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FDA Counting on Global Strategy To Better Secure Supply Chain

The FDA's work toward tighter supply chain control through international regulatory cooperation is falling short, but a new global strategy may speed up the agency's progress, a top FDA official says.

The next several years are critical in the agency's transformation to a "global agency," John Taylor, the FDA's acting principal deputy commissioner, said March 14 at a Pew Charitable Trusts conference in Washington, D.C., on drug supply safety.

To achieve adequate supply chain control, Taylor said, the FDA needs novel and updated enforcement tools, a global alliance of regulators, new authorities to create proactive tools for product safety,

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McNeil Gets Consent Decree After Period of Manufacturing Woes

The FDA has said enough is enough to McNeil Consumer Healthcare over its repeated manufacturing problems, issuing a consent decree that indefinitely closes one plant and places oversight over two others.

The agency said the Johnson & Johnson subsidiary, which has been plagued with recalls of its OTC drugs relating to cGMP violations, will not be able to reopen its troubled Fort Washington, Pa., plant until a litany of changes have been made.

The March 10 decree, filed in a Pennsylvania federal court, sets strict timeframes McNeil must meet or face fines, further recalls and additional shutdowns. Its also names as defendants McNeil's vice president of quality, Veronica Cruz, and Hakan Erdemir, the company's vice president of operations, for violating federal law by distributing adulterated drugs.

Within 30 days of the decree, McNeil needs to outline its plans to destroy all lots of drugs in its possession or recalled since

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adequate funding for inspections, examinations and sample collections and analysis, and updated systems, including IT support, to assist with increased workload.

Moving forward, the agency will follow an action plan with four primary components:

- Partnering with foreign counterparts to create a global coalition of regulators;
- Working to build a global data-information system and network, and proactively sharing data with partners;
- Building additional intelligence-gathering capabilities with an increased focus on risk analytics and a transformed IT capability; and
- Leveraging the efforts of public and private sector third parties and industry to allocate FDA resources based on risk.

Some of this work is already underway, but needs to be "taken to the next level," Taylor said, including greater coordination and enforcement of regulatory standards across nations, even if those standards are not identical.

Regulatory authorities with greater experience and resources must work together to help build regulatory systems in countries with developing systems or fewer resources, he added.

The FDA will also enhance its intelligence-gathering capabilities, with an increased focus on risk analytics and IT capability. The agency will create tools to quickly assess regulatory data across various information resources.

"We must also create a modern means to share data globally, and we must use those data and advanced analytics to proactively prevent and identify problems," Taylor said.

The FDA will also develop programs in each product type it regulates and in inspection programs within those categories, for approved public and private third parties to conduct inspections and other oversight activities.

The agency must establish a review and audit infrastructure to verify that information and to ensure that it can quickly take follow-up enforcement action.

So far, the FDA's adoption of new oversight strategies and its work with foreign partners has not substantially increased coverage of its safety activities, Taylor said.

Some programs are facilitating the shift toward common safety standards, but the FDA has only used these alternatives to its own standards in limited circumstances, he said.

"At the current rate of progress, and through the current mechanisms, it would take decades to reach a comprehensive set of common standards." that would allow the FDA to leverage the work of third parties, domestically and abroad, according to Taylor.

But working alone to ensure U.S. product safety, the FDA's efforts have sometimes fallen short, and foreign inspections still lag behind domestic inspections (*DGR*, November 2010). — April Hollis

Sterility Issues Lead to J&J Product Recall

Another Johnson & Johnson (J&J) product is being recalled — the fifth recall in less than a month — amid sterility concerns.

The latest recall follows the UK's Medicines and Healthcare Products Regulatory Agency (MHRA) issuance of a notice March 2, alerting British healthcare providers of the possible defect. The MHRA says the packages may not have been completely sealed and the contents may not be sterile.

The action involves 585,000 strands or 104 batches of sutures sold under various names — Ethilon, Ethibond, Mersilene and Mersilk — by J&J subsidiary Ethicon.

The UK action follows an Ethicon recall last month of 700,000 vials of a liquid wound-sealing product, Dermabond, amid reports of discoloration and concerns it may take longer than expected to set (*DGR*, March). — David Pittman

FDA Zeroes in on Compliance History for Inspection Decisions

ATHENS, Ga. — Companies that have a track record of non-compliance with GMPs should come under greater FDA scrutiny and be more likely to get inspected, the FDA's associate commissioner for regulatory affairs has suggested.

Speaking March 15 at the International Good Manufacturing Practices Conference, Dara Corrigan said the FDA must "be able to shift our resources to the high-risk areas, which means the high-risks firms."

"We should be looking at those companies with a history of non-compliance. They deserve more scrutiny, and they will have more scrutiny," she added. "And we are looking at ways to better track a company's history over time."

Warning Letter Increase

Corrigan didn't elaborate on how the FDA would handle or examine a company's history, but said there should be rewards for those companies who meet or exceed standards.

"We need to have a way of looking at those [companies] and really assessing where the risk is," said Corrigan, who took office in September and oversees a field staff of roughly 4,000 inspectors. "Good companies deserve FDA's respect."

Corrigan noted a 42 percent increase in the number of warning letters issued between fiscal 2009 and 2010. She also said 68 percent of warning letters from 2010 were issued within a four-month period.

However, Corrigan said warning letters aren't always a good metric for the amount or quality of compliance enforcement the FDA does.

Corrigan acknowledged FDA Commissioner Margaret Hamburg's work to cooperate with foreign governments and inspectors to better ensure the quality of products made overseas and shipped to the U.S.

