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IN THIS ISSUE

CDRH Begins Reorganization Towards Team-Based Approach

CDRH has launched a major shakeup that will create several new offices—including one "super office" for product evaluation and quality.

The overhaul—which begins on March 18 and is set to be completed by Sept. 30—will revamp the center's premarket and postmarket program functions into a team-based configuration. The integration will involve many current components of device reviews, quality, surveillance and enforcement.

The center has previously been organized according to the stage of the product's life cycle, an arrangement that "allows employees to become specialized by function but doesn't always promote the type of communication and collaboration that is proving essential" to device innovation, CDRH said.

(See **CDRH**, *Page 2)*

Australia Proposes New Device Classifications to Align With EU Regs

Australia's TGA released five new draft guidances that propose changes to the classification of numerous medical devices to align more closely with European Union regulations.

The guidances consider the EU's Medical Device Regulation and the potential impact on Australia's regulatory requirements. The five guidances propose changes in device classification for:

- Active implantable devices and their accessories;
- Devices used in direct contact with the heart, central circulatory or central nervous systems;
- Medical devices that administer medicines or biologicals by inhalation;
- Human cells, tissues and organ storage solutions and in vitro fertilization (IVF) media; and
- Substances introduced into the body via a body orifice or applied to the skin.

(See **TGA**, *Page 4)*

CDRH Warns of Device Shortages Following Sterilizer's Suspension

CDRH warned that more than 100 device manufacturers and hundreds of devices face potential shortages following an EPA order to stop medical equipment sterilizer Sterigenics' Willbrook, Illinois facility from sterilizing products with ethylene oxide.

The order bars the facility from beginning any new sterilization cycles using ethylene oxide, which gave off emissions that the Illinois EPA feared would "present an imminent and substantial endangerment to residents and off-site workers" located near the facility. The U.S. EPA found that the ethylene oxide created "elevated cancer risks" after it performed ambient air sampling last year.

The seal order — which resulted from the company's refusal to pause its operations voluntarily — will remain in effect until it is withdrawn by the EPA's acting director.

CDRH said it doesn't know of any related device shortages yet but that the Sterigenics facility's workload consists of over 90 percent medical devices.

"The FDA is reaching out to medical device manufacturers to understand which manufacturers are affected by the cessation of operations at this sterilization facility. At this time, the FDA believes that more than 100 manufacturers and hundreds of devices may be affected," the agency said. — James Miessler

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Instead of evaluating a device "only at one point in time—for instance, to evaluate whether a device meets the standard for approval, or to evaluate postmarket data involving a device safety signal—reviewers, compliance officers and other experts" will now work in teams to carry out device oversight as a device goes through development and commercialization, the center said.

The reorganization will merge certain offices into three new ones, including one "super office," the Office of Product Evaluation and Quality (OPEQ), which will combine the Offices of Compliance, Device Evaluation, Surveillance and Biometrics, and In Vitro Diagnostics and Radiological Health. OPEQ will adopt a total product life cycle approach to device oversight.

Two teams will be formed under the new Office of Policy to deal with guidance, legislation, special projects, and regulatory documents.

The new Office of Strategic Partnerships and Technological Innovation will combine the Science & Strategic Partnerships, Digital Health, Health Informatics and Innovation teams. CDRH noted that the teams will not see a change in their functions.

The plan will also realign center management services to optimize administrative functions and update the center's communications. Some center contacts will change with the overhaul, CDRH noted. The changes in contact information will be added to the center's online management directory.

CDRH began piloting a more integrated approach to device safety throughout the Total Product Life Cycle in June 2018. The center says reorganization will "enhance communication among CDRH staff and enable more efficient activities across the life cycle from premarket review to postmarket surveillance." — James Miessler

BRIEFS

Senators Introduce Bipartisan Bill to Repeal Device Tax

Sens. Pat Toomey (R-Penn.) and Amy Klobuchar (D-Minn.) introduced legislation, the Protect Medical Innovation Act (S. 692), that would end the nationwide medical device tax.

