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FDA Warns Olympus, Fujifilm, Pentax for Failing To Comply With Postmarket Surveillance Order

The FDA issued warning letters to duodenoscope manufacturers Olympus, Fujifilm and Pentax for failing to comply with federal law requirements to conduct postmarket surveillance studies to assess the effectiveness of reprocessing the devices.

The three manufacturers faced intense scrutiny after the Centers for Disease Control and Prevention linked cases of multi-drug resistant bacteria to duodenoscopes in 2013. The CDC reported that the infections were happening even though users followed the manufacturer's cleaning and disinfection or sterilization instructions.

The FDA said that between January 2013 and December 2014 it received 75 reports involving about 135 patients suffering from carbapenem-resistant Enterobacteriaceae transmissions linked to these devices.

(See **Warns**, *Page 2)*

TGA Announces Overhaul of Medical Product Advertising Regulations

Australia's Therapeutic Goods Administration will impose heavier sanctions for violations of its regulations on device advertising, but the agency also will phase out its requirement that certain advertisements be pre-approved in favor of a more self-regulated rule.

The current pre-approval system will remain in place through July 2020, with the TGA using the next two years as a transition period to ensure advertisers have access to the information they need for compliance.

The TGA's rule requiring advertisers to secure prior approval before referencing serious diseases will remain in place even after the pre-approval requirement is phased out.

The TGA also will amend its Therapeutic Goods Advertising Code to help advertisers understand the requirements, impose

(See **Overhaul**, *Page 2)*

Warns, *from Page 1*

All three companies received warning letters in 2015 for a range of problems related to duodenoscopes, including failure to inform the FDA in a timely manner about patient injuries (*IDDM*, Aug. 24, 2015).

At the time, the FDA ordered the three companies to conduct postmarket surveillance studies to determine whether healthcare facilities were able to properly clean and disinfect the devices.

As part of their approved study plans, all three manufacturers were required to conduct a study to sample and culture reprocessed duodenoscopes that are in clinical use, to learn more about issues that contribute to contamination, as well as a human factors study to assess how well trained hospital staff are following the reprocessing instructions.

To date, Olympus has failed to conduct data collection, and Pentax and Fujifilm have failed to provide sufficient data, as required for their respective studies to sample and culture reprocessed duodenoscopes that are in clinical use, the agency said.

Olympus and Pentax also have not complied with requirements for their respective human factors studies to assess how well hospital staff follow reprocessing instructions. Fujifilm has been meeting its requirements for its human factors study, the agency said.

"The FDA has taken important steps to improve the reprocessing of duodenoscopes, and we've seen a reduction in reports of patient infections, but we need the required postmarket studies to determine whether these measures are being properly implemented in real world clinical settings and whether we need to take additional action to further improve the safety of these devices," said Jeff Shuren, director of the FDA's Center for Devices and Radiological Health.

In June 2017, the FDA introduced new requirements for validating instructions for use and for validation of cleaning, disinfection and sterilization in premarket notification submissions for 11 types of devices, including laparoscopic tools and a variety of endoscopes (*IDDM*, June 12, 2017).

The FDA has worked with all three duodenoscope manufacturers to review validated processing instructions and to take corrective actions to remove and replace models from the market with faulty designs that made them difficult to clean and reprocess.

The FDA said it expects the three companies to submit plans by March 24 that outline how study milestones will be achieved. For the sampling and culturing study, the FDA expects 50 percent of samples collected in the study to be processed by Aug. 31, and 100 percent by the end of 2018.

For Olympus' and Pentax's human factors studies, the agency expects 50 percent of testing to be completed by May 31, and 100 percent by June 30.

Read the Olympus warning letter here: www.fdanews.com/03-13-18-OlympusWL.pdf.

Read the Fujifilm warning letter here: www.fdanews.com/03-13-18-FujifilmWL.pdf.

Read the Pentax warning letter here: www.fdanews.com/03-13-18-PentaxWL.pdf.

Overhaul, *from Page 1*

more objective assessments for what constitutes a breach, and address inconsistences between rules for medicines and rules for medical devices.

As of July 2018, the TGA will become the sole body responsible for handling complaints about advertising of medical devices. It is currently developing a web form for lodging complaints.

