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Production at Zimmer's OSP Plant To Resume in Coming Months

Zimmer expects to resume production of many of its orthopedic surgical products (OSP) within the next two or three months as it corrects quality system problems that forced it to halt certain operations at its plant in Dover, Ohio.

"Our remediation plans continue as scheduled as we expect to have most, if not all, of the OSP products back into production by the end of this year — many in the next two or three months," CEO David Dvorak said during the company's second-quarter earnings call.

The firm halted the manufacture of many patient care products, such as wound debridement kits, at the facility after an FDA inspection identified deficiencies at the plant. The production stoppage is estimated to cost the firm $70 million to $80 million in lost revenue this year (*GMP*, May).

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Anika Therapeutics Gets Warning Letter

The FDA cited Anika Therapeutics, which supplies ophthalmic and joint health products to Bausch & Lomb and Johnson & Johnson subsidiary DePuy Mitek, for not having a hand-washing sink outside its sterile gowning room after the firm's quality assurance (QA) department deemed it unnecessary.

"Because of your QA management's decision that the lack of a hand washing sink in such basic septic manufacturing operations is acceptable, we are concerned that an effective quality system has not been implemented and maintained," the FDA told the company in a July 2 warning letter.

The letter cited Anika for quality systems violations for viscosupplementation product Orthovisc, a hyaluronic acid solution injected into joint spaces. DePuy markets the device in the U.S.

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Chief Financial Officer James Crines does not anticipate getting all of that lost revenue back when the products are relaunched in 2009.

Zimmer has had a rough year. Just last month, it suspended U.S. sales of its Durom acetabular cups, used for total hip replacements, until the firm revises surgical instructions and retrains physicians. The suspension is expected to cost the company $20 million to $30 million, it said.

Zimmer halted distribution of the cups after examining its manufacturing process and data from more than 3,100 device users in the U.S. and abroad. The investigation revealed incidents of cups loosening and a revision surgery rate of 5.7 percent when they were not placed in a specific manner, or when "crucial technique steps" were not taken, the company said.

There was no evidence of any material, design or manufacture defects, it added. The investigation concluded that surgeons who do not use specific surgical techniques have a lower success rate.

The device is a cobalt-chromium alloy cup designed for use with Zimmer's Metasul Metal-on-Metal Tribological Solution LDH for total hip replacement. It has a titanium plasma-sprayed coating. It was launched in Europe five years ago for hip resurfacing — an alternative to hip replacement — but the FDA has not approved it for that use. It also is available in Canada, Australia, India, Korea and Argentina for hip resurfacing.

Expansion in Indiana

Aside from the various product withdrawals the firm has encountered this year, Zimmer plans to expand its 2,800-employee Warsaw, Ind., operations. The company will invest more than $19 million to add more space to its foundry operations and create 100 new jobs. The annual output of the Warsaw plant will grow by approximately 1.3 million castings per year, Zimmer said.

The company will receive up to $400,000 in performance-based tax credits from the Indiana Economic Development Corp. based on its plans for creating new jobs.

"The demand for joint replacements continues to grow worldwide," Dvorak said.

Separately, Zimmer has voluntarily recalled a surgical instrument used in minimally invasive knee-implant surgeries.

The company had received reports that some tibial broach impactors, which are used to prepare the tibial bone for an implant, had broken during surgery. Zimmer said other instruments could be used for this purpose.

Zimmer has notified the FDA and affected customers. It said it does not expect the recall to materially impact its sales. — Christopher Hollis, Elizabeth Collins

IOPI Northwest Gets Warning Letter For Lack of Quality Audit

IOPI Northwest allegedly failed to conduct a quality audit for a device to diagnose speech and swallowing disorders, earning it a warning letter.

An inspection of the company's manufacturing facility in Carnation, Wash., revealed several GMP violations with its Iowa Oral Performance Instrument, including failure to establish auditing procedures, the letter says.

The June 25 letter, posted recently to the FDA website, claims the company also did not establish procedures for corrective and preventive actions and complaint handling.

Other violations noted include incomplete device history records, poor maintenance of acceptance activities and improper records showing testing, reviews or approvals of finished devices.

