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INSIDE THIS ISSUE

Genzyme's Fabrazyme, Cerezyme shortage continues, hits salesPage 3

McNeil Fort Washington inspection finds QA responsibility issues.....Page 5

Rust, debris in hoses lead to warning for Italian drug-maker RibbonPage 6

FDA draft guidance harmonizes regional powder density texts.....Page 6

483 InsiderPage 7

Draft guidance harmonizes texts on bacterial endotoxin testsPage 8

AMPAC warned for conditions at API manufacturing site.....Page 9

Sanofi Egyptian anti-counterfeiting initiative focused on training.....Page 9

Keystone products seized after contractor's GMP violations.....Page 10

FDA to start Part 11 inspections after seeing compliance issuesPage 11

FDA Considers Reinstating Warning Oversight to Boost Quality

Since FDA Commissioner Margaret Hamburg ended prior legal review of warning letters last summer, their quality has declined, drugmakers say, prompting the agency to evaluate the policy change.

“I have noticed what appears to be a diminution in the quality of warning letters — issues ranging from typographical errors to lack of legal support for assertions,” Jennifer Bragg, partner at Skadden, Arps, Slate, Meagher & Flom, told *DGR*.

In line with Hamburg's commitment to ensure that the FDA's work is factually and legally correct, the agency is evaluating the impact of the change, spokeswoman Karen Mahoney told *DGR*. That evaluation should be completed by the end of September.

Last summer, Hamburg ended an agency policy requiring prior legal review of all untitled and warning letters (*DGR*, September 2009).

(See **Warnings**, Page 12)

FDA Reviewing McNeil Remediation Plan as Recalls Take Toll on J&J

The FDA is reviewing Johnson & Johnson (J&J) subsidiary McNeil Consumer Healthcare's plan to fix manufacturing quality issues as the company has suspended operations at its Fort Washington, Pa., facility.

McNeil will make a significant investment in manufacturing facilities and laboratories, including installation of new equipment, the company announced last month. It also will reorganize operations, cutting about 300 positions at the troubled plant.

McNeil plans to hire outside experts to provide additional product quality assurance. In addition, the company will develop a comprehensive program to ensure sustainable compliance with regulatory and its own quality requirements.

(See **J&J**, Page 2)

J&J, from Page 1

The plant will be out of service while the changes are made, and McNeil expects most products manufactured there will not be available before the end of the year. Other J&J plants will manufacture many of the products previously produced at Fort Washington.

The company had already halted manufacturing at that plant and has been under investigation by a House committee as a result of several recalls of OTC medicines, including a so-called “phantom recall” of defective Motrin (*DGR, July*).

Other products affected by the recalls include liquid infants’ and children’s Tylenol, Zyrtec and Benadryl.

When the Fort Washington plant reopens, McNeil expects staffing to be substantially lower, the company said.

Lawsuits

In the meantime, J&J has been hit with five lawsuits seeking class-action designation in the wake of the recalls of OTC children’s medications.

The lawsuits, filed last month in the U.S. District Court for the Northern District of Illinois, accuse McNeil of suppressing information about the safety of its products, including their potential harmful effects on children.

The company’s three major recalls in an eight-month period due to quality problems prompted the FDA to look into hundreds of adverse events, including 37 deaths, linked to the recalled products (*DGR, June*).

The company’s action “clearly shows not only an utter disregard for the safety and welfare of the children who use their products, but also a definite pattern of defrauding its consumers by actively misrepresenting through various advertisements that their products were safe, effective and better than other brands or generic products

when in reality, their products were unsafe and may even be dangerous to the children who use them,” according to one of the complaints.

The plaintiffs in the cases are seeking unspecified compensatory, treble and punitive damages.

The FDA is considering criminal penalties against McNeil, CDER Office of Compliance Director Deborah Autor said at a congressional hearing in May.

The House Committee on Oversight and Government Reform also is investigating the matter.

Earnings Hurt

The recalls have also affected earnings and are expected to cost J&J \$600 million in annual lost product sales.

