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IN THIS ISSUE

FDA Finalizes Guidance on Postmarketing Safety Reporting for Combination Products

The FDA has outlined the ways companies are expected to comply with postmarketing safety reporting (PMSR) requirements for combination products in final guidance issued Monday.

The 44-page guidance goes in depth on the numerous types of combination product PMSR reports, what information should be included in them, and hypothetical scenarios to help companies understand them better.

Combo products that contain device constituent parts must be submitted no later than five work days after remedial action is required to prevent a reportable event from occurring again — such as a recall. The guidance describes a situation in which the applicant of a prefilled rescue inhaler approved under an NDA discovers a design flaw that prevents drug delivery and causes the inhaler to fail. The product's defect is found in others on the market and can

(See **Postmarketing**, *Page 2)*

FDA Testing Supports A Streamlined Review of SaMD

The FDA's retrospective testing has been completed, and the results indicate a regulatory decision can be made using the information acquired from a streamlined review of software as a medical device (SaMD).

This conclusion comes as part of the FDA's 2019 mid-year update of its software pre-certification program. The pre-cert program entered its test phase earlier this year, with the goal of confirming that the streamlined review pathway created for SaMD products provides the same assurance of safety and effectiveness for SaMD as the FDA's traditional review pathway for medical devices. The FDA set out to test the excellence appraisal and streamlined review components using SaMD regulatory submissions that have previously been reviewed.

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Postmarketing, *from Page 1*

fail in the same manner — risking serious injury or death. This warrants a five-day report, the agency says.

Serious and unexpected adverse events in combo products containing a drug or biological constituent part must be submitted within fifteen calendar days. Products marketed under a device application have up to 30 calendar days.

For example, a product approved under an NDA that contains a delivery device for a drug would require a fifteen-day report if the device breaks during drug delivery and causes hemorrhaging and patient hospitalization, because "hemorrhage is both a serious and unexpected adverse experience" and was caused by use of the product, the agency explains.

The guidance includes a table that can be used to track how, when and where to submit PMSR reports to the FDA. It also describes situations in which sponsors can combine their submissions to comply with multiple reporting requirements at once.

The FDA in April delayed enforcement of the combination product requirements until July 2020 to give companies time to prepare their IT systems for tracking and reporting the adverse events. Companies that make vaccine-related products have until January 2021.

Read the final guidance here: www.fdanews.com/111788.pdf. — James Miessler

Streamlined, *from Page 1*

To facilitate this, the pre-cert team developed a mock excellence appraisal summary "based on pilot participant site visits and public comments," according to the FDA. The team also created streamlined review packages by extracting elements from the original submission. Software reviewers then conducted a mock review, which ultimately led to the team validating the use of a streamlined review of SaMD.

"Reviewers conducting the mock review generally reported that a regulatory decision could be made using the information acquired from the mock excellence appraisal summary and the streamlined review package," noted the FDA.

But there was also room for improvement, with the test team identifying ways to simplify the process for sponsors and reviewers alike. The team recommended a more structured format, and results from retrospective testing also informed the development of a streamlined review for prospective testing, which is already in progress.

Next steps for the FDA include testing the pre-cert model on new SaMD submissions, which will ultimately determine whether or not results from the pre-cert pathway align with the results of the traditional pathway and satisfy the FDA's regulatory requirements for safety and effectiveness.

Read the FDA's mid-year update here: www.fdanews.com/08-01-19-MidYearPreCert2019.pdf. — Tiffany Winters

France Issues EU's First Cybersecurity Guidelines

France's National Agency for Safety of Medicines and Health Products released new cybersecurity recommendations for medical devices designed to minimize the risk of cyber attacks.

The recommendations are aimed at manufacturers so they can take the necessary precautions to minimize risk, prevent malicious attacks on their devices and keep data from being compromised.

The guidelines discuss best practices, guidelines and appropriate standards for cybersecurity from initial development to commercialization and post-market monitoring.

