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IN THIS ISSUE

EMA Answers Industry Questions on MDR/IVDR

The European Medicines Agency released a new question and answers document on its Medical Devices Regulation and In Vitro Diagnostic Regulation in an attempt to answer mounting questions from industry.

The agency released a similar document early in the year, but the new Q&A provides more details on how the new regulations will be implemented starting May 26, 2020 for devices and May 26, 2022 for IVDs.

The new Q&A adds information on how combination products will be regulated, and which division will review certain combination products, as well as the process for selecting notified bodies, how the new regulations will affect mutual recognition procedures and timelines for changes to devices.

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Court Says Methods for Appointing PTAB Judges Are Unconstitutional

In a case that involves two medical device companies, the Federal Circuit Court of Appeals has ruled that the method for appointing Patent Trial and Appeal Board's administrative patent judges is unconstitutional.

Smith & Nephew petitioned PTAB to conduct an inter partes review of Arthrex's patent for a knotless suture securing assembly. After a briefing and trial, PTAB invalidated the patent.

On appeal, Arthrex argued that the appointment of the board's Administrative Patent Judges by the Secretary of Commerce violates the Appointments Clause of the Constitution, so their case wasn't heard by constitutionally-appointed judges.

The appeals court agreed, finding that the PTAB director does not have enough oversight over the judges. The three-judge panel vacated the board's decision and remanded the case to a new panel of patent judges.

FDA Offers Advice on Drug Master Files For CDER-Led Combination Products

Sponsors of CDER-led drug-device combination products that include electronics or software should include specific technical information in their Type V drug master files, the FDA said in a draft guidance.

The guidance applies to combination products that include devices such as those used for drug delivery — an electromechanically driven pen injector with software that analyzes dosing, for example.

Following CDER's review of a Type V drug master file, the device information may be used to support multiple CDER submissions, including an IND, NDA, ANDA, BLA, or amendments and supplements to those applications, or another DMF, the agency said.

"Because of rapid advances in technology, the device constituent part in… combination products could be modified frequently," the agency noted, adding that sponsors should submit an amendment to a Type V DMF for any modifications to the device constituent part.

Read the draft guidance here: www.fdanews.com/10-28-19-DraftGuidance.pdf. — James Miessler

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For combination products, the EMA follows similar rules as the FDA when it comes to which division will review the device or drug. For example, if the action of the device is primary, then the combination product will be regulated as a medical device and must be CE marked. If the drug is primary, then the product is regulated as a medicinal product.

Companies are "free to choose the notified body they engage with," the EMA said, noting that the only requirement is that the notified body must be designated to carry out conformity assessment procedures for the device type for which a certification is sought.

If a combination product forms a single integral product that is not reusable, the product is governed by the Medicinal Product Directive 2001/83/EC. Examples of integral products are pre-filled syringes, pre-filled pens, nebulizers recharged with a specific drug, patches for transdermal drug delivery and pre-filled inhalers.

Article 117 of the MDR amended directive 2001/83/EC. The change means that, for a device component with CE marking, devicemakers must include a declaration of conformity or the EU notified body certificate with their marketing authorization applications. In some cases, an opinion from a notified body on the conformity of the device part may be submitted, the agency said.

The EMA clarified that Article 117 will not apply to marketing authorization applications submitted before May 26, 2020.

Devicemakers will need to provide a new declaration of conformity when substantial changes are made to a medical device component that affect performance and safety characteristics.

Mutual Recognition Procedures

The mutual recognition procedure, in which an authorization of a device in one EU member state is recognized by another member state, and the repeat use procedure — the use of a mutual recognition procedure for recognition of a marketing authorization by another member state — are new applications for marketing authorization, and devicemakers will need to meet all MDR requirements if an application is submitted after May 26, 2020, including Article 117 for integral devices.

UDI requirements are not applicable to integral combination products if the product is regulated as a medicinal product, when the device component is ancillary.

For integral devices with a CE Mark, the UDI may be assigned to the device itself. However, the UDI should not appear on the labeling or outer package of the medicinal product, the EMA said.

Read the EMA Q&A here: www.fdanews.com/11-07-19-EMA.pdf.

Senators Voice Concerns About FDA's Software Precertification Program

Three Democratic senators raised new concerns about the FDA's digital health pre-certification program and pressed the agency for more clarity.

The Oct. 30 letter from Sens. Elizabeth Warren (D-Mass.), Patty Murray (D-Wash.) and Tina Smith (D-Minn.) came one year after another letter to the FDA outlining similar concerns.