The agency recently joined the 37-member Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme, and now has confidentiality agreements with 20 countries.

The FDA also has foreign offices in China, India, Latin America and Europe, but Corrigan admitted there still needs more work in the area.

A GAO report last year also suggested improved coordination between the FDA's overseas offices as well as long-term strategic planning.

Overseas Inspections

"There is a very current debate in FDA to figure out whether we should actually place more people overseas versus having to fly them out," she said.

A 2010 GAO report found that while on the rise, the number of inspections of foreign plants pales in comparison to those done on domestic facilities (*DGR*, November 2010).

Corrigan, who began her government career as a trial lawyer for the Justice Department in 1990, also addressed other pressing issues regarding her office.

About 40 percent of her department's work force is comprised of new investigators hired in the last three years.

"A lot of these investigations and inspections are complicated, especially in drug manufacturing," she said. "It takes a while to get people up to speed."

In February, Deborah Autor, director of the FDA's Office of Compliance, said that a lack of resources to conduct foreign inspections is part of the reason why the agency has a huge backlog of ANDA applications.

The FDA also needs people devoted to high-level drug inspections.

"We're creating a cadre of specially-trained professional inspectors," Corrigan said.
— David Pittman

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December 2009, that were made at its Fort Washington, Lancaster, Pa. and Las Piedras, Puerto Rico, facilities.

The FDA also ordered McNeil to cease production at Fort Washington until it completes a lengthy 10-step remediation process. The remediation plan spans seven of the order's 26 pages. The company previously said it hoped to reopen the plant mid-year after it closed in April 2010, a timetable that now looks all but impossible.

Remediation Plan

McNeil said that it expects the consent decree to govern the company's operation of the three plants for at least five years following the completion of the remediation plan.

In July, the company said it was developing its own plan, which included making significant investment in manufacturing facilities, reorganizing operations and developing a comprehensive program to ensure sustainable compliance with regulatory and its own quality requirements (*DGR*, August 2010).

The decree's remediation plan includes hiring an independent cGMP consultant for each facility. The consultant must certify the plant's equipment and manufacturing processes are compliant before the FDA inspects the facility.

McNeil must also outline a quality control plan and employee training programs to ensure GMP knowledge and processes.

Although facilities in Lancaster and Puerto Rico can remain open, they must complete the steps or face closure.

If McNeil violates the decree, the FDA may order the company to cease production in Lancaster and Las Piedras and recall products.

The agency could also levy fines of $15,000 a day and an additional $15,000 for each violation of the law up to $10 million a year.

Recalls have hammered McNeil's facilities in the past year.

As one recent example, the company in January recalled nearly 43 million bottles of Tylenol 8 Hour, Tylenol Arthritis Pain, Tylenol upper respiratory products, Benadryl, Sudafed PE and Sinutab that were made at the Fort Washington, plant before it closed (*DGR*, February 11).

The FDA issued McNeil a warning letter Jan. 15 for being too slow to alert the FDA and consumers to trace amounts of a wood-treating chemical in some of its products, including its OTC drug Tylenol.

At least one analyst predicted the consent decree. Wells Fargo analyst Larry Biegelsen said in January he continues to "see some uncertainty regarding Ft. Washington's targeted mid-year reopen after a mid-Dec. Form 483."

To view a copy of the consent decree, visit www.fdanews.com/ext/files/Certified_Filed_Consent_Decree_USA_v._McNeil_PPC.pdf.
— David Pittman

GMP Issues Behind FDA Hold On RegeneRX Drug Trial

The FDA has put a clinical hold on a Phase II trial for RegeneRX Biopharmaceuticals' investigational drug RGN-352, a formulation of Thymosin beta 4 (TB4) to treat acute myocardial infarction, after discovering deviations from cGMP regulations at the contract manufacturer for the drug.

RegeneRX has not disclosed the name of the manufacturer or the nature of the issue that led to the hold, but the company March 16 said the FDA's action is not directed at the safety of RGN-352 or its clinical development plan, and other trials will not be affected.

The FDA did not return requests for comment on the nature of the hold.

RegeneRX is developing TB4, a novel therapeutic peptide, in a number of different formulations for various treatments. RGN-352 is an injectable formulation of the drug for treatment of cardiovascular and central nervous system conditions. — Wilson Peden

FORM 483 INSIDER

Form 483 Reveals McNeil Plant's Trouble Before Spate of Recalls

Workers at McNeil Consumer Healthcare's troubled Fort Washington, Pa., facility routinely ignored abnormal test results for various products that were later recalled, according to a six-observation Form 483.

FDA inspectors found McNeil workers continued to release batches of Benadryl Allergy Fast Melts after obtaining out-of-specification (OOS) and out-of-trend (OOT) results from August 2008 to March 2010.

The agency's Philadelphia District Office also notes no OOS or OOT investigations were conducted for Sudafed PE Cold and Cough Caplets from April 2009, to March 2010, despite results that warranted further view.

Both products were affected by recalls in the last six months (*DGR,* February).

McNeil also sought outside advice on the chemical 2,4,6-tribromoanisole (TBA) and learned analytical testing can detect haloanisole below people's sensory threshold.

But despite continued problems with the odor at the plant and in products, "such quantitative testing was not preformed," according to the form, which came after an Oct. 27, 2010, to Dec. 9, 2010, inspection.

McNeil also used bottles that may have been exposed to haloanisole to package Tylenol 8 Hour caplets.

That product was included in the 43 million bottles of product recalled by the company in January.

