptics, relates that of the 1,085 patients responding who had been switched to a generic AED, 59% said their seizures worsened, and medication side-effects increased for 49%. *Supra* note 4 at 4. Another study compared the rate at which epilepsy patients in Ontario switched back from generic AEDs to the branded version with the rate of “switchbacks” to non-AED branded drugs. The authors found the high rate of switchbacks for those on generic AEDs (12.9-20.9%) compared to non-AED switchbacks (1.5-2.9%) especially significant because of Ontario’s law that compels generic substitution and the high hurdles it erects for patients to switch back. F. Andermann, et al., *Compulsory Generic Switching of Antiepileptic Drugs*, EPILEPSIA, 48(3): 464-469 (2007), at 468.

FDA has firmly expressed its confidence in generic AEDs. One agency official stated that while it is “aware that there are reports of breakthrough seizures . . . with the use of generics,” FDA has “seen no credible evidence that the drugs are responsible.”⁵ Patient groups like the American Epilepsy Society have requested that FDA conduct clinical studies to test bioequivalence, but the agency has yet to take such an action.

Controlled/Extended-Release Drugs. These products, part of a new frontier in pharmaceutical patient care, are intricately designed to provide specific medication doses over a time period. They replace certain immediate release drugs which patients needed to take two or three times a day. FDA’s use of standards designed for older immediate-release drugs to test generic bioequivalence on these new extended-release products has been under fire in recent years.

³ Michael J. Berg, MD, *Generic AEDs: Current Standards and Recommendations*, Johns Hopkins Advanced Studies in Medicine, Vol. 8 No. 7 (July 2008), at 218. “The FDA takes the unequivocal position that ‘products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product.’” *Id.* citing U.S. FDA, Office of Generic Drugs, Approved Drug Products with Therapeutic Equivalence Evaluations. 28th ed. 2008. Available at: <http://www.fda.gov/cder/ob/docs/preface/eclink.htm>.

⁴ *In Their Own Words: Epilepsy Patients’ Experiences Changing the Formulation of the Drugs they Use to Prevent Seizures*, Epilepsy Foundation (Mar. 2009) at 3, available at http://www.epilepsyfoundation.org/medicationswitching/Consumer_Survey_Report%20Recommendations.pdf (emphasis added).

⁵ *Generic Substitution: Why the Controversy*, Mar. 5, 2008, available at http://professionals.epilepsy.com/page/hallway_generics.html (quoting Dr. Russell Katz, Director, Division of Neurology Products).

In 2006, FDA approved a generic version of extended-release antidepressant Wellbutrin XL. Soon after insurance companies and government prescription benefits programs switched patients to generic Bupropion, scores of depression sufferers began logging complaints into medical consumer websites such as The People's Pharmacy and ConsumerLab ranging from returned symptoms to claimed suicide attempts. See Dan Childs, *Generic Drugs: Dangerous Differences?*, ABC News, Oct. 15, 2007. People's Pharmacy alerted FDA to the complaints, and ConsumerLab performed an independent *in vitro* test which revealed that the generic released 34% of the drug into the bloodstream in the first two hours, compared to 8% for Wellbutrin. Melinda Beck, *Inexact Copies: How Generics Differ from Brand Names*, WALL ST. J., Apr. 22, 2008. Six months after committing to an investigation of the patient complaints, FDA reiterated in a report that the generic and branded products were bioequivalent, and thus Bupropion was safe and effective. What FDA failed to note, and about which Wellbutrin XL's producer strongly objected in a Citizen Petition and a lawsuit, was that the agency tested bioequivalence in *only* the 150 mg version of the generic, rather than in *both* the 150 and 300 mg doses in which the branded and generic are available. In response to information that most of the patient complaints centered on the 300 mg dose, FDA reportedly has agreed to consider conducting bioequivalence tests on that dose, but has yet to do so. Becky Jungbauer, *FDA Revisits Wellbutrin Generic – Again*, THE PINK SHEET, Sept. 29, 2008, at 3.

With more than twenty controlled-release generic drugs awaiting FDA approval, the agency must seriously assess whether, as a former FDA Associate Commissioner recently wrote, “[m]easurements that don't include time variables [can] assure bioequivalence for this class of drugs.” Peter Pitts and Robert Goldberg, *Getting it Right with Modern Drugs*, WASH. TIMES, Mar. 2, 2009.

Locally Acting Medicines. This complex type of drug is designed to go directly to the “site of activity” and remain there, rather than be absorbed systemically into the bloodstream. According to federal statutes, regulatory provisions, and principles of sound science, when testing generics of such medicines, FDA should utilize bioequivalence tests that go beyond examining rate and extent of the product's concentration in blood. See, e.g., FDA ORANGE BOOK, at viii, available at <http://www.fda.gov/cder/orange/obannual.pdf>. But recent FDA actions on pending generic applications for locally acting drugs reflect a troubling drift from rigorous standards towards tests that can compromise patient safety.

One particularly illuminating example involves Vancocin, an antibiotic that remains the only FDA-approved treatment for, and last line of defense against, a deadly gastrointestinal bacteria, *Clostridium difficile*. FDA had consistently stated that *in vivo* clinical trials were the norm for generics of drugs like Vancocin. See ViroPharma Inc. letter to FDA, Docket No. 2006P-0124 (May 31, 2006), at 3. But FDA's Office of Generic Drugs in March 2006 decided to abandon *in vivo* trials for a generic of Vancocin, instead opting for testing in a lab how the product dissolves in solution (i.e. *in vitro*). FDA arrived at such a dramatic reversal with no public input or transparent deliberation. Rather than directly inform the public or Vancocin's manufacturer, ViroPharma, FDA first announced the change to a capital market analysis firm. *Id.* at 5. The testing change touched off a firestorm of opposition from ViroPharma, supported by doctors, patients, research institutes and medical societies such as the Infectious Diseases Society of America. A University of Massachusetts professor and clinical practitioner wrote to FDA, “Approving a generic version based on a new process resting on less-than scientifically obvious assumptions and shepherded through with more attention to expediency than transparency is playing Russian roulette with the most vulnerable populations.” Maraya Zilberberg, MD, MPH letter to FDA, Docket No. 2008-D-0626 (Jan. 20, 2009), at 3.

