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IN THIS ISSUE

IMDRF Releases Guidance On Pathways for Personalized Devices

The International Medical Device Regulators Forum (IMDRF) has released a draft guidance laying out regulatory pathways for personalized medical devices.

The IMDRF recommendations represent best practices for harmonizing the regulation of personalized medical devices across international jurisdictions.

The guidance recommends applying existing regulatory pathways to medical devices intended for a particular individual, while also identifying special considerations for regulating each category of medical devices.

The IMDRF Personalized Medical Devices Task Group noted that current guidance fails to take into account recent developments in the device industry such as 3D printing methods based on patient CT scans.

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

GS1 Issues New Guidelines That Reflect New UDI Requirements

GS1 released updated guidance to help devicemakers comply with new unique device identifier requirements under the FDA's updated standards.

The new guidelines identify the GS1 identification and barcode standards that correlate to the FDA's UDI Rule requirements and explains how to implement the standards within the context of the FDA rule.

"As with all GS1 standards and solutions, this Implementation Guideline is voluntary, not mandatory," the standard-setting organization said. "It does not provide any guidance or advice regarding regulatory compliance."

The 62-page guidance document provides updates on GS1 company prefixes and barcode scanners as well as updates on the global trade item number (GTIN) data structure and how to determine which GTIN structure to use and what barcode options are available.

(See **GS1**, *Page 2)*

European Commission Issues Q&A On Requirements for Notified Bodies

The European Commission's Medical Device Coordination Group (MDCG) released a Q&A on requirements for notified bodies (NBs) under the EU's medical device and in vitro diagnostic regulations (MDR/IVDR).

The eight-page guidance addresses concerns NBs may have about their organizational structure, when they can provide pre-certification services, their authority prior to notification and how to ensure compliance with impartiality requirements.

Individual EU member states inform the Commission and other member states that a body has been designated to conduct conformity assessments. NBs may not accept applications under the MDR/IDVR until a day after their notification is published on the online Nando (New Approach Notified and Designated Organizations) information system.

A notified body's organizational structure may differ depending on the legal entity and organization it belongs to, the guidance says. Holding companies, for instance, may need to provide an organizational chart of their head office that describes the functional and managerial relationships.

Pre-certification services may not be rendered before the manufacturer files an application, such as for clinical data review or assessment of a quality management system. Such services must take place "under the scope of the application," the guidance states.

Read the coordination group's guidance here: www.fdanews.com/06-07-19-NotifiedBodies.pdf. — James Miessler

IMDRF, *from Page 1*

Many regulatory authorities have already defined the term "custom-made" device and have introduced exemption provisions for regulating custom-made devices to cover special cases when mass-produced devices did not meet the needs of individual patients.

Because custom-made devices, including implantable devices for particular patients, are now available on a much larger scale, some jurisdictions are noticing the questionable use of custom-made device exemptions, with more patients receiving higher risk classification medical devices under these exemptions.

The working group had previously released a final guidance that defined personal medical devices and distinguished between personalized medical devices and custom-made medical devices. Personalized devices describe devices intended for a particular individual, but custom-made devices are not patient-matched, the guidance says (*IDDM*, Nov. 16, 2018).

The new guidance includes a decision tree for determining whether a device is a personalized medical device or not and which pathway it should take.

Makers of custom-made devices should determine the classification of the device if it were not custom made, the group suggests. For higher-risk custom-made devices such as implantable devices, manufacturing should be undertaken in a facility that is subject to third-party oversight, the group said.

The group recommends that custom-made devices and their manufacturers be registered or notified to regulatory authorities where they are supplied.

Read the IMDRF guidance here: www.fdanews.com/06-07-19-imdrf.pdf.

GS1, *from Page 1*

The GTIN is used to represent the device identifier portion of the UDI. The application and use of each segment can vary depending on the GTIN structure being used, and specific rules are defined within the GS1 general specification.

"In order to ensure the uniqueness of your GTINs going forward, it is imperative that any GS1 member that has a GS1 company prefix that aligns its labeler code submit a request to the U.S. FDA for continued use of their labeler code," the guidance says. It notes that device companies may have more than one GS1 company prefix.

Read the GS1 guidance here: www.fdanews.com/06-06-19-GS1.pdf.

MedTech Europe Faults EU Plan For Harmonizing Standards

Harmonized standards are key for applying Europe's new medical device and in vitro diagnostics regulations, but the European Commission's latest draft of the standards to be considered is filled with technical errors that would result in a lack of standardization, MedTech Europe said.