Read the TGA's announcement here: www.fdanews.com/03-13-18-TGA.pdf. — Zack Budryk

Warning Letter Roundup: FDA Warns Firms for Misbranding, Quality Issues

The FDA issued warning letters to three devicemakers, citing misbranding and significant quality deficiencies.

Dexcowin: The FDA was not impressed with Korean devicemaker Dexcowin's responses to a Form 483 it received following an August 2017 inspection of its facility in Seoul. The FDA received two responses from the manufacturer of portable dental X-rays, but then issued a 13-item warning letter.

The company's devices were deemed to be misbranded because the Korean devicemaker failed or refused to furnish material or information on medical device reporting, and it had not established records of the results of tests for electronic product radiation safety.

The firm also failed to immediately report accidental radiation occurrences in at least two instances. The warning letter noted that the two incidents still had not been reported.

"Due to an influx of battery complaints, your firm switched battery suppliers. However, your firm did not process this corrective action through its CAPA system," the FDA said. The agency said the firm's response that it would include all 2017 CAPAs in an upcoming review was insufficient because a retrospective review was warranted.

Device validation procedures didn't include predefined methods, operating conditions or acceptance criteria to ensure the device conformed to user needs and intended uses, the FDA said.

The inspection revealed inadequate procedures for identifying, documenting, validating and verifying design changes before they're implemented. The agency said the firm's response did not measure up because it failed to include a retrospective review of other design changes to ensure they were appropriately validated and verified.

The firm had no documentation that testing equipment was qualified for its intended purpose, and it had not maintained device history records.

Document controls were also found to be questionable. For example, the company made updates to procedures on numerous occasions without documenting the date the procedure was updated.

The FDA said it would refuse entry of the company's products into the United States until all non-conformances are corrected.

Laser Dental Innovations: FDA investigators uncovered numerous quality system deficiencies during a December 2017 inspection of Laser Dental Innovations' San Jose, California plant.

The firm was hit with a Form 483 at the end of the inspection, but the agency was not satisfied with the response, and issued a warning letter to the laser fiber optic surgical device manufacturer.

The quality system failures ranged from inadequate corrective and preventive actions, failure to maintain complaint files, failure to establish procedures to control the design of devices, failure to ensure that all products received conform to requirements, and failure to establish procedures to ensure that device history records are maintained in accordance with the device master record.

The FDA inspector observed that the firm failed to document several CAPAs, and that records didn't include a root cause analysis or investigation details. Moreover, no details were provided in the response to the 483 on how the problems would be remedied for complaints associated with broken or improperly functioning collets in the LiteSaber handpieces.

Design history files for the LifeSaber 10mm hand piece and StarLite Fiber Optic devices didn't include records for design validation or design verification, and the company told the investigator that the records "did not exist."

Laser Dental Innovations also failed to establish supplier contracts or supplier evaluations.

The warning letter notes that the firm had not conducted an internal quality system audit since 2011.

(See **Warning***, Page 4)*

India's CDSCO Proposes National Accreditation for Device, IVD Labs

India's Central Drugs Standard Control Organization is requiring laboratories that test medical devices and in vitro diagnostics to register with the agency.

The registrations will allow CDSCO and other government agencies to maintain updated information on all laboratories involved in testing of medical devices and IVDs.

CDSCO issued the order in light of the country's new Medical Device Rules that became effective Jan. 1, marking the first time that India regulated medical devices separately from drug products.

Under the new rules, the Central government may designate any laboratory that has facilities for testing and evaluating devices and IVDs as a central medical device testing laboratory. However, no laboratory may be designated without first being accredited by the National Accreditation Board for Testing and Calibration Laboratories (NABL).

Laboratories that go through the accreditation process will need to inform CDSCO about which devices and IVDs can be tested at their facilities, as well as the persons involved in the testing. Laboratories that are deemed suitable may be officially designated as central medical device testing labs.

Applicants for the central medical device testing laboratory designation should send a valid copy of the NABL certificate to CDSCO along with the scope of the test for which it is accredited, a copy of the testing protocol and test method for each of the test parameters, and a list of equipment with calibration status and manufacturer details.

India will soon release a new national list of IVDs that could be used to improve access to reliable diagnostic tests in public hospitals for high burden diseases such as HIV, tuberculosis and malaria, according to the Indian Council of Medical Research.

The list could be expanded later to create a list of essential diagnostics, similar to India's list of essential drugs, which could be used to set price caps.