"While the marketing of medical devices is well regulated from a regulatory point of view, the culture of cybersecurity is very heterogenous within [medical device] manufacturers," ANSM said. "This is mainly due to a lack of awareness of cybersecurity requirements, a failure to take cybersecurity into account in the device design and development process, and the absence of specific regulatory texts or recommendations for cyber security."

ANSM stressed that under the new EU Medical Device Regulation software is deemed to be an active device if it is used to diagnose, prevent, monitor, predict or treat a disease or disability. Software is also considered a medical device if it provides information by means of in vitro examination of specimens from the body, including organ, blood and tissue donation.

In safeguarding software from cyber attacks, ANSM differentiates between safety and security. The key difference is that operating safety mainly involves accidental faults while security includes intentional faults. The cyber security document only deals with security recommendations.

The ANSM recommendations focus mainly on the availability and integrity of medical device integrating software, where a malicious attack could have harmful repercussions on patient health. The recommendations include various risk analysis methods as well as recommendations for choosing controlled firewalls in internet-exposed areas, setting up system partitioning, and documents and tools are provided as a reference.

Compliance security requirements under ISO 13485:2016 are provided as are approaches to guarantee integrity, availability, confidentiality and auditability.

ANSM is accepting comments on the draft recommendations until Sept. 30. Comments will be circulated to manufacturers in December.

Read the Guidelines here: www.fdanews.com/08-01-19-ANSM.pdf.

China Launches Pilot Program For Unique Device Identifier System

China's National Medical Products Administration is gearing up to implement a unique device identification system and it's establishing a pilot program that will focus on high-risk implantable devices first.

The pilot will focus mostly on devices such as heart and brain implants and prostheses, but it will also include devices from other categories for testing purposes. The project will include device manufacturers, distributors, sponsors and production management involved in the device lifecycle.

The launch marks an important step in the modernization of China's medical device supervision system, the NMPA said.

The objective is to establish a nationwide unique identification system framework for devices, and the pilot will focus on applications of unique identifiers to track adverse events, product recalls and traceability.

Provincial state FDAs will participate in the program as well as selected foreign devicemakers, distributors, coding agencies and associations. The NMPA will set standards and guidelines for establishing a UDI system and advise companies on how to carry out the work. State FDAs will coordinate the pilot project and test the platform.

Industry Supports Reclassification Of Surgical Staplers, But Adds Caution

Most comments on FDA's draft guidance for reclassifying surgical staplers supported the move to reclassify devices from Class I to Class II but some cautioned that the rule could adversely affect access to surgical staplers.

The devices are currently not required to submit a premarket notification to the FDA before marketing. The reclassification would mean the agency could require premarket review and establish special controls for the staplers, including performance testing and demonstration of usability. It would also allow for "specific labeling elements" to support safe use.

Prior to issuing the guidance, the FDA issued an alert in April warning of the risks of surgical staplers for internal use and implantable surgical staples. 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 health care providers.

Reclassification

The agency subsequently held a May meeting of the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee to discuss the reclassification of surgical stapler devices for internal use from Class I (general controls) to Class II (special controls).

Both Medtronic and Johnson & Johnson said in their comments that they supported the FDA's proposal to reclassify all internal surgical staplers as Class II devices.

Medtronic presented an analysis of the safety and performance data of its internal staplers at the May advisory committee meeting, "confirming both their favorable safety profile and the absence of any safety signals," the devicemaker said in its comments.

The company raised concerns about the FDA's proposal to require additional bench and animal testing on devices that have been in use for years and have an established safety profile. It said these requirements are unlikely to provide clinically meaningful information and, in fact, could adversely affect patient access. It urged the agency not to apply testing controls retroactively on devices that have been cleared through the 510(k) process and already have established safety profiles.

These concerns were echoed by the panel, Medtronic said, noting that the panel had recommended that the FDA work with industry stakeholders to develop clinically meaningful special controls. Medtronic asked the FDA to work collaboratively with industry to evaluate and address the panel's request for a uniform color-coding system for all stapler reloads.

