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IN THIS ISSUE

FDA Offers Advice on Benefit-Risk Considerations for Device Submissions

The FDA outlined in two new guidances how to assess the risks and benefits of medical devices for premarket submissions as well as for de novo classifications and humanitarian device exemptions.

The level of uncertainty regarding the benefits and risks of a device depends primarily on the type of premarket decision and the context. "The appropriate uncertainty…would depend on the circumstances, including the totality of information about the device," the agency says, in a guidance on how to deal with uncertainty.

"The continuous, robust generation of evidence throughout the premarket and postmarket setting … is important to continuously refine our understanding of how medical devices are used and perform," the agency says.

At the top of the list of considerations, the agency writes that the scope of probable benefits of the device must be considered, including if the probable benefits are greater than what's been observed in

(See **Guidances***, Page 2)*

European Commission Issues New Vigilance Guidance

The European Commission issued new guidance on when devicemakers operating in the EU need to issue Field Safety Corrective Actions and how they should prepare field safety notices.

The guidance introduces a new manufacturer incident report and a new template for field safety notices. It also introduces device-specific vigilance guidance and provides more detail on coordinating vigilance activities with regulators.

Under the new EU regulations, devicemakers must have procedures to review post-market experience to ensure that any needed corrective actions are carried out, and they are required to report incidents and recalls to their national authorities.

(See **Vigilance***, Page 4)*

Guidances, *from Page 1*

alternative therapies and diagnostics. The duration, frequency, magnitude and likelihood of benefits should be considered, the agency says, as well as the device's impact on clinical management and patient satisfaction.

The FDA adds that the risks associated with a device should be taken into account. Device-related serious and non-serious adverse events, procedure-related complications, probability of a harmful event, and duration of harmful events are included in this category, as well as the number of different harmful even types associated with the device and their collective severity.

In addition to objective measures of probable benefits and risks related to a new device, the FDA considers the patient's perspective in evaluating appropriate uncertainty. Patient-centric metrics, such as validated health-related quality of life scales and patient-reported outcomes, can be a factor in device approvals, the draft guidance adds.

At the time of approval or de novo classification, the agency writes that "patient perspectives on benefits and risks may reveal reasonable patients who are willing to tolerate a very high level of risk to achieve a probable benefit, especially if that benefit results in an improvement in quality of life." Additionally, variation in risk tolerance among patients compels the FDA to "consider evidence relating to patients' perspective of what constitutes a meaningful benefit when determining if the device is effective" when assessing data in a PMA application or de novo request.

For de novo requests, the FDA says that the risks associated with a device largely contributes towards its assessment of uncertainty and the overall risk-benefit profile. The agency may allow greater uncertainty if the device presents minimal risks or if special controls can mitigate risks, it said.

Other considerations include the device's public health need, including the benefit-risk profile of the device compared with available treatments and/or standard of care, as well as the feasibility of generating extensive clinical premarket data based on appropriate considerations.

The type of decision being made is also important, the FDA adds. "There is generally likely to be more uncertainty surrounding a device's benefit-risk profile based on the evidence submitted in an HDE application, as compared to a PMA, because the standards for approval are different," the agency writes.

In the guidance document, the FDA gives hypothetical case examples on approaches to conventional uncertainty, modest uncertainty, and high uncertainty for PMA considerations of breakthrough devices as well as medical devices that treat rare diseases.

Read the guidance on Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device Premarket Approvals, De Novo Classifications, and Humanitarian Device Exemptions here: www.fdanews.com/08-29-19-Consideration.pdf.

Read the guidance on Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications here: www.fdanews.com/08-29-19-Determinations.pdf. — Brandon May

Industry Critical of EC's Plan For Reprocessing Single-Use Devices

Devicemakers were critical of the European Commission's specifications for reprocessing single-use devices, with many comments raising concerns about specifications were released earlier this summer.

Some comments said the Commission lacked the legal authority to implement the requirements, and others said it should revise or delete many of the specifications.

The commission released a draft regulation that offers specifications for reprocessing single-use medical devices that appears to offer flexibility, but it received pushback from industry for being too restrictive (*IDDM*, Aug. 12).