McNeil, which closed the Fort Washington plant last April, agreed to a consent decree March 10 that indefinitely closes the facility.

McNeil declined to comment on the form. The 483 is available at www.fdanews.com/ext/files/McNeil-483.pdf.

Syringe Batches at Center of 483 For Pfizer's Pearl River Plant

An FDA inspection of Pfizer's Pearl River, N.Y., plant resulted in 22 Form 483 observations.

During a previous third-party inspection of the plant, Pfizer found hair and fibers adhered to syringe stoppers, the FDA's New York District Office notes.

The company identified batches that used the stoppers; "however, the investigation did not identify five other batches of Prevnar 7v which used the syringe and stopper batches," the Oct. 1, 2010, form states.

Pfizer also failed to investigate a black speck on the glass of a syringe barrel found during an inspection of retention samples, the FDA's Sept. 14, 2010, to Oct. 1, 2010, inspection found.

The company is working to address the observations, Pfizer spokesman Rick Chambers told *DGR*. The Form 483 is available at www.fdanews.com/ext/files/Pfizer-483.pdf.

Form 483 Notes Several Issues With Genzyme Kidney Drug

Manufacturing issues with chronic kidney disease drug Hectorol have resulted in a multi-item Form 483 for Genzyme.

The company failed to check that 10 finished lots of Hectorol (doxercalciferol) were free of particulates, the FDA's New Jersey District Office says.

"The initial non-conformance report and subsequent CAPA investigation failed to indentify all potentially impacted lots," states the Jan. 31 form to the Ridgefield, N.J. plant.

An automated machine in the plant rejected more than 6,200 vials of Hectorol. However, FDA inspectors found no evidence to identify the source of particulates found in rejected vials.

Genzyme did not return a request for comment by press time. A copy of the 483 is available at www.fdanews.com/ext/files/Genzyme-483.pdf.

Law Firm Asks FDA to Disclose Legal Enforcement Actions

A Washington, D.C., law firm is pushing for the FDA to create a website that will disclose more information on legal enforcement actions.

The request, sent by Hyman, Phelps and McNamara, cites a memorandum to executive departments and agencies that President Barack Obama issued in January as the basis of its request.

The memo requests "agencies with broad regulatory compliance and administrative enforcement responsibilities develop plans to make public information concerning their regulatory compliance and enforcement activities accessible, downloadable, and searchable online" by May 18.

"There is no reason why the FDA cannot place on its website public notice for every enforcement action that is publicly filed in court," the law firm says in a letter March 11 to FDA Chief Counsel Ralph Tyler.

The firm says it would like to see a new website provide the names and judicial districts of all lawsuits filed by the government with regard to activity regulated by the FDA. They would also like the names and judicial district of all lawsuits filed against the FDA and/or its officials in connection with FDA regulatory or enforcement activities, as well as all briefs and other pleadings publicly filed in such cases.

FDA's Tyler has received the letter and his office is in the process of compiling a formal response, spokeswoman Karen Mahoney told *DGR* March 14. — Virgil Dickson

APP Recalls Oncologic Irinotecan Over Fungal Contamination

APP Pharmaceuticals is recalling five lots of the oncologic irinotecan HCl injection after several reports of particulates found in vials.

The company says it received three customer complaints of foreign material from one lot, later identified as fungal microbial contaminant.

Although a preliminary investigation indicates the particulate was only found in the one lot, as a precautionary measure, APP is recalling lots produced before and after the affected lot.

The recall involves a total of 90,000 vials, Matthias Link, a spokesman for Fresenius Kabi, APP's parent company, told *DGR*.

The recalled lots involve 100 mg/5mL (20 mg/mL), 5 mL single-dose vials and 40 mg/2mL (20 mg/mL), 2 mL single-dose vials.

A chemotherapeutic agent given intravenously that is non-sterile has the potential to cause infections, which could be fatal if a patient is immunocompromised. However, the company says it is not aware of any adverse events.

An FDA MedWatch report issued March 28 recommended that healthcare providers and patients report any adverse events that may be related to the product.

Irinotecan is used for the treatment of metastatic colorectal cancer and is a generic version of Pfizer's Camptosar. — Jonathan Block

FDA May Send Warning Letters to Clients of Noncompliant Suppliers

ATHENS, Ga. — The FDA may begin issuing warning letters to drugmakers when their contracted suppliers fall out of agency compliance, signaling further agency efforts to strengthen the safety of pharmaceutical supply chains.

Too often, FDA inspections find drug companies aren't properly qualifying their suppliers, Steven Wolfgang, a consumer safety officer at CDER's Office of Compliance, said last month at the International Good Manufacturing Practices Conference. The fallout has resulted in patient harm, such as the deaths from the 2007 Chinese tainted heparin crisis.

The agency recently issued a warning letter to a contracted supplier and copied all the companies it had supplied products to. The outside companies were not listed on the warning letter, but were notified of the FDA's action against their supplier.

Wolfgang said the next logical step is to begin handing letters to all companies in the supply chain if the industry doesn't take more efforts to ensure the quality of products.

The materials in any given drug can change hands numerous times and can come from several countries, Wolfgang said. Drugmakers' names are on the labels of their finished products, so they must take more action in ensuring the quality of materials they receive and the manufacturing processes used to make those imported products.

Steven Niedelman, an industry consultant with law firm King & Spalding, told *DGR* that supplier quality issues are a top concern for many companies. "If this helps stem the tide of problems and gets the attention of industry, they will take a more proactive approach to assure the quality of their suppliers before they enter into long-term contracts."