Earlier this month, India released final audit fees for notified bodies under its new medical device regulations (*IDDM*, March 5).

Read the CDSCO notice here: www.fdanews.com/03-13-18-Indialabs.pdf.

Warning, *from Page 3*

Opternative: The FDA handed Opternative a warning letter after a review of its website found it was marketing an online eye examination mobile medical app device without marketing clearance.

The agency cited the firm for failing to secure pre-market approval for the app as well as for misbranding because the company failed to notify the FDA it was introducing the device to the market.

The FDA demanded that Opternative immediately cease marketing the product.

Read the three warning letters here: www.fdanews.com/03-16-18-ThreeWLs.pdf.

PEOPLE ON THE MOVE

Anika Therapeutics appointed **Joseph Darling** as CEO. Darling brings more than 20 years of experience in executive management and leadership. He previously served at Abbott Laboratories, Baxter Healthcare, Smith & Nephew, CONMED, and Wyeth-Ayerst.

Exogenesis Corporation named **Dmitry Shashkov** as president and CEO. Shashkov previously served as president and CEO of H.C. Stark Fabricated Products and in several roles at Honeywell Specialty Materials. Prior to Honeywell, he worked at McKinsey & Company, managing projects in chemical, pharmaceutical, and telecommunication industries. Exogenesis is commercializing NanoAccel, a technology that modifies materials at a nanoscale level. It has entered into commercialization agreements with Vallum Corporation to produce enhanced interbody devices for spine fusion procedures.

483 Roundup: Three Device Facilities Hit for Procedural Deficiencies

The FDA cited two device manufacturers and an importer after inspections identified issues with procedures, including product acceptance, complaint handling and medical device reporting.

Fendental MFG: The specification developer and initial importer based in Medley, Florida, drew a Form 483 from the FDA for procedural issues, including complaint handling, after an inspection in December.

The firm did not have a purchasing control procedure or recorded evaluation of its contract manufacturer and own-label product suppliers, making it unable to ensure products and services it received conform to specifications.

It also failed to implement its acceptance procedure for receipt, sampling and storage of products. The firm did not document incoming acceptance activities for any finished devices received.

Fen Dental also had an inadequate complaint handling procedure. It did not require investigation of events that must be reported to the FDA, including the assessment of whether a device failed specifications; whether the device was used for treatment or diagnosis; and any relationship of the device to the event. Its record retention period for complaint files was also inadequate, the agency said.

In addition, one of the firm's medical device reporting procedures did not require the electronic submission of MDR event reports.

SafetyFix Medical Technologies: The FDA issued the Saint Louis, Missouri device manufacturer a Form 483 for device record issues and procedural failures following a November inspection.

The investigator found observed that the firm's device master record (DMR) for fixation screws did not define certain specifications, including for packaging, labeling, acceptance criteria and quality assurance.

The device history record for the same product also did not have documentation of primary labeling, and the agency said the facility had shipped loose, unlabeled fixation screws since 2016.

The firm also had design validation problems. It lacked objective evidence to show that its easy out screw design was validated using initial production

(See **483s***, Page 6)*

Service Report or Complaint?

One of the most confusing issues medical device manufacturers face when servicing their products is determining when a service issue qualifies as a complaint and whether the event must be reported to the FDA.

Servicing is the maintenance and repair of medical devices and falls under 21 CFR 820.200 – Servicing.

The intent of the regulations is to ensure that servicing is correctly performed and verified according to the company's specifications, and that the serviced device is suitable for the intended use.

The regulations require devicemakers to document service reports and include information about the device serviced, the date of service, type of service, test and inspection data, and device identification number.

Devicemakers need a system for screening repair and service reports to determine whether they should be logged as complaints. Although not every service report is a complaint, a service report initiated as the result of a complaint needs to be cross- referenced in the complaint handling system.

If a manufacturer receives a service report representing an adverse event, the report is automatically deemed a complaint and needs to be processed accordingly. All deaths and serious injuries require investigation, regardless of whether it was alleged that the device contributed to the adverse event.

For 90 percent of the market, field service is a devicemaker's main interface with the customer. Field service representatives are a manufacturer's eyes and ears and should be trained to recognize when a service issue qualifies as a complaint and how to follow the company's complaint management SOP.

