

REGULATION

FDA Steps Up Action Against Counterfeit Drugs, Warns US Consumers Against Fake Medicine from Mexico

The US Food and Drug Administration (Rockville, MD, www.fda.gov) released its annual report on May 18 explaining the agency's campaign against counterfeit prescription drugs. The report says FDA's Office of Criminal Investigations (OCI) launched 58 inquiries in 2004 (up from 30 in 2003) "involving hundreds of thousands of fake dosage units."

Combating counterfeit drugs strategy status report

Critical components	Completed	Ongoing
Track and trace (RFID)	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Authentication technologies	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Electronic pedigree	<input type="checkbox"/>	<input checked="" type="checkbox"/>
States adopt stricter laws	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Secure business practices	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Reporting via MedWatch	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Counterfeit alert network	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Internal rapid response	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Educate consumers and health professionals	<input type="checkbox"/>	<input checked="" type="checkbox"/>
International collaboration	<input type="checkbox"/>	<input checked="" type="checkbox"/>

The report credited the increase to stepped-up enforcement action, increased collaboration with state and private agencies, and increased manufacturer vigilance.

The report does not say how many of those 58 initiated investigations have produced or are likely to produce arrests or product seizures. It does include an appendix that summarizes seven drug-counterfeiting cases that closed during the past year:

Counterfeit Lipitor

- During the first quarter of 2005, three men pled guilty to federal criminal charges in a multimillion dollar Lipitor smuggling and counterfeiting conspiracy. To date, eight people have been indicted, four have pled guilty, and another was convicted by a trial jury.
- In September, a Belize citizen was convicted and sentenced to 10 months incarceration and one year probation.

Counterfeit human growth hormone

- In March 2004, a Texas man pled guilty to four counts of conspiracy to introduce misbranded and unapproved new drugs into interstate commerce, counterfeiting human growth hormone, and possessing controlled drugs with the intent to distribute. Two other persons involved in these offenses were previously convicted and sentenced.

Counterfeit Viagra

- In 2004, a counterfeiter pled guilty to conspiracy, trafficking in counterfeit goods, and a felony violation of the Federal Food, Drug and Cosmetic Act, admitting he conspired with a manufacturer in Beijing to import thousands of counterfeit Viagra tablets into the United States. He was fined \$6000 and sentenced to 18 months in prison, followed by three years probation.
- In January 2005, a Southern California man pled guilty to importing counterfeit Viagra from China and manufacturing 700,000 counterfeit Viagra tablets at a laboratory in the United States. An accomplice was convicted of similar charges in September 2004. The total value of the counterfeit Viagra in this case is more than \$5.65 million.

Counterfeit Serostim

A June 2004 indictment charged an individual with obtaining counterfeit Serostim (a formulation of somatropin human growth hormone) and selling it to bodybuilders. A collaborator pled guilty to similar charges in February 2003.

Counterfeit labeled pharmaceuticals

In October 2004, an Alabama drug wholesaling company was convicted, fined \$24,000, and sentenced to five years probation.

World Express Rx

In January 2005, a San Diego man was sentenced to serve a 51-month prison term and to forfeit substantial cash proceeds for his role in operating a large Internet pharmacy scheme. The illicit drugs included products counterfeited in Mexico, India, and Pakistan, which were then smuggled into the United States. At least 14 other individuals also are being prosecuted in California or Florida as part of this conspiracy.

Warning on Mexican border-town counterfeits

Earlier in May, FDA took the unusual step of warning Americans against counterfeit Lipitor, Viagra, "and an unapproved product promoted as 'generic Evista'" sold in Mexican border-town pharmacies.

The "generic Evista" was made or distributed by Litorio, whose label claimed that it was manufactured in Monterrey. FDA obtained it from a pharmacy in Agua Prieta (Sonora, Mexico), and conducted the analysis in conjunction with the National Association of Boards of Pharmacy.

The ersatz Lipitor and Viagra came from pharmacies in Juarez, Los Algodones, Nogales, and Tijuana. FDA reports that the counterfeit labels were in English, rather than the Spanish used on genuine Mexican drugs. Pfizer analyzed the samples of both drugs, FDA said.

