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IMDRF Flags Lack of 'Global Alignment' in Cybersecurity

Devicemakers should assess cybersecurity risks throughout the product lifecycle, the International Medical Device Regulators Forum (IMDRF) says in a new draft guidance that calls for "convergence of global healthcare cybersecurity principles and practices."

The "current disparate regulations across governments lack the global alignment needed to ensure medical device cybersecurity," IMDRF says.

The guidance flags the shared responsibility for cybersecurity among stakeholders, noting that the increasing use of wireless and network-connected devices has resulted in a surge of cybersecurity incidents that have rendered devices and hospital networks inoperable.

The guidance outlines general principles to facilitate international regulatory convergence and it includes recommendations for stakeholders on pre-market and post-market best practices.

(See **IMDRF**, *Page 2)*

FDA Investigates Implantable Devices That Contain Metals

The FDA called for feedback on a newly released report on biological responses to metal implants and says it's investigating possible adverse events linked to the devices.

The agency said it wants to learn more about how patients respond to materials used in such devices and it's inviting comments on gaps in the science and what approaches the FDA should consider.

"Based on our evaluation, we believe the current evidence, although limited, suggests some individuals may be predisposed to develop a local or systemic immune or inflammatory reaction when exposed to certain metals contained in select implantable devices," the agency said.

The most common metals and alloys used in implants include stainless steel, cobalt-chrome ally, titanium, and nickel-titanium alloy (nitinol). Other metals such as gold, platinum, silver, iridium, tantalum and tungsten are common.

(See **Metals**, *Page 4)*

IMDRF, *from Page 1*

It urges device manufacturers, healthcare providers, regulators, and users to employ a risk-based approach to designing and developing medical devices that offer cybersecurity protection.

The IMDRF recommends that stakeholders actively participate in information sharing organizations to ensure communication of cybersecurity incidents, threats and vulnerabilities that may affect the safety, effectiveness, integrity and security of devices and the connected healthcare infrastructure.

Pre-Market Considerations

"Proactively addressing cybersecurity threats at the design stage can better mitigate patient harm than engaging in reactive, post-market activities alone," the guidance stresses. Manufacturers need to consider secure communications, data confidentiality, data integrity, user access, software maintenance, hardware or physical design and reliability and availability.

Devicemakers should consider how data transfer to and from the device is secured to prevent unauthorized access or modification. They should determine how the communications between devices/systems will authenticate each other, if encryption is required, and if terminating communication sessions after a pre-defined time is appropriate.

Risk analysis should focus on the exploitability of the cybersecurity vulnerability and the severity of patient harm if the vulnerability were to be exploited. Risk assessments should tie design to threat models, clinical hazards, mitigations and testing. The validation of the design phase testing should consider how and where the device is used.

Software verification techniques should be used to ensure the software complies with specifications and to minimize the risk of anomalies, the guidance recommends.

Post-Market Management

Since cybersecurity threats will continuously evolve, devicemakers should proactively monitor, identify and address vulnerabilities as part of their post-market management strategy, and should develop a plan before market entry. Items to consider would include post-market vigilance, vulnerability and disclosure, patching and updates, recovery and information sharing, IMDRF says.

Legacy devices are a particular concern as they can't reasonably be protected against current cybersecurity threats. As such, they remain a challenge for all stakeholders, and devicemakers should continue to monitor legacy devices for critical vulnerabilities and provide a "best-effort response" and maintain ongoing risk documentation.

IMDRF urges legacy device manufacturers to:

- Design and develop devices so that, at a minimum, they "meet a security baseline and include mechanisms for updates and patches" over their clinically useful life;
- Monitor legacy devices for critical vulnerabilities and "provide a best-effort response and maintain ongoing risk documentation aligned to the total product life cycle" as a part of risk management; and
- Clearly communicate the end of life and end of support dates of the devices as part of the procurement and installation process including a communication of customer responsibilities at these time points. This helps healthcare organizations understand their responsibilities and device risk.

Read the full draft guidance here: www.fdanews.com/10-04-19-IMDRF.pdf.