Excerpted from the *FDAnews* management report: *Complaint Management for Devicemakers: From Receiving and Investigating to Analyzing Trends*.

483s, *from Page 5*

units, lots, batches or their equivalents. The risk analysis was also inadequately documented, as its product design failure modes and effects analysis was unsigned, undated and only in a draft form.

In addition, the firm did not have adequate requirements that must be met by its suppliers. It accepted a contract manufacturer without confirming the supplier could meet product specifications and it lacked documentation to show that a consulting firm it employed was evaluated and approved as a supplier of services.

The firm also lacked written medical device reporting procedures.

Geri-Gentle Corporation: A December inspection of Geri-Gentle Corporation's South Plainsfield, New Jersey facility earned the company a Form 483 from the FDA, citing a lack of supplier requirements and incoming product acceptance procedures.

The agency's investigator found that the firm did not have any written procedures in place to define requirements for suppliers, contractors and consultants, and did not have any procedures for monitoring their performances. It also had no written quality agreements or contracts for quality control in place for them.

The firm also lacked written procedures for receiving acceptance activities. For example, it did not define the acceptance activities required to be performed when receiving finished devices for requirement conformity, such as inspections, label reviews, tests and reviewing certificates of analysis. It also did not document the acceptance or rejection of incoming finished devices.

The firm did not properly establish written procedures that describe how the firm will prevent product mix-ups by controlling non-conforming finished products that it might receive from suppliers or contractors.

In addition, complaint review and evaluation procedures, as well as written procedures for corrective and preventative action and medical device reporting, were not adequately established.

Read the three Form 483s here: www.fdanews.com/03-16-18-Three483s.pdf.

FDA Issues Advisory On Neurovascular Embolization Coils

The FDA sent a letter to health care providers warning of the potential for increased image voids when using magnetic resonance angiography (MRA) imaging for follow-up of certain post neurovascular embolization coil procedures.

Because aneurysms treated with coils may have residual filling or may recur, patients are at risk for late hemorrhage, so follow-up imaging is performed as needed.

When MRA is performed on patients implanted with neurovascular embolization coils containing 304V stainless steel — either as part of the coil implant, or left behind as part of the detachment process — the images may contain larger than expected MR artifact, or image voids, when compared to other metals, the agency said

The reduced quality of the MRA images in these cases can result in inaccurate clinical diagnoses and inappropriate medical decisions.

Digital subtraction angiography (DSA) has traditionally been used for imaging aneurysms after coiling, but as MRA image quality and accessibility improve, more health care providers are choosing to use MRA imaging, the agency noted.

The FDA is "not asking manufacturers to phase out the non-MR conditional products," FDA spokesperson Stephanie Caccomo told *FDAnews*.

However, the agency recommends that health care providers "be aware of the presence of 304V stainless steel in the coil system(s)." If they are uncertain about a particular coil system, they should contact the device manufacturer for specific recommendations regarding the use of MRA with their product.

If the implanted coil system contains 304V stainless steel, health providers should consider using an X-ray-based DSA instead of an MRA, the agency said.

If health care providers use devices without any labeled information about their safety in the MR environment, said Caccomo, the devices "should be assumed to be MR unsafe." The FDA did not disclose which devices contain 304V stainless steel because "materials used by manufacturers are considered proprietary information," she said.

When choosing to use MRA for follow-up, providers should use imaging parameters including a high readout bandwidth and the shortest possible echo times to minimize image artifact, and they should be certain that the MRI system meets all conditions provided in the MRI conditional labeling of the coil system (e.g., magnetic field strength in units of Tesla)."

The agency urged providers to report any image artifacts via the Medwatch online reporting form, including the manufacturer, the brand of coil, the imaging parameters used and any follow-up action taken. — Donna Scaramastra Gorman

APPROVALS

FDA Grants 510(k) Exemption For Denture Repair Kits

The FDA issued an order exempting over-the-counter denture repair kits from 510(k) clearance requirements in response to a petition submitted by Hyman, Phelps & McNamara for the class II devices.

The agency determined that the product's risks and characteristics were well established and that premarket notification was not necessary to provide reasonable assurance of the product's safety and effectiveness, as long as it remains compliant with existing special controls.

The OTC products consist of materials like powder and liquid glues meant to be applied permanently to a denture to fix breaks or cracks. The agency believes that any changes in the device that could impact its safety or effectiveness will be readily detectable by routine analysis and nonclinical testing.