In the Oct. 10, 2018 letter, the three senators included more than 20 questions on the program, including the FDA's legal framework, the qualification process, monitoring and postmarket surveillance, and the agency's ability to oversee digital health products.

At the time the senators said the agency should be focused on ensuring it has the tools and capacity

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BRIEFS

Danish Regulator to Double Device Unit Staffing, Launch Analytics Center

The Danish Medicines Agency will more than double the staff in its medical devices unit in 2020 as it aims to "massively build up capacity."

The agency is also establishing a new medical device data analytics center to better handle the growing volume of data to monitor devices under real world conditions. The center will be the first of its kind in Europe, the agency said.

In addition, the center will set a regulatory framework for data in terms of how they are obtained, protected and used in the interest of public health and in line with "data-ethical standards," it said.

The move comes at a time when the industry is quickly evolving with new products and technologies such as 3D printing emerging, but it also is a response to the EU Medical Device Regulation that comes into force next year.

The unit is reorganizing into four teams including: an international collaboration team; a premarket team to handle notified bodies, approval of clinical trials and applications for exemption; a team responsible for medical devices on the market, including registration of manufacturers, and market surveillance.

India's CDSCO to Regulate All Devices by Year End

India's Ministry of Health and Family Welfare reported that all medical devices will officially be overseen by the Central Drugs Standard Control Organization by the end of 2019.

Under the provisions of the 2017 medical devices rules, all foreign devicemakers must comply with conformity assessment requirements, which means obtaining a conformity assessment certificate and registering their devices on the National Register of Medical Devices before they can be marketed in the country.

In addition, a draft law proposes compensation to patients for faulty medical devices. The Medical Devices Bill 2019 applies to all locally made and imported medical devices. The draft law includes penalties and jail terms for placing a device on the market without a conformity assessment certificate.

EU's Medical Device Coordination Group Promises 50 Guidances on EU MDR

The European Commission's Medical Device Coordination Group plans to release 50 guidance documents on the EU Medical Device Regulation and the In Vitro Diagnostic Regulation.

Most of the documents will cover oversight of notified bodies and clinical investigations. Several documents in the works relate to unique device identification, including integration of UDI in devicemakers' quality management plans, and guidelines on specific product types.

Other guidances are expected on nomenclature. One on standards and one for market surveillance for Class I devicemakers is expected before year end.

Read the full list her: www.fdanews.com/11-07-19-guidance.pdf.

Senators Press FDA on 'Progressive Approval' for Medical Devices

Two senators pressed the new acting FDA Commissioner Brett Giroir and CDRH Director Jeffrey Shuren in a Nov. 4 letter on the agency's proposal to create a "progressive approval" pathway for medical devices.

Sens. Elizabeth Warren (D-Mass.) and Patty Murray (D-Wash.) noted former FDA Commissioner Scott Gottlieb had said in July 2018 that the agency's conditional approval pathway for animal products would not be appropriate for human medical products.

The pathway, which the agency proposed in April, would "allow certain medical devices onto the market before manufacturers completely demonstrated the device's safety and effectiveness," potentially creating risks for American consumers, the senators said.

Warren and Murray wrote to express their disappointment that the agency no longer stands behind the comments made by Gottlieb. The senators previously pressed the agency for information on the proposal in June.

The lawmakers also asked for details of eligibility criteria for the pathway, the agency's approach to post-market data collection, and its ability to remove medical products from the market once they have been approved.

Read the Senators' letter here: www.fdanews.com/11-07-19-FollowupLetter.pdf.
— Jordan Williams

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to guarantee that software products that perform medical device functions are safe and effective and to hold companies that skirt the rules accountable.

"Instead, the Pre-Cert Pilot focuses heavily on the potential of standards for design, validation, and maintenance of software and the ability to capture post-market data to reduce premarket review time or eliminate the need for premarket review altogether," it said (*IDDM*, Oct. 12, 2018).

The FDA responded to the senators' original concerns in June, but the new letter includes new questions on the program.

The senators were particularly concerned about the "excellence appraisal" the FDA plans to use for an organization-level review of a software as a medical device manufacturer to evaluate an organization's capability for developing, testing, and managing software throughout a product's lifecycle.

The senators pressed the agency about the limits of flexibility that would be applied to devicemakers and what type of data or evidence the agency is considering. The senators asked the agency to provide a copy of a mock excellence appraisal summary that was used in a recent pilot program.

In addition, the letter raises concerns about the appropriateness of the de novo pathway as a statutory basis for the program, as well as the plan to rely on real world performance analytics from organizations.