In the second quarter alone, the shutdown of the Fort Washington plant and related recalls cost J&J \$200 million, Chief Financial Officer Dominic Caruso said last month during the company’s second-quarter earnings call.

The quarter’s sales also were also hurt by U.S. healthcare reform legislation — to the tune of about \$90 million, he added.

The company disclosed during the call that it recently received a grand jury subpoena from the U.S. Attorney’s Office for the Eastern District of Pennsylvania regarding the recalls.

Both the U.S. attorney’s office and the company declined to provide *DGR* with additional details.

For the quarter, worldwide sales of consumer products fell 5.4 percent to \$3.6 billion, J&J said.

As a result of the plant shutdown, recalls and pricing pressures in Europe, the company also downgraded its full-year profit outlook. — April Hollis, David Belian and Jonathan Block

Genzyme's Fabrazyme, Cerezyme Shortage Continues, Hits Sales

Supplies of two of Genzyme's drugs, Fabrazyme and Cerezyme, will continue to be limited over the next month as the company deals with disruptions in production and an FDA consent decree for manufacturing violations.

Lots of Fabrazyme (agalsidase beta) are expected to be tight in August, with some regions having no supply through September, the company said in an update last month. Short-term shipping delays of Cerezyme (imiglucerase for injection) in some regions may cause a shift in patients' infusion schedules.

Fabrazyme and Cerezyme, used to treat Fabry and Gaucher's diseases, respectively, have been in short supply as a result of contamination at the company's Allston, Mass., plant last year. Genzyme agreed to a consent decree with the FDA to resolve several GMP violations in the past year (*DGR, June*).

Shire Benefits

The shortage has led the Committee for Medicinal Products for Human Use (CHMP) to recommend European physicians who prescribe Fabrazyme consider switching patients to Shire's Replagal (agalsidase alfa).

The European Medicines Agency committee made the recommendation last month after Genzyme said it would not be able to produce enough Fabrazyme for the 600 patients on the drug in Europe.

New Fabry patients should be prescribed an alternate treatment, such as Replagal, the CHMP said. Fabrazyme patients treated at lower than 1 mg/kg a week should consider switching to Replagal, while those at the 1 mg/kg dose should continue with Fabrazyme.

The CHMP has also recommended approval of Shire's Vpriv (velaglucerase alfa) for Gaucher's disease, which would compete with Cerezyme.

Genzyme's manufacturing issues also weighed heavily on second-quarter results, but the company said it has made significant progress in resolving the situation that has limited the supply of Cerezyme and Fabrazyme.

Genzyme reported last month that Cerezyme revenues dropped to \$138.7 million in the quarter, while Fabrazyme revenues fell to \$39.5 million. By comparison, the figures for the second quarter of 2009 were, respectively, \$298.1 million and \$134.3 million. During the quarter, Cerezyme shipped at 50 percent of demand while Fabrazyme shipped at 30 percent.

Revenue Down

Overall, revenue in the quarter fell 12 percent compared to the same period last year.

Despite the revenue slide, "when you take Fabrazyme and Cerezyme out of the equation, the rest of the business grew 13 percent," CEO Henri Termeer noted during Genzyme's second-quarter earnings call.

Genzyme expects to ramp up shipments of Cerezyme in August and Fabrazyme in the fourth quarter. In addition, the company also expects a 30 percent improvement in Fabrazyme productivity thanks to FDA approval of a new working cell bank used in its manufacture, Scott Canute, president of Genzyme's global manufacturing and corporate operations, said.

Supplies will be further improved when the agency approves a new manufacturing facility in Framingham, Mass., which the company expects at the end of 2011, Canute added.

Although some patients have switched to Shire's treatments, most patients have remained loyal to Genzyme's products, Senior Vice President John Butler noted.

Progress on the drug supplies can be obtained at supplyupdate.genzyme.com. — Jonathan Block, LaCrisa Butler

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McNeil Fort Washington Inspection Finds QA Responsibility Issues

McNeil Consumer Healthcare's quality control unit failed to fully follow responsibilities and procedures at the company's Fort Washington, Pa., facility, such as for rejecting contaminated materials, an FDA inspection report says.