Panther Orthopedics Receives 510(k) Clearance for PUMA System

Panther Orthopedics won FDA approval for its implantable orthopedic fixation device used in the treatment of orthopedic trauma and sports medicine.

(See **Approvals**, *Page 8)*

Approvals, *from Page 7*

The device delivers continuous compression during bone healing and it allows for a 2.8 mm pilot hole that preserves bone tissue. The system was designed to solve the problems experienced with the use of stiff metal screws that restrict normal physiological joint motion and with flexible fixation devices that creep and lose compression.

FDA Approves 23andMe's Home Breast Cancer Testing

The FDA approved 23andMe's at-home screenings for three breast cancer mutations.

The genetic testing company will report the test results as part of its Health and Ancestry product.

Women who carry one of the three BRCA1 and BRCA2 gene mutations are at substantially increased risk for developing breast and ovarian cancer.

Oral Fluid Drug Screen Device Gains 510(k) Clearance

Premier Biotech received 510(k) clearance for OralTox, a rapid oral fluid drug screen device.

The device uses oral fluid as a testing matrix and detects up to 12 drugs simultaneously. Unlike for urine testing, the collection can be fully observed without privacy concerns and it is resistant to alteration.

The test can detect amphetamine, cocaine, marijuana, methamphetamine, opiates and phencyclidine (PCP), and the test can be sent to a laboratory for confirmation. It also offers confirmations of presumptive positive results.

Zebra Medical Scores CE Mark For Brain Bleed Detection Algorithm

Zebra Medical Vision received a CE mark for its brain bleed detection algorithm for integration into its deep learning imaging analytics platform. The algorithm can detect intracranial hemorrhage.

The platform also offers automatic detection for low bone mineral density, vertebral fractures, fatty liver, coronary artery calcium, emphysema and more.

Polyganics Gets Breakthrough Designation For Liver and Pancreas Sealant Patch

The FDA granted breakthrough designation to Polyganics' Liver and Pancreas Sealant Patch designed to prevent leakage after hepato-pancreato-biliary procedures.

The device is made from a proprietary polymer that seals off surgically treated tissues during the healing process.

The Dutch company received a grant of $1.4 million from the European Fund for Regional Development last December for clinical validation of the device.

Roche's Hematology Testing Solution Gains 510(k) Clearance

Roche's cobas m 511 integrated hematology analyzer received 510(k) clearance from the FDA.

The device identifies, counts and categorizes white and red blood cells and platelets, and presents digital images of the cell types.

The cobas m 511 combines a cell counter, stainer, slidemaker and digital morphology analyzer.

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Regenerative Medicine: *Steps to Accelerate Development*

With the 21st Century Cures Act, attention is being focused on the use of human cells and tissue to treat serious and underserved conditions.

The FDA created a new regulatory paradigm in November 2017 when it issued four guidances — 2 final and 2 draft — aimed at explaining, streamlining and accelerating development of regenerative therapies.

Key among these developments is the creation of a new Regenerative Medicine Advanced Therapy (RMAT) designation that offers applicants an abbreviated pathway to approval, working closely with the FDA throughout the process.

Regenerative Medicine outlines the RMAT pathway and breaks down requirements regenerative medicine developers must meet to qualify. The FDA granted RMAT designation to 12 organizations in 2017 — the first year of the program. Now is the time to get in the mix, work with the FDA to develop the program and improve your chance of being one of the next RMAT designees.

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- How to apply for RMAT designation
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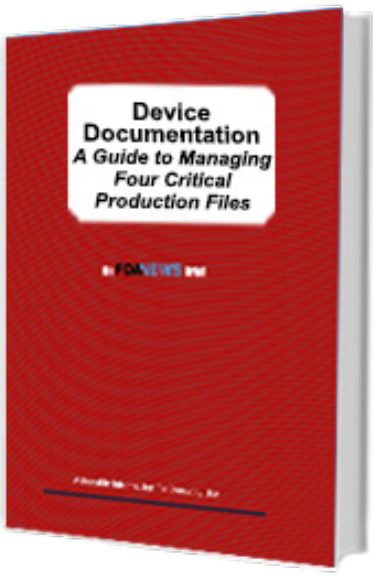

Device Documentation: *A Guide to Managing Four Critical Production Files*

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