Brazil Requires Pre-Approval For Custom-Made Devices

Brazil's ANVISA issued a new regulation for custom-made medical devices that includes new requirements for manufacturing, marketing and importing such devices.

In line with International Medical Device Regulators Forum, Brazil's regulation (RDC 305/2019) makes the distinction between custom-made devices, patient-specific devices and adaptable devices.

Under the definition, custom-made devices are made specifically for individual patients and manufacturers must seek approval from ANVISA to manufacture those devices.

Patient-specific devices are those that have been modified for a specific person's anatomy using anatomical imaging or other sizing techniques. Manufacturers of these devices also must seek approval to manufacture a patient-specific device. The agency is allowing a 24-month transition period for manufacturers of these devices that are currently marketed in Brazil.

A device that is mass produced but later adjusted or modified based on a device manufacturer's instruction is considered an adaptable medical device. No transition period is available for these devices.

Patient-specific Class III and Class IV medical devices will be reviewed on a case-by-case devices, ANVISA said.

EU Medical Device Regulation Sets New Requirements for Trials

Devicemakers planning to market products in the European Union need to understand new EU rules that spell out when clinical research is required and impose requirements for conducting trials.

The clinical research provisions of the EU Medical Device Regulation (MDR) will take effect in May 2020 and will require devices that are Class III or implanted in a patient's body to be proven safe and effective in a clinical trial.

The MDR is more complex than the Medical Device Directives (MDD) previously in effect in the EU, says device quality systems expert Dan O'Leary of Ombu Enterprises. The process for applying to conduct a trial also will be more involved, he says.

The first step is to determine whether the device falls under one of several exceptions to the clinical investigation requirement, including devices that are a modification of a device already marketed by the same manufacturer that has been demonstrated to be equivalent to the original.

Clinical equivalence also can exempt a device from the trial obligation if it is used for the same clinical condition or purpose — including severity and stage of disease — at the same site in the body and in a similar population based on age, anatomy or physiology.

The MDR alters some of the components of a trial application. For example, the investigator's brochure must include risk management information on devices employing a medicinal substance, human tissue or animal tissue.

The sponsor also must provide a detailed description of the specific medical or surgical procedures involved in using the device. Here they are looking for any deviation from normal clinical practice, O'Leary says.

"Where they are different, the MDR wins," O'Leary says.

An additional element of the informed consent process under MDR requires sponsors to explain to the patient possible treatment alternatives, including follow-up measures if participation is discontinued.

Although devicemakers currently approved to conduct a trial under MDD will be grandfathered in under the MDR, O'Leary warns sponsors to stay on top of the changes. Even grandfathered trials should make sure all their documentation lines up with the new requirements, he says. "So that even though you started under the MDD, … you have the MDR requirements for the design dossier content covered, because you don't want to get surprised at the end." — Colin Stoecker

FDA Issues Advice for Intravascular Devices With Lubricious Coatings

In a newly released guidance, the FDA spells out what manufacturers need to consider when labeling catheters, wires and delivery systems with lubricious coatings used during minimally invasive diagnostic and therapeutic vascular procedures.

The agency notes that coatings may sometimes separate from intravascular devices and it has seen serious adverse events from hydrophilic and hydrophobic coatings in devices and wires.

The agency notes that several causes of coating separation have been reported but says no specific manufacturer or brand of the devices carries a higher risk of coating separation than others.

Proper device selection, adequate premarket testing and preparation are needed to reduce clinical use-related issues of devices with lubricious coatings. The guidance covers the information devicemakers should include in labeling submitted in premarket applications or premarket notification submissions for Class 2 and Class 3 devices.

The agency includes recommendations for device and coating descriptions, writing an Indications for Use statement, device-related warnings, communicating preparation steps the user should follow in the clinical setting, and providing statements of potential and known adverse effects associated with coating loss.

Read the guidance full here: www.fdanews.com/10-10-19-Coating.pdf.

Wheelchair Manufacturer Warned for Misbranding

The FDA issued a warning letter to 21st Century Scientific for misbranding powered wheelchairs.