Read the Oct. 30 letter here: www.fdanews.com/11-07-19-Letter.pdf.

Contract Manufacturer Cited for Validations, Nonconforming Product

Lax process validation, inadequate control of nonconforming product and failure to implement CAPA procedures were a few of the concerns the FDA highlighted during an inspection of Mark Two Engineering's Miami Lakes, Florida facility.

Process validation activities were found to be unacceptable because they didn't include acceptance criteria, production records and inspection data records, the FDA said. Inspection records also lacked the operator's initials and dates.

The agency investigators said that six of seven CAPA procedures were missing critical information, including root cause evaluation, effectiveness checks and corrective action plans. The 483 said the contract manufacturer of medical device components didn't perform trending of complaints and nonconforming products.

For example, one complaint investigation identified the possible root cause as failure to follow proper line clearance procedures as an isolated occurrence. However numerous complaints also addressed this root cause failure, and complaints and CAPAs were not reviewed to determine if corrective actions were implemented, the agency said.

The contract manufacturer had not implemented procedures to control nonconforming products, not all material review record forms included the disposition of nonconforming products, and evaluations of the nonconforming products doesn't include the need for an investigation.

Other observations on the eight-item 483 included failure to maintain equipment and supplier evaluations, and failure to establish procedures for receiving, reviewing and evaluating complaints by a formally designated unit.

Read the Mark Two Engineering Form 483 here: www.fdanews.com/11-07-19-marktwoengineeringinc483.pdf.

Changes to FDA Inspection Protocols

Since 2013, the FDA has been working toward a realignment of its inspection structure, including shifts in personnel as well as priorities.

The changes include an increased focus on inspectors with technical expertise around various kinds of medical devices and emerging technologies. In practice, this means devicemakers will see two inspectors at a time, rather than one. The first will be a general quality system investigator, while the second will be someone with specialized knowledge about the type of device a company manufactures — such as implantables, nanotechnology or stents.

Devicemakers should expect to always see one inspector who is extremely familiar with the type of device they're making. John Avellanet, managing director and principal of Cerulean Associates suggests having a subject-area expert on hand for the inspection, someone who can answer technical questions and explain things to an inspector clearly.

This also means that if the subject-area expert goes on vacation, or is out sick, a backup expert should be available, or at least on call. For small companies, this might mean contacting a professor at a local university who helped develop the technology, or someone who did some testing and clinical trials for the product.

The agency has trained its investigators on the basics of data integrity, and it has plans to do more specialized data-integrity training as well as training in emerging technologies, such as 3D printing.

Companies that can demonstrate consistent quality benchmarks could see fewer regular inspections as a result of the FDA's ongoing effort to better allocate its limited resources.

One of the top priorities for CDRH is to move toward "a culture of quality and organizational excellence," according to Cisco Vicenty, program manager for the CDRH's Case for Quality initiative. In practical terms, this means CDRH is Looking at how it can help drive a "quality mindset" within the medical device industry, strengthening product and manufacturing quality across the board.

Excerpted from the FDAnews management report: *CDRH in Transition — Navigating the New Culture of Quality*.

Device Re-Packager Lacks Procedures To Control Labeling, Device History

Alt Medical Devices' Miami, Florida plant lacked procedures to control labeling activities and procedures for maintaining device history records to show that its devices were re-labeled and re-packaged according to specifications, FDA investigators found.

In a nine-item Form 483, they noted a history of documentation lapses and failure to establish quality control procedures.

For example, device history records for bio-microscopes re-labeled and re-packaged by the firm weren't available for inspection, and inspectors said the firm lacked procedures for controlling and documenting acceptance activities such as incoming inspections, in-process functional testing for devices.

In addition, the firm lacked supplier control procedures for monitoring and documenting approved suppliers for devices re-labeled and re-packaged. Written procedures that define requirements and methods for reportable events submitted to the FDA were also lacking, as were procedures for CAPA events and conducting quality audits, the 483 said.

Read the Alt Medical Devices Form 483 here: www.fdanews.com/11-07-19-altmedicaldevices483.pdf.

Contract Manufacturer Fails to Validate Equipment, Document Complaints

Failure to validate equipment and to establish CAPA procedures were among the QMS failures discovered during an FDA inspection of contract manufacturer Custom Milling Center's Golden, Colorado facility.

The contract manufacturer failed to validate its process for equipment used in manufacturing Class II dental devices, and the documentation didn't include all requirements defined in the process validation procedures.