The letter cites a statement that was on the company's website: "The IOPI is registered with the FDA, but it is not 'approved' because the FDA does not approve medical devices."

The letter informs the company, "Establishments, not devices, are registered with FDA" and adds that the agency does approve certain Class III devices. It told the company to correct such misstatements.

The letter is available at www.fda.gov/foi/warning_letters/s6855c.pdf. — Nick Wills

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Production operations for Amvisc and Amvisc Plus, which are general-purpose viscoelastics used during cataract procedures, also were cited. The products are marketed by Bausch & Lomb.

The company's facility in Woburn, Mass., manufactures the devices. Staarvisc II and Shellgel, also produced at the site, are cited in the letter as well.

Complaint Handling

Another concern the FDA raised was how the firm handled complaints. "We observed that when you receive a complaint, you are not contacting the original complainant to obtain the information required to make a thorough investigation. Instead you are only dealing with the distributor, even though you are provided with the complainant's name," the FDA says in the letter.

Information concerning the number of events, the final diagnosis and specific treatment were not always obtained. "Without this information, it is difficult to make a conclusion that further investigation is not warranted or an event is not reportable under 21 C.F.R. Part 803," the letter says.

"Additionally, we observed complaints of cases of inflammation, endophthalmitis and toxic anterior segment syndrome … involving your ophthalmic products," the FDA says. "We are concerned that thorough investigations are not being conducted on these complaints to determine that a root cause is not due to ... validation deficiencies."

The agency mentions a complaint from a distributor regarding 10–15 cases of inflammation that may have occurred after using Amvisc. The complaint was received July 7, 2006, and was closed Aug. 1, 2007. The FDA says there was no documentation in Anika's file to demonstrate that it attempted to get more information from individual complainants.

The FDA also cited problems with the firm's aseptic processing operations.

Environmental samples to monitor aseptic manufacturing were not taken, the letter says. Media fills to validate aseptic processing did not completely simulate routine manufacturing for sterile bulk concentrate for Amvisc, Amvisc Plus, Staarvisc II, Shellgel and Orthovisc. Specifically, process simulations did not incorporate numerous manual aseptic steps on the same equipment and times routinely used during actual manufacturing.

In addition, the company released two of three lots manufactured during an environmental excursion in a gowning room before an investigation of the problem was completed, the letter says.

That investigation began last October and was closed in March with no root cause determination. However, lots manufactured during the excursion were released last November, prior to the QA department approving them for release in March. A report revealed that the investigation was performed on the wrong room — one with an uncontrolled environment.

In a separate event, the firm initiated an investigation in June 2007 into contaminated sterile bulk concentrate. The investigation determined that the contamination might have resulted from an inner lid of the batch vessel. The contamination was believed to have resulted from a high fill volume that allowed the product to contact an identified item, the letter says.

A corrective and preventive action (CAPA) to examine the possibility of a maximum fill volume was approved by the QA department late last August. The FDA investigator observed that the CAPA had not been closed at the time of the inspection, which was conducted in March, and investigators were not able to review any documentation showing a preventive action was implemented, the letter says.

Further, the company did not sample its purified water system appropriately because it did not collect samples from a collection hose that is not flushed, cleaned or sanitized prior to collection during routine use, the letter says.

The company said it was cooperating with the FDA, and a plan to remediate the issues has been developed. Product quality is Anika's highest concern, and it is committed to investing in the best quality systems, the company said. The warning letter can be accessed at www.fda.gov/foi/warning_letters/s6860c.pdf. — Christopher Hollis

Advanced Bionics, FDA Settle Dispute

Cochlear implantmaker Advanced Bionics has agreed to pay a $1.1 million fine for shipping products that used components from an unapproved supplier. The firm's president and co-CEO, Jeffrey Greiner, agreed to pay a $75,000 fine.

The settlement closes an administrative complaint originally filed by the FDA last November and amended in March. The agency initially sought a $1.1 million fine from Greiner, the maximum it can impose on an individual or company (*GMP*, April). Neither the company nor its president admitted liability in the settlement.

