INTERNATIONAL DEVICES & DIAGNOSTICS MONITOR

Vol. 2, No. 33
Aug. 22, 2016

IN THIS ISSUE

FDA Hands Out 15 Warning Letters To Devicemakers for GMP Violations

The FDA has posted 15 new warning letters to device manufacturers for GMP violations: 14 to foreign manufacturers and one to a U.S. company.

The UK took the lion's share of letters, raking in five, with China getting three letters, followed by Germany with two. Italy, France, Argentina and the Philippines also received one warning letter each.

The companies ranged from manufacturers of orthopedic implants, surgical cutting devices, carbon monoxide monitors and contact lenses to makers of menstrual cups and teeth whitening devices.

The FDA noted that it would refuse entry to 10 of the companies' products until the required corrections were made, and it would not be approving PMAs for Class III devices for 11 of the companies that received warning letters.

(See **Warning Letters**, *Page 2)*

FDA Issues More Warnings on Custom Ultrasonics Reprocessors for Duodenoscopes

The FDA is recommending that health care facilities stop using an endoscope reprocessor system from Custom Ultrasonics to disinfect duodenoscopes.

The warning covers all Custom Ultrasonics' System 83 Plus Automated endoscope reprocessors but notes that the reprocessors may be used to reprocess other flexible endoscopes, just not duodenoscopes.

The communication was triggered by an urgent medical device recall that Custom Ultrasonics issued in May advising users to stop using its System 83 Plus AERS for duodenoscopes. As part of the recall, the company is providing customers with a label to affix on the reprocessors warning that they are not indicated for reprocessing duodenoscopes.

(See **Duodenoscopes**, *Page 4)*

Warning Letters, *from Page 1*

The most-cited deficiency was failure to establish adequate corrective and preventive procedures (21 CFR 820.100), with 11 firms receiving warnings.

The FDA made clear that fixing CAPA procedures would not be enough to satisfy inspectors. They expected to see retrospective analyses that documented past problems and that the firms understood the source of the failures. In addition, inspectors wanted the firms to address how they would remedy nonconforming product that had been released to the market.

The next-cited warning related to procedures for receiving, reviewing and evaluating complaints by a formal unit within the company. FDA handed out nine citations to companies for lax complaint procedures.

At number three was design validation and verification procedures to ensure design requirements meet specifications and their intended usage requirements.

Along these same lines, about nine firms fell short when it came to maintaining device history records and device master records.

A number of firms received citations for failing to establish acceptance procedures to ensure that requirements for in-process products are met. Many also failed to document acceptance activities, the warning letters said.

Other firms failed to submit medical device reports or to establish written MDR procedures, the agency said. Other often-cited deficiencies included inadequate purchasing controls, failure to establish procedures for quality audits and failure to conduct necessary audits.

Highlights from the warning letters include the following citations:

(See **Warning Letters**, *Page 6)*

Company	Country	Types of Products Manufactured	No. of Citations on Warning Letter	Warning Letter Date
Mooncup Ltd.	UK	Menstrual cups	3	May 27, 2016
Helica Instruments	UK	Electrosurgical cutting and coagulation devices and accessories	12	May 13, 2016
Master And Frank Enterprises	China	Surgical drapes and gowns	4	May 10, 2016
F.P. Rubinstein Y Cia SRL	Argentina	Laser-powered surgical instruments	15	May 5, 2016
Aussiemed	Germany	Biofeedback devices	5	March 3, 2016
Novastep	France	Bone staples, screws, plates and intermedullary implants	5	July 28, 2016
Beyond Technology Corp.	China	Teeth whitening devices, dental floss	3	July 19, 2016
C World KSG	Philippines	Contact lenses	4	Feb. 18, 2016
Implants Int'l	UK	Orthopedic implants	6	Feb. 18, 2016
A.R.C.O.S. Srl	Italy	Compression socks	11	Aug. 3, 2016
Spiegelberg Gmbh	Germany	Intercranial pressure monitoring products	8	Aug. 3, 2016
Shenzhen Creative Industry	China	Class II patient monitors, fetal dopplers, oximeters	8	Jan. 15, 2016
Omega Laser Systems	UK	Laser systems	10	Feb. 17, 2016
Bedfont Scientific	UK	Carbon monoxide monitors	8	Feb. 4, 2016
W&R Investments	U.S.	Flexible CO2 laser waveguide	6	Aug. 5, 2016

Expert Advice on Getting Medical Device Reports "Inspection Ready"

Complaints are one of the most commonly cited sections in FDA device warning letters.

"Every MDR has an associated complaint with it. So, what that means is in order to understand how to properly implement MDRs, we've got to understand how to properly implement complaints," Dan O'Leary said.