Numerous documentation lapses were observed for corrective and preventive action procedures, including missing signatures and risk assessments of CAPA actions. The agency found no analysis of processes, work operations, quality audit reports, quality records, service records, complaints, returned product and other sources of quality data.

The investigators reviewed at least 13 customer complaints and all 13 were missing documentation of device history record reviews or dispositions, and none were finalized with signatures and dates of reviews and closures. Four complaints failed to specify the product associated with the complaint.

The firm had not established a device master record for manufacturing patient-specific Class II dental abutment medical devices and device history records were not established, the 483 said.

Read the Custom Milling Center Form 483 here: www.fdanews.com/11-07-19-custommillingcenterinc483.pdf.

Georgia Attorney General Moves To Shutter BD Sterilization Plant

Georgia's Attorney General filed a complaint to temporarily stop Becton, Dickinson from operating its Covington medical device sterilization facility "in an unlawful manner."

The state claims that from Sept. 15, 2019 through Sept. 22, 2019, BD violated the Georgia air quality rules when it "negligently allowed the release of 54.5 pounds of ethylene oxide into the atmosphere, which upon further investigation has been determined to have been caused by a lack of diligence and prolonged operator error rather than an equipment malfunction."

"In addition, BD has failed to take all responsible precautions to prevent fugitive emissions of ethylene oxide in a timely manner as required by the Act, the Rules and its Air Quality Permit," the Office of the Attorney General said.

The state said that BD should be shut down until it demonstrates to the Court that it has completed the following actions:

- Trained all technicians on the proper operation of all valves in the facility;
- Completed corrective action to prevent a future release from all vacuum exhaust valves at the facility by installing blanks on the outlets to all vacuum exhaust valves to prevent flow regardless of valve position or condition; and
- Installed necessary pollution control equipment to capture fugitive emissions of ethylene oxide at the facility and route them to a control device with at least 99 percent efficiency.

"Today's action by the state of Georgia is a result of BD's lack of response to these recent violations, which is in stark contrast to the response that Governor Kemp and EPD have gotten from other similar medical commercial sterilizers in Georgia that have complied with EPD's requests and are progressing in their efforts to reduce ethylene oxide emissions," said AG Chris Carr.

APPROVALS

WaveForm Gains CE Mark For Glucose Monitor

Wilsonville, Oregon devicemaker WaveForm announced that it received the CE Mark for its Cascade continuous glucose monitoring system, a device that displays its readings on a mobile app.

Using a disposable sensor that patients can wear for up to two weeks, the device sends measured glucose data to its accompanying mobile app via a Bluetooth transmitter every minute, with no additional receiver device necessary.

The monitor can be used for making diabetes treatment decisions for pregnant women, patients requiring dialysis and children aged two years and older.

DiFusion's New Biomaterial-Using Spinal Implant Gains FDA Clearance

The FDA has handed 510(k) clearance to DiFusion for its Xiphos-ZF spinal implant, the first device of its kind to use the new biomaterial Zfuze.

The biomaterial's surface is negative charged, microporous, and hydrophilic rather than hydrophobic, allowing it to support bony ingrowth while keeping the mechanical properties and imaging capabilities of traditional PEEK (polyetheretherketone) implants.

Zfuze can be injection molded, 3D printed or machined, and surface treatments such as laser etching and nano-surfacing can be performed on the material, DiFusion said.

Focal Healthcare's Prostate Fusion Biopsy Solution Gains CE Mark

Focal Healthcare has received the CE Mark for its Fusion Bx 2.0, a semi-robotic prostate fusion biopsy solution that enables urologists to perform targeted prostate biopsies.

The system uses a simple interface and comes with a semi-robotic arm used to maintain probe steadiness during biopsies. It also displays a 3D

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

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model for prostate and MRI target visualization in real-time.

The Fusion Bx 2.0 features automatic motion compensation to account for patient movement, maintaining imaging and allowing procedures to continue uninterrupted.

FDA Clears Okami's Vascular Occlusion System

The FDA granted Okami Medical 510(k) clearance for its Lobo vascular occlusion system, a device used in the occlusion of peripheral blood vessels.

The low-profile braided occluder is a minimally invasive device for rapid and focal occlusion of a wide range of arterial targets.

The system is compatible with microcatheters, allowing it to navigate the peripheral vasculature. It self-expands upon deployment and can conform to multiple targets, including curved vessels.

Tractus' Catheter Earns FDA Clearance

Tractus Vascular has received 510(k) clearance for its Tractus crossing support catheter (CSC), which has been cleared in various lengths and guidewire compatibilities.