The FDA has taken additional steps to focus attention on the issue as well. Late last year, a former FDA official said the agency is working on revising GMP regulations that would require companies to audit raw material suppliers (*DGR*, November 2010). — David Pittman

FDA Border Protection Plan to Cut Down on Counterfeit Drugs

The FDA will soon begin working more closely with other federal agencies — including Customs and Border Protection (CBP) — as it hopes to nab more counterfeit drugs entering the U.S. drug supply chain.

The two agencies will develop a plan to catch more illegal drugs at ports by the end of fiscal 2011.

"As part of this process, FDA and CBP will examine the flow of imported pharmaceutical products through different ports of entry, identify all available legal authorities and develop best practices to enhance collaborative enforcement efforts," states a 17-page report delivered to Congress and Vice President Joe Biden in March.

The recommendations came from the Counterfeit Pharmaceutical Inter-Agency Working Group, which was comprised of members of various federal agencies, including the departments of Justice, Commerce and Homeland Security.

The Justice Department and Homeland Security will also continue to work internationally to combat counterfeit pharmaceuticals. The agencies still intend to work with internet-hosting sites such as GoDaddy, Google and Microsoft, to crack down on illegal online pharmacies.

"PhRMA supports and commends the Administration for its commitment to protecting patient health and safety by safeguarding the closed U.S. drug supply system from the global counterfeit medicine epidemic," PhRMA President John Castellani said.

However, in a media conference call March 11, PhRMA Assistant General Counsel Kendra Martello stopped short of calling for increased fees to help FDA fund overseas inspections. A GAO report

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Pharma Manufacturing in Japan Largely Spared by Quake

As Japan continues to deal with the aftermath of a massive 9.0 earthquake and ensuing tsunami, it appears the country's pharmaceutical industry and U.S. companies with operations there have not suffered extensive damage.

Luckily, for most Japanese pharmas, the earthquake rocked the northeastern part of the country, 200 miles away from urban centers such as Tokyo, Osaka and Kobe, where many companies have offices or facilities.

A preliminary survey conducted by *DGR* of several U.S.-based pharmaceutical companies that have operations in Japan has found that at this stage, for the most part, no major damage has been reported.

Employees Safe

"We have received word that our colleagues at Eisai's headquarters office in Tokyo are safe," Eisai U.S. Senior Director for Corporate Communications Lynn Kenney told *DGR*, adding the company's facilities at the Tsukuba Research Laboratories and the Koishikawa Knowledge Center in Tokyo housing Eisai product creation systems headquarters have suffered damage, but all employees there are safe.

However, the company has a large employee base in Sendai, one of the areas hardest hit by the earthquake, "and we have not been able to reach all of our employees due to communications systems being down," she noted.

"Regarding our facilities, worldwide security and business continuity teams are working closely with local management to assess our facilities thoroughly for any damage," Johnson & Johnson spokeswoman Carol Goodrich told *DGR*. The company "is in communication with local relief agencies to determine local needs."

Covidien Vice President for Public Relations Bruce Farmer told *DGR* that all of its 1,500 employees in Japan have been accounted for and none of its facilities suffered major damage.

Although Bausch & Lomb does not conduct any manufacturing in the country, Mike McDougall, the company's vice president for corporate communications and public affairs said that its operations went back March 14.

Abbott has about 2,400 employees in Japan in offices in Tokyo, Chiba (near Tokyo) and Fukui.

Japan's pharmaceutical market is considered the second largest in the world, according to IMS Health, which projects it will reach $100 billion in sales this year. — Jonathan Block, Virgil Dickson

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last year found that agency inspection of foreign plants pales in comparison to domestic ones.

"We support increased appropriations to help FDA carry out its vital mission," she said. "We have not taken a position on that."

Martello also said PhRMA supports greater flexibility for the FDA in overseas inspections and stronger criminal penalties for counterfeiters.

"International harmonization will be an important issue for FDA to focus on as it moves forward," she said.

Following an infusion of counterfeit heparin and resulting patient deaths, the safety of the U.S. drug supply chain has garnered a great deal of attention recently.

A group of Republican lawmakers recently opened a Congressional investigation into the FDA's handling of the 2007 tainted heparin crisis (*DGR*, March).

In February, approaches to a track and trace system for prescription drugs that would make it easier to root out counterfeits were discussed at an agency-industry workshop (*DGR*, March).

The interagency report is available at www.whitehouse.gov/sites/default/files/omb/IPEC/Pharma_Report_Final.pdf. — David Pittman

Former KV CEO Gets Hefty Fine, Jail Time for FDCA Violations

Former KV Pharmaceutical CEO Marc Hermelin has been fined and will do jail time for the distribution of misbranded products, including oversized morphine tablets.

Hermelin, who also served as the chairman of the company's board, pleaded guilty March 10 to two misdemeanor violations of the Food, Drug, and Cosmetic Act (FDCA), and admitted KV distributed misbranded morphine sulfate tablets in 2007 and 2008. As part of his sentence, Hermelin was ordered to pay a $1-million fine, forfeit $900,000 and serve a sentence of 30 days in jail.

The government charged that Hermelin, as the responsible corporate officer for KV and its subsidiary Ethex, had the authority and responsibility to prevent and correct FDCA violations at both companies.

Therefore, Hermelin was ordered excluded from participation in federal healthcare programs under guidance from the HHS Office of Inspector General (OIG) and Ethex was dissolved.

Misbranded Tablets

The oversized morphine tablets contained more morphine than was specified in its label, deeming it "misbranded" under federal law. In June 2008, KV discovered the oversized tablets and reported them to the FDA in addition to publicly recalling several lots (*DGR*, December 2008).

