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Globalization of the Pharmaceutical Supply Chain: What are the Risks?

The FDA's Difficult Task

by Jill Van Den Bos

The Food and Drug Administration (FDA) is the gatekeeper of the U.S. pharmaceutical market. Its role in this capacity is to ensure the safety and efficacy of the drug supply. This role, however, is not an easy one. A few high-profile drug withdrawals over the years, including Thalidomide, Fen-Phen and Vioxx, and other post-marketing "black box" warnings, including widely prescribed antidepressants, have highlighted the difficulties of the FDA's function and caused the agency to become the subject of some fairly public criticism and congressional scrutiny. A 2007 article in *Fortune,* titled "FDA damned if it does, damned if it doesn't," illustrated the difficulties of being the FDA: criticized for being "too cozy with the industry" or for getting tough and thereby "standing in the way of new medicines."[i]

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Globalization: The New Thorny Issue

More recent developments surrounding the globalization of the pharmaceutical supply chain appear poised to provide the context for the next assault on the FDA's ability to protect the American public from unsafe or ineffective drugs. Previous post-marketing discoveries of safety issues may eventually pale in comparison to safety issues presented by globalization of pharmaceutical manufacturing.

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[i] Simons, John. FDA damned if it does, damned if it doesn't. Nov. 9, 2007. Accessed 01-07-2009. Available at: *http://money.cnn.com/2007/11/08/magazines/fortune/simons_fda.fortune/index.htm.*

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Whereas most ingredients used to be manufactured in the United States, 80 percent of active ingredients are now manufactured in China and India. Regulation of these manufacturers is limited and variable.[ii]

For example, Chinese pharmaceutical companies that produce active pharmaceutical ingredients (APIs) are regulated by the State Food and Drug Administration. However, companies that are officially part of another industry, such as chemical companies, also manufacture APIs and are not regulated in the same manner. Of the 80,000 or so chemical companies in China, the number that manufacture APIs is unknown. Furthermore, the State Food and Drug Administration in China does not monitor the manufacturers of intermediate compounds, the building blocks for APIs.[iii]

Although many globally produced APIs wind up on the U.S. pharmaceutical market, the FDA lacks the overseas capacity to inspect foreign manufacturers. Indeed, the FDA may not have accurate information on foreign manufacturers that are subject to investigation. As such, fewer than two percent of these facilities are examined by the FDA.[iv] In fact, investigators from the House Energy and Commerce Committee recently accompanied FDA officials on inspections of drug plants in China and India. They concluded that the FDA was unable to provide basic information such as the number of firms exporting to the United States, and overseas FDA inspectors lacked necessary logistical support. Since the FDA only conducts about 20 inspections per year, it would take the FDA 13 years to inspect all of the manufacturers of bulk ingredients with its current staff.[v]

As a result of the globalization of the supply chain, there are greater opportunities for the production and dissemination of unsafe drugs in the United States.[vi]

Counterfeit Products

Counterfeit drugs are substandard medicines whose composition and ingredients do not meet the correct scientific specifications and are fraudulently mislabeled with respect to a product's identity or source. This can come about in several ways:

- ingredients are mislabeled as API when they are impure or inactive,
- the correct API is replaced with an incorrect potency/dosage,
- the correct API is replaced with a cheaper version, or
- an expired API is labeled with a new and false expiration date.[vii]

The FDA estimates that 10 percent of medicines on the global market are counterfeit. This value has been closer to one percent in markets such as the United States and Canada, and much higher in developing markets. In 2005, there were 100 reported incidents of counterfeiting in the United States and 42 seizures. The production of counterfeit drugs does not occur in large infrastructure or facilities, but is carried out in ordinary households, small cottage industries or in backyards. Counterfeiting is highly lucrative because of high demand and low production costs. There is no deterring legislation in most countries because there is no fear of being apprehended and prosecuted. The willingness of patients to buy medicines through the Internet has

[ii] Bogdanich, Walt. F.D.A is Unable to Ensure Drugs are Safe, Panel is Told. Nov. 2, 2007. Accessed 01-07-2009. Available at: *http://www.nytimes.com/2007/11/02/washington/02FDA.html*.