Some lots of a raw material that had known contamination with gram-negative organisms were approved for use in manufacturing several finished lots of children's and infants' Tylenol drug products, according to the April 30 Form 483, posted online last month.

"Responsible firm officials did not adhere to GMP regulations," the form adds, and employees are not given training in cGMPs and written procedures required by GMP regulations.

CAPA Failure

McNeil also failed to follow its procedures requiring that a corrective and preventive action (CAPA) be initiated when systemic GMP issues or significant trends are identified and associated with nonconformance events, consumer complaints, manufacturing events and significant trends.

For example, no CAPA was initiated for several batches from May 2009 to April 2010 where foreign material, particulate matter or contamination were observed, the form says. No CAPAs were initiated for 46 consumer complaints regarding foreign materials, black or dark specks during the same period.

McNeil's control procedures failed to validate the manufacturing processes that caused variability in the characteristics of the drug product, another citation says.

The company also did not conduct a thorough investigation or any additional analytical testing for certain lots of Infants' Dye-Free Tylenol Suspension Drops cherry 80 mg/0.8 mL

that were super potent and failed a release specification for an acetaminophen assay.

No review of the batch production and packaging records was conducted for lack of effect regarding the drops, as the quality department's evaluation of complaints determined that no quality issues were warranted, the letter says.

Agency inspectors also found a lack of adequate lab facilities for testing and approval or rejection of components and drug products.

During an April 19 walk-through of the microbiological laboratory, inspectors found several deviations, including a large exposed gap in the ceiling above an incubator. Additionally, an incubator had a large amount of visible gray and brown dust/debris on the bottom of the chamber under the shelves where media-filled containers and media hold-time studies were located.

The following day, inspectors observed that labeling was stored throughout the warehouse, accessible to personnel with access to the raw material/component storage areas, instead of being stored in a locked cage with limited access.

Storage Issues

Drug components and labeling in unrestricted status were stored in the open incoming inspection area in the warehouse, along with materials in quarantined and blocked status, the form says.

The quality issues, many of which McNeil identified in its own quality reviews and communicated to the FDA, are unacceptable and not indicative of how the company intends to operate, J&J said at the time. The Form 483 is available at www.fdanews.com/ext/files/McNeilConsumerHealthcare.pdf.

In related news, the company said last month that a J&J/Merck manufacturing facility that makes OTC products received an FDA Form 483 after a recent inspection.

(See [Inspection](#), Page 8)

Rust, Debris in Hoses Lead to Warning for Italian Company

Ribbon SRL, an Italian antibiotics maker, has received an FDA warning letter for GMP deviations related to equipment cleaning and process simulations.

FDA inspectors observed that cleaned multi-use hoses, used in the production of cephalosporin intermediates, had white residue or brown rust-like residue on the connection surface and the interior of the transfer hose. The presence of rust, deterioration and debris in product contact equipment used to manufacture sterile drug products is unacceptable, according to the May 27 letter recently posted online.

The FDA acknowledges details Ribbon provided on its general cleaning rules, but the company did not provide adequate information on its controls to ensure contaminated hoses are not used in manufacturing. Ribbon also did not include evidence of corrective actions to remove the rust, deterioration and debris, the letter adds.

The company's response should include the steps in the production process in which the hoses are used, as well as documentation that cleaning procedures are adequate to prevent product contamination. Ribbon also should provide the investigation report with its findings, including the cleaning methods performed, as well as the corrective and preventive actions.

Other citations in the letter said process simulations did not represent actual production operations for the company's sterile active pharmaceutical ingredient.

In addition, the company's test material and validation procedures compromise the recovery of microbial contaminants. The company's response to a post-inspection Form 483 does not provide scientific evidence and documentation that the placebo medium used during process simulation adequately supports growth promotion of viable organisms. The FDA requests Ribbon's

rationale and supporting study summary report for using each of the placebo growth media in its process simulations.

