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IN THIS ISSUE

FDA Reaffirms Flexibility On GCP Compliance for Device Trials

In a March 19 webinar, the FDA amplified its commitment to exercising discretion when devicemakers seek waivers for new requirements that aim to support quality and integrity of clinical data and protection of human subjects by incorporating good clinical practice (GCP) standards.

A final rule on human subject protection, which went into effect on effect Feb. 21, requires that data from medical device trials be gathered in accordance with GPCs. It applies to data that supports investigational drug exemption applications, 510(k) submissions, and de novo classification requests, as well as applications for premarket approval, product development protocols and humanitarian device exemptions. It also applies to bench and in vitro diagnostic studies of de-identified specimens.

The final rule aligns with the FDA's vision that patients deserve access to high quality, safe and effective devices, said John Doucet,

(See **GCP**, *Page 2)*

European Commission Releases Long-Awaited Details on Eudamed, Nomenclature System

The European Commission released long-awaited guidance on Eudamed (the European Database on Medical Devices) and the device nomenclature system that will be used for the EU's new medical device and in vitro diagnostic regulations.

The document is the first draft guidance the commission has released that provides details the functional specifications of the Eudamed database for devices and IVDs. The new regulations go into effect on May 26, 2020 for devices and on May 26, 2022 for IVDs.

Eudamed is "a keystone for the implementation of the new regulations," enabling device traceability and better market surveillance, the commission said.

The guidance covers legal requirements for stakeholders, including unique device identifiers, clinical investigations, vigilance, and

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lead reviewer at FDA's Office of Device Evaluation. But the agency also recognizes that companies are conducting more multi-national investigations and often rely on foreign clinical data.

In the webinar on implementation of the final rule, the agency said it may grant waivers in cases where informed consent is impossible to approve, such as for research on leftover human specimens and where sharing subject medical data is prohibited by local laws.

To improve chances for FDA approval of a noncompliant application, companies should outline steps researchers took or will take to ensure credible, accurate data and to ensure human subjects are adequately protected, said co-presenter Dina Stolman, a consultant and past medical officer in FDA's Center for Biologics Evaluation and Research. Applicants should include a cover letter clearly stating the waiver request, she added.

It's good practice to communicate with the review team before going into the pre-market submission phase, but it's not mandatory, Stolman said. "You can come in with a reason for noncompliance and that [can be] an acceptable reason."

Companies can also request a waiver before beginning a study.

The agency issued a guidance in 2018 outlining how to meet the agency's requirements, request waivers and provide the required information to support clinical data submissions.

Read the guidance here: house link: www.fdanews.com/03-28-19-GCPGuidance.pdf.

Read the final rule here: house link: www.fdanews.com/03-28-19-GCPFinalRule.pdf.
— Gienna Shaw

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specific requirements for manufacturers, notified bodies and other actors.

The Eudamed system includes a public website for anonymous users to search and view publicly available data and a restricted website for database content management with access to all data an authorized user has the right to access.

Distributors and importers that assume the obligations of device manufacturers also assume responsibility for unique device identification labeling, the commission said. This means that distributors and importers must apply for registration as manufacturers and receive a single registration number, according to Article 16 of the device regulations (*IDDM*, Oct. 26, 2018).

However, if the manufacturer is identified on the label rather than the distributor or importer, the manufacturer is responsible for meeting the UDI obligations under the quality system regulation. Released by the Medical Device Coordination Group (MDCG), which is comprised of representatives from all EU member states, the guidance clarifies roles and responsibilities for device and IVD manufacturers.

The commission also released guidance on device and IVD nomenclature to support the Eudamed database and to serve as a reference throughout the decision process. The guidance was developed in cooperation with the MDCG, and the EC adopted the proposals that the MDCG had floated in 2018.

The EC said the Italian National Classification of Medical Devices (CND) nomenclature will be mapped to the Global Medical Device Nomenclature (GMDN) and will be made available in the future Eudamed.

"The correspondence between the nomenclatures will be visible to operators and incorporated in the future database," the commission said. "This will allow all operators registering their device to find CND nomenclature equivalent to a GMDN code."