The draft specifications lay down the rules for applying EU regulations 2017/745 for medical devices, allowing reprocessing of single-use devices where permitted by individual EU member states.

The Commission stressed that certain single-use devices are not suitable for reprocessing, such as those that emit radiation, incorporate drugs, or are used in invasive procedures on the central nervous system. Also excluded are implantable devices, devices with batteries that cannot be changed, or that have cutting or scraping blades that can't be changed or sharpened before the next procedure.

Commenters were particularly vocal about Article 5, which requires manufacturers to list technical information about their devices on their websites.

The European Coordination Committee of the Radiological, Electromedical and Healthcare IT Industry (COCIR) said that there was "no legal obligation to communicate information on the website of the manufacturer or the authorized representative."

MedTech Europe submitted a similar comment, stressing that the manufacturers' technical documentation is proprietary information, and the manufacturer is under no obligation to list such information.

COCIR said there is no legal obligation for a manufacturer to provide access to technical documentation, and it said the regulator's expectations should be further specified or the provision should be deleted.

The U.S.-based Association of Medical Device Reprocessors (AMDR) had similar concerns, citing confusion among its member who believe the specifications are intended to apply to EU MDR-regulated reprocessors.

MedTech Europe said it was not clear whether the implementing regulation applies only to reprocessing of single-use devices conducted by health institutions for their own in-house use.

AMDR took issue with the list of devices that should not be reprocessed under Article 3 as being too restrictive and said the entire section should be deleted. "Devices that cannot or should not be reprocessed will not be able to demonstrate compliance with these Common Specifications and will therefore not be reprocessed," AMDR said. The substance of these or CE marking requirements "sets a sufficient bar to prevent inappropriate devices from being reprocessed."

MedTech Europe scolded the commission for sending out a consultation over the summer holiday and said stakeholder consultations should be better timed.

Read the comments here: www.fdanews.com/08-29-19-Feedback.pdf.

China Introduces New Pricing Policies To Reshape Medical Device Market

China's State Council unveiled a plan to drive down high prices for medical devices and substitute expensive imports with locally made products.

The move echoes China's approach to controlling drug prices. The government said it will take similar measures to "clean up" the market for high-value medical devices.

"The pricing measures will bring significant pressure on multinational devicemakers, because most of their products currently have not been subject to price controls," Katherine Wang,

(See **China***, Page 4)*

Vigilance, *from Page 1*

But the directives and the guidance in MEDDEV 2.12-1 rev. 8 contain "very little detail on the vigilance obligations for manufacturers," according to attorneys at Sidley. As a result, many manufacturers find that vigilance reporting can be a confusing.

The additional guidance removes a requirement for the national competent authority to consult with manufacturers when preparing a National Competent Authority (NCA) report. It may not always be appropriate or justified for the manufacturer to be consulted or informed of a NCA report in cases where there is a serious risk to the safety of patients or other users but where no corrective action has yet been established, Sidley noted.

However, the guidance does require that the manufacturer always be consulted when an NCA report is prepared in response to a Field Safety Corrective Action being performed by the manufacturer. When a manufacturer is consulted, the NCA must provide a deadline for comments.

The Commission clarifies that "it is both the nature of the action taken, and the reason giving rise to the need for the action which defines whether an action is a FSCA."

The manufacturer's incident report has also been updated and includes some new concepts. It introduces new structures and International Medical Device Regulators Forum coding and terminology. It also includes a definition of similar incidents and requires trend data for those. Other new concepts that come into force in January 2020 include a unique device identification (UDI) system and the concept of a single registration number (SRN).

The guidance explains the role of a vigilance taskforce in communicating with other stakeholders including the manufacturer and when such a taskforce should be used.

"For the more involved and complex issues, the establishment of a specific vigilance taskforce may be required," the guidance says, noting that the composition of such a taskforce should include the competent authority with the original concern as well as other competent authorities, the manufacturer or its authorized representative, and notified bodies.

Read the European Commission's guidance here: www.fdanews.com/08-29-19-Guidance.pdf.

China, *from Page 3*

partner at the Shanghai office of law firm Ropes & Gray, told *FDAnews*.

The cost containment measures include price cuts through group purchasing organizations and the creation of a more transparent supply chain.