The complaint, which was adjudicated by an FDA administrative law judge, alleged that Advanced Bionics shipped its HiRes90k implantable cochlear stimulator after the company changed its supplier for a critical component. The firm did not notify the FDA of the supplier change.

"The failure to submit supplemental information prevented the FDA from being able to evaluate the potential impact of the changes on the safety and effectiveness of the device," the agency said.

In March 2006, Advanced Bionics recalled 613 units of the HiRes90k cochlear stimulators made with components from the unapproved supplier. The recall was initiated because excessive moisture could leak into the units, potentially causing device failure and requiring surgery.

In its complaint, the agency said Advanced Bionics shipped two devices that were implanted after the March recall.

Alfred Mann, co-CEO of the company and CEO of biopharmaceutical firm MannKind, originally founded Advanced Bionics. Boston Scientific purchased the company in 2004 for $740 million plus future milestone payments but later divested the auditory division of Advanced Bionics. — Christopher Hollis

Boston Scientific Expects Warning Letter to Be Lifted This Quarter

Boston Scientific is anticipating that the FDA will lift its corporate warning letter this quarter, paving the way for approval of the firm's next-generation drug-eluting stent.

Taxus Liberte, which is designed to be a more flexible and deliverable stent than its predecessor Taxus Express, is approved in Europe where it leads the market, the company told *GMP*. Although the warning letter is holding up approval of all of the company's pending products, except those manufactured by its Guidant division, Taxus Liberte is the most significant.

Two years ago, the firm received the corporate warning letter citing insufficient quality management practices and "serious regulatory problems" at numerous facilities (*GMP*, February 2006). The letter has cost Boston Scientific a hefty sum, but those expenses are starting to subside, allowing the company to deploy resources elsewhere.

"The resources come in two flavors in this regard. One is just the outside help that we've had for a couple of years here, and we're kind of past that stage. So the tens of hundreds of millions of dollars we've spent that way have begun to diminish," James Tobin, CEO of Boston Scientific, said last month during the company's second-quarter earnings call.

"As far as our own engineering core goes, there's still process validation ongoing. There's still a lot of work to be done. You are never done, and we're still finishing up the last parts of various aspects of this," Tobin continued. "But we're beginning to see the opportunity to shift some of our engineering resources back into [value improvement programs]. … So we have a large inventory of good ideas that now we can start to implement."

Freeing up engineering resources is important to the company. Last year, Samuel Leno, chief financial officer of Boston Scientific, indicated that engineers who typically drive standard costs down 5 percent to 8 percent were working on compliance issues from the warning letter (*GMP*, October 2007).

During the second quarter, the company established a reserve to write off obsolete inventory for Taxus Express once the firm switches to marketing Taxus Liberte. Although Leno said it is probable the corporate warning letter would be lifted this quarter, he emphasized that the timing was really up to the FDA. — Christopher Hollis

Expert: Avoid Import Detention With Knowledge of FDA Import Policy

If a device manufacturer encounters problems at the U.S. border, it can reduce the likelihood of a full-blown product detention by understanding the FDA's import policy and knowing how to work with U.S. customs personnel, a former FDA attorney says.

"There is often more than one way to skin a cat," Benjamin England, founder of Benjamin L. England & Associates, said at an FDAnews audioconference.

Firms attempting to import healthcare products into the U.S. may have entry denied because they fail to provide data the FDA has no legal authority to demand. "It happens far more often than people realize," England said.

The FDA's refusal authority stems from 21 USC 381, which gives it the right to refuse products that appear on examination of samples "or otherwise" to be unsanitary, adulterated, misbranded, or forbidden or restricted for sale in the country of origin.

The appearance standard can be a fairly low level of evidence, England said, as Congress gave the FDA discretion to determine what amounts to an appearance of a violation. The "or otherwise" clause is even more nebulous and hard to pin down, he added. It can be based on examination

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Warning Letter Cites Firm's Handling Of Malfunctioning Muscle Stimulators

A rash of adverse incidents that occurred after Encore Medical had identified a problem with its muscle stimulators has resulted in a warning letter from the FDA.

Between May 2006 and last December, the firm received 64 complaints of patients being shocked or burned from an over-voltage malfunction in its muscle stimulator EPR product line.