The agency statement noted that US and Mexican officials are cooperating in an effort to curtail trade in counterfeit drugs and that Mexico's Federal Commission for the Protection from Health Risks has recently shut down 19 pharmacies and confiscated 105 tons of fake medicines.

—Douglas McCormick



MANUFACTURING

GlaxoSmithKline and FDA Agree on Consent Decree

GlaxoSmithKline (GSK, London and Philadelphia, www.gsk.com) and the US Food and Drug Administration (Rockville, MD, www.fda.gov) have reached an agreement on a consent decree regarding corrections at the company's Cidra, Puerto Rico, manufacturing facility.

GSK's Cidra plant manufactures the tablets—"Paxil CR" (paroxetine hydrochloride controlled release, for depression) and "Avandamet" (combination rosiglitazone maleate and metformin hydrochloride, for diabetes)—seized by federal marshals at three locations last February. FDA had obtained the warrant, citing manufacturing errors that produced some tablets with out-of-specification levels of active ingredient.

In a prepared statement, GSK said that it "has identified the source of the manufacturing issues related to both products, and has already implemented revisions to those manufacturing processes." GSK expects to resume manufacturing and distribution of Avandamet and Paxil CR to the United States and elsewhere "in mid-year," well ahead of industry analysts' predictions.

The consent agreement also "requires that all corrections and the firm's compliance with CGMP requirements be certified by a third-party expert," in addition to continuing FDA monitoring, according to FDA's statement. The agreement holds GSK to a well-defined procedure for reporting and correcting process shortcomings discovered during this review.

GSK will post a \$650-million performance bond to ensure that the product seized in February is "appropriately destroyed or reconditioned." GSK says that it "anticipates meeting all requirements of the bond within 90 days following entry of the decree." Although the proposed decree provides for penalties as much as \$10 million per year if the company does not hold to its terms, GSK emphasizes that FDA is not imposing any fines or penalties at this time.

The draft consent decree was presented to the US District Court of the Eastern District of North Carolina on April 27, and will take effect after it is signed by GSK and FDA and entered by the court.

—Douglas McCormick

EDUCATION

Graduate Program Focuses on Pharmaceutical Technology

In an effort to educate students about the role of technology in the pharmaceutical and biotechnology industries, the Wesley J. Howe School of Technology Management at Stevens Institute of Technology (Hoboken, NJ, <http://howe.stevens.edu>) has created a new graduate program in pharmaceutical technology management.

"There had been an interest in developing a program focused on the pharmaceutical industry," says Joel Dobbs, program director of pharmaceutical technology management at Stevens Institute. "The Wesley J. Howe School focuses on the area of technology management and organizations that derive economic value through technology, which certainly describes the pharmaceutical business."

Last fall, the school met with 16 senior pharmaceutical executives and leading industry consultants to determine what skills students will need to become leaders in the pharmaceutical industry as well as to learn more about the challenges that companies are facing, which future employees must be prepared to handle.

"One of the big things that came across universally was that the companies needed people who really understood the pharmaceutical business soup to nuts," Dobbs says. "They want people who can understand how to translate technological possibilities into business benefits and can develop strategies that can exploit the technologies that are emerging."

To meet this need, the school created a graduate certificate program with four courses, "Managing Technology and Innovation," "Managing Pharmaceutical Research and Development," "Sales, Marketing and Supply Chain Management," and "Introduction to Pharmaceutical Manufacturing." The courses also can be taken as part of master's degree programs with a concentration in pharmaceutical technology management.

Students will learn about the strategic management of technology and overall drug development process. Courses use case studies that document real situations and how pharmaceutical manufacturers have approached various dilemmas. Compliance and anticounterfeiting measures are also covered extensively, according to Dobbs. The school also is in talks with major pharmaceutical companies to teach classes from their sites in the evenings to give students a first hand look at what goes into a successful manufacturing plant.

The new curriculum will launch in Sept. 2005. According to Dobbs, there has been a significant interest in the program.

—George Koroneos

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MANUFACTURING

New Chemical Reaction Method Accelerates Indole Production

A new chemical reaction pioneered by researchers from the University of Toronto (Toronto, ON, Canada, www.utoronto.ca) simplifies the production process for indole rings, a basic molecular frameworks commonly used in pharmaceutical products such as cholesterol-reducing drugs.