Read the documents here: www.fdanews.com/03-28-19-eudamed.pdf and www.fdanews.com/03-28-19-MDNomenclature.pdf.

FDA Moves to Improve Mammography Quality Standards

The FDA issued a proposed rule aimed at modernizing mammography quality standards and better positioning the agency to act when violations are found.

The agency plans to require that only digital accessory components specifically FDA approved or cleared for mammography be used in mammography facilities, or that facilities use components that otherwise meet the requirements in the rule.

In other proposed changes, the agency would directly notify patients and healthcare professionals that mammography at a facility did not meet quality standards and that reevaluation or repeat of the mammogram at another certified facility may be needed, if the facilities themselves are unwilling or unable to notify them.

In addition, the rule would strengthen record-keeping requirements to minimize information loss and improve access to patient mammography records.

Read the proposed rule here: www.fdanews.com/03-28-19-ProposedRule.pdf.

FDA Releases Draft Guidance On Device Establishment Inspections

The FDA issued a new draft guidance laying out how the agency is updating uniform inspections—other than for-cause inspections—to reflect the FDA Reauthorization Act of 2017.

The three-page draft spells out how agency staff will communicate prior to and during inspections. The investigator will notify the owner, operator, or agent in charge of a medical device establishment by telephone within "a reasonable time" before the inspection. The pre-announcement should generally be no less than five calendar days in advance.

The notification should include information about the type and nature of the inspection, such as whether it is scheduled as abbreviated, comprehensive, or pre-approval. FDA standards for reasonable estimated timeframes of inspections generally range from three to six continuous business days.

Inspection duration is impacted by factors such as the complexities of the firm's operations, availability of knowledgeable staff, and the nature of observed deficiencies.

It may be necessary to extend an inspection for a number of reasons, including for FDA to follow-up on post-market safety information such as recalls, Medical Device Reports, and complaints received by the agency.

Generally, inspections of both domestic and foreign device establishments should take place within a standard timeframe and occur over consecutive business days. But exceptions to these timeframes may be appropriate in some circumstances, the agency says.

The FDA still has authority to conduct unannounced, for-cause inspections.

Read the draft guidance here: www.fdanews.com/03-29-19-Inspectionsguidance.pdf.

FDA Warns Two Breast Implant Makers Over Post-Approval Studies

Two breast implant manufacturers were served with warning letters after the FDA found they failed to comply with post-approval study requirements.

The FDA found that the two silicone gel-filled breast implant makers – Johnson & Johnson's Mentor Worldwide of Irvine, California and Sientra of Santa Barbara, California – violated the requirement that they conduct post-approval studies to assess the long-term safety and risks of their implants.

The agency found both companies were in violation of two of the seven post-approval study requirements which were set as part of their 2013 premarket approval applications.

"Post-approval requirements are critical to ensuring the safety and effectiveness of the medical products we regulate," said FDA Commissioner Scott Gottlieb.

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The FDA called out Mentor's for low recruitment, poor data and low follow-up rates in its warning letter and noted "serious deficiencies" in the company's post-approval study for its MemoryShape breast implant. The agency found the devicemaker failed to evaluate the long-term clinical performance of MemoryShape implants under general use conditions and failed to enroll the 2,518 women required for the study. The FDA also noted significant data inconsistencies, including poor patient accounting and missing race and ethnicity data.

In a response to the warning letter, Mentor noted that the FDA "did not raise any specific safety or quality concerns." Mentor also said it encountered challenges enrolling the number of women required as part of the post-approval study due to a "low preference" for textured devices like MemoryShape. More than 90 percent of breast implants in the U.S. are smooth surfaced devices, the company said.

Sientra was cited for similar violations concerning its Silicone Gel Breast Implants. The FDA said the company failed to evaluate the long-term clinical performance under general use conditions and failed to follow study subjects annually for ten years. The manufacturer had a follow-up rate of just 61 percent, which is below the target follow-up rate.

Sientra did not respond to a request for comment.