The government alleged although KV knew of other oversized tablets and that one of its machines could randomly produce them, the company did not inform the FDA of this.

In May 2010, Ethex pleaded guilty to two felony offenses as a result of its failure to file required reports with the FDA concerning the oversized tablets. Ethex was then ordered to pay $28.1 million in fines and was placed on probation for five years.

In a related federal case in St. Louis, after the oversized drugs were acknowledged, the FDA conducted an inspection of KV's facilities and found numerous drug-production problems and other potential violations. The Justice Department then filed a civil suit against KV and Ethex, asking the court to have the companies and the executive officers take immediate action to remedy the problems. A federal court issued an order requesting that the executive officers fix the production problems. — Molly Cohen

FDA Warns Drugmakers About Fragment Formation in Vials

In response to several recalls, the FDA is warning drug manufacturers of the potential formation of glass fragments in injectable drugs filled in small-volume glass vials.

The agency says glass has advantages over other packaging materials. However, there is still the potential for glass, under certain conditions, to shed thin, flexible fragments called glass lamellae from the interior surface of the container directly into the drug.

The agency says the lamellae are difficult to detect by visual inspection.

Last September, Amgen recalled lots of its anemia drug Epogen (epoetin alfa) and Centocor Ortho Biotech's Procrit (epoetin alfa) due to glass lamellae (*DGR*, October 2010).

The same problem affected Sandoz a month later, forcing the company to voluntarily recall lots of its methotrexate injections (*DGR*, December 2010).

Earlier this year, Cumberland Pharmaceuticals recalled six lots of overdose drug Acetadote (acetylcysteine) because of glass particles (*DGR*, February).

Most recently, American Regent voluntarily recalled potassium phosphate and sodium thiosulfate injections because of glass lamellae formulation (*DGR*, February).

While no adverse events have been reported from glass lamellae, they could cause embolic,

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Bill Would Increase Penalties For Prescription Drug Thefts

Citing a dramatic spike in thefts of prescription drugs and medical devices, a group of democratic senators March 8 introduced legislation to crack down on medical product heists at every point in the supply chain.

Among other things, the SAFE Doses Act (Strengthening and Focusing Enforcement to Deter Organized Stealing and Enhance Safety) would increase federal penalties for pharmacy theft and give authorities additional tools, including wiretaps, by bringing drug thefts under the Racketeer-Influenced and Corrupt Organizations (RICO) Act.

Sens. Amy Klobuchar (Minn.), Charles Schumer (NY), Jay Rockefeller (W.Va.), Sherrod Brown (Ohio), Bill Nelson (Fla.) and Bob Casey (Pa.) are co-sponsoring the bill.

The legislation would:

- Increase possible sentences for theft of controlled substances from pharmacies;
- Increase sentences for theft of medical products and subsequent transportation and storage;
- Strengthen penalties for stolen medical product "fences," including parties who knowingly obtain stolen products for resale;
- Enhance sentences when ingestion of a stolen substance results in death or when the defendant is a participant in the supply chain;
- Make medical product theft subject to the RICO Act; and
- Provide for civil penalties and the forfeiture of monetary gains from stolen goods.

The FDA issued alerts twice last year about the potential dangers to patients from stolen drugs. In April 2010, the agency warned of several cases involving adverse reactions in patients who had taken stolen drugs and sent a letter to drugmakers urging them to develop contingencies to respond when thefts occur (*DGR*, May 2010). In August, the FDA issued a release after a number of patients suffered ill effects related to stolen insulin. — Meg Bryant

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thrombotic and other vascular events when administered intravenously, or when administered subcutaneously, could lead to the development of foreign body granuloma, local injection site reactions and increased immunogenicity, the FDA warns.

According to the FDA, several conditions may lead to a higher incidence of glass lamellae formulation:

- Vials manufactured by a tubing process are less resistant than molded glass vials and may shed more easily. However, the processing conditions can be designed to mitigate the potential for later delamination;
- Drug solutions formulated at high pH and with certain buffers like citrate and tartrate;
- Length of time the drug is exposed to the inner surface of the container;
- Room temperature storage requirements; and
- Terminal sterilization has a significant effect on glass stability.

The FDA recommends several actions to help prevent lamellae formulation. For "at-risk" products, vial surface alkalinity can be minimized through selection of highly resistant, non-alkaline earth borosilicate glass.

Appropriate selection of vendors is also important as well as proper quality control of incoming vials.

The agency also advises manufacturers to re-examine their supplier quality management program and reminds manufactures current good manufacturing regulations require drug containers not be reactive or additive so as to alter the safety or quality of the drug. — Molly Cohen

Fabrazyme, Thyrogen Supplies Run Into Manufacturing Snag

Supplies of Genzyme's Fabry disease drug Fabrazyme have hit another snag as the company announced further manufacturing problems for a drug already in short supply.

The company halted production of a lot of Fabrazyme (agalsidase beta) when the finished batch was rejected for not meeting release criteria, Genzyme announced March 23.

"Our current plans are to fill and finish all future lots of Fabrazyme at a contract manufacturing facility that is already handling a large portion of Fabrazyme fill/finish," Genzyme said.

The company previously moved the fill/finish activities to a contract manufacturer site in Ireland after a consent decree forced the closure of Genzyme's troubled Allston, Mass., plant (*DGR*, December 2010).

Genzyme said in January Fabrazyme supplies aren't likely to be on track until a new production facility in Framingham, Mass., comes online later this year (*DGR*, February).