During an inspection of the firm's Coeur d'Alene, Idaho facility, agency investigators found that the firm didn't notify the FDA of its intent to introduce its Bounder powered seating wheelchairs to the market. The firm was marketing the wheelchairs as a modification option to its Bounder VA power wheelchair and other systems.

According to product labeling, the modifications added device functions such as lifting the user, tilting the user and bringing the user to a standing position. Advertising also showed the wheelchair being used in rugged terrain, and the agency said these modifications were significant changes that require the company to submit a 510(k) premarket notification.

The September 2018 inspection also revealed that the firm had not submitted a medical device report to the FDA following a serious injury. The firm became aware of a serious injury to a wheelchair user on May 16, 2017, but it failed to submit an MDR.

The agency said the company didn't establish internal systems that provide for timely identification, communication and evaluation of events subject to MDR requirements. Investigators flagged numerous deficiencies in the company's MDR processes, including a lack of instructions for conducting an investigation of each MDR reportable event.

The warning letter also cited the firm for its failure to fully document adverse events.

Read the warning letter here: www.fdanews.com/10-10-19-21stCenturyScientificWL.pdf.

Metals, *from Page 1*

The agency is also investigating amalgam used to fill teeth. Amalgam contains liquid elemental mercury and powdered alloy composed of silver, tin, copper and other metals.

"A more systematic research approach incorporating all possible clinical manifestations and underlying pathogenetic mechanisms is needed for enabling a timely detection and preventive treatment of adverse outcomes pertaining to implant reactivity," the report states.

The agency has scheduled a public meeting of the Immunology Devices Panel of the Medical Devices Advisory Committee on Nov. 13-14 to discuss immunological responses to metal-containing products regulated as medical devices.

Read the FDA report here: www.fdanews.com/10-10-19-Metals.pdf.

Ashlar Medical Falls Short On Design Validation, Risk Analysis

Ashlar Medical failed to perform design validation and risk analysis for its rediFLOW, rediPORT, rediFILL and associated firmware and software since 2015, the FDA found in a inspection of the firm's Natchitoches, Louisiana facility.

The company had not investigated the causes of deficiencies identified in a 2017 agency inspection, including issues with design control, quality audits, complaint handling, medical device reporting and purchasing controls, the 483 said.

The firm failed to evaluate "risks to distributed product, manufacturing processes and quality system potentially affected by those deficiencies," the agency said.

Requirements for suppliers were also not defined or documented, and written MDR procedures did not include an internal system that provides for timely identification and evaluation of reportable events, the agency said.

The firm had not evaluated complaints for MDR reportable events since 2015 when it began to manufacture and distribute the devices.

In addition, the firm's CAPA procedure did not require verification or validation of the actions taken.

Read the Form 483 here: www.fdanews.com/10-10-19-ashlarmedicalllc483.pdf.

Quality Plan, Quality Audits Lacking At Hospital Therapy Products

Management at Hospital Therapy Products failed to establish a quality plan, quality audits, or procedures for management reviews, a May 7-14 inspection of the firm's Wood Dale, Illinois inspection revealed.

During a previous 2017 FDA inspection, the firm was also cited for failing to establish quality audits,

(See **Therapy**, *Page 6)*

Complaint Classifications

Establishing a classification system for complaints helps organize your analysis. The customer is complaining the device is deficient in meeting one or more essential design output areas including: identity; quality; durability; reliability; safety; effectiveness; and performance.

If you are going to use this classification method, make sure your complaint SOPs clearly define each type and staff are trained to make decisions based on those definitions.

Ultimately, the devicemaker must make a key decision about each complaint: Does the complaint allege a serious incident — one that might have led or might lead to a death, a serious deterioration of someone's state of health or a threat to public health?

If the answer is yes, the complaint must be reported to the FDA or other regulator based on their regulations. If the complaint is determined to be "nonserious," it does not need to be reported but it must be recorded, investigated and classified for analysis purposes.

It's the way you use the results of this analysis that regulators emphasize. They want to know that you are tracking and identifying any significant increase in frequency or severity or other outlier uncovered in complaints and that you are using that information to make continual improvements.

