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IN THIS ISSUE

Editor's Note: Due to summer breaks, *International Devices & Diagnostics Monitor* will not be published July 22. The next issue will be published Aug. 5.

FDA Releases Final Rule On Appeals of CDRH Decisions

The FDA issued a final rule on appealing CDRH's significant decisions about medical devices, including procedures for submitting requests and timelines for the agency's responses.

The rule, which goes into effect Aug. 1, covers requests for review of significant CDRH decisions relating 510(k) premarket notifications, premarket approval applications and humanitarian device exemptions. It also covers requests for breakthrough device designations, or investigational device exemptions.

Under the final rule, a request for review must be submitted no later than 30 days after the decision. The FDA must schedule a meeting within 30 days of a request and make a decision no later than 30 days after that. If there's no in-person or teleconference meeting, the FDA must issue a decision within 45 days of the request.

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

EU Regulators Say Some Devices May Not Be Available Due to MDR Delays

The European Commission acknowledged that there will likely be shortages of some devices due to delays in implementing the EU's Medical Device Regulation (MDR) and In Vitro Diagnostics Regulation (IVDR).

In a new fact sheet, the commission said that the biggest change concerns the new risk-based classification of in vitro diagnostic devices and the role of notified bodies.

Under the new regulations, each IVD will be assigned to one of four risk classes, which means that approximately 85 percent of all IVDs will need notified body oversight under the IVDR, compared to 20 percent previously.

Devices or services sold via the internet are now explicitly covered by the MDR and IVDR. These changes "could have consequences for

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CDRH, *from Page 1*

The rule also establishes procedures for requesting supervisory review of other CDRH decisions not covered under the FDA Safety and Innovation Act and the 21st Century Cures Act.

The agency said the final rule "provides transparency and clarity for internal and external stakeholders: and gives requesters "new predictability through binding deadlines for FDA action on a request for supervisory review."

Read the final rule here: www.fdanews.com/07-05-19-FinalRule.pdf. — Gienna Shaw

Delays, *from Page 1*

the availability of medical devices for health institutions," the commission said.

"For instance, manufacturers may choose to stop the production of certain medical devices. Furthermore, if certain medical devices do not get their certificates on time these products may become temporarily unavailable."

Many Class I devices were up-classified to Class IIa or higher under the new regulations, which means they were allowed to self-declare in the past but will not have a valid NB certificate and will not qualify for the grace implementation period that the MDR grants (*IDDM*, June 22).

So far, only two notified bodies—BSI and TUV SUD—have been designated under the MDR/IVD, and "there is no indication that a significant number of notified bodies will be designated in the next months," according to the European Coordination Committee of the Radiological, Electromedical and Healthcare IT Industry.

"By now, 38 notified bodies have applied for MDR," Gert Bos, executive director and partner at QServe, told *FDAnews*.

Bos said the European Commission remains optimistic that it will designate up to 20 notified bodies by the end of the year, but most observers expect just 10 NBs to be designated by the end of the year in a best-case scenario, and 20 by the MDR implementation end of May 2020, he said.

Then all the work needs to be done during the grace period for compliance of certain products by 2024. Most critical will be products that cannot use the grace period and that will need an MDR certificate by May 2020 — such as re-usable surgical instruments. "That will be extremely hard to manage in time," said Bos, who was formerly head of the notified body at BSI-Germany.

Last month, the Swiss notified body QS Zurich said it will no longer pursue NB designation. The announcement came just a week after London-based Lloyd's Register Quality Assurance said it would not offer its NB services under the new regulations. (*IDDM*, June 22).

The commission's fact sheet also lists information that must be supplied on device and IVD unique device identifiers. It includes a checklist that devicemakers can use to assess their preparedness to implement the new regulations.

Read the fact sheet here: www.fdanews.com/07-05-19-ECFactsheet.pdf.

FDA Issues Draft Guidance On Labeling of Combination Products

The FDA released draft guidance on the content and formatting of Instructions for Use (IFU) for prescription drugs, biologics, and drug- or biologic-device combinations.