The commission's standardization request includes a list of standards to be considered for harmonization under each regulation, and the request proposes timelines for adopting the standards. However, MedTech Europe said that if the standards were to be implemented, they would result in a deficiency of harmonized standards.

"This situation will lead to a lack of alignment between notified bodies with respect to the conformity assessment procedure and potential confusion within the system as a whole, possibly allowing non-state-of-the-art products to enter the market," MedTech Europe says in a new position paper.

MedTech Europe said that list of standards in Annexes I and II of the standardization request lacks several key horizontal standards for both IVDs and medical devices that are "vital to ensure safety and performance." In addition, references to these standards are already listed in the EU's Official Journal under IEC 61326-1, ISO 14708, ISO 14630 and ISO 17664.

Timelines 'Misaligned'

Annexes I and II specify timing for adoption, but the timelines "appear to be misaligned with the enforcement dates of the new regulations. For example, the EN 60601 series related to basic safety and essential principles of [medical devices] are due to be adopted by May 27, 2024, which is four years after the date of application of the MDR on May 26, 2020," the association said.

The requested standards also hinder device-makers from complying with applicable regulations, because manufacturers need to conform to the general safety and performance requirements that take into account the state of the art. However, "it may be possible that state-of-the-art would not be considered if manufacturers were to apply the [proposed standards]," the paper states.

Given the time-intensive process to approve a standardization request, such a closed list "hinders CE-marking of innovation devices," the association said.

Rewriting Needed

The current Annex III of the draft standardization request would effectively halt the harmonization of standards that reproduce the requirements sets out in the regulations, MedTech Europe said, stressing that this approach "would require extensive rewriting of standards to ensure no cross-over or the exclusion of standards only because of editorial issues."

MedTech Europe is calling on member states, notified bodies and standards organizations to contact the Commission to emphasize the potential long-term impact on product availability, approval, safety and innovation with a direct consequence to patient safety and the delivery of state-of-the-art healthcare.

In related news, seven device and IVD stakeholders including MedTech Europe, released a joint statement that calls on the Commission and member states to accelerate the implementation of the regulatory system "to prevent a 'cliff-edge' scenario for patients, healthcare professionals and healthcare systems in Europe.

The letter notes that the implementation date for the new regs is less than a year away but the system is far from being functional. "Immediate action is needed now to avoid severe disruption of product supply to patients and hospitals as well as to safeguard the innovation capacity of the sector in developing new life-saving and life-transforming technologies," the joint letter states.

Read the position paper here: www.fdanews.com/06-06-19-Medtech.pdf.

FDA Issues Final Guidance On the Q-Submission Program

CDRH released final guidance for device sponsors on requesting feedback or meetings with agency officials ahead of investigational device exemption (IDE) or other marketing submissions under the Q-Submission program.

The program was established in 1995, initially to provide sponsors a way to get FDA feedback on IDE applications prior to submission. Over time, it evolved to include feedback on premarket approvals, humanitarian device exemptions, De Novo requests, and 510(k) submissions, as well as to assess whether a clinical trial requires submission of an IDE, the agency explained.

Q-Sub interactions can include pre-submissions for marketing applications, submission issue requests—usually relating to hold letters—and study risk determinations to assess whether a planned device clinical trial is a significant risk, non-significant risk, or exempt from IDE regulations.

Read the full guidance here: www.fdanews.com/06-06-19-QSubmissions.pdf.

Japan, South Korea Seek to Speed Device Access, Secure Safety

At the recent International Medical Device Regulators Forum (IMDRF) meeting in Moscow, Japanese and South Korean regulators said they plan to introduce mechanisms to allow for rapid access to needed devices and in vitro diagnostics.

Japan recently adopted its "Sakigake" pathway for breakthrough biologics that allows for provisional approval based on limited clinical data, and it is considering a similar pathway for devices. The new device pathway would need to be approved by legislation.

The proposal would allow for rapid practical use of needed devices "based on the premise of ensuring safety," Japan's Pharmaceuticals and Medical Devices Agency (PMDA) said. Such a system would use patient registries or similar electronic tracking for enhanced postmarket surveillance.

Similar to the Sakigake classification for drugs, it would require that an innovative device or in vitro diagnostic represents an urgent medical need and the premarket application would have to be the first in the world.