Effective complaint management is a complex undertaking, involving staffing, training, data storage, trend analysis, reporting, information sharing, and meeting federal and international quality standards.

Complaint management involves all levels of a devicemaker's business: manufacturing, research, customer service, sales, field service, quality assurance, regulatory affairs, all the way up to the executive suites where the big decisions are made.

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

Lax Change Design Procedures Found at Vasamed

Failure to establish procedures for design changes and for acceptance of incoming product, were among the quality management lapses uncovered during a May 13-16 FDA inspection of Vasamed's Eden Prairie, Minnesota plant.

The devicemaker manufacturers the Sensilase PAD-IQ, which measures skin perfusion to detect arterial vascular health.

Agency investigators found that design plans were not reviewed, updated and approved as the design and development of the device evolved. A user interface board design change for the PAD-IQ was completed in 2016, but documentation control procedures were not established.

Engineering change orders are required, and they should include a drawing, marketing literature, labeling, technical specification, work instruction, operating procedures, material specification and parts that are under control of the Vasamed documentation system, the agency said. However, this was not done for at least five major processes.

In addition, the device history record didn't demonstrate that the device was manufactured in accordance with quality management practices, because none of the records included primary identification labeling.

The firm also identified issues with nonconforming product, but it had not opened a vendor action request to correct a complaint, as is required by its CAPA procedures.

Read the Form 483 here: www.fdanews.com/10-10-19-vasamedinc483.pdf.

Therapy, *from Page 5*

but the firm has "continued to fail to conduct quality audits since the last FDA inspection," the 483 says.

Corrective and preventive action activities were not properly documented as evidenced by three CAPAs that were initiated since the agency's previous inspection.

The firm was also cited for failure to have a quality policy at the last inspection, and FDA inspectors were handed a document titled "Quality System Policies, Procedures and Requirements," but the document failed to reference a quality policy, the 483 says.

"Your firm failed to have a quality manual and/or plan that describes and references the firm's organizational structure and/or quality documents that will assure your firm's compliance with quality policy," the 483 says.

Another repeat observation from the 2017 inspection was that the firm failed to establish written management review procedures. Inspectors noted that on May 7, they were initially told that no formal management reviews had been held since the last FDA inspection.

In addition, numerous documents lacked a signature by a "quality designee."

Read the 483 here: www.fdanews.com/10-10-19-hospitaltherapyproductsinc483.pdf.

FDA Streamlines Application Process For Oncology Combination

A new final guidance from the FDA allows some sponsors of oncology products to file a single application for use of an investigational diagnostic in their trial rather than filing for the drug and device components separately.

Under the new guidance, sponsors of trials combining a new oncology drug with a new in vitro diagnostic (IVD) device will submit an investigational new drug application to the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER), including information about the investigational IVD in question.

CDER or CBER then will consult with the Center for Devices and Radiologic Health (CDRH) to determine whether the IVD presents a "significant risk" and requires the sponsor to submit to CDRH a separate application for investigational device exemption.

The guidance applies only to new IND applications and does not address IND-exempt trials.

Read the final guidance here: www.fdanews.com/10-10-19-IVDGuidance.pdf.

New FDA Guidance On 510(k)s for Guidewires

The FDA offers new advice for devicemakers on 510(k) submissions for guidewires used in coronary, peripheral and neurovasculature in a final guidance released last week.

The FDA notes that guidewires are not required to include directions for lay use, but labeling must include adequate information for the intended user. The information should cover indications, routes, methods, effects, frequency and duration of administration as well as contraindications, side effects, and any relevant hazards.

Submissions for guidewires should include: a device description; a predicate comparison; biocompatibility; sterility; pyrogenicity; shelf life and packaging; non-clinical bench testing; and clinical performance testing, the agency says.

A new 510(k) submission is required for modifications that would affect either the safety and/or efficacy of the device. Examples that would require a new submission include changes to guidewire material, coating, and tip configuration. Changes to device packaging would not likely warrant a new 510(k) submission, the agency says.