Labeling

J&J went a step further and requested that FDA provide confirmation that its products meet these new expectations and, if not, grant an expedited pre-submission meeting for "all impacted manufacturers to discuss the assessment and align on the pathway forward."

The guidance recommends that manufacturers place visible contraindications on their products regarding their use on tissues for which stapling is overly risky, including a statement noting that the device shouldn't be used to staple necrotic, friable, ischemic or edematous tissues.

Medtronic said it did not support adding such statements to labeling, and it urged the FDA to work with industry to "develop a consistent framework for labeling across the class of internal stapling devices, with a focus on helping surgeons make appropriate choices for the patients."

Additional clarity is needed on several of the FDA's labeling recommendations, J&J said. For example, the company recommended that the warning require, "A statement to avoid the use of the stapler on large blood vessels, such as the aorta."

"Many of our stapling products include a contraindication for use on the aorta (Do not use on the aorta), and the addition of a softer warning may lead to confusion by surgeon users that use on the aorta could be acceptable," J&J explained.

Radiation Safety Apparel Maker Fails to Report Complaints

Devicemaker Protech Leaded Eyewear failed to develop Medical Device Reporting procedures and didn't investigate complaints, the FDA's Dec. 6-14, 2018 inspection of its Lake Park, Florida plant revealed.

The maker of radiation safety apparel received numerous complaints about broken lenses in its safety glasses, holes in protective gloves, and many of these "were not reviewed, evaluated or investigated. Some of these complaints, especially the glove failures, could be MDR reportable," the Form 483 said.

The firm didn't analyze processes, work operations, quality records, service records, complaints, returned product and other sources of quality data to identify potential causes of the nonconforming product, the FDA said. It also didn't employ appropriate statistical methodology to detect recurring quality problems.

For example, procedures for the first-pass yield system to track nonconformances internally for aprons and eyewear was not followed nor was it done consistently to track supplies, product numbers or returned products for replacement and servicing.

Potential suppliers weren't evaluated or documented, and document control procedures were not adequately maintained, the FDA said. For example, documents "geared solely for ISO requirements are not toward FDA requirements," the FDA said. In addition, none of the company's procedures had approval dates or signatures.

Read the Protech Leaded Eyewear Form 483 here: www.fdanews.com/08-01-19-protechleadedeyewear483.pdf.

When Not to Report

Manufacturers do not need to submit a medical device report (MDR) to the FDA when information about the event would cause a person qualified to make a medical judgment to reach the conclusion that the device did not cause or contribute to a death or serious injury, or that a malfunction would not be likely to cause or contribute to death or serious injury if it were to recur.

But companies need to be very careful about how they implement this particular provision of the regulations. The FDA has issued warning letters to some companies saying that reliance on the medical judgment or statements from a physician who used the product is not always satisfactory when determining MDR reportability.

The FDA expects devicemakers to look at the totality of the complaint information when making this determination.

There are three additional situations in which a devicemaker is not required to file an MDR:

- When complaints come from multiple sources about the same event and patient, they can file just one report;
- When information about the event is incorrect and an investigation determines that no device-related issue occurred; and
- When the device involved in the complaint was manufactured by another company.

In this case, the company receiving the complaint should pass it on to the FDA with a cover letter explaining the situation.

Things to Keep in Mind

A company's MDR system must be able to identify all potential sources of reportable events. There is a tendency to think that the complaint system is the only way these events become known to the company. Although it is a major source of MDR information, it is not the only one.

For example, a manufacturer conducts a limited market release to get feedback on a product from a certain subset of customers before full-scale production and release. The company needs to evaluate this feedback — often collected through questionnaires — for complaints that require action and reporting.

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

FDA Warns Clinicon For Lax Testing, Validation of Sterilization Processes

The FDA issued a June 20 warning letter to Clinicon for quality system lapses related to its SureProbe Class II sterile probe following an April 3-4 inspection of the firm's Oceanside, California facility.

Clinicon's sterile laser probes are used for the incision, excision, vaporization, ablation, coagulation or cauterization of soft tissues.