The 2.3 percent medical device excise tax — a tax paid whenever a purchase is made — became active in 2013. In July 2018, the House voted to permanently repeal the tax, with 283 members of Congress voicing their support for revocation.

AdvaMed strongly opposes the tax, arguing that it should be repealed so the industry can "make the multi-year investments in R&D and infrastructure necessary to sustain the innovation ecosystem and take the next leap forward in patient care."

Administration Seeks $55 Million For Device Database in Fiscal 2020

The Trump administration's budget request for fiscal year 2020 calls for $55 million for a safety database that the FDA says will allow the agency to track a device through its total lifecycle.

The FDA is one of the few government agencies that would get a bump in federal spending under the administration's fiscal 2020 budget request.

"This capability to better leverage pre-existing and new data in near real time is essential for implementing the FDA's new approaches for digital health technologies, breakthrough devices, use of real-world evidence and cybersecurity," the agency said. "Overall, this will make medical device reviews, post-market surveillance and cybersecurity efforts significantly more efficient and informative."

FDA Promises Draft Guidance on Staplers

The FDA said it plans to issue draft guidance on surgical staplers and implantable staples as reports of nasty side effects continue to mount.

The agency said it wants manufacturers to include labeling to improve the safety record of the devices that have become common in surgery. Between 2011 and 2018, medical staples have been associated with 41,000 adverse events, including 366 deaths and more than 9,000 serious injuries, the FDA said in a letter to healthcare providers.

The agency said it will host an open meeting of its General and Plastic Surgery Devices Panel Advisory Committee following the release of the draft guidance.

FDA Reclassifies Contraception Software as Class II (Special Controls)

The FDA reclassified software applications for contraception as Class II medical devices with special controls, making them exempt from premarket notification requirements.

The agency moved the device type from automatic Class III into Class II (special controls) because it determined that the change "will provide a reasonable assurance of safety and effectiveness."

The special controls include clinical performance testing to show the software's effectiveness and human factors testing to show users can correctly use the application based on the directions for use. Other controls include software verification, validation and a hazard analysis.

Brain Implant Trials May Need To Include Home Use

Sponsors of brain implant trials seeking an investigational device exemption may be asked to demonstrate that their devices can work in "realistic home use environments," the FDA said in a new draft guidance.

In general, the FDA doesn't grant IDEs for brain implants because it considers them significant-risk devices. But the agency may consider granting exemptions to trials of implants aimed at repairing catastrophic spinal damage or lost limbs if sponsors can show in their protocols that their trials approximate "realistic home-use environments."

Read the draft guidance here: www.fdanews.com/02-28-19-Brainimplant.pdf.

EMA Issues Guidance On New Device, IVD Rules

The European Medicines Agency issued final guidance on new rules for certain in vitro diagnostics and medical devices.

European Union Regulation 2017/745 and Regulation 2017/246 introduces new roles and responsibilities for both the EMA and national competent authorities pertaining to medical devices.

The new regulations will apply to any marketing authorization application for a medicinal product with an integral medical device submitted as of May 26, 2020.

The EMA strongly suggests submitting the certificate or declaration of conformity or notified body opinion as part of the initial application. If after authorization, the sponsor makes a substantial change to the design or intended purpose of the device component, any required certificate or declaration of conformity should be submitted as part of the variation/extension application.

The regulation will not apply to currently authorized products except in cases involving additional or full replacement of the device component or substantial design changes to the device component, the agency said.

Given the "ever-increasing pace of innovation and the blurring of traditional boundaries" between medicines and devices, the agency expects to assume new responsibilities in regulating complex medicines with a medical device component.

"The big challenge we face is to ensure we have the appropriate expertise and resources to adequately carry out these new tasks," said EMA's Executive Director Guido Rasi.