"The government is going to introduce multiple means to bring down prices of high value medical consumables, and multinational companies will experience more direct impact than their local peers because of significant price differences," Wang said.

To control pricing, the National Healthcare Security Administration (NHSA) will negotiate the purchase prices and reimbursement rates for high-value devices to be listed in the national Basic Medical Insurance reimbursement scheme. Long term, the NHSA intends to gradually introduce a diagnosis-related group payment system so that hospitals and physicians will have incentives to use lower-priced devices.

In the meantime, the government is rolling out a volume and category-based group purchase pilot program for public hospitals to target high-value products. The group purchasing and price negotiation models are both derived from China's drug reimbursement system, Wang said, which was designed to do away with preferential pricing for foreign drugmakers.

Three provinces have already started group purchases for selected consumables. One province — Anhui, in eastern China — claimed it reduced the price of orthopedic implants by 53.4 percent and reduced the price of intraocular lenses by 20.5 percent on average.

483 Roundup: Three Firms Cited For Design Controls, Quality

The FDA flagged three devicemakers for quality and other deficiencies observed during inspections.

Dharma Research: Dharma Research failed to validate its processes or to qualify equipment used for its dental gel, the FDA said following a March 6-18 inspection of the firm's Miami, Florida facility.

The company failed to validate storage conditions for its Etchant gel prior to the final syringe packaging, and there was inadequate documentation of control methods, monitoring and data collection for the sealing of the prophylaxis paste cups, the agency said — noting this as a repeat observation from 2014.

Another repeat observation was failing to establish design control procedures for the Class II dental product or to provide a reference to all records related to the design and development process, such as user needs, design inputs and outputs, and design verification and validation activities.

The FDA said the company's production processes were not developed, conducted, controlled and monitored to ensure that a device conformed to specifications.

"Your firm has failed to adequately identify hazards associated with all stages of the device life cycle, from product design to procurement to production and post-market use with the goal to estimate, evaluate, control and monitor risks associated with each life-cycle stage," the 483 said.

Health-Chem Acquisitions: Management at Health-Chem Acquisitions failed to ensure that every functional area responsible for the design and manufacturing of hCG test strips was properly resourced for achieving quality and compliance function, the FDA said following a Jan. 17-Feb. 20 inspection of the company's Pompano Beach, Florida plant.

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

Special Issues for Medical Device Reporting Procedures

Devicemakers need to consider three special issues when developing or revamping medical device reporting (MDR) procedures.

Reporting to other regulators: U.S. devicemakers often report to regulators in other countries, which may have different requirements. The FDA recommends that companies develop U.S.-specific MDR procedures rather than try to establish a global procedure to meet all requirements. An alternative would be to provide the MDR procedure as a clearly defined section of a global document.

The two-year malfunction "rule:" Traditionally, there has been an unwritten rule that if a company reports a malfunction and that problem doesn't occur for two more years, it doesn't have to report that issue anymore. The two-year period is referenced as a suggestion in the agency's 1997 guidance on Medical Device Reporting for Manufacturers. However, in a 2011 warning letter to Animas Corp., the FDA stated that devicemakers should not blindly apply that time period and stop reporting. Instead, a company interested in ending reporting on a given issue should discuss the issue with the agency.

Contract manufacturers: The 1997 MDR guidance recommended that both the devicemaker and any contract manufacturer report MDRs unless they have a written agreement that the FDA has approved that only one will report them. Make sure that if you have contract manufacturers, it's crystal clear between you, the contract manufacturer and the FDA who is reporting MDRs.

Some things can be left out of MDR procedures. For instance, the FDA no longer requires annual certifications, so the agency has recommended that devicemakers remove references to these from their procedures. The same applies to baseline reports. Device manufacturers that have references to either of these documents in their existing procedures should delete them.

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

483s, *from Page 5*

Health-Chem manufactures HCD diagnostic products such as pregnancy and fertility kits, cholesterol and glucose monitoring, and diagnostics for drug and alcohol screening.

Personnel with knowledge of the firm's market withdrawals, submissions and design controls were not present during the inspection to provide concrete responses regarding the basis for the market withdrawal of the pregnancy test, the FDA said.