The warning letters are part of the FDA's ongoing efforts to streamline and modernize how the agency implements post-market actions outlined in the Medical Device Safety Action Plan.

Read the Mentor warning letter here: www.fdanews.com/03-28-19-MentorWorldwideWL.pdf.

Read the Sientra warning letter here: www.fdanews.com/03-28-19-SientraWL.pdf.

— Tiffany Winters

CAPA Data and Documentation

Once the CAPA team is in place, it is time to look at data and documentation systems:

- Take an inventory of all processes and data elements/sources involved in manufacturing your products, paying particular attention to any data that may indicate product quality or other problems, and define the measurements to be taken from those sources and establish processes to analyze the measurements. You may need to include data from suppliers and contract manufacturers;
- Identify trends while analyzing your quality data and to act on what you learn. In other words, use trending techniques to catch—and address—quality problems early.
- Develop reporting and record-keeping systems that are either electronic or paper-based to organize records and data and form the framework of your CAPA system; and
- Consider using automated electronic tools for collecting data and investigating, documenting and tracking corrective and preventive actions for all types of nonconformities.

Policies and Procedures

Once a CAPA team is in place and data and documentation have been reviewed, the next steps involve establishing policies and procedures:

- Establish SOPs that cover all CAPA activities, such as data monitoring, collection and trending; controlling and investigating nonconforming products; record-keeping and organization; and documenting all CAPA activities;
- Establish systems to conduct failure investigations and root cause analyses that will tell you where CAPA plans are needed and help you develop CAPA plans to deal with the quality problems.
- Establish verification or validation requirements for CAPA plans before implementation that prove that the actions taken will fix the root causes and mitigate the failures found;
- Prepare a system for evaluating CAPAs for completeness, set deadlines for when the CAPAs will close and plan to meet those deadlines; and
- Develop templates and train staff to write reports on completed CAPAs and create processes to have management review and approve reports.

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

Full Range Rehab Hit For Repeat Observations

Cincinnati, Ohio-based Full Range Rehab failed to file Medical Device Reports within 30 days of receiving information that one of its devices may have caused or contributed to a serious injury, according to a 483 issued to the firm following a Jan. 30-31 inspection.

The FDA said the firm failed to document any corrections for the previous eight observations covering its CAPA system. Moreover, five of the eight observations were repeat observations of repeat observations, including failure to establish an internal audit procedure or to conduct internal audits.

The agency said the firm's complaint handling procedure did not define all customer complaints. Additionally, the agency found the firm did not record any repairs or complaints. The facility's quality and compliance manager told inspectors the firm does not routinely record or document device repairs.

Other repeat observations included inadequate device history records and failure to maintain a device master record.

Read the Form 483 here: www.fdanews.com/03-28-19-fullrangerehabllc483.pdf.

Valtronic Falls Short on CAPAs And Nonconforming Products

Contract device manufacturer Valtronic netted a Form 483 for inadequate CAPA procedures, nonconforming products and a failure to document validations at its Solon, Ohio plant.

The FDA, which inspected the facility from Dec. 12-19, 2018, said Valtronic was not using nonconformance data as a quality data source for its CAPA system or analyzing the data for potential corrective and preventive actions.

At least two CAPAs were opened in 2017 to address delamination issues, but both were not completed and did not address investigative activities. One was closed as "unsuccessful," while the other had no further action taken at all.

The firm's process validation activities and results were also found to be lacking as they failed to include equipment variables and other key criteria. For example, there was no record of who conducted validation activities and durability studies were not conducted.

The agency also found that the manufacturer's nonconforming product procedure was incomplete. Specifically, the company didn't include defects found on one of the lines during manufacturing.

Read the 483 here: www.fdanews.com/03-28-19-aaltronictechinc483.pdf.

DoubleDay Cited for Failure To Control Nonconforming Products

DoubleDay Acquisitions failed to control products that didn't meet specifications at its Moraine, Ohio manufacturing facility, the FDA discovered during a Dec. 10-14, 2018 inspection.

DoubleDay, which provides cold chain solutions, failed to document nonconformances for its AcuTemp AX56L blood storage refrigerator during in-process manufacturing, the agency said.