An indole is a benzene ring that is made of a six-member carbon-containing ring attached to a five-member nitrogen-containing ring. To make these privileged structures, researchers use a palladium catalyst to form two chemical bonds: a nitrogen-carbon and a carbon-carbon formation. These indole-containing compounds can then be used to produce known chemical agents, a lead structure, or a new derivative for a pharmaceutical. "This new process shortens the process for making the indole skeleton and to produce compounds that could not be made easily by other methods," says Mark Lautens, a University of Toronto professor who codeveloped the technique with graduate student Eric Fang.

The palladium catalyst is designed to

be quick and cost-effective. "It uses relatively inexpensive, commercially available material starting materials and takes only 2 or 3 steps to get to the final product," explains Lautens. Typical processes require 6–10 steps to complete.

In addition, the researchers use boronic acid to make the carbon-carbon bond, which is more environmentally friendly than many available alternatives. "To make a hundred kilograms of these best-selling drugs, there are often hundreds of liters of solvent used, not to mention the many purification processes involved," says Lautens. "This reaction is a cleaner, more-efficient chemistry that would eliminate multireactions and thus saves on solvents, which are often considered a hazardous waste."

Although the technology is not currently being used for commercial use, the researchers hope to partner with a pharmaceutical company to modify the process for large-scale production. The University of Toronto filed a provisional patent for

the technique in March 2005 and licensed the technology to the university's innovations foundation.

—Kaylynn Chiarello

DRUG DELIVERY

Cytogen and Dowpharma to Develop Targeted Anticancer Product

Cytogen Corporation (Princeton, NJ, www.cytogen.com) and Dowpharma, a business unit of The Dow Chemical Company (Midland, MI, www.dow.com) have joined forces to develop a new, targeted therapy to treat prostate and other cancers.

The team will use Dowpharma's "MeO-DOTA" bifunctional chelant technology to attach a beta-emitting radionuclide lutetium-177 as a payload to Cytogen's "7E11-C5.3" antibody. This monoclonal antibody targets prostate-specific membrane antigen (PSMA), a protein often expressed by the most aggressive clones of prostate cancer cells and tumors.

Dowpharma's technology will bind the therapeutic radioisotope to the same murine monoclonal antibody used in Cytogen's "Prostascint" molecular imaging procedure for detecting the spread of prostate cancer with a gamma camera. According to the company, it is the first and only commercial product that targets PSMA. Researchers are hopeful the technique will offer improved diagnosis and treatment for prostate cancer.

Said William Goeckeler, PhD, senior vice-president of operations at Cytogen, "DOTA-based bifunctional chelating agents have been shown to provide exceptional stability to [e]nsure that therapeutic radionuclides do not separate from the monoclonal antibodies that target them to tumors."

—Kaylynn Chiarello

MANUFACTURING/EDUCATION

Purdue Pharmaceutical Manufacturing and Education Center Opens its Doors

Purdue University's (West Lafayette, IN, www.purdue.edu) Chao Center for Industrial Pharmacy and Contract Manufacturing (www.thechaocenter.com) is scheduled to open for business this month after two years of construction (*Pharm. Technol.* 27 [10], 22 [2003]).

The \$6.5-million, 12,000-ft² facility will develop drugs to treat diseases that mainly affect underprivileged populations. The center also will focus on producing less-profitable drugs that are made in small volumes. In partnership with Eli Lilly and Co., the first product expected to come off the manufacturing line will be an antibiotic for treating multiple drug-resistant tuberculosis. Batch testing will begin next month.

As one of five university-affiliated manufacturing plants in the United States, the center will give students opportunities to learn about pharmaceutical production through internships and scholarships. In a press release, John M. Pezzuto, Purdue's Dean of the College of Pharmacy, Nursing, and Health Sciences said, "Purdue pharmacy students will be able to familiarize themselves with good manufacturing practices procedures as they watch these processes in a working manufacturing and development facility."

The plant currently is undergoing the final stages of regulatory approval.

—Kaylynn Chiarello