Of those complaints, 58 were made after the company had identified the malfunction, the letter says.

Although Encore had developed software to detect the over-voltage and shut down the device, it only installed the revision in stimulators that were in stock or that had been returned. The software revision was not installed in devices already distributed and in use.

In a similar incident with its Vectra Genisys product line, Encore became aware in 2005 of a malfunction in which diodes were failing on boards used to control ultrasound devices.

It modified the products in stock but did not replace the diodes in ultrasound devices in distribution, the letter says. As a result, a number of the devices had to be returned and replaced last year.

During the FDA inspection, the firm failed to provide the investigator with written documentation of its corrective and preventive action (CAPA) activities.

In the warning letter, the FDA acknowledges Encore's efforts to address its concerns. The company has revised its written CAPA procedures, provided documentation for a corrective action, recalled the muscle stimulators to install the software revision and recalled the ultrasound devices because of the high rate of diode failure.

However, it has not provided data to demonstrate the software revision will be effective over the lifespan of the device, the letter says. The agency requests verification and validation plans and reports for the software.

MDR Failures

Encore also was cited for failure to submit medical device reports (MDRs) within 30 days for some complaints concerning over-voltage malfunctions that resulted in a shock, burn or high output to the patient. Several of the reports it did submit did not correctly indicate the type of reportable event.

The company reported two incidents as malfunctions rather than serious injuries. One of these MDRs did not mention that the patient had received a burn that blistered and turned black. The patient had to be prescribed medication. The report also did not indicate that skin grafts were considered to ensure a complete recovery without scarring.

The other MDR did not include the fact that the patient received a shock, which provoked a panic attack, and screamed, panted, mumbled incoherently and eventually became unresponsive.

The firm's response on the MDR issue is only partially adequate, the FDA says. Before the close of the January inspection, Encore submitted 15 MDRs for complaints of user shock or burning due to malfunctions of muscle stimulators between July 17 and Oct. 5, 2007. It also amended an MDR standard operating procedure, retrained personnel, re-reviewed complaints and submitted three new MDRs.

However, the company did not submit MDRs for 48 similar complaints received prior to July 17, 2007. Those complaints must be filed as MDRs, according to the letter.

Encore could not be reached for comment by press time. The warning letter is available at www.fda.gov/foi/warning_letters/s6845c.pdf.
— April Astor

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of prior shipments, adverse events associated with the product in the U.S. or foreign markets, or the prior compliance history of the product, foreign manufacturer, exporter, importer or geographic region or country of origin.

Having a product subjected to FDA import screening can result in several possible actions: a request for documentation, a request for sampling and examination notice, a detention recommendation or a "may proceed" notice.

According to England, FDA-regulated imports increased by about 272 percent to roughly 8 million commercial lines of entry from 1991–2000. By 2007, the agency had jurisdiction over 17 million lines of entry, he said, noting that the number has been doubling every five years and is not expected to stabilize.

The FDA physically examines only about 0.7 percent of foreign products arriving at U.S. borders, a figure England said is somewhat deceptive because the agency employs a risk-based approach determined by the type of product. "I can tell you the FDA inspects zero percent of plastic forks," he said. Many refusals are made without the product being inspected.

Most of the import program is based on guidance. Many of the procedures the FDA follows are unpublished, making it hard for firms to find out about them. "There are no clear stated procedures regarding a myriad of issues importers and exporters encounter with FDA," England said. Since there are variations in the ways different FDA district offices process imports, it is "like having a dozen FDAs to deal with," he added.

England offered advice on eight critical stages of border entry:

- Review stage — "Find out what they [the FDA] like to see and give it to them. ... The goal is to convert a conditional customs release to an unconditional release."
- Correspondence stage — Firms must be ready with copies of supplier filings, batch certifications, notification and affirmation of compliance codes and "have all proof of accurate identifiers available."
- Sample/exam stage — Firms need to hold the product until a release is given. The "FDA will sample the largest lot number in the shipment and extend the results to other lots. … That's the 'or otherwise.'"
- Detention stage — "Remember a detention is not a final action. The FDA is often wrong." Firms should provide the requested data as soon as possible. If it is in FDA databases, the fact that a company cannot get it is not an actual violation of the law.
- Reconditioning stage — Simple reconditioning or relabeling may suffice to bring a detained product into compliance.
- Refusal stage — This is usually final, so firms should immediately appeal to the supervisor of the individual who made the decision.
- Redelivery stage — Usually exportation or destruction of refused goods is required within 90 days of refusal. However, by seeking a rescission of the refusal, firms may be able to stop the clock.
- Liquidated damages stage — Firms that fail to redeliver refused goods face liquidated damages at three times the invoice value. This is the time to present an argument against the FDA to customs officials.