On December 16, 2008, FDA issued a Federal Register notice announcing a “draft guidance” which it termed a “clarification” of its earlier recommendations for determining bioequivalence for generic formulations of Vancocin. The guidelines would permit *in vitro* testing in some situations, while requiring *in vivo* clinical reviews in others. 73 Fed. Reg. 76362. In its comments, ViroPharma argues that the guidance “is not a clarification. Nor is it an evidence-based BE method,” and that “OGD is asking patients to rely on this ‘close enough’ approach to bioequivalence for a drug where the consequences of getting it wrong can be major surgery or death.” ViroPharma Inc. comments, Docket No. 2008-D-0626 (Mar. 18, 2009), at iv. In addition, ViroPharma sued FDA under the Freedom of Information Act (FOIA) on December 16, 2008 for failing to respond to its FOIA request for the agency's administrative record of its 2006 decision on *in vitro* testing. ViroPharma's 2006 Citizen Petition, the FOIA suit, the FDA's draft guidance proposal, and the application for a generic of Vancocin all remain unresolved.

FDA has set aside traditionally stringent bioequivalence standards when assessing generic applications for other locally acting drugs. The public, as well as the manufacturers of the Lidoderm topical patch, first learned of the agency's departure from clinical testing for topical products through an FDA letter to a generic company seeking to copy Lidoderm. The patch, which treats acute pain suffered by those recovering from herpes, is designed to concentrate medicine at the site of damaged skin, and not be circulated systemically. Despite this, FDA endorsed tests that examine plasma concentrations in an *in vitro* fashion, a method used for transdermal skin patches that act systemically (i.e. enter the bloodstream). Lidoderm's manufacturer is opposing FDA's bioequivalence test change, arguing that a "one-size-fits-all" approach to topical products violates agency regulations and imperils patients. Amended Citizen Petition of Endo Pharmaceuticals Inc., Docket No. 2006P-0522 (Aug. 29, 2007). FDA has yet to act on Endo's petition or the generic company's application.

Risks of Government Inaction. The Food and Drug Administration's formal offering of a draft guidance on bioequivalence testing for Vancocin, as well as its convening of a Pharmaceutical Science and Clinical Pharmacology Advisory Committee meeting last July on generic approval standards, indicates that the agency is conscious of concerns over bioequivalence. Perhaps FDA has realized that simply restating the mantra that approved generics are identical to the branded drugs they replicate will not satisfy the growing number of critics to agency policies. But taking action only after being compelled by negative publicity or threat of legal action is not a sustainable approach either. Unfortunately fundamental changes on bioequivalence, if any, are not imminently forthcoming. As an account of the July advisory committee meeting noted, "If the July 23 meeting . . . is any indication, FDA appears years away from changing approval standards for generics of drugs with complex dosage forms." Becky Jungbauer, *'Difficult' Bioequivalence Issues Make Limited Progress at Advisory Cmte.*, THE PINK SHEET, July 28, 2008.

Patients, as well others with a stake in bioequivalence determinations, will bear the risks and costs of ponderous bureaucratic process. In this era of health care cost containment, generic drug use will continue to rise and, because such products are either not tested in humans at all or only in healthy subjects, if a generic is not therapeutically equivalent, sick patients will be the first to know. Ineffective drug treatments on conditions like epilepsy and depression will lead to further medical care, including possible hospitalization, potentially overcoming the cost savings generics may provide.

The risks of inaction are also great for branded and generic pharmaceutical manufacturers. Branded drug makers face damage to their reputations and relationships with customers if a non-equivalent generic is ineffective or does harm. Under the reasoning of a recent California appeals court ruling, they also risk liability exposure if a generic does harm.⁶ While individual generic drug makers also face reputational harm and liability exposure if their products cause injury or do not perform adequately, the damage would likely be far more widespread. One or several high-profile incidents that shake public faith in the equivalence of generics could cripple the consumer confidence that the entire industry has earned over the last two decades.

The stakes are also high for FDA and government policy makers. FDA, wracked by a bribery scandal in the late 1980s involving generic drug oversight, has campaigned aggressively to shape public opinion on generics, and proudly touts its role in reducing health care costs. To ensure that FDA retains the public's confidence on generic approvals, the agency's new leadership should ensure that bioequivalence decisions adhere to federal statutes and regulations, are made in a transparent manner, and are based on sound science, not cost savings.

A quarter century ago, lawmakers dramatically altered American health care with the passage of the Hatch-Waxman Act. The law expanded competition and access to medications, and set the stage for generic drugs to play the leading role in health cost containment that many current reform proposals have scripted for them. As reform debates and action proceed, our policy makers must ensure, through greater oversight and scrutiny, that FDA is approving, and will continue to approve, generic products which are fully equivalent, and similarly safe and effective, as the original medications they duplicate.

⁶*Conte v. Wyeth, Inc.* 168 Cal. App. 4th 89 (2009); *but see Schrock v. Wyeth*, 601 F. Supp. 2d (W.D. Ok. 2009).