Genzyme is also warning healthcare professionals that global supplies of Thyrogen will be limited through July, possibly causing temporary shortages in some countries.

Thyrogen Shortage

While Genzyme transferred fill/finish activities of some of its products to Hospira last year, the move led to a low inventory of Thyrogen (thyrotropin alfa for injection), spokeswoman Erin Emlock told *DGR*.

On top of that, "we had a batch recently that was supposed to go to Europe that was not released," Emlock added.

The European Medicines Agency said it was informed by the company that a manufacturing issue will result in a supply shortage and the company will meet about 45 percent of EU demand through July.

— David Pittman, Molly Cohen

Dakota Labs Gets Warning for GMP, Labeling Violations

Dakota Laboratories has received a warning letter for significant violations of cGMP regulations and for mislabeling two drugs.

The FDA's Minneapolis District Office discovered a number of cGMP and product sterility issues during a June 22 to 23, 2010, inspection of Dakota's Mitchell, S.D., facility.

Dakota failed to establish written procedures "to prevent microbiological contamination of drug products purporting to be sterile," the FDA says. Dakota released several batches of eye drops without validating their sterility, and did not assure that filters were adequately suitable.

Dakota also did not investigate environmental data that failed to meet company limits, neglecting to test water used in the production of its Ortho-K Eye Drops and its Women's Eye Drops. Moreover, the company "does not have an adequate system for monitoring environmental conditions," the letter states.

Because of the severity of Dakota's cGMP violations, the FDA suggests Dakota, "engage a third party consultant having the appropriate cGMP expertise," to assist the company in assessing its practices.

The FDA also takes issue with the labeling of two of Dakota's products, Ring Relief ear drops and Iwise pink eye drops. Both products are labeled homeopathic, but "these products are prescription drugs … because they are intended to treat diseases that require diagnosis and treatment by a physician," according to the letter.

Dakota has been working with a number of cGMP consultants to address the violations noted in the warning letter, company President Charles Voellinger told *DGR*.

The Dakota warning letter can be found at www.fdanews.com/ext/files/11.pdf.

— Kevin O'Rourke

GAO Says FDA Oversight Is at 'High-Risk' for Mismanagement

The FDA's oversight of medical products remains a "high-risk" area for mismanagement, according to a recent update to the GAO's High-Risk Series, which points to ongoing issues with the agency's inspection of overseas facilities and postmarket safety monitoring.

The series highlights federal government operations GAO determines to be at risk for "fraud, waste, abuse, and mismanagement" or that require "transformation to address economy, efficiency, or effectiveness challenges."

The FDA was first added to GAO's High-Risk List in 2009, after the office determined the agency "needs to enhance its oversight of medical products to better protect public health." That update criticized the FDA's inspections of foreign facilities as well as the agency's monitoring of clinical trials and review of promotional materials.

Since then, the FDA has continued to struggle with foreign inspections (*DGR*, November 2010). While the agency has opened new offices overseas, it still lacks performance goals and a plan to address potential staffing challenges.

The FDA's approach to choosing facilities for inspection is also inconsistent with the GAO's recommendation that the agency inspect facilities with the highest public health risk potential at a comparable rate, regardless of whether they are in the U.S. or overseas.

In addition, the agency continues to struggle with postmarket safety monitoring, another weakness noted in the 2009 report. The 2011 update expresses concern that some FDA staffers consider premarket responsibilities a higher priority, and that staffing and technological issues limit the agency's capacity to conduct safety studies.

GAO is also concerned that the FDA is not routinely monitoring postmarket studies for drugs expedited under the accelerated approval program, and notes the agency has not developed criteria for withdrawing drugs that fail to confirm clinical benefit under the program.

The report acknowledges some progress in this area though, pointing to FDA initiatives to improve reporting of adverse events and make tracking more efficient.

Despite these improvements, the FDA has a long way to go, GAO says. Before the high-risk designation can be removed, the agency must:

- Strengthen its resource management and strategic planning;
- Develop results-oriented performance measures;
- Create a workforce plan for new overseas offices; and
- Implement a rigorous postmarket safety program. — Wilson Peden

FDA Cross-Contamination Guidance Addresses Beta-Lactam Antibiotics

The FDA has issued new guidance to help manufacturers decide when separate buildings are necessary to prevent non-penicillin beta-lactam antibiotics from cross-contaminating other pharmaceuticals.

If the products are made in the same facility, the area dedicated to manufacturing a non-penicillin beta-lactam must be structurally isolated from areas where other products are manufactured, the March draft guidance states.

Beta-Lactam compounds' chemical structure is believed to initiate allergic reactions in some patients.

Beta-lactam antibiotic manufacturers should also establish stringent controls to prevent cross contamination, the guidance says. For example, manufacturers must use separate air-handling systems for sensitizing non-penicillin beta-lactams and other products.

The FDA has handed out warning letters for cross-contamination risks, including one to Venezuelan-based Laboratories L.O. Oftalmi last May related to beta-lactam antibiotics (*DGR*, October 2010).

The new draft guidance is available at www.fdanews.com/ext/files/UCM246958.pdf.
— David Pittman

Guidance: Manufacturers Need Contingency Plans at Plants

In the wake of a devastating earthquake in Japan, the FDA is urging drugmakers to develop contingency plans to use during emergencies that result in many workers absent from manufacturing plants.

The agency's guidance, finalized last month, provides suggestions for the development and implementation of a plan to continue producing medically necessary drug products (MNPs) during a crisis to avoid shortages that could impact public health.