Read the Q&A document here: www.fdanews.com/02-28-19-EMA.pdf. — Zack Budryk

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TGA, *from Page 1*

Australia currently has a separate category for active implantable medical devices, called Class AIMD and the agency proposes to classify these as Class III devices, which would simplify the TGA classification scheme. Implantable accessories to implantable devices are currently classified as Class III devices in Australia and these would remain unchanged.

The EU MDR classifies devices into four classes (Class I, Class IIa, Class IIb and Class III), with active implantable devices and their accessories comprising the highest risk, Class III category.

For sponsors, the proposed TGA changes would mean that all Class III devices, including non-implantable accessories would require conformity assessment documents. This would also include software that drives an active implantable device. The agency is proposing a transition date from August 2020.

The TGA guidance proposes a Class III classification for any surgically invasive medical device that is in contact with heart, central circulatory or central nervous systems regardless of the duration of use or intended indications.

Under the EU MDR, surgically invasive devices intended for short-term use are classified as Class IIa unless they control, diagnose monitor or correct a defect.

Some devices, such as heart valves and balloon catheters are currently classified as Class IIa devices in Australia, and the up-classification would mean that sponsors would have to present conformity assessment certificates along with other regulatory requirements associated with higher-risk devices.

The TGA is proposing a new rule that would classify all invasive devices that administer inhaled drugs as Class IIa unless their mode of action has an essential impact on the efficacy and safety of the drug or they treat life-threatening conditions, in which case they would be classified as Class IIb devices. Currently, there are no specific classification rules for devices that administer drugs or biologicals via inhalation.

Read the five guidances here: www.fdanews.com/03-14-19-Consultations.pdf.

483 Roundup: Four Device Firms Cited for GMP, Other Failures

The FDA hit four facilities for various failures including inadequate validations, CAPAs, written procedures and supplier evaluations.

Datascope: Failure to establish validation procedures or to conduct risk analysis for its Cardiosave hybrid intra-aortic balloon pumps landed Datascope a nine-item Form 483 following a July 30 to Oct. 3, 2018 FDA inspection of its Maywah, New Jersey facility.

Numerous test protocols, including for software design validation and risk management processes were found to be lacking, inspectors said. For example, severity ratings were inconsistent with those identified in a hazard analysis and risk management report. In addition, none of the battery packs for the aortic balloon pump passed acceptance criteria.

A design change procedure failed to identify new or altered risks or hazards or the potential failure of the device to address fluid ingress after modifications were made. The agency inspector found that there "was no design plan documentation" for numerous design changes.

The FDA said the firm's design verification didn't confirm that design output met design input requirements. For example, design verification of the performance testing was conducted in 2011, but no verification was performed for software updates since 2011 despite several software updates.

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

Ten Inspection Objectives

When examining CAPA systems, FDA investigators focus on 10 specific areas:

1. Compliance with the Quality System Regulation (QSR);
2. Sources used to identify problems;
3. Examination of unfavorable trends;
4. Quality of the data information system:
5. Statistical methods;
6. Failure investigations;
7. Corrective action;
8. Evaluation of corrective action's effectiveness;
9. Verification that corrective and preventive actions were implemented and documented; and
10. Dissemination and management review of CAPA results.

Investigators will check to see if a manufacturer has an understanding of the terms and concepts involved in CAPA management, such as nonconformances, quality audit, corrective action and preventive action. So CAPA procedures must include definitions of these and other terms. The FDA doesn't specify what definitions to use.

Quality systems expert Dan O'Leary, president of Ombu Enterprises, recommends looking to the QSR and international standards such as ISO 8402:1994, ISO 9000:2005 or ISO 9000:2015 to develop definitions, but be sure to cite the source in each case.

FDA investigators will check the kind of data collection and monitoring a devicemaker conducts as part of efforts to catch trouble when, or even before, it occurs. The sources a company uses to identify nonconformities should include data and information collected during manufacturing, such as acceptance activities, and after distribution, such as complaint, service and returned product records. Quality audits, installation reports and litigation records also are acceptable sources.