[iii] Bogdanich, Walt. Chinese Chemicals Flow Unchecked Onto World Drug Market. Oct. 31, 2007. Accessed 01-07-2009. Available at: *http://www.nytimes.com/2007/10/31/world/asia/31chemical.html*.

[iv] Barnes, Kirsty. F.D.A. Failure on Foreign Inspections Frightening. Nov. 5, 2007. Accessed 01-07-2009. Available at: *http://www.outsourcing-pharma.com/Contract-Manufacturing/FDA-failure-on-foreign-inspections-frightening*.

[v] Bogdanich, Walt. F.D.A is Unable to Ensure Drugs are Safe, Panel is Told. Nov. 2007. Accessed 01-07-2009. Available at: *http://www.nytimes.com/2007/11/02/washington/02FDA.html*.

[vi] World Health Organization. Substandard and Counterfeit Medicines Fact Sheet No. 275. Nov. 2003. Accessed 01-07-2009. Available at: *http://www.who.int/mediacentre/factsheets/fs275/en/*.

[vii] World Health Organization. Substandard and Counterfeit Medicines Fact Sheet No. 275. Nov. 2003. Accessed 01-07-2009. Available at: *http://www.who.int/mediacentre/factsheets/fs275/en/*.

been quickly recognized by criminals as a profitable way to supply counterfeit medicines to unsuspecting customers.[viii] Counterfeiters have targeted a wide range of modern drugs in the areas of cancer, erectile dysfunction, cardiology, hormones, steroids and antihistamines.[ix]

Pharmaceutical counterfeiting has been described as the perfect crime: if the patient's condition improves, there is no investigation. If the patient's condition deteriorates, it will be attributed to the medical condition or disease.[x]

What is the Risk?

Counterfeit drugs can have two basic impacts on patients: the active ingredient is less than the stated dose, or missing altogether; or the drug is downright harmful in that it contains what amounts to poison. Both of these situations occur with alarming frequency.

In the first case, patients will be taking drugs that do not have the expected therapeutic effect, leading to ineffective treatment and therapeutic failure, which can be disastrous depending on the condition being treated. To make matters worse, this happens while spending money that is expected to lead to therapeutic benefit—the patient and the health plan are paying for this ineffective treatment. As an example, a recent study by the World Health Organization (WHO) found that 38 percent of antimalarial drugs in pharmacies in Southeast Asia contained no active ingredient.[xi]

In the second case, patients will be taking drugs that may have the expected therapeutic effect, but also have an additional deleterious effect. Again, the impact can be disastrous, as illustrated by a 2008 case of tainted heparin in the United States. In this case, up to 50 percent of the active ingredient was replaced with oversulfated chondroitin sulfate, a cheaper ingredient that has similar properties to that of heparin.[xii] At least 95 Americans died and hundreds had severe allergic reactions after taking this counterfeit drug.[xiii]

What is the possible cost to a health plan if a commonly prescribed drug, such as a statin, were replaced with a counterfeit drug? Statins (HMG-CoA reductase inhibitors) are a class of drugs prescribed to reduce hyperlipidemia, which is high levels of fatty molecules (cholesterol and triglycerides) in the blood. Hyperlipidemia is, in turn, associated with increased speed of hardening of the arteries, leading to increased risk for heart disease, stroke and other vascular diseases. Statins are generally effective, if potentially costly, at reducing the morbid outcomes of hyperlipidemia.[xiv]

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[viii] Organisation for Economic Co-operation and Development. The Economic Impact of Counterfeiting and Piracy. 2008. Accessed 01-07-2009. Available at: *http://books.google.com/books?id=1z2p2MRNwvoC&pg =PA362&lpg=PA362&dq=pharmaceutical+counterfeiting+perfect+crime&source=bl&ots=V5bCPHIfJ8&sig=iF4wf4tkubRjbLIgmIMu0dbiU7s&hl=en&ei=ZZycSYSWGeDkmQfE9JngBA&sa=X&oi=book_result&resnum=4&ct=result.*

[ix] Messplay, Gary C. and Heisey, Colleen. Is It Real or Is It Counterfeit? Securing our drug supply chain. September 2005. Accessed 01-07-2009. Available at: *http://www.hunton.com/files/tbl_s47Details%5CFileUpload265%5C1503%5CContractPharma_sept05.pdf.*