Even if the FDA releases a product, customs can demand redelivery for 30 days, England said. This usually occurs when the agency can show that information it relied upon to issue the release was somehow flawed.

At each stage, firms can benefit from face-to-face encounters with compliance officers and their supervisors. "Meet with them when things are going well, too. Don't be a stranger," England said, noting that discussing a firm's internal compliance or how it verifies data and qualifies vendors may prove useful in obtaining releases later. — Meg Bryant

New Reactors for Medical Isotopes Needed to Address Supply Issues

To minimize disruptions in medical imaging, the Atomic Energy of Canada Limited's (AECL) National Research Universal (NRU) nuclear reactor needs to be replaced, according to a group of experts convened by Health Canada.

Their report, released by the Canadian health minister last month, recommends exploring opportunities to bring new nuclear reactors on line to produce medical isotopes, which are used with positron emission tomography and single photon emission CT machines and cannot be stored because of their short shelf life.

The NRU reactor, which is more than 50 years old, produces roughly half of the global medical isotope supply. When it was shut down for almost a month last year due to a maintenance issue, the impact was significant.

Plans to build new reactors were nixed earlier this year. In May, AECL announced the immediate discontinuation of the MAPLE project, which included building two new nuclear reactors and a processing facility.

AECL said the decision would not affect the medical isotope supply as the NRU's operating site license is authorized through October 2011.

MDS, an Ontario-based company that processes medical isotopes for diagnostic radiopharmaceuticals, filed a $1.6 billion lawsuit last month against AECL, the firm's isotope supplier, and the Canadian government over the discontinuation of the MAPLE project, which would have supplied MDS with isotopes.

MDS is suing for damages and breach of contract and is seeking arbitration proceedings with AECL. A Canadian federal crown corporation, AECL is structured like a private business but is owned by the government.

AECL signed a contract with MDS in 1996 to complete the MAPLE project in 2000 as a replacement for its NRU reactor. Although MDS noted that by 2005, the MAPLE project was "five years behind schedule and costs had more than doubled," it mediated an agreement with AECL in 2006 that the project would continue and the reactors would be brought into service this year, ensuring the firm a 40-year isotope supply.

The implications of AECL's abandonment of the MAPLE project for the diagnostic community are long-range, Robert Atcher, president of SNM (formerly known as the Society for Nuclear Medicine), told *GMP*.

"The MAPLE reactors were supposed to provide a smooth transition from the NRU reactor to a more modern production capability. With the cancellation of that project, we are now without any current or planned alternative production capacity that would extend beyond about five years," he said.

Plans for the Reactor

As a result of last year's outage, AECL and the Canadian Nuclear Safety Commission (CNSC) contracted with Talisman International to conduct an independent review of the reactor. They announced last month that they had accepted 15 recommendations detailed in that review, all of which are aimed at preventing similar situations in the future.

One of the recommendations is that CNSC and AECL develop a formal process to quickly determine whether, and under what conditions, continued operation of the NRU reactor may be justified "during off-normal conditions."

"To address the review team's findings and recommendations, CNSC has put a corrective action plan in place with aggressive timelines," Michael Binder, CNSC president, said.

The report submitted to Canada's health minister is available at www.hc-sc.gc.ca/hcs-sss/alt_formats/hpb-dgps/pdf/pubs/2008-med-isotope/2008-med-isotope-eng.pdf. The Talisman International report can be found at media3.marketwire.com/docs/talisman%5feng.pdf. — Elizabeth Collins

Supplier-Agreement Failures Result in FDA Warning

X Spine Systems' failure to correct quality problems, document complaint assessments and establish quality requirements for suppliers was cited in a warning letter.