Devicemakers should also examine their historical records, such as component test results, for shifts or trends that could predict a potential nonconformance. Investigators want to see evidence that such trends were studied and appropriate preventive actions considered.

The primary complaint in FDA warning letters featuring CAPA citations is that, although the devicemaker had established CAPA procedures, it did not follow or document them properly.

Excerpted from the FDAnews management report: *Creating QSR-Compliant CAPA Systems: A Practical Guide for Devicemakers*.

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Datascope also failed to document corrective and preventive actions or statistical analyses of failures. Investigators noted that procedures for rework of nonconforming product was not adequately established. In addition, suppliers were not properly vetted o confirm they could meet specifications.

Nurses Assist: Failure to identify actions needed to correct and prevent microbial contamination landed Nurses Assist an FDA Form 483 following an Oct. 15 to Oct. 25, 2018 inspection of the firm's Haltom City, Texas facility.

The maker of senior care products for institutions initiated and closed at least 32 nonconformances due to bioburden issues since July 2017, but it didn't establish procedures to confirm that corrective actions were effective.

For example, the manufacturer failed to validate the effect of a sterilization process for sterile water and saline bottles that are packaged in tracheostomy care kits.

The agency cited the firm for failure to establish procedures to prevent contamination by substances that may have an adverse effect on product quality. Specifically, inspectors observed a leaking filter in a system used for manufacturing USP sterile water and saline, as well as a rusty metal support above the saline mixing tanks that were not closed properly.

Wellman Advanced Materials: Written procedures were found to be missing for a range of quality parameters at Wellman Advanced Materials' Johnsonville, SC, plant during a Dec. 10-13, 2018 FDA inspection.

The compounder of thermoplastic resins lacked written procedures for the quality control unit or records of annual evaluations or reviews for FDA-regulated products.

Records indicated that GMP training had not been conducted since 2014 and training for laboratory personnel was not documented.

"GMP training is not conducted on a continuing basis and with sufficient frequency to assure that employees remain familiar with GMP requirements," the agency said.

Belluscura: The FDA hit Plano, Texas devicemaker Belluscura with a Form 483 for failing to properly document evaluations of potential suppliers to ensure that their products conformed to specified requirements.

In a Nov. 19-29, 2018 inspection, the agency noted that the facility evaluated prospective suppliers using a questionnaire prior to an audit but had failed to do that for two of its suppliers.

Read the Datascope Form 483 here: www.fdanews.com/03-12-19-datascopecorp483.pdf.

Read the Nurses Assist Form 483 here: www.fdanews.com/03-12-19-nurseassistllc483.pdf.

Read the Wellman Advanced Materials Form 483 here: www.fdanews.com/03-12-19-wellmanadvancedmaterialsllc483.pdf.

Read the Belluscura Form 483 here: www.fdanews.com/03-12-19-belluscurallc483.pdf.

TGA Ends Three Year Transition to ISO 13485:2016

Australia's Therapeutic Goods Administration reached the end of its three-year transition period to the 2016 version of ISO 13485 and devicemakers using the updated standard to show Quality Management System (QMS) conformity are now expected to have their systems up-to-date.

As of March 1, all ISO 13485:2003 certificates issued by the TGA are now expired and may not be extended. Only 2016 QMS certificates can now be issued by the agency to manufacturers who have been audited according to the new standard.

The agency said manufacturers must provide evidence in their conformity assessment applications that their QMS has been implemented in harmony with ISO 13485:2016. Applications submitted before the period ended should still be able to use the 2003 standards, but the agency said it would alert applicants if additional QMS evidence is needed before it can issue a conformity assessment certificate.

Devicemakers that have a current TGA-issued conformity assessment certificate for part one of the device regulations (excluding clause 1.6, part 4 or part 5) don't need to submit any additional information, nor do manufacturers not currently seeking TGA approval for substantial changes or recertification.