Once the pathway is designated, the device-maker would receive a priority consultation, and the review time would be six months instead of 12 months.

Also at the meeting, South Korean officials discussed plans to introduce a unique device identification system and an enhanced adverse event portal that's already in place.

The UDI system will be introduced in stages, starting with highest-risk Class IV devices in July. Class III devices will come online in July 2020, Class II in July 2021, and Class I in July 2022.

As with Japan, South Korea's focus is on getting innovative devices and diagnostics to patients faster while also securing the supply chain.

Read the PMDA presentation here: www.fdanews.com/06-06-19-Japan.pdf.

Read South Korea's presentation here: www.fdanews.com/06-06-19-SouthKorea.pdf.

Houston Devicemaker Called Out for Numerous Violations

The FDA cited Houston, Texas devicemaker Talon for a multitude of transgressions at its facility, including problems with validations and complaint investigations.

The FDA investigator logged a whopping 13 observations during the March 11-28 inspection—including four repeat violations from an inspection in 2011.

The agency took issue with the facility's design change procedures, which did not include specific instructions for steps such as how the change would be identified, documented, verified or reviewed for implementation. The company implemented multiple design changes that did not undergo verification.

The investigator found that customer complaint investigation records lacked required information. For example, some corrective actions only included email notification addresses.

The firm's servicing procedure was also inadequate, as it did not include instructions for ensuring that servicing adhered to specified requirements.

Read the full Talon Form 483 here: www.fdanews.com/06-06-19-talonansstechco483.pdf. — James Miessler

Sources of Error for Verification and Validation

All verification and validation testing must be concerned with variability, also known as error.

There are, essentially, two sources of error. The first source, the most common and most-focused-on by devicemakers, is the variability of the device or component itself, according to Steven Walfish, president of Statistical Outsourcing Services. This is the standard deviation and represents the part-to-part variability in the process.

The second source is measurement variability, which refers to variability in the measurement of a device characteristic or output due to the instrument used. The question asked here is: "How much variability will I get when I take the exact same unit and measure it repeatedly with the same instrument?"

This source of error becomes particularly important when a company wants to look at variability within a part versus variability part-to-part. "If my measurement system variability is very high, then I'm going to need to test the same unit more times than necessarily testing multiple units," Walfish said. "It becomes very important when we start to talk about how we're going to partition out our sample size."

Thus, companies must periodically perform a measurement system analysis (MSA). Walfish suggested that devicemakers should do so before undertaking any data collection and decision-making. MSAs also should be repeated periodically on a maintenance basis.

"Always, always, always get this measurement system under control," Walfish said. "Under the variability prior to doing any data collection and, more importantly, before you do any decision-making about the design."

Some key activities that could warrant an MSA include:

- Making product design decisions;
- Performing process validation;
- Improving phase in a black/green belt project; and
- Conducting a final product inspection.

Walfish placed extra emphasis on the first bullet point, saying, "If we're going to make a decision about the product design, we want to make sure that our measurement system is adequate, and if we've already done a measurement system analysis, that it's still valid, before we go about making any decisions about product design."

Finally, Walfish cautioned against focusing only on Type I errors — the so-called producer risk — when developing sampling plans.

While company risk is important, devicemakers also need to consider the FDA's priority, which is risk to the patient, or Type II errors. Thus, the agency would like to see sampling plans that also control for this type of risk.

Excerpted from the FDAnews management report: *Choosing the Best Device Sample Size for Verification and Validation.*

EC Releases New Guidance On Eudamed Data Exchange

After months of criticism of the European Commission for the slow release of guidance on the EU's new medical device regulations, the Commission released a flurry of documents on the Eudamed data exchange.

The guidance notes that there are several entry points for inputting and downloading data into the Eudamed database:

- The user interface, which involves manual input of data;
- The XML upload/download option, which is semi-automated. The XML data must be validated against the provided Eudamed DTX service; and
- The data exchange machine-to-machine (M2M) system, which allows for automatic data exchange between an external backend system, with data automatically transmitted to Eudamed in XML format with the same validation conditions.

The manual user interface model is the simplest option from a data handling, manipulation, and implementation perspective, because the user only needs a computer and an internet connection.

The guidance notes that the machine-to-machine option "may be too costly" considering the many architectural, technological and operational issues, if the frequency and volume of the data transfer remains low.