[x] Organisation for Economic Co-operation and Development. The Economic Impact of Counterfeiting and Piracy. 2008. Accessed 01-07-2009. Available at: *http://books.google.com/books?id=1z2p2MRNwvoC&pg=PA362&lpg=PA362&dq=pharmaceutical+counterfeiting+perfect+crime&source=bl&ots=V5bCPHIfJ8&sig=iF4wf4tkubRjbLIgmIMu0dbiU7s&hl=en&ei=ZZycSYSWGeDkmQfE9JngBA&sa=X&oi=book_result&resnum=4&ct=result.*

[xi] Loewy, Madas. Deadly imitations: counterfeit drugs are a growing global enterprise and a major threat to health in both the developed and the developing world. Jan. 1, 2007. Accessed 01-07-2009. Available at: *http://www.thefreelibrary.com/Deadly+imitations:+counterfeit+drugs+are+a+growing+global+enterprise...-a0185654331.*

[xii] Bogdanich, Walt. Heparin Find May Point to Chinese Counterfeiting.. March 20, 2008. Accessed 01-07-2009. Available at: *http://www.nytimes.com/2008/03/20/health/20heparin.html.*

[xiii] Bate, Roger. The Wrong Message in a Bottle. Nov. 15, 2008. Accessed 01-07-2009. Available at: *http://www.nytimes.com/2008/11/15/opinion/15bate.html.*

[xiv] Pletcher MJ, Lazar L, Bibbins-Domingo K, Moran A, Rodondi N, Coxson P, Lightwood J, Williams L, Goldman L. Comparing Impact and Cost-Effectiveness of Primary Prevention Strategies for Lipid-Lowering. Annals of Internal Medicine, Feb 17, 2009, 150(4):243-254.

Statins are taken by many people. Statins, as a class, have the second highest per member per month claim cost (PMPM) among all drug classes for the commercially insured at $6.47, and the highest PMPM for the Medicare eligible population at $37.81. If a commonly prescribed statin were replaced with a counterfeit version having no active ingredient, the resulting cost to a health plan would include the price paid for the counterfeit drugs themselves plus the cost of nontreatment for the populating taking this statin. If instead this target statin were replaced with a counterfeit version having no active ingredient and also containing a chemical that caused a severe allergic reaction requiring long hospitalizations for even a small portion of affected patients, the cost to a health plan could be substantial. Add to this the more important costs in terms of health to the patients themselves.

The FDA estimates that 10 percent of medicines on the global market are counterfeit.

There are many relevant variables that would come into play, naturally, including time until the "bad" drugs were discovered, the size of the population impacted, type of drug and what condition it treated. However, this "what if" exercise suggests that the costs in terms of health, quality of life and dollars could be substantial if a relatively big "slip" occurred.

The Future

In recent years the FDA has responded to the threat of counterfeit pharmaceuticals by stepping up efforts to improve the safety of the nation's drug supply. One method has been to encourage the use of technologically advanced tags that electronically label drug packages. Radiofrequency identification (RFID) enables manufacturers and others in the drug supply chain to track drug products, making inserting counterfeit products into the supply chain more difficult.[xv]

In November 2008, the FDA opened an office in Beijing, China. The FDA plans to open more offices in China as well as in other international locations.[xvi] Congress has also taken an interest in the safety of the drug supply chain, with possible legislative action that may include tracking requirements.[xvii]

Another FDA initiative, announced Jan. 14, 2009, is a voluntary program called the Secure Supply Chain pilot program to promote and improve the safety of drugs and APIs manufactured outside the United States. To do this, the FDA will select 100 applicant companies that meet certain criteria to participate.[xviii] "The program creates incentives for drug manufacturers to develop and maintain secure supply chains," according to Deborah Autor, director of the office of compliance in the FDA's Center for Drug Evaluation and Research.[xix]

Although the U.S. pharmaceutical market is still one of the safest in the world, the impact of the globalization of pharmaceutical manufacturing has brought with it a well-deserved element of fear that is galvanizing the FDA and others into action.

"Best safety lies in fear."

—*Hamlet*, William Shakespeare. ■

[xv] Food & Drug Administration. Radiofrequency Identification Technology: Protecting the Drug Supply. March – April 2005. Accessed 01-07-2009. Available at: *http://www.fda.gov/fdac/features/2005/205_rfid.html*.

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