The device history record showed the first test for the refrigerator failed, but this nonconformance wasn't documented and the failed test was discarded instead of being kept with the device history record, the agency noted.

Inspectors also chastised the company for not establishing and documenting procedures for reworking nonconforming products. For example, the firm failed to document in-process rework performed on the AX56L units — including preapproval and approval of the rework and the rework's impact on the finished devices.

In addition, corrective and preventive procedures did not include documentation of all activities. Six of 11 quality reports were issued for damaged and unusable parts from the sample supplier, but the firm did not file any supplier corrective action reports.

Read the Form 483 here: www.fdanews.com/03-28-19-doubledayacquisitionsllc483.pdf.

EU Advisory Group Calls for Urgent Clarification of Exemptions

A key advisory group to the European Commission called for urgent clarification of certain device exemptions under Article 54(2) b of the EU's Medical Device Regulation (MDR).

The article lays down three criteria that exempt devices from the premarket clinical evaluation consultation procedure involving expert panels.

The EU Medical Device Coordination Group (MDCG) said the commission's guidance on the article is unclear and has raised concerns among EU member states.

As written, the exemption would apply "where the device has been designed by modifying a device already marketed by the same manufacturer for the same intended purpose, provided that the manufacturer has demonstrated to the satisfaction of the notified body that the modifications do not adversely affect the benefit-risk ratio of the device.…"

MDGC said the interpretation of this article is unclear, notably the application of the word "marketed."

The advisory group points out that in Article 54(2)a the certificates are referred to as those issued under the new regulation, but in Article 54(2)b, there is no indication of whether a device already marketed refers to devices already marketed under existing EU Directives or the MDR.

Timing is Critical

The timing is critical because new procedures are being launched for establishing expert panels, and the way the article is interpreted will have an impact on the future workload of expert panels as well as budgets, the group said.

The MDGC said that the "device already marketed" reference cannot be intended to refer to a device already marketed uniquely under the new regulation.

The group argued that if legislators had wanted to restrict the application of point "b" to devices marketed uniquely under the MDR, they should have explicitly stated that as they did for point "a."

The group stressed that in respect to devices that have been marketed already under the relevant EU Directives, the word "modification" should be meant as "limited only to those modifications needed in order to comply with the new legal requirements introduced by the MDR."

The devices will be subject to all applicable new MDR requirements, including those related to clinical evaluation and would need to be assessed by notified bodies against these new requirements, the MDGC said.

Read the notice here: www.fdanews.com/03-28-19-MDRexemptions.pdf.

Medstar Agrees to Pay $35 Million To Settle Kickback Charges

Healthcare company MedStar Health will pay $35 million to settle claims that it made illegal kickbacks to a cardiology group in exchange for referrals for various cardiovascular procedures including implants of medically unnecessary stents.

The Department of Justice alleged that MedStar Union Memorial Hospital, MedStar Franklin Square Medical Center and MedStar Health — all based in Maryland — set up a kickback scheme with Mid Atlantic Cardiovascular Associates (MACVA), a Pikeville cardiology group, that operated for approximately five years under the guise of professional services agreements. The scheme violated the False Claims Act, the DOJ said.

The department claimed that MACVA sent Union Memorial hospital referrals for profitable cardiovascular procedures for Medicare-covered patients, including cardiac surgery and interventional cardiology procedures, from 2006 to 2011.

The agreement also covers allegations that MedStar received Medicare payments from 2006 to 2012 for medically unnecessary stents performed by a one-time employee of MACVA, John Wang, who later worked for MedStar. Additionally, it resolves a lawsuit brought by former patients of Wang alleging the doctor, MedStar and Union Memorial established a pattern of falsely submitting Medicare claims for medically unnecessary percutaneous transluminal coronary angioplasties with stent placement procedures. — James Miessler

FDA Lays Out New Guidance On Anthrax Testing Devices

The FDA released new guidance for device-makers hoping to sell equipment to test for anthrax and other dangerous bacteria.