The FDA is planning to issue a proposed rule some time in 2019 on adopting ISO 13485:2016, and said it will hold a panel committee meeting after it releases the proposal. It will also develop, in collaboration with industry, a report comparing ISO 13485:2016 and QS regulation. — James Miessler

APPROVALS

FDA Approves New Indication For Abbott's MitraClip

The FDA approved a new indication for Abbott Vascular's MitraClip heart valve repair device for reducing mitral regurgitation, a leakage of blood backward through the mitral valve into the heart's left atrium.

The device was first approved in 2013 for reducing mitral regurgitation in certain patients whose significant mitral regurgitation and heart failure symptoms resulted from abnormalities of the mitral valve. The new indication is for treatment of patients with normal mitral valves who develop heart failure symptoms and moderate-to-severe or severe mitral regurgitation because of diminished left heart function.

Admedus Earns CE Mark For Collagen Bioscaffold

Admedus earned the CE Mark for its Vascu-Cel collagen bioscaffold, a device used in a wide variety of vascular surgical procedures.

The device is strong but pliable and designed for good suturability. It is bioengineered using the company's proprietary ADAPT technology and has been used with success in cardiac repairs and reconstructions.

The bioscaffold reduces the need for agents to stop bleeding due to its hemostasis capabilities and is ready for use off the shelf with no rinsing required.

Sonavex's Blood Flow Monitor Cleared

Sonavex's blood flow monitoring device EchoSure received 510(k) clearance from the FDA, allowing surgeons to monitor a patient via a mobile device.

The ultrasound technology "may enable detection of vascular compromise earlier than clinical observation alone, providing opportunities for more rapid intervention and improved patient outcomes," said Sonavex President and Chief Medical Officer Devin O'Brien Coon.

The device uses deep learning algorithms with 3D ultrasound imaging to visually and quantitatively measure a patient's blood flow in real-time after microvascular and vascular surgeries.

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

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Alcyone Lifesciences Gains Breakthrough Device Designation for ThecaFlex

Alcyone Lifesciences earned a breakthrough device designation from the FDA for its ThecaFlex DRx system, indicated for patients aged three or older who need chronic bolus intrathecal treatment.

The device, which is made up of a subcutaneous port and an intrathecal catheter used to access cerebrospinal fluid, helps treat patients with life-threatening, debilitating central nervous system disorders.

The device is designed for patients who cannot undergo lumbar punctures due to spinal anomalies or who are resistant to lumbar punctures needed for therapy administration.

FDA Hands Paige.Ai Breakthrough Designation for Cancer Diagnosis Tool

The FDA awarded Paige.Ai breakthrough device designation for an artificial intelligence system designed to diagnose cancer.

The diagnostic tool reviews digitized slides through an arrangement with a cancer center and funding is available for digitization of four million slides.

The software uses an algorithm that is trained with expert cancer diagnoses and is the first publicly announced AI tool for diagnosing cancer.

Agfa Receives 510(k) Clearance For Imaging System

Agfa received 510(k) clearance from the FDA for its DR 800, a multipurpose imaging system that offers radiography, fluoroscopy, tomography and other advanced clinical applications.

The image processor is equipped with software for better brightness control, enhanced noise suppression and veiling glare reduction.

The device includes software that processes the tomographic slices it generates from a tomographic sweep and can reconstruct images in less than a minute.

Co-Diagnostics Gains CE Mark For ZDC Multiplex Test

Co-Diagnostics received the CE Mark for its Logix Smart Zika/Dengue/Chikungunya in vitro diagnostic test and the company is now producing the multiplex test at its facility in Salt Lake City, Utah.

The Logix Smart test detects the three mosquito-transmitted viruses in patients and distinguishes between them by analyzing their RNA. If a specimen tests positive for Zika, a cerebral spinal fluid sample can be taken to look for neurological infection.