As part of the guidance, the FDA recommends manufacturers discuss with suppliers actions to avoid or mitigate disruptions in the supply chain.

The agency suggests a plan should address each location's specifications as part of a broader plan to address multiple sites within a company.

MNP Priorities

The FDA recommends companies identify the percentage of resources routinely dedicated to the manufacture of MNPs and conduct quality risk assessments to help identify activities that can be reduced, delayed or substituted.

People or positions within the company should be identified who have the authority to activate or deactivate the plan and any other necessary decisions.

Companies should also prioritize their MNPs, with special attention given to products for which the company is the sole provider or supplies a significant share of the U.S. market, and products vulnerable to shortage.

The agency points out MNPs may include products for maintenance of dependent populations, as well as products related to the particular emergency.

The FDA acknowledges that during an emergency, CDER is prepared to exercise enforcement discretion on statutory and regulatory requirements, provided the product remains safe and effective and has adequate identity, strength, quality and purity.

The FDA also encourages manufacturers to notify CDER when an emergency plan is activated and deactivated.

Lastly, the FDA recommends companies maintain records that support decisions to changes approved during the plan for manufacturing and release of MNPs.

The guidance, planning for the Effects of High Absenteeism to Ensure Availability of Medically Necessary Drug Products, is available at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM196497.pdf. — Molly Cohen

FDA, USP and Industry Working to Improve Drug Quality Standards

In an effort to bolster the safety and reliability of widely used drugs, the U.S. Pharmacopeia (USP) is partnering with FDA and the Consumer Healthcare Products Association (CHPA) to update quality standards for more than three dozen products.

The initial effort is focused on a priority list of drugs and ingredients identified by the FDA as being susceptible to counterfeiting or raising other concerns.

The list — which includes 30 acetaminophen monographs, seven diphenhydramine monographs and monographs for inactive ingredients copovidone, crospovidone, povidone and talc — is part of a larger USP standards modernization initiative targeting about 700 small molecule and 96 excipient monographs.

In addition to the initial list, the FDA will recommend other drug and ingredient standards for updating as it sees fit.

FDA Commissioner Margaret Hamburg has endorsed the USP project. But the CHPA has expressed concern that not enough attention has been given to product degradants.

The CHPA proposed working with the USP and FDA to ensure industry input in the process and has established working groups to study and propose degradant standards for acetaminophen and diphenhydramine.

USP CEO Roger Williams said he welcomes CHPA's involvement. — Meg Bryant

Pfizer Recalls Pain Drug Embeda, Prostate Drug, Antidepressant

Pfizer has recalled all lots of its chronic pain medication Embeda due to a defect found during testing, a move that could keep the drug out of pharmacies for months.

Roughly 100,000 bottles of Embeda (morphine sulfate/naltrexone HCl) extended release capsules are being pulled from the market because of stability issues, Pfizer said March 16.

"We are investigating the cause and will make every effort to return the product to patients as soon as possible," company spokesman Rick Chambers told *DGR*. "We do expect Embeda will be off the market for many months."

Pfizer said it hasn't received any adverse event reports, and the issue is unlikely to cause them.

"During routine stability testing of representative samples, elevated levels of sequestered naltrexone degradants were found," Chambers said. "Naltrexone HCl is contained in the core of Embeda and is sequestered when the medicine is used as prescribed."

Pfizer acquired Embeda as part of its $3.3 billion purchase of King Pharmaceuticals in October. The FDA approved Embeda in August 2009 as the first abuse-resistant prescription opioid. The naltrexone blocks the morphine's euphoric effects.

Recalls in March and April last year caused Embeda's sales to drop an estimated $2.9 million, according to SEC filings. King also voluntarily recalled two lots of the drug in late 2010 because of post-manufacturing testing unrelated to product safety.

Sales of Embeda nearly reached $34 million for the first nine months of 2010, according to SEC filings from King.

Other Recalls

Pfizer subsidiary Greenstone is also recalling two generic drugs — one used to treat depression, the other used by men with enlarged prostate — due to a labeling snafu.

The Peapack, N.J.-based generic-drug maker said March 26 it was recalling the antidepressant citalopram as well as finasteride, which is indicated for benign prostatic hyperplasia.

Bottles labeled citalopram may in fact contain finasteride and vice versa, the company says. The possible labeling mishap was caused by Indian third-party manufacturer Aurobindo, Pfizer spokesman Rick Chambers told *DGR*.

Citalopram 10-mg tablets (100-count bottle) and Finasteride 5-mg tablets (90-count bottle) with lot number FI0510058-A on the label should be returned, Greenstone says. Citalopram is the generic equivalent of Forest's Celexa and finasteride is equivalent to Merck's Proscar.

Health Warnings

Greenstone warned of possible ramifications for cessation of treatment. In particular, patients who discontinue use of citalopram abruptly may experience a worsening of depression or other discontinuation symptoms. Finasteride should not be used or handled by pregnant women, as it can cause birth defects.

Approximately 2,600 bottles of both drugs were affected, of which 700 were on market, according to Chambers. Pfizer is conducting an investigation into the cause of the mix-up and does not expect a shortage of either drug, Chambers added. No adverse events have been reported.

The FDA in February issued an import alert banning importation of antibiotics made at one of Aurobindo's plants. The company supplies a number of injectable and solid oral-dose products to Greenstone.

Earlier this month, the two companies signed a licensing agreement that will have Aurobindo expanding the number of generic products it manufactures for Greenstone.