Based on his own research, about a third of all device warning letters have MDR citations — with 40 percent including citations for complaint handling.

Define, Document and Implement

Manufacturers should first have a process in place that explains how a designated unit or individual in the facility is going to handle and evaluate complaints.

That is where a flow process comes in handy. It involves writing down and documenting all decisions, incorporating tools such as a flow chart that outlines each step and a well-structured form to help you in this process.

"You're going to document the forms or database elements for complaints, and then you're going to implement the process. And don't forget to train the people involved and create the appropriate training records," O'Leary advised.

Manufacturers should have protocols in place to cover all regulatory requirements, ensuring that complaint and MDR processes "interlock" with one another.

"Oftentimes problems occur when you're transferring information from one of these systems to another. So, make sure that they hang together. Review all the procedures together to make sure that you've got everything covered, [that] there's no gaps and no contradictions," he said.

He also advised interlinking the complaint and data analysis process to avoid silos. "This means, perhaps, that your designated complaint unit is also going to handle the MDRs, so that it's all done in a uniform way."

Internal audit programs are the best way to ensure the robustness of your QMS, he emphasized. This involves checking all of these processes to ensure that they "are running the way that you intend that they run."

Audit Schedule

An audit schedule should review the following elements on a regular basis: conformance to complaint, analysis, and MDR procedures; complaint investigation decisions and records; MDRs submitted on time, and records in the MDR event files.

For each of these elements, manufacturers should create a checklist based on established procedures and work instructions.

Internal quality auditors should ensure that the sample size of records isn't too small. This runs the risk of not catching rare problems, leaving room for the FDA investigators to find them instead. "So, make sure that your sample size is large enough that you're going to get all of the required records," he advised.
— Jennifer Lubell

TGA Maps Transition to ISO Quality Management Standard

Australia's Therapeutic Goods Administration will transition to the ISO 13485:2016 standard governing medical device quality management systems over the next three years.

The agency clarified that the 2003 standard and the 2016 standard will co-exist during the three-year transition period.

Users of ISO 13485:2003 should work with the TGA or their EU Notified Body or the Medical Devices Single Audit Program organization to schedule an upgrade audit during the transition period. — Tamra Sami

Duodenoscopes, *from Page 1*

The FDA said it is reviewing additional reprocessing validation data provided by Custom Ultrasonics, and is continuing to work with the company to correct violations uncovered during an April inspection.

The company has had a tumultuous compliance history. The FDA entered into a 2007 consent decree with Custom Ultrasonics due to repeated violations of the quality system regulation.

The FDA ordered Custom Ultrasonics to recall its AERs last November, following a slew of infection outbreaks related to duodenoscopes.

Ongoing Problems

The move came after reports of inadequately reprocessed duodenoscopes were linked to infection transmission in hospitals across the country, and followed an inspection that found a number of violations, including the inability to validate that the AERs could adequately wash and disinfect endoscopes to mitigate the risk of patient infection.

At that time, the FDA determined that the company had not adequately addressed the problems. To lessen the risk of infection transmission, the agency recommended that healthcare facilities currently using Custom Ultrasonics AERs adopt alternative methods to reprocess flexible endoscopes as soon as possible (*IDDM*, Nov. 20, 2015).

This is not the first time Custom Ultrasonics has fallen under FDA scrutiny after entering the consent decree. In 2012, the agency ordered the company to stop manufacturing and distributing all AER device models and components, and ordered their recall after the company failed to obtain clearance following a significant change to the software operating system for one of the reprocessors.

Custom Ultrasonics subsequently obtained clearance, and the products were permitted to remain on the market.

In January, a Senate report found that the FDA's system for monitoring the safety of devices failed to quickly identify and resolve the spread of antibiotic-resistant infections linked to duodenoscopes. In September 2013, the FDA started investigating how closed-channel duodenoscopes could spread infection despite proper cleaning, but the agency did not alert the public of the risks for 17 months, says the report (*IDDM*, Jan. 15).

Three other duodenoscope manufacturers also failed to meet regulatory requirements — Olympus submitted incomplete and misleading medical device reports, and Pentax and Fujifilm filed late and incomplete reports (*IDDM*, Aug. 21, 2015).

Earlier this year, the FDA strengthened controls on reprocessing of certain products, including AERs, in response to the infections linked to the duodenoscopes. In final guidance, the FDA required manufacturers of the products to include data validating the effectiveness of their reprocessing methods as part of their 510(k) submissions (*IDDM*, March 13).