The data exchange model is the most complex. Because it allows a bulk download of sensitive data, the application connected to Eudamed will need to comply with a "series of security requirements," the Commission said. This solution should only be considered if the amount of data to be uploaded or downloaded can't be entered manually, and there will be frequent exchanges of data between systems.

The guidance provides a decision tree to help authorized representatives or importers, devicemakers on which option makes the most sense to meet their compliance duties. Another decision tree is provided for notified bodies to make its determinations.

The Commission also released a separate document offering technical details on data exchange related architecture and data modeling for performing M2M connectivity.

This document covers high-level concepts such as the entity model, the service model the data exchange communication patterns and service definitions.

In May, The European Commission released new details on the datasets devicemakers should include in the Eudamed database for unique device identifiers under the new MDR and IVDR. The overriding principle for the database is that each UDI device identifier (DI) inherits the attributes of its linked Basic UDI-DI—the primary identifier of a device model and the main key for records in the UDI database that's referenced in certificates and EU declarations of conformity (*IDDM*, May 10).

Read the Eudamed Data Exchange Guidelines here: www.fdanews.com/06-06-19-Eudamed.pdf.

EMA Publishes Draft Guidance on Combo Device Quality Requirements

The European Medicines Agency issued a draft guideline on quality requirements for combination devices, opening the guidance up to a three-month public consultation.

The guideline, which applies to devices required for administering, dosing or using medications, is meant to improve the consistency and transparency of information included in regulatory submissions for those products. It also includes a proposed template for notified body opinions on device conformity to general safety and performance regulations.

Specifically, it details device information sponsors need to include in their initial marketing authorization applications and during their products' lifecycle, such as a description of the manufacturing process, the container closure system, and functional performance and stability studies. For example, sponsors should discuss and justify the suitability of the device for the particular drug product and perform interaction studies using a risk-based approach.

If the combination product includes a drug product intended to be sterile, the device's sterility should be verified by referring to its CE certificate. Maintenance of sterility throughout the product's use, as well as the final medicinal product's shelf-life, should also be documented, the guideline says.

Read the full draft guidance here: www.fdanews.com/06-04-19-EMA.pdf. — James Miessler

APPROVALS

FDA Clears Misonix Ultrasonic Surgical System

The FDA has handed Misonix 510(k) clearance for its Nexus ultrasonic surgical platform, which integrates multiple solutions for surgical applications into a single device.

The system combines all the features of the company's ultrasonic tools—BoneScalpel, SonicOne and SonaStar—to enable bone, tumor and tissue removal capabilities. Nexus' smart technology makes the platform easier to setup and use.

Nexus features a new digital algorithm that provides more control and efficiency, and increased power to improve tissue resection rates. Misonix will launch the platform on the U.S. market in July.

Ignite Orthopedics Radial Head Arthroplasty System Cleared

Ignite Orthopedics has received 510(k) clearance for its Radial Head Arthroplasty System, the firm's first product to receive FDA clearance.

The company's Radial Head Arthroplasty System is designed to treat patients with fractured or degenerative arthritis of the proximal radius. Radial head fractures account for approximately one-third of all elbow fractures.

The system allows a spacer to be placed when joint stability requires added height. A surgeon can insert the spacer without having to dislocate the radius, which can disrupt the surrounding soft tissue and slow down surgery.

Acandis Stent Retriever Device Receives CE Mark

Acandis has earned the CE Mark for its new stent retriever, the Aperio hybrid thrombectomy device, which is compatible with vessel diameters from 1.5 mm to 5.5 mm.

The retriever is used to restore arterial flow in patients diagnosed with ischemic stroke due to large intracranial vascular occlusion. It can be delivered through common 0.021" microcatheters.

Acandis said the retriever's design, which features small closed cells and large open cells, provides good vessel wall alignment, improved device expansion and efficient clot retention.

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

Approvals, *from Page 7*

FDA Clears Leica Biosystems Digital Pathology System

The FDA granted Leica Biosystems 510(k) clearance for its Aperio AT2 DX system, an automated scanning and viewing platform.

The high-throughput device automatically scans pathology slides, delivering whole images quickly. It also allows the user to view the slides through the device.

The platform will be coupled with clinical management software to serve as an integrated digital pathology workflow solution upon launch, the company said.

DiaSorin Molecular's VZV Assay Cleared

DiaSorin Molecular has nabbed the FDA's clearance for its Simplexa VZV Direct assay, a molecular diagnostic test used to detect the varicella-zoster virus (VZV).