IFUs should be "written in nontechnical language and clearly state the actions a patient should take to use the product," the agency says. The guidance recommends using active voice and commands, with sentences that start with an action verb. It also provides sample labeling that covers all elements of an IFU from dosage and usage to storage and disposal.

The agency notes that the main purpose of an IFU is to provide "detailed, action-oriented, step-by-step written and visual instructions in a patient-friendly manner." The FDA recommends including any relevant information from the prescribing information that describes how to use the product, as well as any additional details necessary for safe and effective use.

The FDA also includes recommendations for design and layout, including the use of easy-to-read fonts, sequential numbering with step numbers bolded, and visuals. The agency also recommends a balance between the text, visuals and whitespace to ensure readability and comprehension.

When reviewing IFUs, the agency looks for "scientific accuracy and consistency with the FDA-approved prescribing information' for the product, the guidance states.

Read the full draft guidance here: www.fdanews.com/07-01-19-IFU.pdf. — Dave Stroup

Canada Establishes New Premarket Requirements for Device Cybersecurity

Health Canada issued new guidance on its premarket requirements for medical device cybersecurity.

The agency's final guidance spells out what needs to be submitted as part of a license application or amendment to show that a device is secured against "intentional or unintentional unauthorized access."

New requirements in the final guidance address pre- and post-market compliance, including monitoring and responding to emerging risks. The agency also requires safeguards such as passwords to protect against unauthorized tampering.

"While the idea that medical devices could be used for intentional harm may sound like science fiction, the risk is real enough to warrant precautions from medical device regulators," the agency said.

Health Canada considers cybersecurity a component of a medical device's lifecycle that can impact safety and effectiveness. As such, it should be considered when designing a device (*IDDM*, Dec. 14, 2018).

The final guidance complements Health Canada's recently released Action Plan on Medical Devices that seeks to improve how devices get on the market and strengthens monitoring and follow-up for devices already in use (*IDDM*, June 4).

Outside Networks

The updated guidance covers strategies to reduce potential risks associated with devices that contain software and technology that enable communication with outside networks. The new requirements apply to all devices that connect to software, from Class I to Class IV. There are additional requirements for Class III and Class IV applications such as detailed verification and validation testing summaries and reports of supporting evidence on cybersecurity testing.

"Failure to submit the additional information with an application could result in a request for additional information under subsection 35(1) of the regulations at any time during the review," the agency said.

Manufacturers should consider design controls that allow the device to detect, resist,

(See **Canada**, *Page 4)*

MedTech Europe Lays Out Plan to Help EU Member States With New MDR

Device association MedTech Europe released a seven-point plan to help EU member states tackle the looming MDR/IVDR implementation deadlines.

The plan points out gaping holes in critical infrastructure. The call to action covers notified bodies for certification of new products, recertification, Eudamed, quality guidance, scientific bodies and harmonized standards.

MedTech Europe notes that the system is far from being functional with the implementation date for the MDR less than a year away. It says the first step is to designate notified bodes more quickly.

It urges member states to "acknowledge that we are not on track," and to prepare for the lack of notified bodies. It calls for an EU-wide solution that ensures that manufacturers can continue CE marking.

The association suggests removing as much bureaucracy from the process as possible to accelerate NB designations. Regulators should also consider the NB's past track record under the former directives, "instead of re-assessing everything from A to Z," it said.

Another proposed solution is to create a staged re-certification procedure for NBs to follow that would give priority to product families that can't use the grace period that allows a delay in implementing the requirements.

MedTech Europe calls for the new Eudamed database to be deployed with workable IT specifications and implementation timelines, and for regulators to publish guidance documents as soon as possible.

Read the seven-point plan here: www.fdanews.com/07-05-19-MedTechEuropeIVDRMDR.pdf.

Canada, *from Page 3*

respond and recover from cybersecurity attacks. The controls include secure communications, data security, user access, software maintenance, and reliability and availability.