The April inspection revealed that the firm didn't document validation of its packaging process, and there was no revalidation or reassessment of the sterilization process since 2015, the warning letter says. The initial validation was conducted by a contract sterilizer.

When asked for further documentation of the packaging process for sterile devices, the inspectors were provided with information about a sealing procedure that requires a visual inspection for leaks. The firm said no package integrity testing was performed to show that the packaging procedure was developed according to protocol with pre-approved acceptance criteria, test data "or any final report to validate the sealing process can maintain [a] sterility barrier," the FDA said.

In addition, the firm was not calibrating or maintaining the pneumatic heat sealer used to create the sterile barrier on the laser probes. The company provided an inspection showing a measuring and test equipment procedure that was dated in 2010, but it had no other documentation related to the sealer operating records.

The firm was unable to provide inspectors with procedures on how device history records are maintained, and there were no records available to demonstrate that testing procedures were conducted or that sterilization was conducted.

The FDA said that following the inspection, Clinicon sent a letter dated April 12 that said an additional reply would be forthcoming; however that reply never came.

Read the warning letter here: www.fdanews.com/08-01-19-CliniconWL.pdf.

France Establishes Pilot in Preparation For New EU Device Regs

France's National Medicines Agency has established a pilot project to prepare for implementation of the new EU Medical Device Regulation and In Vitro Diagnostics Regulation.

The pilot project is focusing on new requirements for clinical investigations and the agency will work with industry stakeholders to ensure that authorizations for Class III implantable devices, and Class IIa and Class IIb invasive devices meet the new framework.

The MDD requires a clinical investigation authorization scheme for invasive Class IIa and Class IIb devices and Class III implantable devices as well as an ethical review of the CI at each member state. A single submission is required on the European EUDAMED database, which will gather information related to clinical trial and will be accessible to the public.

The regulation also requires that multi-site trials conducted in several member states have coordinated assessment procedures for applications and amendments as well as a single decision for each member state. This process is mandatory from May 26, 2027, and before that time as soon as the EUDAMED portal is operational.

Ongoing since November 2018, France's pilot project has involved all stakeholders in order to define the different stages of the evaluation process on an organizational level as well as the solutions provided between the ANSM and the Human Protection Committees (CPP).

The ANSM reported that the pilot has strengthened relations with the CPPs.

APPROVALS

FDA Clears New Indications For Lyme Disease Diagnostics

The FDA has OK'd four diagnostic tests with new indications for diagnosing Lyme disease.

"The tests cleared today are the first time that a test has been indicated to follow a new testing paradigm in which two tests called enzyme immunoassays (EIA) are run concurrently or sequentially" rather than the current two-step Western Blot test, the agency said.

The new assays are easier to interpret in the laboratory due to the streamlined methods for running the tests, CDRH said.

Elekta's Radiation Therapy System 'Unity' Gains Canadian Clearance

Canada's Canadian Nuclear Safety Commission has given the go-ahead for the clinical use of Elekta's Unity magnetic resonance radiation therapy (MR/RT) system.

The system uses an MRI scanner and a linear accelerator backed by adaptive software to adjust doses of radiation therapy based on daily changes in the tumor's shape, size and position and the surrounding healthy tissue.

Elekta CEO Richard Hausmann says the system is "changing how leading cancer centers deliver radiation therapy, reshaping the dose in real time and targeting hard-to-treat cancers that previously could not be treated effectively with radiation."

FDA Approves Intersect ENT's Sinus Implant Delivery System

Menlo Park, California devicemaker Intersect ENT said that the FDA has approved the delivery system for its Propel Mini sinus implant.

The company's new Straight Delivery System is designed to place the Propel Mini steroid releasing sinus implant in the ethmoid sinus. The implant helps keep the sinus open during delivery of mometasone furoate, a steroid medication used to treat skin conditions.

The sinus implant helps to improve the outcomes of frontal and ethmoid sinus surgery.