Read the FDA warning here: www.fdanews.com/08-17-16-FDAwarning.pdf. — Tamra Sami

Edwards' Transcatheter Heart Valves Approved in Intermediate-Risk Patients

In an industry first, the FDA approved an expanded indication for transcatheter heart valves for patients with aortic valve stenosis at intermediate risk for death or complications from open-heart surgery.

Previously, transcatheter heart valves were only approved for patients at high or greater risk for death or complications from surgery. Roughly one-third of patients referred for open-heart surgery for aortic valve replacement fall into the intermediate-risk category.

Patients with severe aortic valve stenosis generally need heart valve replacement to improve blood flow. Open-heart surgery has been the gold standard for aortic valve replacement in intermediate risk patients, but it involves a larger incision and longer recovery time than the minimally invasive procedure used to insert the transcatheter heart valve.

Manufactured by Edwards Lifesciences, the Sapien 3 transcatheter heart valve consists of a catheter-based artificial aortic heart valve and accessories used to implant the valve via the femoral artery. The valve is attached to a balloon-expandable, cobalt-chromium frame, and is pushed through the blood vessels until it reaches the diseased aortic valve, which is expanded by the balloon and is anchored to the diseased valve. Once the new valve is in place, it opens and closes properly, allowing the blood to flow in the correct direction.

The Edwards Sapien XT transcatheter heart valve consists of a catheter-based artificial aortic heart valve and accessories much like the Sapien 3, and it comes in three sizes: 23 mm, 26 mm, and 29 mm.

The approval was supported by clinical studies in 1,021 intermediate-risk patients implanted with the Sapien XT heart valve, and in 1,078 intermediate risk patients implanted with the Sapien 3 valve. The two studies demonstrated a reasonable assurance of safety and effectiveness of both transcatheter heart valves in intermediate-risk patients.

As part of the approval, Edwards is required to conduct a post-approval study to follow patients treated with either device for 10 years to monitor safety and effectiveness.

The devices are contraindicated in patients who can't tolerate blood thinning medication as well as patients being treated for a bacterial or other infection.

The Sapien XT was also approved in 2015 to treat patients who had previously received tissue aortic valves that failed. — Tamra Sami

Potential For Glass Particles Prompt Cook Medical Global Recall

Cook Medical announced a global recall of 8,750 units of its Roadrunner UniGlide hydrophilic wire guides due to the possibility of glass particles in the coating of the wire guide units.

Netherlands-based DSM Biomedical B.V., Cook Medical's supplier of the hydrophilic coating for the wire guides, recalled certain lots of material due to concerns about glass particles ranging in size from 4 to 280 µm.

Cook received one lot of the affected recalled coating, which prompted the company to initiate the global recall. The company said it was taking the action as a precautionary measure.

The wire guides deliver percutaneous catheters into the peripheral vascular system. Potential adverse events could include vessel damage, bleeding and embolic particulate in the circulatory system. Cook Medical has not received any reports of adverse events.

Cook requested customers and distributors to quarantine and discontinue use of all recalled units. For a full list of affected products and lot numbers, read the notice here: www.fdanews.com/08-19-16-Cookrecall.pdf. — Tamra Sami

Warning Letter, *from Page 2*

- China's Master and Frank Enterprise submitted a Failure Mode and Analysis risk analysis for its surgical drapes and gowns, but the FDA concluded that the FMEA was inadequate because it didn't consider all potential hazards if the products didn't conform to specifications. For example, it didn't address potential biohazardous materials and physical contaminants that may be introduced from the surgical gowns into the surgical environment.

- The UK's Helica Instruments was citied for failing to establish and maintain adequate procedures to control nonconforming products. For example, the firm's nonconforming product procedure didn't adequately address the identification, documentation, evaluation, segregation and disposition of nonconforming product; nor did it address nonconformance evaluations and investigations or the need to notify those responsible for the nonconforming product, the warning letter says. The firm's procedure also lacked detail when it came to rework and reevaluation activities including whether there were any adverse events from the rework of the electrosurgical cutting and coagulation devices and accessories.

- CAPA procedures and complaint handling were found lacking at Argentina's F.P. Rubinstein Y Cia. The FDA noted that the firm's CAPA procedure that was opened to address validation records was closed without performing the required validation. The letter noted that this was a repeat observation from an inspection in October 2014. The firm also failed to evaluate complaints of burns patients received from the firm's laser-powered surgical instruments. The letter notes that eight out of eight complaints sampled did not include MDR evaluations, and four complaints did not have the phone number of the complainant or a description of the complaint. The agency noted that this also was a repeat observation. The firm also did not maintain device history records, which was another repeat observation, the warning letter notes.