Sponsors must include detailed descriptions for how the devices should be used, the chemicals involved in the tests, how to test the devices how specimens should be stored and how the device should be shipped and how to interpret and report test results, the agency says.

The companies must also include a statement that says, "The interpretation of test results requires experienced clinical personnel who have training in principles and use of microbiological culture identification methods and infectious disease diagnostics and have the necessary awareness to report an identification of B. anthracis and coordinate with local or state public health directors."

Approval applications should also include "descriptive information" on the studies that sponsors conducted to test their devices.

The 22-page guidance says that the FDA is worried about false negatives, false positives, risks to lab workers and "unique, device-specific risks." To that end, device sponsors will have to conduct a risk analysis before they submit anything to the FDA and describe the risk analysis.

FDA Commissioner Scott Gottlieb said the recommendations in the final guidance "provide a clear and predictable review pathway."

Read the FDA guidance here: www.fdanews.com/03-29-19-FDAguidance.pdf. — Bill Myers

APPROVALS

CardioFocus' Endoscopic Ablator Gains CE Mark to Treat Atrial Fibrillation

CardioFocus received the CE Mark for its HeartLight X3, an endoscopic ablation system used to remove harmful tissue in the body and perform pulmonary vein isolation procedures.

The third-generation product combines a motor control system with laser energy and direct tissue visualization to block abnormal electric pathways responsible for atrial fibrillation.

Atrial fibrillation is a quivering or irregular heartbreak that can cause stroke, heart failure and other adverse events.

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FDA Approves Impulse Dynamics' Heart Failure Device

The FDA approved Impulse Dynamics' implantable Optimizer Smart System for treating heart failure.

The breakthrough device, which received a 12-0 vote from the FDA's Medical Devices Advisory Committee in December 2018, is intended for patients who have mildly to moderately reduced left ventricular ejection fractions and aren't eligible for cardiac resynchronization therapy.

The device delivers an electrical pulse just after the heart contracts to modulate the strength of the heart muscle contraction rather than the rhythm.

Brightwater's Biliary Stent System Cleared by FDA

The FDA issued 510(k) clearance for Brightwater Medical's biliary stent system, designed to remove the need for an invasive procedure in treating biliary duct obstructions.

Used by interventional radiologists, the device enables stent release in less than a minute during an in-office visit or at bedside, eliminating the need for sedation or repeated drain insertions.

The stent system helps to treat biliary duct obstructions, which can lead to serious complications including sepsis, liver damage or biliary cirrhosis.

FDA Clears Masimo's CO-Oximeter

Masimo received 510(k) clearance for its Rad-67 Pulse CO-Oximeter, a device used to measure the oxygen carrying state of hemoglobin in a blood sample.

The portable device performs spot-check monitoring using its DCI-mini sensor, which analyzes total hemoglobin, carboxyhemoglobin, methemoglobin and arterial oxygen saturation.

The single-device solution is suited for use in both clinical and non-clinical settings, such as emergency rooms, physician's offices and pre- and post-surgery situations.

Zimmer Biomet Earns FDA Clearance For Robotic Spine System

The FDA cleared Zimmer Biomet's Rosa One Spine System, a device used for robotically assisted minimally invasive complex spine procedures.

The device includes 3D intraoperative planning software and a navigation toolkit to enhance placement accuracy.

The system combines real-time patient tracking capabilities with robotics and navigation to aid in minimally invasive and complex thoracolumbar spine procedures.

FDA OKs Device for Treating Heart Failure

The FDA approved Impulse Dynamics' Optimizer Smart system, an implantable pulse generator designed to treat moderate to severe heart failure.

The device treats patients who are unable to use other heart failure devices, such as cardiac resynchronization therapy. The device is implanted under the skin in the upper left or right chest area and attached to three leads implanted in the heart.

After implantation, the physician tests and programs the device, enabling it to give electrical impulses to the heart during regular heartbeats and assist in squeezing.

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Complaint Management for Devicemakers: *From Receiving and Investigating to Analyzing Trends*

Complaint management is essential to a functioning quality management system.

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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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