Defective Generic Pill Revives Quality Concerns

WASHINGTON (AP) — More Americans than ever are taking generic drugs, as blockbuster medicines like Plavix and Lipitor become available in low-cost versions. But the government's revelation this week that it mistakenly approved a defective generic antidepressant could stoke longtime concerns about the quality of knockoff drugs.

The Food and Drug Administration on Wednesday asked Teva Pharmaceuticals to withdraw its drug Budeprion XL 300 after testing showed the drug did not properly release its key ingredient. The drug is supposed to be equivalent to GlaxoSmithKline's popular antidepressant Wellbutrin XL, which is prescribed to treat depression, anxiety and symptoms of nicotine withdrawal.

The announcement marked an about-face for regulators, who said in 2008 that the two drugs were essentially the same, despite hundreds of complaints from patients who said they experienced side effects such as headaches, anxiety and insomnia after switching to the generic drug. The FDA has withdrawn generic drugs before, but this appears to be the first case driven by consumer complaints, which continued to pile up after the FDA said the drug was working correctly.

"The lesson is that everyone — from pharmacists to physicians to the FDA — needs to take these reports seriously," said Dr. Tod Cooperman of ConsumerLab, a privately-held company that independently tests drugs and nutrition products. Cooperman added that the vast majority generic drugs work appropriately but that, "consumers will be the first to know when there is a problem."

ConsumerLab first drew attention to the issue with Budeprion XL in 2007. The company published an analysis of the two drugs, indicating Budeprion XL released its active ingredient at a much faster rate than Wellbutrin. The FDA completed its own study in August that confirmed those findings.

But FDA officials said Thursday it would have been irresponsible to make scientific decisions based on patient reports, which can be influenced by a host of individual factors, including their disease.

"When these reports come in we don't know exactly what is going on with the patient," said David Read, regulatory counsel for the FDA's office of generic drugs. "Is it a failure of the drug or is it a coincidence they are experiencing some sort of problem? It's something to discuss between them and their physician."

Read pointed out that in the last five years the FDA has only had to correct itself on the equivalence of three drugs. Two cases involved drugs from Dr. Reddy's Laboratories: an antidepressant and an antifungal medication. The third case involved an anti-seizure drug from Upshur-Smith Laboratories.

The FDA approved the first generic versions of Wellbutrin XL in 2006, including Budeprion. The generic drug is made by U.S.-based Impax Laboratories Inc. and sold by Israel-based Teva Pharmaceutical Industries Ltd.

Teva said Wednesday that it halted shipments of the drug last Thursday after being contacted by the FDA. The company pointed out that there is no safety issue with the pill.

The Generic Pharmaceutical Association, a trade group for generic drugmakers, moved quickly to defend the track record of both the FDA and its companies.

"There are approximately 10,000 FDA-approved interchangeable generics in the U.S.," said Ralph Neas, the group's CEO and president. "The recall by a single manufacturer of one strength of a generic drug should in no way cast doubt on the impeccable reputation of the generic industry or the FDA."

The generic pharmaceutical industry has never been more successful. With prices 50 to 70 percent below the original product, generic drugs are favored by government and private insurers, pharmacies and patients. Last year, generic drugs made up 80 percent of the 4 billion prescriptions written in the U.S., an all-time high driven by a wave of patent expirations. In the last year some of the best-selling drugs ever made have gone generic, including the high cholesterol pill Lipitor and the blood thinner Plavix.

And complaints about generic drugs are rare, although they have cropped up before. The FDA's stance has been that generic drugs are chemically and medically equivalent to the original products. The agency has hammered home that message in pamphlets and posters with slogans like "Generic Drugs Make the Grade," and "Generic Drugs Measure Up."

But the same streamlined process that makes generic drugs so cheap can open the door to problems like those seen with Teva's antidepressant. Developing and testing an original prescription drug can take more than a decade and cost upwards of $1 billion dollars, according to the Pharmaceutical Research and Manufacturers Association. The high price tag on most new drugs reflects the cost of years of trials that often involve hundreds of patients.

By comparison, generics are much less expensive because manufacturers are not required to repeat those costly studies. Instead the FDA asks companies to show that the drug is the same dose, strength and functions similarly in the body. In most cases, that means conducting a small study of 25 to 35 people showing that the generic drug is absorbed into the bloodstream at the same rate as the original drug. Usually regulators require a test of one dose of the drug, and then apply those results to other dosages.

FDA officials said Wednesday that this practice led to the mistaken approval of Teva's antidepressant. The FDA approved the drug based on a study of the 150 milligram dose of the drug, assuming the 300 milligram version of the drug would

function similarly. An agency follow-up study showed that only 75 percent of the 300 milligram dose was actually being absorbed into the bloodstream.

"Based on the information we had available at that time we concluded that the 150 milligram strength was doing what it should, and that it was acceptable to extrapolate those findings to the 300 milligram strength" said Barbara Davit, director of bioequivalence for FDA's office of generic drugs.

Davit said the agency traditionally tests the lower dose of antidepressant drugs to avoid unnecessarily exposing patients to high doses. Davit said that approach "is no longer appropriate," and that the agency will test the highest dose when approving future versions of the drug.

In fact, while the FDA continues to tout the quality of generic drugs to the public, the agency has taken a more critical tone in discussions with industry. Earlier this year, the FDA's commissioner urged industry executives to put more focus on quality.

More than 225 drugs are currently in short supply, according to the American Society of Health-System Pharmacists, and many are cheap, generic drugs like sedatives, antibiotics and painkillers. Some of the shortages have been caused by manufacturing shutdowns due to plant contamination and other serious problems.

"Generic manufacturers need to be doing even more to ensure the quality of their products_for example, sharing best practices," Dr. Margaret Hamburg told members of the Generic Pharmaceutical Association. "And you have a particular responsibility to step forward when a product you are producing is medically necessary."

Despite the tough love from FDA officials, the agency continues to dedicate resources to bolster the image of generic drugs. Recent legislation passed by Congress includes FDA funding to study how differences in the color, shape and size of generic drug tablets can influence patients' view of their quality, compared to traditional products.

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