- China's Beyond Technology Corporation failed to establish procedures to prevent contamination of equipment or products, the warning letter said, drawing attention to rodent infestation in the buildings where teeth whitening devices and dental floss was manufactured. — Tamra Sami

FDA Extends Comment Period For Infectious Disease Dx Guidance

The FDA has extended the comment period from Aug. 11 to Sept. 12 for its draft guidance on infectious disease next-generation sequencing diagnostic devices.

Released May 13, the guidance spells out how the agency plans to regulate diagnostics that detect infectious disease organisms, antimicrobial resistance and virulence markers.

Tagged as Class II devices, the FDA will regulate infectious disease NGS Dx devices based on a "one-system" approach, similar to the way it regulates molecular-based diagnostic devices. The guidance notes that in contrast to human sequencing diagnostics, infectious disease sequencing diagnostics generally require rapid and actionable results, "as delayed or incorrect diagnoses can result in fatalities."

The guidance was drawn from stakeholder input during an April 13, 2015 meeting that stressed the need for more advanced testing to better detect and identify infectious disease organisms. Stakeholders stressed that next-generation sequencing can replace previous methods with a single approach (*IDDM*, May 13).

The guidance proposes the use of an alternative comparator to validate NGS-based tests for infectious diseases. To that end, the agency developed the FDA-ARGOS [FDA dAtabase for Regulatory Grade microbial Sequences] database to supply validated regulatory-grade microbial genomic sequence entries collected from public databases.

FDA Adcom Recommends Approval for Baebies' Seeker Analyzer for Newborns

An FDA advisory committee unanimously agreed that Baebies' Seeker analyzer should be approved to detect lysosomal enzymes in newborns.

The Clinical Chemistry and Toxicology Devices Panel had originally expressed concerns about false positives and negatives associated with the diagnostic test, but it ultimately decided that the benefits outweighed the risk and the Instruction for Use statement could indicate the limitations.

Baebies, Inc. is seeking a *de novo* classification for the system, which includes the Seeker analyzer, the Seeker 4-plex assay kit, Seeker cartridges, the Spot Logic software and quality control materials. The diagnostic uses digital microfluidic technology to measure lysosomal enzymes associated with Mucopolysaccharidosis Type 1 disease, Pompe disease, Gaucher disease and Fabry disease.

Reduced activity for any of the four enzymes identified should be followed up by other confirmatory diagnostics, the agency said.

The test does have numerous limitations. For example, enzymes vary by age and by seasons since enzymes are impacted by temperature and humidity. Thus, the Instructions for Use statement should recommend that users set their own cutoffs, the panel recommended.

Limitations were also noted with analytical performance of the device around the high risk cutoff. The panel noted that it was "somewhat concerned" with the analytical performance but concluded that it was adequate to support its proposed intended use within the limited population. — Tamra Sami

UK Warns of Underdosing With Roche's Accu-Check Insulin Pump

The UK is warning of a risk of incorrect insulin dosage caused by leaking cartridges used with Roche's Accu-Check Insight insulin pump system.

The Medicines and Healthcare products Regulatory Agency said that cartridges inserted incorrectly can leak insulin, resulting in under-delivery of insulin, which could lead to rapid deterioration of health, diabetic ketoacidosis or death.

Roche released an urgent Field Safety Notice detailing the problem and offered advice and additional training on the use of the device.

Leaking cartridges can be detected by regularly checking the pump a few hours following the cartridge change as the insulin would be visible through condensation in the pump's cartridge compartment, the company said in the field alert.

Roche said it is updating its handling instructions immediately and will provide updated user manuals shortly at a later stage. In the meantime, users should:

1. Check the cartridge every time it is changed, including the rubber plunger at the bottom of the cartridge. Users should not use the cartridge if there is any damage or leakage seen or if the rubber plunger has been drawn above the white label band at the bottom of the cartridge.
2. Always hold the pump in an upright position when inserting the new cartridge.
3. Change the adapter tube every time the cartridge is changed.
4. Make sure the nose of the adapter is inserted into the notches of the pump's housing at a right angle when placing a new adapter on the bayonet socket of the cartridge compartment. Otherwise the needle located in the nose of the adapter could bend and lead to leakage of insulin into the cartridge compartment.
5. Turn the adapter clockwise all the way until it stops. The adapter is correctly positioned when it is aligned with the pump's housing.

Read the alert here: www.fdanews.com/08-18-16-Rocherecall.pdf. — Tamra Sami

BRIEFS

FDA Classifies Three Devices as Class II

The FDA made determinations for three *de novo* requests for classification this week.