The final guidance replaces the agency's Coronary and Cerebrovascular Guidewire Guidance released in January 1995.

Read the full guidance here: www.fdanews.com/10-10-19-510kguidance.pdf. — Brandon May

APPROVALS

Erchonia Laser Gains 510(k) Clearance for Temporary Pain Relief

The FDA cleared Erchonia's Erchonia Violet and Red Laser (EVRL) device for the temporary relief of chronic neck and shoulder musculoskeletal pain.

The handheld, smart phone-sized low-level laser is the first violet laser (405nm) to receive FDA market clearance for the use on an indication related to pain, the company said.

The product uses low-level laser therapy to avoid the side effects of traditional treatments and different wavelengths to stimulate different types of healing.

Epica Grabs FDA Clearance For Tomography Imaging System

The FDA granted 510(k) clearance to Epica International's SeeFactorCT3 imaging platform, a device that combines three different imaging systems.

The robotically-controlled platform includes CT, fluoroscopy and digital radiography imaging systems, a detachable patient table and chair, and a sterile drape used for interventional procedures.

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

Approvals, *from Page 7*

The ultra high-resolution system can be moved to patients in an intensive care unit or emergency room and can be operated by physicians, surgeons, dentists, or other qualified professionals.

Gore Earns CE Mark For Atrial Septal Defect Occluder

Gore earned the CE Mark for its Cardioform atrial septal defect (ASD) occluder, a device that closes abnormal openings in the heart.

The minimally invasive device is designed for transcatheter closure of ostium secundum atrial defects and it can be retrieved and repositioned. The device can close defects ranging from eight to 35 millimeters in diameter.

The occluder was recently granted approval by the FDA for the treatment of ASDs.

FDA Clears Exogenesis' Hernia Mesh

Exogenesis received 510(k) clearance from the FDA for its hernia mesh, a device indicated for repairing abdominal wall hernias and abdominal wall deficiencies that require reinforcing material.

The device consists of monofilament medical grade polypropylene and has a surface treated with the company's Accelerated Neutral Atom Beam technology.

The mesh provides long-term tissue support and its large pores encourage tissue ingrowth.

Laser Associated Sciences Blood Flow Monitor Cleared

Laser Associated Sciences' non-invasive blood flow monitoring system, FlowMet-R, received 510(k) clearance from the FDA for detecting peripheral artery disease and gauging the efficacy of treatments.

The device clips onto a patient's toe and uses a small laser diode and camera to measure blood flow, providing insight on surgical effectiveness.

"By directly measuring limb perfusion during surgeries, physicians can see for the first time whether peripheral blood flow [is] being improved in real time," says Laser's CEO Sean White.

Australia Approves Smartphone Diagnostic For Acute Pediatric Respiratory Disease

Australia's Therapeutic Goods Administration (TGA) has approved ResApp's ResAppDx-EU, a smartphone-based app for diagnosing and managing respiratory disease in pediatric patients.

The app previously received the CE Mark, which 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.

Luminex Grabs FDA Clearance For MRSA Nasal Swab Assay

The FDA granted Luminex 510(k) clearance for its Aries MRSA assay, an in vitro diagnostic test that uses nasal swabs to directly detect methicillin-resistant Staphylococcus aureus (MRSA).

The diagnostic is run on Luminex's Aries system, that features six FDA cleared and seven CE marked assays and can also run lab-developed tests.

MRSA is usually spread by direct contact with an infected wound or contaminated hands, often those of healthcare providers, according to the CDC.

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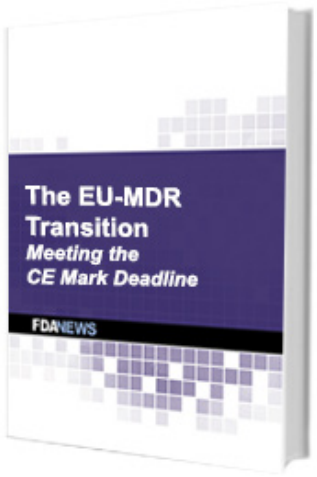

The EU-MDR Transition: *Meeting the CE Mark Deadline*

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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