Zika, dengue and chikungunya all have similar symptoms — such as joint pain and severe fever — and thus can be misdiagnosed by physicians.

Saranas Wins Novo Designation For Endovascular Bleed Monitor

The FDA granted Saranas a de novo designation for its Early Bird endovascular bleed monitoring system.

The Early Bird incudes a vascular access sheath equipped with sensors to detect and monitor bleeding from blood vessels that have sustained damage from endovascular procedures like TAVR and hemodynamic support device placement.

The company said that the Early Bird is the only device on the market designed for early bleed detection.

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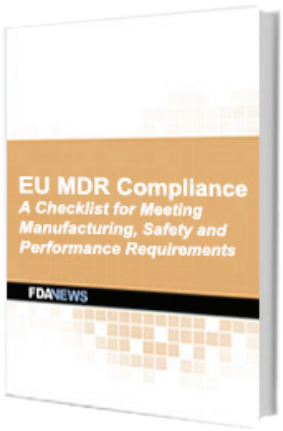

EU MDR Compliance: *A Checklist for Meeting Manufacturing, Safety and Performance Requirements*

The new EU Medical Device Regulation is massive… complex… and confusing… and you must be ready to comply by May 26, 2020.

When the European Union revised its system of rules for medical device manufacturers in 2017, it replaced a longstanding set of directives on specific topics with one large document that covers all aspects of making devices in EU countries.

Not only did they consolidate all the rules, they gave them greater weight. Previously, medical device directives provided guidance but did not have the force of law. The new MDR, however, contains mandates that are legally enforceable by EU member countries.

The FDAnews report **EU MDR Compliance** can help. Our editors have combed through the regulations, picking out the most minute compliance points and building them into a checklist of 200+ requirements you can use to confirm that you are satisfying all the EU mandates for device manufacturing. The report provides:

- Definitions of key terms in the EU MDR
- Knowing where to find specific requirements in the 150+ page regulation
- Checklists that walk you through every aspect of manufacturing, safety and performance requirements
- A training tool for employees new to the regulations

EU MDR Compliance: *A Checklist for Meeting Manufacturing, Safety and Performance Requirements* is the tool that collects all the requirements, explains them and itemized them in an easy-to-use form to ensure compliance.

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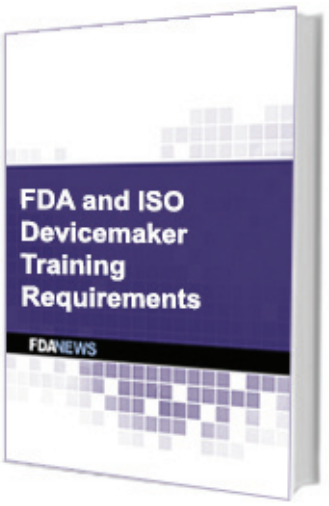

FDA and ISO Devicemaker Training Requirements

Device manufacture is a complicated business, but few areas are more rulebound than QMS. Many a devicemaker has come up short trying to stay abreast of the FDA's QSR, ISO 13485:2016, and other ISOs while trying to comply with competence, training and awareness rules.

It takes more than teaching simple skills to achieve the state of job readiness and performance required of devicemakers' workforces. Regulators agree that a comprehensive training program should consider employee education, experience, background and skills. What they don't agree on is what those concepts mean and how to incorporate them into training.

FDA and ISO Devicemaker Training Requirements breaks down training requirements in both the FDA's QSR and international standards ISO 13485, 9001 and 10018 — among others — shows where they overlap and where they differ and provides a plan for developing a training program that fills in all the gaps. You will learn:

- The four elements of competency
- Definitions of key terms and requirements
- The concept of a "designated individual" and the qualifications for the role
- The importance of a well-written job description
- The difference between a "job" and a "role"
- Factors in employee awareness and how to foster them
- How to evaluate your training program for compliance and effectiveness

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