The firm failed to establish design control procedures because the formal design history file was not maintained for hCG analog and digital test strip systems. There was no documented evidence that design review meetings were carried out, the agency said.

The diagnostics maker also didn't establish the type of evaluation needed to qualify suppliers or to maintain evidence that suppliers met such requirements.

Stimwave: FDA investigators found Stimwave Technologies' complaint handling procedures and corrective and preventive actions for its implantable pain treatment devices were not up to par, during a Jan. 29-Feb. 15 inspection of the firm's Pompano Beach, Fla. Facility.

The company makes wireless pain relief products called the Freedom spinal cord stimulator and the StimQ peripheral nerve stimulator that target nerves causing chronic pain. Faulty devices were returned to the manufacturer for not charging, not connecting or powering on and overheating, but many of the complaints were not entered into the firm's complaint handling system.

Software-related allegations of performance problems were not documented and handled through the firm's complaint handling system, which meant that complaints were not evaluated to determine if the events should be reported to the FDA.

Numerous complaints of injuries from infections associated with the implanted devices, as well as problems due to the migration of the devices were reported but not immediately followed up as MDRs.

The firm's CAPA procedures didn't include requirements for analyzing quality data using appropriate statistical methodology to detect recurring quality problems, the 483 said, noting that the firm only began documenting returned products as of Aug. 31, 2018 until the time of the inspection.

Procedures for design change were found to be lacking because they didn't require validation or verification of all design changes, inspectors said, pointing to software validation problems.

Read the Dharma Research Form 483 here: www.fdanews.com/08-29-19-dharmaresearchinc483.pdf.

Read the Health-Chem Acquisitions Form 483 here: www.fdanews.com/08-29-19-healthchemacquisitionsllc483.pdf.

Read the Stimwave Technologies Form 483 here: www.fdanews.com/08-29-19-stimwavetech483.pdf.

Third Circuit Appellate Court Nullifies Five of Mallinckrodt's Patents

A federal appeals court ruled that Praxair did not infringe on Mallinckrodt patents for its gas cylinder for inhaled nitric oxide.

Mallinckrodt, the name-brand manufacturer of INOmax (nitric oxide gas), sued Praxair in 2015 for alleged patent infringement by its generic product Noxivent. The complaint in the U.S. District Court of Delaware claimed in part that Praxair's NOxBOXi delivery mechanism infringed on several device patents, and that the gas itself infringes the patent when used with Mallinckrodt's cylinder.

In a 2017 trial, the judge ruled that Mallinckrodt's patents for the drug were invalid, and that Praxair had not infringed on the device patents.

In an Aug. 27 ruling, the Third Circuit Court of Appeals upheld the decision, noting the Delaware district court correctly interpreted the "plain language" of how the cylinder "verifies" the nitric oxide being released. The court also found that since Praxair's system does not 'verify' the gas, it does not infringe on Mallinckrodt's patent.

Mallinckrodt said it will consider all its legal options to challenge the ruling. — Jordan Williams

Cancer Patients Sue Sterigenics Over Factory Emissions

Dozens of cancer patients have sued Sterigenics in Cook County, Illinois for damages related to ethylene oxide emissions from its Illinois factories.

The lawsuits, filed in Cook County Circuit Court, allege that the company failed to monitor how much ethylene oxide (EtO) was being emitted from their plants.

EtO is a chemical commonly used for sterilizing medical and pharmaceutical products that cannot support conventional sterilization with high-temperature steam. Federal and international agencies identify the chemical as carcinogenic in humans.

The individuals, who live in areas surrounding the plants, allege that they developed cancer from being exposed to the chemical for years.

The new lawsuits follow a federal court ruling that the company can be sued in Cook County as opposed to federal court in Illinois.

U.S. District Judge Rebecca Pallmeyer wrote that Sterigenics can be sued in Cook County, writing that the company's compliance with federal law has nothing to do with matters in Illinois. The ruling sent eleven similar cases filed last year back to Cook County.

APPROVALS

ResApp Gains CE Mark For Respiratory Disease Diagnostic App

ResApp has earned the CE Mark for its ResAppDx-EU, a smartphone-based diagnostic test for acute pediatric respiratory disease.