When the FDA inspected the firm's Miamisburg, Ohio, facility April 7–18, it found several GMP violations. The company responded in May, but the agency sent a warning letter July 15, listing a dozen alleged failures X Spine must address.

The FDA had cited the firm for revising a package insert for its Spider Cervical Plating System last September without notifying customers that a previous insert would not guarantee a specified sterility assurance level.

Although X Spine responded that a "field advisory notice" would be sent immediately to customers with unimplanted devices to assure they followed the current package insert, the agency says this response was not adequate. "It does not address how you will assure that the appropriate corrective and preventive action will be taken when a nonconformance is identified in the future," the warning letter says.

The agency also cited the company for failing to establish quality requirements for suppliers and for not having supplier agreements requiring notification of design or manufacturing changes that might affect products.

X Spine replied that it had sent questionnaires and agreements by June 30 to Level I suppliers of implantable devices and revised its supplier-approval procedure to include quality requirements. The agency asks the company to provide copies of the questionnaire, new agreement and the revised approval procedure.

The company also was cited for four alleged failures involving design. It did not demonstrate that the design of the Spider Cervical Plating System was developed according to quality-system regulation, for example, in that it did not approve the design and development plan or address sterilization requirements in design inputs, the letter says.

The company told the FDA it would complete training by Aug. 15 and update its design history file and revise its product design procedure by July 30. The agency requests an update and supporting documentation for these actions.

Failure to establish procedures to address incomplete, ambiguous or conflicting design inputs was the second design failure listed in the letter. The firm said it would include these by July 30 in a "product design procedure map," the letter says.

The third design failure was not having complete procedures for verifying that design output meets input. X Spine's "'Product Design Procedure Process Map' defines design verification as 'inspections that occur during the course of assembly, manufacturing and processing' [but] the procedure does not address how your firm will demonstrate the design outputs meet the design inputs," the letter says.

The fourth design failure was not addressing risk analysis in design procedure, the letter says, noting that the company's process map does not address when or how risk analysis is to be done.

The letter also says the firm had inadequate complaint-handling procedures — specifically, it had no documentation of medical device report assessments for five complaints received after January 2006. Recorded dates, specific investigator names and results of failure investigations for four complaints also were undocumented, the letter says.

The agency, acknowledging the company's commitment to revise its complaint form and review all complaints for complete investigations by June 30, requests a copy of the results of those investigations.

X Spine did not return calls for comment by press time.

The warning letter is available at www.fda.gov/foi/warning_letters/s6865c.pdf. — Renee Frojo, David Grant

Complaint Handling Draws Warning Letter for Contact Lens Maker

Numerous complaints involving the possible malfunction of diagnostic contact lenses were overlooked by Volk Optical, according to a recent FDA warning letter.

In its response to Form 483 observations, Volk indicated it would re-evaluate and inspect the three complaints listed by an FDA investigator. But the investigator had used those complaints only as examples, the warning letter says, and Volk was required to complete failure investigations for all 19 complaints sampled for review. That sample was taken from 1,070 complaints received by Volk within the past year.

Every complaint must be reviewed to determine if additional failure investigations or corrective actions need to be taken, the letter says.

The company also was cited because its complaint procedure failed to follow FDA requirements for analyzing sources to identify existing and potential malfunctions of the devices in question. This procedure should include analyzing the types of complaints and the reasons for returns.

The letter adds that Volk lacked thorough documentation for all steps in its complaint procedure.

As part of its response, Volk said its complaint-handling procedure would be revised and implemented this month. The FDA requested copies of the new procedure for a follow-up review.

Volk also was warned that its Wide Field Lens was not in accordance with FDA design control requirements. The letter notes the following deficiencies:

- The only documented review of the product was conducted prior to the approval of the design, so it was not performed at the appropriate stage of development;
- The design verification tests for the outside diameter of glass, field of view and spatial resolution were performed before approval of the design inputs, and the weight-of-glass test was not performed;
- No acceptance criteria were established before the design was validated, and only one site was used for testing;
- No design transfer procedures were established; and
- There is an incomplete master record for the lens, which has not been approved.