Cybersecurity should be incorporated into the risk management process for every device that consists of or contains software, and manufacturers should develop a framework for managing cybersecurity risks throughout their organizations the agency said.

All cybersecurity risk control measures should be verified and validated against the device's design requirements and specifications, the agency said, and manufacturers should be able to trace all validation activities back to these design requirements and specifications.

The guidance includes a table listing design control considerations as well as explanations of the relationship between the cybersecurity risk management process and the safety risk management process as defined in ISO 14971. An additional appendix includes various example of security risks and the tests that manufacturers should conduct to counter those risks.

Read the final guidance here: www.fdanews.com/07-05-19-cybersecurityguidance.pdf.

483 Roundup: FDA Cites Three Firms for Complaints, Validations

The FDA rapped three devicemakers for a variety of violations including complaint handling, validations and failure to establish procedures for process changes.

Pacific Medical Group: Failure to investigate complaints that certain devices did not meet specifications resulted in a Form 483 for Pacific Medical Group of San Clemente, Calif., following a Feb. 6 to March 14 FDA inspection.

The facility was cited in 2014 for failing to investigate returned fetal cable transducers and electrode cables that were not functioning. It also failed to investigate the root cause of the failure of the devices, which reoccurred after devices were returned to customers. At least 17 devices were reported as not functioning.

"Your firm failed to investigate the device malfunction, resulting in a use of the device [that] caused [a] burn or red mark on a patient," the agency said, adding that the firm also failed to evaluate complaints for medical device reportability to the FDA.

Investigators found no records of corrective and preventive actions, or records of risk management activities for fetal transducers, the agency said.

In addition, the firm had not established design control procedures and it lacked design history, design specifications and design change records of fetal transducer.

The facility also failed to conduct design validation studies following a change in supplier for a cable. And the facility' procedures for final inspection and product acceptance didn't

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

Linking Complaints to Risk Management

Complaints, adverse events and MDRs all provide information about instances when production, storage or use of a device may not be going as intended. These can be situations in which previously unrecognized hazards exist or known hazards unexpectedly arise, such as a particular manufacturing facility not following all quality management procedures, says quality expert Dan O'Leary of Ombu Enterprises.

Some common risk management activities to take in such cases include evaluation of all prior activities, examination of manufacturing procedures to see if something needs to be updated and performance of internal audits to identify causes of known issues and to catch unknown hazards before they have a chance to make it to the complaint or MDR stage.

The globally accepted risk management standard for medical devices, ISO 14971, sets forth a method for analyzing hazards, predicting the resulting harm and estimating the severity and probability of the risk associated with a particular device. Devicemakers usually conduct this analysis in the design phase, which allows them to take steps to reduce risk to an acceptable level. They then monitor production and post-production information, such as complaints and MDRs, and react accordingly.

While not all device manufacturers apply ISO 14971 specifically, the broader concept it presents of risk management from design through marketing can be applied to meeting U.S. regulations.

To estimate risk, a devicemaker must first identify all hazards that can occur during correct use of a device in normal conditions. O'Leary recommends against using failure mode and effects analysis (FMEA) for risk assessments, as this technique only addresses singular faults. Device companies must look at hazards associated with a sequence of events.

The severity and probability of the potential hazards, as well as the probability of the hazard occurring and the probability that it leads to patient harm are used to measure the degree of risk. Under this scheme, the inputs for risk analysis include hazards and hazardous situations. The output is the estimated risks.

Once the risk has been analyzed and quantified, the devicemaker can tackle the task of risk reduction, which means putting measures in place that reduce the risk to acceptable levels.

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

FDA Warns of Security Holes In Medtronic's Insulin Pumps

Certain models of Medtronic's MiniMed insulin pumps have potential cybersecurity risks and should be swapped out for newer models, the FDA advised.

The company recalled multiple pumps, including the MiniMed 508 and ten MiniMed Paradigm models and is now offering alternative pumps that don't have the security vulnerabilities.

Hackers may be able to connect wirelessly to the devices and change the settings, giving them control over insulin delivery to the patient, the agency said. This could cause hypoglycemia or halt the delivery of insulin.