Micro Interventional Devices' Permaseal, indicated for soft tissue approximation of cardiac apical tissue during transcatheter value replacement, will be deemed a Class II device, the FDA said, which is the classification the company had requested n June 25.

Class II devices require special controls to provide reasonable assurance of safety.

Sommetrics' cNEP Airway Management System was also classified a Class II device, despite a *de novo* request for Class I.

The airway management system is a silicone rubber collar that is attached to the neck and provides negative suction through a regulated vacuum source to provide a patient airway during mild to moderate sedation.

Lastly, Jan Medical's cranial motion measurement device Brain Pulse was also classified as Class II with special controls. The Brain Pulse detects and amplifies skull motion caused by pulsatile flow from the cardiac cycle.

FDA Grants Ninth EUA for Zika Dx

The FDA granted an Emergency Use Authorization for InBios' International's Zika diagnostic to confirm the presence of Zika virus antibodies.

The ZIKV Detect IgM Capture ELISA detects Zika virus IgM antibodies in human sera.

Confirmation of the presence of anti-Zika IgM antibodies or other flavivirus IgM antibodies requires additional testing. The EUA marks the ninth Zika diagnostic the FDA has granted an emergency use authorization.

Levita's Magnetic Surgical System Cleared

Levita's magnetic surgical system was granted FDA clearance and received its CE Mark. The system was initially indicated for gallbladder removal surgery, but it is also used to magnetically retract and maneuver the gallbladder, which reduces the number of incisions.

Masimo Gets CE Mark for RAS-45 Sensor

Masimo gets the CE Marking of RAS-45, which is a single-use adult and pediatric acoustic respiration sensor for rainbow Acoustic Monitoring of respiration rate.

The respiratory acoustic monitoring system is noninvasive and continuously measures respiration rate using an adhesive sensor with an integrated acoustic transducer, RAS-45, that is applied to the patient's neck. The sensor is for patients who weigh more than 22 lbs.

FDA grants 510(k) to Conventus

Conventus Orthopaedics received a 510(k) clearance from the FDA to market its new Conventus Cage device for fractured ulnar bone repair.

The device system employs the shape memory properties of nitinol to expand within the bone which creates a structure that prevents a collapse of the fracture repair. This eliminates the use of plates and screws.

The device is used for the treatment of distal and proximal ulna fractures.

FDANEWS

Customer Service
(888) 838-5578 • +1 (703) 538-7600
customerservice@fdanews.com

Editor: Tamra Sami
+1 (703) 538-7634
tsami@fdanews.com

Ad Sales: Jim Desborough
+1 (703) 538-7647
jdesborough@fdanews.com

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

Reporters: José Vasquez, Cynthia Jessup, Derek Major **Managing Editor:** Jim Stimson **President:** Cynthia Carter

Mastering the FDA's Import Rules

U.S. authorities are holding imports more than ever before, particularly at ports that have a history of holding products, and imports from India.

This management report will tell you how to develop a top-notch import compliance program that will keep you in the "safe zone" when it comes to your dealings with the FDA and Customs. You'll gain a clear understanding of the FDA's expectations and qualifications and Customs' operational processes.

You'll also learn:

- The inside scoop from a former FDA import official on the FDA's latest priorities and expectations
- What to do to minimize your risk of delays, detentions and refusals
- How to work closely with suppliers, contract manufacturers and labelers to significantly reduce your hold times
- How to conduct a gap analysis to identify weaknesses in your existing compliance program
- How the FDA operates its import process and uses its main tool — PREDICT
- The importance of proper declarations and other good importer practices to ensure compliance with FDA regulations

Don't take the chance of having your imports held at Customs for reasons that aren't obvious or clear to you.

It's your chance to save your company time … money … and tiresome headaches.

FOUR EASY WAYS TO ORDER

1. **PHONE:** Toll free (888) 838-5578
   or +1 (703) 538-7600
2. **WEB:** www.fdanews.com/51352
3. **FAX:** +1 (703) 538-7676
4. **MAIL:** FDAnews
   300 N. Washington St., Suite 200
   Falls Church, VA 22046-3431

☑**Yes!** Please send me ____ copy(ies) of ***Mastering the FDA's Import Rules*** at the price of $397 for each PDF.

Name _____

Title _____

Company _____

Address _____

City_____ State _____ Zip code _____

Country _____

Telephone _____

Fax _____

Email _____

METHOD OF PAYMENT

❑ Check enclosed (payable to FDAnews)

❑ Bill me/my company. Our P.O.# _____

❑ Charge my credit card:
❑ Visa ❑ MasterCard ❑ American Express

Credit card no. _____

Expiration date _____

Signature _____
(Signature required on credit card and bill-me orders)

16FLYR-N