According to reports, Pfizer has recently been considering selling its Greenstone unit, as part of a possible strategic shift to a smaller, pharma-only company. — David Pittman, Kevin O'Rourke

Excipients Also Used as Actives May Cause Issues for Industry

As the FDA continues to clamp down on drug supply chains, some companies are concerned that an ill-defined sliver of drug ingredients will drive suppliers to increase costs or reduce supply.

Atypical actives are chemicals listed as active pharmaceutical ingredients (APIs) but used commercially as excipients or for other uses. Although the FDA doesn't keep count of how many such chemicals exists, Europe lists more than 100.

The atypical actives' dual use has caused headaches for industry because if a drug or dietary supplement maker lists a product as an API, that maker's supplier and its plants would be subject to a more stringent set of FDA standards.

Supplier Surprise

In some cases, suppliers have been surprised when FDA inspectors arrived because they didn't know their clients used what they believed was an excipient as an API, according to attendees at a Parenteral Drug Association workshop March 9 and 10 in Bethesda, Md.

"We were all in shock how often this was happening," David Schoneker, global regulatory affairs director for Colorcon, an excipient maker in Harleysville, Pa., said.

Colorcon, for example, stopped producing a product called Cal-Carb, a calcium carbonate-based excipient used primarily as filler in pills. Some drugmakers used Cal-Carb as an API, which led the FDA to show up at Colorcon's plants for inspections and issue a multi-item Form 483.

"We were trying to make clear that this was an excipient and that it was not suitable as an API," Alexa Smith, global regulatory services manager for Colorcon, said.

But that didn't seem to matter to some of the company's clients. Colorcon concluded there were too many problems with producing the product as an API rather than solely as an excipient.

These expectations for excipient suppliers may increase costs or reduce supply, if excipient makers submit to inspections or cease production of the atypical active. Either option means more hurdles for drugmakers.

What Can Be Done?

CDER Consumer Safety Officer Steven Wolfgang recommended drug companies audit their materials' supply chain and ensure the quality and integrity of the ingredients they use. But some drugmakers have found excipient and raw material suppliers unwilling to divulge information or yield to FDA inspections.

Schoneker suggested creating a new set of standards for atypical actives to complement those for excipients and APIs, noting the industry needs better quality standards for suppliers.

However, Pfizer's Director of Quality and Regulatory Policy Janeen Skutnik-Wilkinson pointed out that suppliers have no obligation to sell to pharmaceutical companies and quality standards could limit products. "We have to work with them to fit their systems rather than ask them to fit our models," Skutnik-Wilkinson said.

Further regulation of excipient makers could cause some suppliers, such as Colorcon, to stop production altogether.

Representatives from the FDA and the European Medicines Agency spoke with less urgency on the topic than industry attendees. While the FDA has done little to address the issues around atypical actives, Wolfgang encouraged drug companies to take a proactive stance on the issue.

"You're seeing a movement towards developing standards," Wolfgang said. "Now is the time to start thinking about those standards."

Wolfgang told *DGR* afterward that the FDA isn't working toward new atypical active standards and, that if new standards were to come, they likely would be developed within industry and not the FDA. — David Pittman

FDA, EMA to Do Parallel Reviews For QbD Application Components

Under a new pilot program, NDAs submitted to the FDA and European Medicines Agency (EMA) with quality by design (QbD) components will undergo parallel review from both regulatory agencies.

The pilot, which will run from April 1 until March 31, 2014, at which time the agencies will assess and issue a joint outcome of the program, the EMA says.

The dual review will neither expedite nor lengthen the approval process, FDA spokeswoman Morgan Liscinsky told *DGR*.

Reviewers from both agencies will assess, separately, the quality/chemistry, manufacturing and control section of submissions.

In Europe, the pilot will apply to new MAAs and quality-related scientific advice requests.

Meanwhile, in the U.S., the program will cover NDAs, sNDAs and chemistry manufacturing control meeting requests.

One goal of the pilot program is to ensure International Conference on Harmonisation guidelines are implemented consistently in both regions.

The agencies request interested applicants notify both agencies three months in advance of submission. — Molly Cohen

EMA Signs Agreement With International Regulatory Body

The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (known jointly as PIC/S) signed a new cooperation agreement with the European Medicines Agency (EMA) to strengthen their cooperation in areas of common interest related to good manufacturing and distribution practice (GMDP).

The agreement, signed Dec. 28 and released Feb. 18, will focus on sharing resources and avoiding duplicative activities.

PIC/S will work mostly with the EMA's Compliance and Inspection Sector, and the arrangement runs for two years.

The exchange of information between the two organizations may include legislation and guidances prepared by both entities, timings of public consultation and publication of documents, confidential or restricted information exempt from public disclosure and confidential information shared during official meetings.

Both organizations will exchange information in regards to auditing schedules to avoid duplication.

The cooperation agreement is available at www.ema.europa.eu/docs/en_GB/document_library/Other/2011/02/WC500102054.pdf. — Molly Cohen

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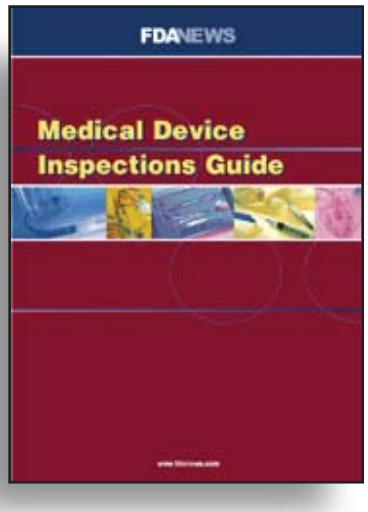

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