The Department of Homeland Security also issued a cybersecurity alert for the insulin pumps, noting that the "vulnerability may allow an attacker with access to one of the affected products to intercept, modify, or interfere with the wireless radio frequency communications to or from the product. "This may allow attackers to read sensitive data, change pump settings, or control insulin delivery," DHS said.

Medtronic issued a June 27 security bulletin on the cyber vulnerability. "As of the date of this bulletin, we have received no confirmed reports of unauthorized persons changing settings or controlling insulin delivery because of this vulnerability," the company said.

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identify or specify required tests to be performed to meet specifications.

Preservation Solutions: A Feb 19 to March 12 FDA inspection of Preservation Solutions' Elkhorn, Wisconsin facility revealed that the firm failed to correctly validate its aseptic processes for manufacturing and processing sterile organ transplant preservation solutions.

Test data didn't support specified requirements for several lots of product, and the firm didn't handle this as a protocol deviation or failure for the initial or subsequent testing. It also failed to meet ISO requirements referenced in the product.

"Your firm lacks an approved process validation for the bag leak test of the sterile organ transplant preservation solution at the time of final packaging for distribution," the Form 483 says, noting that complaints were received that led to a recall of the solution.

An investigation identified additional units from different lots that were in available inventory that were subject to leaks, but the units were released as acceptable without detecting the bag leaks.

The FDA investigators found that the firm replaced the clean room floor in the aseptic processing area but failed to perform qualification studies to evaluate the potential bioburden impact of the floor replacement.

Performance Health Supply: Failure to establish procedures for process changes as well as documentation and CAPA lapses led to a seven-item Form 483 for Performance Health Supply following an April 8-17 FDA inspection at its Cedarburg, Wisconsin facility.

The supplier of physical therapy products failed to follow procedures for a process change request for a new water system that was installed to eliminate manufacturing nonconformities. The firm also failed to validate the system and to evaluate risk.

The investigator noted that a change request was also missing for a software update performed on the waterjet system. The firm received at least four complaints that the product didn't meet specifications following the software upgrade. Also lacking were established process parameters for injection molders used to manufacture orthotic splints.

Read the Pacific Medical Group Form 483 here: www.fdanews.com/07-05-19-pacificmedicalgroup483.pdf.

Read the Preservation Solutions Form 483 here: www.fdanews.com/07-05-19-preservationsolutions483.pdf.

Read the Performance Health Supply Form 483 here: www.fdanews.com/07-05-19-performancehealthsupply483.pdf.

BRIEFS

EU Creates Expert Panels To Review MDR Implementation

The European Commission is creating expert panels to review the implementation process for the EU's new medical device and in vitro diagnostics regulations after numerous industry groups have sounded alarms over the delay in implementing the new regulations.

With less than one year to go for devices to meet the May 26, 2020 implementation date — IVDs have until May 26, 2022 — the expert panels will assess high-risk devices and "contribute to the prospective improvement of the overall framework" by advising the Commission, the Medical Device Coordination Group, EU member states, notified bodies and manufacturers.

The panels will also take on other tasks such as contributing to the development of common specifications for clinical evaluation of device categories, guidance documents and standards. Experts on the panels will be appointed for three-year renewable terms.

Read the notice here: www.fdanews.com/07-05-19-ECMDIVD.pdf.

Canada Proposes New Device Regs to Improve Safety

Health Canada has launched a new consultation on proposed regulations that could impose additional requirements on devicemakers to make their products safer.

Under the proposal, manufacturers could be required to conduct additional assessments and to provide additional analyses and post-market reviews of their products.

The proposal calls for manufacturers to prepare annual summary reports of all known adverse events, reported problems, incidents, risks, and to notify Health Canada if there has been any change to the risks and benefits of a product.

Comments on the new regulations are being accepted until Aug. 26. Read the proposal here: www.fdanews.com/07-05-19-CanadaGazette.pdf.