The catheter is used during interventional procedures in the peripheral and coronary vasculatures to support a guidewire and enable access in hard-to-reach regions. It allows guidewire changes and gives a channel for saline solutions and contrast media.

The Tractus CSC has been cleared for 0.014, 0.018 and 0.035 guidewire compatibilities and 90, 135, 155, and 170 centimeter lengths.

TGA Approves Mallinckrodt's Uvadex for Use with Cellex Platform

Australia's Therapeutic Goods Administration (TGA) has granted Mallinckrodt approval for use of its cancer drug Uvadex (methoxsalen) with the Therakos Cellex photopheresis system for treating adults with chronic graft versus host disease (cGvHD) and skin manifestations of cutaneous T-cell lymphoma (CTCL).

The treatment — in which blood is removed from the patient by machine and white blood cells are isolated and then exposed to medication, followed by irradiation and return to the patient — is indicated for cGvHD in adults following stem cell transplantation and palliative treatment of skin manifestations of CTCL that doesn't respond to other treatments.

The Cellex platform combines cell collection, photoactivation and reinfusion technologies in a single closed system and can be operated by a single person.

FDA Clears HeartVista's AI-Assisted Cardiac MRI Software

The FDA granted HeartVista 510(k) clearance for its One Click AI-assisted magnetic resonance imaging acquisition software for use in cardiac MRIs.

The software provides standard cardiac views in just ten seconds while the patient breathes freely, taking the complexity and long scan times out of cardiac MRIs.

The software also flags when the image quality is subpar and prompts the operator to reacquire the images if they wish.

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Medical Device Calibration: *A Step-by-Step Guide to Meeting FDA and ISO Standards*

Warning letter citing calibration failures are on the rise — indicating that the FDA is paying more attention to the issue.

Both the FDA and ISO have specific requirements for calibrating medical devices. And — they don't always line up. So devicemakers doing business in the US and abroad need a clear path to compliance if they want to avoid penalties.

Medical Device Calibration: *A Step-by-Step Guide to Meeting FDA and ISO Standards* provides a roadmap that walks devicemakers through each aspect of calibration requirements — showing where the FDA and ISO differ and where they match up — and explains how to combine them to endure full compliance.

You will learn:

- The role of monitoring and measuring in a medical device Quality Management System (QMS)
- Requirements for calibration in FDA's Quality System Regulation
- How to distinguish between accuracy and precision
- The role of traceability in a calibration program
- The audit requirements in both QSIT and MDSAP

The report defines key terms and concepts involved in calibration including proving that calibration practices can be traced back to recognized national and international standards.

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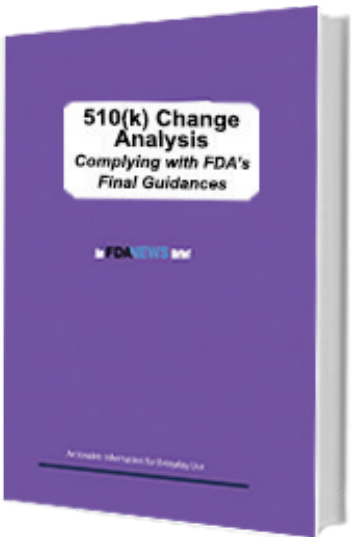

510(k) Change Analysis: *Complying with FDA's Final Guidances*

510(k) Change Analysis: *Complying with FDA's Final Guidances* breaks down the guidances finalized in October, 2017 — *Deciding When to Submit a 510(k) for a Change to an Existing Device* and *Deciding When to Submit a 510(k) for a Software Change to an Existing Device* — and provides a step-by-step method for making the right call for submitting a new 510(k) application. Expert-developed spreadsheets walk you through the questions you must ask and lead you to the proper conclusion.

After reading this book, you'll understand:

- What kinds of changes trigger the need for a new 510(k) application and which don't
- How to evaluate the effect of the change on the device's safety and effectiveness
- How to assess the risk the change may introduce
- The components of risk as described in ISO 14971
- How to follow the complex flowcharts the guidances present
- How to develop a risk matrix
- How to document the decision-making process, including justifying a decision not to file a new 510(k)

In addition to the decision-making spreadsheets that all but do the work for you, the report includes copies of both guidances and an example of a change analysis effort.

Order your copy of the **510(k) Change Analysis** brief for step-by-step instruction on deciding whether you need to submit a new 510(k) if you change an existing device.

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