The CE Mark was supported by data from a pediatric clinical study showing that the app's cough-based diagnosis algorithms had "excellent agreement with a clinical diagnosis," the company said.

The mobile software app is intended for use by clinicians to diagnose lower respiratory tract disease, croup, pneumonia, asthma/reactive airway disease and bronchiolitis in infants and children.

Atrial Management Device Cleared For Expanded Labeling

The FDA granted AtriCure 510(k) clearance for additional labeling claims for its AtriClip left atrial appendage (LAA) management device.

The expanded clearance changes the indication from occlusion of the LAA to exclusion and adds electrical isolation as a labeling claim. Occlusion plugs the opening to prevent blood flow into the LAA, whereas exclusion shuts off or eliminates the appendage from the left atrium.

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

Approvals, *from Page 7*

The agency granted the electrical isolation claim after testing showed that when excluding the LAA using the device, the appendage can no longer conduct electrical activity.

FDA Clears Biobeat's Cuffless Blood Pressure Monitors

The FDA granted Biobeat 510(k) clearance for its blood pressure, oxygenation and heart rate patch and watch monitors.

The devices take away the need for an inflating cuff, enabling remote monitoring and cloud-based healthcare, with data transmitted using either WiFi, Bluetooth, radiofrequency or a smartphone.

The products are the first of their kind to receive FDA clearance, the company said. They previously gained the CE Mark.

Miracor Earns Breakthrough Designation For STEMI Heart Attack Treatment

The FDA granted Miracor breakthrough designation for its PiCSO (pressure-controlled intermittent coronary sinus occlusion) device for treating heart attacks in which a coronary artery is completely blocked.

The device is designed to clear coronary microcirculation by stopping blood delivery into the right atrium through the coronary sinus, to improve blood flow to the area of obstruction after a ST-elevation myocardial infarction (STEMI) heart attack.

ST elevation refers to a reading on an electrocardiogram where the trace is abnormally high. STEMI heart attacks are considered the "classic" heart attacks and occur when a coronary artery has become totally blocked, causing a large portion of the heart to stop receiving blood.

FDA Approves CVRx's Advanced Heart Failure Treatment

The FDA granted CVRx approval for its Barostim Neo system, a technology designed to improve symptoms in patients with advanced heart failure who can't be treated with other heart failure devices.

Advanced heart failure can cause fatigue, palpitation and shortness of breath, leading patients with the condition to receive no benefit from standard treatments.

The Barostim Neo was one of the first therapies to receive the FDA's Breakthrough Device designation, which led to prioritized review of a phase 3 trial in 264 patients, which showed positive safety and effectiveness results.

OrthoPediatrics' Foot Deformity Treatment Earns 510(k) Clearance

The FDA has granted OrthoPediatrics 510(k) clearance for PediFoot, a pediatric-specific system for treating foot and ankle fractures and deformities.

The device is intended for fixating fractures, osteotomies, non-unions, replantations, and small bone and bone fragment fusions in pediatric patients, including the feet, ankles, hands and wrists. It uses the company's variable angle locking technology, which offers five points of fixation.

PediFoot addresses common deformities encountered in pediatric patients, including cavus foot, flatfoot, clubfoot and hallux valgus, the company said.

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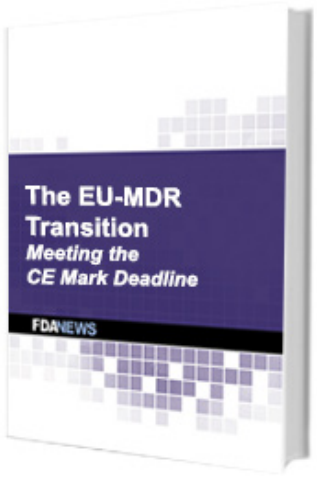

The EU-MDR Transition: *Meeting the CE Mark Deadline*

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

Complaint management is essential to a functioning quality management system.

Understanding the FDA's Quality System Regulation isn't enough — you must also master ISO 13485:2016 and the new EU MDR. They all require devicemakers to conduct trending in some form or another. But none of them tell you HOW.

This new edition of the best-selling **Medical Device Complaint Management** fills in that gap for you.

In addition to teaching the principles of successful complaint management …

- Receiving, documenting and investigating complaints
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