APPROVALS

BioTronik Earns CE Mark For Injectable Cardiac Monitor

BioTronik's injectable cardiac monitor for tracking arrhythmias, the BioMonitor III, has earned the CE Mark and is now available on the European market.

The device is designed to help patients with irregular heart rhythms by detecting and recording suspected arrhythmia and unexplained loss of consciousness caused by low blood pressure.

The monitor works in conjunction with the devicemaker's home monitoring system and requires no patient interaction.

Chembio Nabs CE Mark For Multiplex Diagnostic

Chembio Diagnostics has earned the CE Mark for its point-of-care Dual Path Platform (DPP) multiplex test for the Zika, dengue and chikungunya viruses.

The diagnostic provides simultaneous detection of the antibodies for active and prior exposure to the viruses — an important distinction for treatment.

The test uses a small drop of blood from the fingertip and works in conjunction with the company's DPP Micro Reader device to provide results in approximately 15 minutes.

FDA Clears Benvenue's Expandable Interbody Device

The FDA has handed Benvenue 510(k) clearance for its Luna XD expandable interbody device for use in patients with symptomatic degenerative disc disease.

The minimally invasive device is inserted via a small incision and gives the patient's spine anterior column stability, strength and fusion.

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

Approvals, *from Page 7*

The implant includes a large graft chamber to promote successful fusion and restoration of maximum height.

Viveve Earns FDA Clearance For Collagen Builder

The FDA granted Viveve 510(k) clearance for its Viveve 2.0 system, a cryogen-cooled monopolar radiofrequency device used to rebuild natural collagen in female patients.

The device is used in general procedures for electrocoagulation and hemostasis, using controlled cooling to protect tissue from damage while allowing for greater penetration of its radio waves.

The system uses a small probe that emits cryogen-cooling and radio waves to spur the production of new collagen and tissue reinvigoration.

Quidel Earns 510(k) Clearance For Triage TOX Drug Screen

Quidel Corporation received 510(k) clearance from the FDA for its Triage TOX Drug Screen, 94600, a fluorescence immunoassay for detecting the presence of drug and/or metabolites in human urine of up to nine drug assays.

Results are typically displayed in approximately 15 minutes from the addition of specimen and are stored in the meter's memory to display or print when needed. If connected, the Meter can transmit results to the laboratory or hospital information system.

The test is used with Quidel's Triage MeterPro instrumented system. The company is optimistic that the assay will boost its Triage sales and create further growth for its MeterPro instruments. "We believe that our latest diagnostic screening test can play an important role in providing fast, diagnostic answers to healthcare providers in the emergency and urgent care settings," said Quidel's CEO, Douglas Bryant.

RYAH Medtech Gains CE Mark For Dry Herb Vaporizer

RYAH Medtech has received the CE Mark from the British Standards Institute for its RYAH vaporizer, a device used to administer dry herb medicine.

The vaporizer, which enables patients to precisely control the device's temperature and the dosage they inhale, is expected to launch in Europe in the near future.

The device can stay clean by using RYAH cartridges that prevent material from coming into direct contact with the heating chamber.

Avioq's HIV Assay for Reactive Samples Gains CE Mark

Avioq's VioOne HIV Profile Supplemental Assay has earned the CE Mark and is seeking distribution partners for Europe.

The enzyme-linked immunosorbent assay (ELISA) confirms and distinguishes between individual antibodies directed to various gene products of HIV-1 and HIV-2 in human serum and blood plasma.

The test is specifically used to confirm the presence of HIV-1 or HIV-2 antibodies in specimens that were repeatedly reactive during diagnostic screening procedures.

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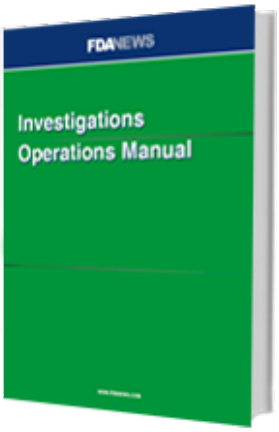

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