The company did not provide a comment by press time. The warning letter is available at www.fdanews.com/ext/files/RibbonSRL.pdf.
— April Hollis

FDA Draft Guidance Harmonizes Regional Powder Density Texts

The FDA plans to accept International Conference on Harmonisation (ICH) standards for bulk density and tapped density of powders as part of an ongoing harmonization project intended to reduce paperwork for drugmakers.

The FDA will publish an annex to the ICH Q4B chapter on evaluation and recommendation of pharmacopoeial texts in a draft agency guidance, according to a notice in the July 14 *Federal Register*. Comments are due Sept. 12.

Acceptance of the standards would allow drugmakers submitting dossiers in ICH regions to use the U.S., European and Japanese pharmacopoeial texts interchangeably with the following conditions:

- For bulk density method 2, the tolerance of the cup volume should be 16.39 ± 0.20 mL;
- For tapped density method 3, the test conditions, including tapping height, should be specified in the results; and
- For measures of powder compressibility, if V10 is used, it should be clearly stated in the results.

Even if the texts are interchangeable, the guidance notes that when sponsors or manufacturers change their existing methods to the Q4B-evaluated pharmacopoeial texts, any change notification, variation or prior approval procedures should be handled according to regional regulatory mechanisms for compendia changes.

The draft guidance is available at www.fdanews.com/ext/files/UCM218825.pdf.
— April Hollis

FORM 483 INSIDER

Impax Inspection Finds Cleaning, Investigation Issues

Impax Laboratories has received a Form 483 with observations related to cleaning procedures and environmental and personnel controls for preventing microbiological contamination of drug product.

For example, the Hayward, Calif.-based company used nonlint-free wipes in all major equipment for minor and major cleaning for all commercial products, according to the April 22 form.

Household, unqualified, nonlint-free, multi-use cloth rag mops were also seen in use with germicide solution in buckets directly outside a room where a lot of tamsulosin 0.4 mg had been manufactured, and the room was undergoing minor cleaning in between lots for further tamsulosin manufacturing, the form adds.

The form also notes the corrective action for an increased trend in metal contamination does not address the root cause of equipment wear.

Impax did not respond to a request for comment by press time. The Form 483 is available at www.fdanews.com/ext/files/Impax.pdf.

FDA 483 to Ruger Chemical Finds Deficient Quality Management

Ruger Chemical's quality management system is deficient, does not require the active participation of management and does not include all available resources, according to a Form 483.

Additionally, the company's quality-related activities are not fully defined and documented, the April 8 form says.

For Rugersone AD-20, an active pharmaceutical ingredient, the laboratory performs only three out of nine tests recorded on the certificate of analysis. The values for other properties, such as organic volatile impurities, residue on ignition

and heavy metals are taken from the raw material's certificate of analysis.

Further, Ruger does not verify analytical results found on certificates of analysis for materials that will be repackaged or further processed.

Ruger did not respond to a request for comment by press time. The Form 483 is available at www.fdanews.com/ext/files/Ruger.pdf.

Sun Gets Form 483 for Lack of Process Validation Assurance

Sun Pharmaceutical Industries has received a Form 483 for lack of assurance that the manufacturing process for its gemfibrozil 600-mg tablets is fully validated and will produce batches of consistent quality.

For example, three validation batches exhibited failures for individual unknown impurities at the six-month and nine-month room temperature stability time points. The six-month results were invalidated after a new column produced passing results, and the nine-month results were attributed to co-eluting peaks during testing.

Although the quality unit reviewed stability data prior to inclusion in annual reports, numerous ANDA reports contained inaccurate data and Sun remained unaware of the errors until the inspection.

The FDA also found inspection of packaging facilities immediately after use is not done to assure that all drug products have been removed from previous operations. An investigation was initiated after broken tablets were found during packaging of oxycodone 15 mg tablets. During the investigation, oxycodone 5 mg tablets were found in the brushes of a packaging line. Those tablets were packaged six days earlier, and the packaging line cleaning was reviewed and approved after packaging of that lot.

Sun did not respond to a request for comment by press time. The Form 483 is available at www.fdanews.com/ext/files/Sun.pdf.