Volk has revised and implemented its design and development procedures and informed the FDA that it is re-evaluating all other insufficient procedures, a task it plans to complete by December. The FDA says it cannot fully evaluate the adequacy of Volk's response until that re-evaluation is complete.

"We're currently focused on resolving all those items in question," Volk President Peter Mastores told *GMP*. "I and the company look at this as an opportunity to improve our products and our systems."

The warning letter is available at www.fda.gov/foi/warning_letters/s6859c.pdf. — Renee Frojo

MDR Failures Becoming Source of Suspicion

Manufacturers should expect heavy FDA enforcement for medical device reports (MDRs) as failure to comply with MDR regulations has created an atmosphere of distrust between the agency and some companies, an expert says.

Since the beginning of the year, warning letters relating to MDRs have constituted 42 percent of all letters issued by the FDA to device companies. This is a jump of 9 percent over the number issued for the same period last year, Pamela Furman Forrest, partner at King & Spalding, said at an FDAnews audioconference.

Out of the 19 warning letters issued between Jan. 1 through July 8:

- 12 were issued because of a failure to develop, maintain and implement written MDR procedures;

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- 10 were for failures to submit an MDR within 30 days of receiving or becoming aware of an adverse event or refusal to provide required information; and
- Three were for failure to investigate and evaluate the cause of an adverse event.

In most cases, common pitfalls included incidents in which companies overlooked seemingly minor complaints, failed to document all steps of a complaint investigation and did not train personnel to report information within the allotted time period.

"As a result, the FDA resorts to micromanaging companies that it becomes frustrated with," Forrest said. "FDA has a very conservative view of MDR requirements."

She said a worst-case scenario involved TMJ Implants, which was cited in July 2007 for failure to file 17 MDRs. When the company told the FDA it was "misinterpreting" the MDRs, the agency responded by fining the corporation and two executives a total of $630,000 — claiming the company was not investigating the complaints thoroughly enough to determine if they were reportable.

To avoid noncompliance, Forrest advised manufacturers to establish effective MDR procedures that incorporate FDA regulations and address full identification and timely communication of any possible adverse events, including minor malfunctions.

Then they should thoroughly log complaints into a database to be carefully screened. "What gets often overlooked are malfunction events that are potentially harmful," Forrest said. "These often get short-shifted and come back to haunt a company."

Manufacturers should assume a particular malfunction will recur, as required by the regulation, rather than assessing the likelihood that it will recur, Forrest said.

Miscalculated internal timelines and attention to reporting deadlines are the second most common pitfall, she said.

According to the FDA, manufacturers are considered to have become aware of a reportable event when any employee becomes aware of it — not when the complaint reaches the regulatory department for analysis.

Everyone in the company can become sensitive in the routing of complaint information if companies make it a priority to comprehensively train relevant personnel, Forrest said.

She also suggested manufacturers stay on the FDA's good side by making good-faith efforts to obtain MDR information. More than one request for information should be made in writing, and all attempts to retrieve information about a complaint should be documented.

As it stands, manufacturers have 30 days to submit individual MDRs for a device that may have caused or contributed to a serious injury or has malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The FDA is implementing changes that are part of the FDA Amendments Act of 2007 that will require 30-day individual MDRs for malfunction of Class II, Class III and other devices as determined by the agency. — Renee Frojo

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Customer Service (888) 838-5578 • +1 (703) 538-7600 customerservice@fdanews.com
Editor: Christopher Hollis (703) 538-7650 chollis@fdanews.com
Ad Sales: Andrew McSherry (703) 538-7643 amcsherry@fdanews.com
Content Sales: Alka Desai (703) 538-7669 adesai@fdanews.com

300 N. Washington St., Suite 200 • Falls Church, VA 22046-3431 • Phone: (888) 838-5578 • +1 (703) 538-7600 • Fax: +1 (703) 538-7676
www.fdanews.com

Reporters: Renee Frojo, Nick Wills, Meg Bryant

President: Cynthia Carter; **Publisher:** Matt Salt; **Editorial Director:** David Grant; **Executive Editor:** Mari Serebrov