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

Approvals, *from Page 7*

Life Spine's Expandable Spacer System Earns Additional FDA Clearance

The FDA has handed Life Spine 510(k) clearance for two new widths of its Prolift expandable spacer system

The agency cleared the device in 8mm–10mm widths, enabling the device to accommodate a wider range of patients that require transforaminal lumbar interbody fusion (TLIF) and posterior lumbar interbody fusion (PLIF) procedures.

"As opposed to traditional static interbodies, Prolift was engineered to reduce the need for surgical steps, such as sequential trialing, and in turn reduce operating time," Life Spine said.

OrthoPediatrics' Cannulated Screw System Cleared by FDA

The FDA has granted OrthoPediatrics 510(k) clearance for its Cannulated Screw System, a device used to treat bone fractures and fusions in smaller patients.

The new screws are made of stainless steel and come in 2.5mm, 3mm, 3.5mm, 4mm, 4.5mm and 5.5mm sizes. It also offers an "all-in-one" option that increases operating room efficiency.

The company's executive vice president, David Bailey, said the device is "innovative as it allows physicians to adequately address the issue when first detected/present."

Ortho Clinical Gains CE Mark For Cardiac Assay

Ortho Clinical Diagnostics has received the CE Mark for an improved version of its Vitros NT-proBNP II product, a diagnostic used to identify heart failure.

The assay is also designed for risk stratification — grouping patients based on their risk and rising risk — of acute coronary syndrome and heart failure.

The enhanced version of the assay has improved assay quality through the use of monoclonal antibodies and an enhanced resistance to potential interferences.

FDA Clears MiRus' Spine Alignment Monitoring System

MiRus' Galileo Spine Alignment Monitoring System has received 510(k) clearance from the FDA for spinal alignment.

The wireless, non-optical device is a real-time measurement system used in segmental and global sagittal spine alignment. It provides surgeons with feedback as they perform corrective procedures in the operating room and confirms that the alignment was successful.

According to the company, the device is the first product approved by the FDA that measures sagittal plane alignment in real-time without the heavy use of repeated imaging.

FDA Clears Wound Dressing For Treating Mustard Gas Injuries

Argentum Medical has received 510(k) clearance for its Silverlon Wound Contact Dressing for the treatment of certain injuries caused by sulfur mustard, most commonly known as mustard gas.

The agency's decision marks its first approval of a product to manage certain blister injuries caused by mustard gas.

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The EU-MDR Transition: *Meeting the CE Mark Deadline*

If you plan to continue putting devices on the European market, you'll need to implement the EU-MDR.

Due to the slow progress in the EU companies are being guided through a soft transition plan.

Dan O'Leary — industry expert with more than 30 years of experience in quality, operations and program management — explains the hybrid system, where you maintain a device certificate under the MDD and a QMS under the MDR.

The EU-MDR Transition: *Meeting the CE Mark Deadline* explains how to take advantage of the soft transition to the new regulation. The soft transition allows companies to retain certain aspects of the current CE Mark applications while following new registration requirements, if their notified bodies approve.

But, what does that really mean?

This report breaks down all the rules and explains all the implications of a soft transition, providing a path to follow to full compliance:

- **Transition Timeline:** All the dates and deadlines on the transition timeline
- **SOPs:** How to develop an SOP for the post market surveillance you will have to conduct under EU-MDR
- **Adverse Events:** How to report adverse events
- **Forms:** What new forms will be required
- **Technical documentation:** How to structure technical documentation for your hybrid system

Start implementing the hybrid MDD/MDR system to keep your products on the European market until the full EU-MDR comes into effect.

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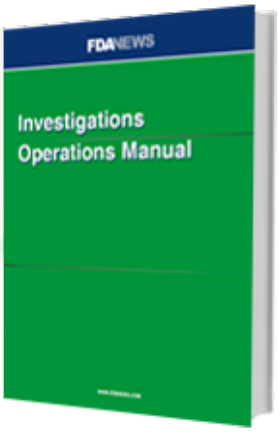

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