Inspection, from Page 5

The observations at the Lancaster, Pa., plant come as the FDA is reviewing McNeil's plan to fix manufacturing quality issues at the company's Fort Washington, Pa., facility (*see story, page 1*).

J&J and Merck will provide a detailed response to the FDA and work diligently to address all observations, J&J spokeswoman Bonnie Jacobs told *DGR*, though she would not provide any further details about the observations.

"It's probably not an accident" that the agency is examining other J&J sites, Fred Branding, an attorney with Reed Smith, told *DGR*. "It could be that FDA is looking at the manufacturing activities at more than one site to see if there's a pattern in practice."

Jacobs declined to specify the names of products produced at the Lancaster site. However, the J&J/Merck Consumer Products joint venture makes heartburn products including Pepcid and Mylanta, and Mylicon, anti-gas drops for infants.

In November 2008, about 12,000 bottles of Mylicon were recalled because the bottles may have contained metal fragments. — April Hollis

Draft Guidance Harmonizes Texts On Bacterial Endotoxin Tests

The FDA is moving to accept International Conference on Harmonisation (ICH) standards for bacterial endotoxin testing as part of an ongoing harmonization initiative to reduce paperwork for industry.

The FDA published an annex to the ICH Q4B chapter on bacterial endotoxins test in a draft agency guidance, according to a notice in the July 19 *Federal Register*. Comments are due Sept. 14.

Acceptance of the standards allows drug-makers submitting dossiers in ICH regions to use the U.S., European and Japanese pharmacopoeial

texts interchangeably. Health Canada will also accept the texts as interchangeable, the draft says.

The texts did not contain acceptance criteria, according to the draft, which advises specifying endotoxin limits in the application dossier unless otherwise specified in an individual monograph.

Even if the texts are interchangeable, the guidance notes that when sponsors or manufacturers change their existing methods to the Q4B-evaluated pharmacopoeial texts, any change notification, variation or prior approval procedures should be handled according to regional regulatory mechanisms for compendia changes.

Regional pharmacopoeial texts for bacterial endotoxins test are USP <85> Bacterial Endotoxins Test, the section in Ph. Eur. 2.6.14. Bacterial Endotoxins and JP 4.01 Bacterial Endotoxins Test.

The draft guidance is available at www.fda.gov/oc/ohrt/ucm219167.pdf.

— April Hollis

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AMPAC Warned for Conditions At API Manufacturing Site

AMPAC Fine Chemicals has been handed an FDA warning letter for conditions at its active pharmaceutical ingredient (API) manufacturing facility.

A Feb. 9 to 19 inspection of the facility found dirt, blistering paint, rust and oil droplets near manufacturing equipment in several building locations, according to the June 25 letter recently posted online.

The company observed paint chips in material while manufacturing temozolomide, but its variance report did not provide enough detail on corrective actions taken after initial corrective actions failed.

AMPAC told the FDA its cleaning procedures would correct the conditions before initiating manufacturing operations. And the company said it has adequate controls and methods of detection to prevent contamination and inadvertent release of product containing foreign matter. However, it does not describe such controls and methods of detection, the letter says.

Another citation notes a processing room was used to manufacture chlorambucil from Jan. 4 to 18 and then released by the quality engineer and production manager Jan. 22 to manufacture another material without performing any cleaning.

AMPAC's 483 response states the occurrence was an "isolated incident" and not indicative of the effectiveness of the facility audit process. However, the company did not describe how it will ensure that cleaning was performed or will be performed before beginning manufacturing operations between different batches of APIs.

The FDA also notes AMPAC stored a drum of returned temozolomide API in a warehouse storage area with other drums of temozolomide API that were labeled as accepted and ready for release. The returned drum was not properly identified, according to the letter.

The company's 483 response states that it has developed new procedures regarding rejected batches, but it has not addressed how it will manage returned APIs, the letter says.

AMPAC did not respond to a request for comment by press time. The warning letter is available at www.fdanews.com/ext/files/AMPAC_Fine_Chemicals_WL.pdf. — April Hollis

Sanofi Egyptian Anti-Counterfeit Initiative Focused on Training

An anti-counterfeiting effort by Sanofi-Aventis' Egypt affiliate is focusing on training and consumer awareness to reduce supply chain breaches.