The diagnostic—which is meant to be used alongside the company's HSV 1 and 2 direct assay—is used with samples of cerebrospinal fluid to detect virus DNA, making it effective in the diagnosis of meningitis and encephalitis.

VZV causes varicella (chickenpox), a highly transmissible disease most commonly experienced in early childhood that can cause acute meningitis.

Israeli Devicemaker Gains De Novo Clearance for Mobile Migraine Treatment

Theranica earned De Novo clearance from the FDA for its Nerivio Migra product, a neuromodulation device designed to treat migraines.

The device is placed on the upper arm and emits electrical pulses that are controlled via smartphone. It is indicated for treating migraines with or without aura—a visual, sensory, motor or verbal disturbance—in adults who don't have chronic migraine.

Clinical data showed that the product "can provide patients with significant relief of pain and other migraine symptoms without the side effects presented by drugs," said Messoud Ashina, president-elect of the International Headache Society.

iThera Medical Earns CE Mark For Imaging System

Munich-based iThera Medical received the CE Mark for its multispectral optoacoustic tomography (MSOT) imaging system that allows radiation- and contrast-agent-free imaging of soft tissue.

The system combines laser excitation and ultrasound detection for the analysis of hemoglobin, lipids, collagen and other chromophores in tissue.

MSOT makes use of the photoacoustic effect in which absorbed light results in the emission of acoustic signals. By tuning the wavelength of the laser, it can identify compounds by their color.

MSOT allows the study of disease processes on a molecular level. Exploratory clinical trials have already been completed for inflammatory bowel disease, various soft tissue cancers, systemic sclerosis, muscular dystrophy, and cardiovascular diseases.

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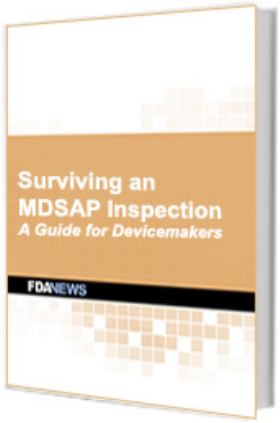

Surviving an MDSAP Inspection: *A Guide for Devicemakers*

Currently, Australia, Brazil, Canada, Japan and the United States are participating in the MDSAP program. If you pass one MDSAP inspection you'll be ready to pursue marketing authorization in five separate countries.

But, if you're going through MDSAP for the first time your experience will be very different from regulatory inspections you've gone through in the past.

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- You'll know exactly what questions the auditor will ask

The prescriptive nature of the MDSAP model makes it relatively easy to prepare for an audit — if you know what to expect. **Surviving an MDSAP Inspection** provides all the information you'll need to understand the MDSAP model. You'll learn:

- The standard schedule for and duration of audits
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- Different types of audits involved, such as initial certification, surveillance, desk and site audits
- How to create a checklist to make sure all your bases are covered
- The MDSAP grading system and how nonconformance issues can be escalated — and consequences of getting a bad grade

The management report also includes a copy of the MDSAP Companion document — the official guide — auditors will follow.

Order your copy of **Surviving an MDSAP Inspection: *A Guide for Devicemakers*** and know what to expect from an MDSAP audit and how to prepare for it.

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EU MDR Compliance: *A Checklist for Meeting Manufacturing, Safety and Performance Requirements*

The new EU Medical Device Regulation is massive… complex… and confusing… and you must be ready to comply by May 26, 2020.

When the European Union revised its system of rules for medical device manufacturers in 2017, it replaced a longstanding set of directives on specific topics with one large document that covers all aspects of making devices in EU countries.

Not only did they consolidate all the rules, they gave them greater weight. Previously, medical device directives provided guidance but did not have the force of law. The new MDR, however, contains mandates that are legally enforceable by EU member countries.

The FDAnews report **EU MDR Compliance** can help. Our editors have combed through the regulations, picking out the most minute compliance points and building them into a checklist of 200+ requirements you can use to confirm that you are satisfying all the EU mandates for device manufacturing. The report provides:

- Definitions of key terms in the EU MDR
- Knowing where to find specific requirements in the 150+ page regulation
- Checklists that walk you through every aspect of manufacturing, safety and performance requirements
- A training tool for employees new to the regulations

EU MDR Compliance: *A Checklist for Meeting Manufacturing, Safety and Performance Requirements* is the tool that collects all the requirements, explains them and itemized them in an easy-to-use form to ensure compliance.

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