Part of the ongoing three-part initiative involves active participation during local training programs for the Egyptian Ministry of Health inspection department and other authorities, educating them on how to distinguish between original and counterfeit products, company spokesman Jack Cox told *DGR*.

"We are training customs, particularly in countries at risk," Cox said, adding the company exchanges information with local police and customs officials.

During the first phase of the effort, an Egyptian delegation, including officials from the Ministry of Health, the Customs Authority and the Ministry of Interior's anti-smuggling unit from the Ministry of France, visited the customs authority in Le Havre, France, to review anti-smuggling measures, Cox added.

The delegation also visited Sanofi's laboratories that detect counterfeit medicines to learn about the techniques used there, including packaging control and chemical analysis of suspected products.

Sanofi is also working to raise public awareness by communicating with public stakeholders and the media to increase regulations addressing counterfeit drugs, Cox said. — April Hollis

Keystone Products Seized After Contractor's GMP Violations

U.S. marshals have seized \$39,000 worth of Keystone Pharmaceuticals' cyanide antidote kits after finding repeated GMP violations at its contract manufacturer.

An FDA inspection last year of contract manufacturer PrimaPharm found continuing GMP violations that had been cited in a 2008 warning letter, the FDA said last month.

At that time, PrimaPharm said it would no longer accept orders from Keystone to manufacture the kits or injections.

However, an FDA inspection of Keystone a month later revealed Keystone had continued to distribute the unapproved drugs in the cyanide kits still in inventory and did not intend to stop, according to the agency. The company has been given numerous opportunities to come into compliance, the FDA notes.

"The FDA is taking this action because Keystone has refused to take these unapproved products

off the market," FDA acting Associate Commissioner for Regulatory Affairs Michael Chappell said.

The FDA had issued a warning letter to San Diego-based PrimaPharm in October 2008, identifying numerous cGMP violations.

For example, PrimaPharm did not establish and follow written procedures to prevent microbiological contamination of sterile drugs, according to the FDA's Oct. 31 warning letter (*DGR*, December 2008).

Media fills used to validate unidentified processes were deficient, and the environmental monitoring program did not include sampling of critical surfaces, the FDA says.

Procedures for cleanroom operations were cited as well.

"These deviations raise significant concerns with sterility assurance of products that were produced under these conditions," the letter says.

Keystone did not respond to a request for comment by press time. — April Hollis

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FDA to Start Part 11 Inspections After Seeing Compliance Issues

The FDA will soon begin inspections to determine companies' compliance with electronic records guidelines under 21 CFR 11 (Part 11).

The agency has seen a variety of compliance issues, ranging from insufficient computer system validation to missing audit trails in critical systems, George Smith, project manager officer in CDER's Office of Compliance, told *DGR* last month. Some of these issues may not have been obvious to industry as many of the citations were made to the predicate rule without Part 11 being mentioned, he added.

What the FDA finds in the new inspections could lead to additional guidance, or the agency could decide to amend the existing Part 11 regulation or amend the current scope and application guidance, Gordon Richman, vice president of Strategic Compliance Consulting for EduQuest, said last month during an FDAnews webinar.

A 2003 guidance set certain conditions covering validation, audit trail, record retention, record copying and legacy systems for which the FDA does not intend to take enforcement action. But violations that do not fall within the guidance's discretion can lead to enforcement action, depending on the importance of the violation, the agency said.

Companies can prepare for inspections by conducting an inventory of all systems and having a simple description, or system overview, of each system, Richman suggested. It is also important to ensure that validation documentation is current and there is a robust change management system.

Drugmakers should be familiar with Part 11 requirements. When evaluating systems for compliance with predicate rules, as well as Part 11, Richman advised prioritizing based on criticality, product impact, risk, visibility and data integrity.

Companies should minimize the potential impact of any gaps and develop a plan for achieving compliance with recordkeeping requirements first.

Additionally, information system/information technology staff should be trained on applicable regulatory requirements.

Another important focus area is good software and systems engineering practices. "This is what the regulators are usually looking for," he said, adding, "Companies fail because they continue to apply poor practices that cannot be justified or defended."

The guidance, "Part 11, Electronic Records; Electronic Signatures — Scope and Application," is available at www.fdanews.com/ext/files/ucm070295.pdf. — April Hollis

Merck Shuts R&D, Manufacturing Sites for Schering Consolidation

Merck will close eight research sites and eight manufacturing plants as part of its restructuring plans following its merger with Schering-Plough.

The drug giant expects to save between \$2.7 billion and \$3.1 billion in annual costs in 2012 as a result, the company said last month. Merck also plans on laying off 15 percent of the combined companies' workforce to achieve a goal of \$3.5 billion in annual savings.

Merck's Cambridge, Mass., research facility is the only U.S.-based site slated for closure. The others are in Canada, Denmark, Germany, the Netherlands and Scotland.

After consolidation, Merck Research Laboratories will have 16 research and development centers worldwide that will focus on seven key areas: cardiovascular disease, diabetes/obesity, infectious disease, oncology, neuroscience and ophthalmology, respiratory and immunology and women's health.

The company's manufacturing sites will shrink from 91 to 77, which include animal health facilities previously scheduled to shutter as part of Schering-Plough's venture with Sanofi-Aventis' Merial.

Merck's \$41.1 billion merger with Sanofi-Aventis took effect last November.
— Jonathan Block

Warnings, from Page 1

To speed up enforcement action, she instructed that the Office of Chief Counsel (OCC) would review only warning letters that have “significant legal issues.”

As a result, the quality of the letters has dropped, Bragg said. “For years, those within FDA who were doing the preliminary drafting of warning letters knew that other eyes would be reviewing the letters before they were issued,” she said.

“This meant that any errors would likely be corrected before the final letter was issued,” she added. “Now that there is not an automatic OCC review of the letters, this internal check no longer exists.”

Lack of prior review may not be the only contributor to the diminishing quality of warning letters. Increasing turnover at the FDA also may be at fault, Bragg said.

“The retirement of a number of senior people, combined with large increases in hiring, means that it is increasingly common for people with less experience to be asked to step in and handle matters that might previously have been handled by their more experienced counterparts,” she said.

Edwin Bills, a compliance expert at Bilanx Consulting, agreed that turnover is a likely factor, noting that the letters from some FDA districts are better than those from others.

“There is still enough experience in management levels to overcome shortage of experience of investigators,” Bills told *DGR*. But unless the agency develops warning letter standards for its staff, he expects continuing turnover in district management will result in more widespread problems with quality and nonenforceable letters.

— Virgil Dickson

BMS Recalls Three Lots of Coumadin Blister Packs

Bristol-Myers Squibb voluntarily recalled three lots of physician sample blister packs of Coumadin after determining that some tablets over time may not meet the specification for isopropanol.

Isopropanol is used to maintain the active ingredient, warfarin, in the crystalline state, and the issue could affect therapeutic levels of the ingredient, the FDA said last month.

A decrease of coumadin, which is prescribed to treat or prevent blood clots, could lead to heart attack or stroke. Too much active ingredient could cause an increased risk of bleeding.

BMS is taking steps to reduce the shelf life of the Coumadin 1-mg product packaged in blister packs from 36 months to 18 months, company spokeswoman Christina Trank told *DGR*.

The recall involves 1-mg blister packs distributed in the U.S. — April Hollis

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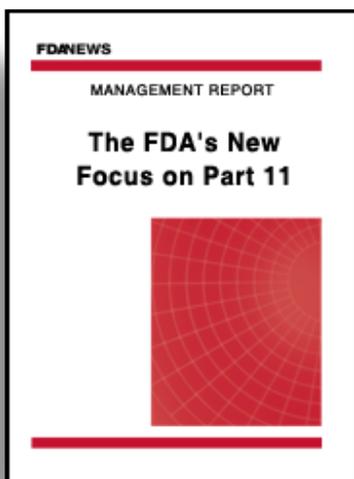
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