INTERNATIONAL DEVICES & DIAGNOSTICS MONITOR

Vol. 4, No. 13
March 26, 2018

IN THIS ISSUE

FDA Postpones Enforcement of Combination Product Rules, Outlines Requirements for Constituent Parts

The FDA issued two guidances on postmarketing safety reporting for combination products, pushing back reporting requirements for certain combination products and clarifying reporting rules for their constituent parts.

In one guidance, titled Compliance Policy for Combination Product Postmarketing Safety Reporting, the agency said it will not immediately enforce certain provisions of the 2016 postmarketing safety reporting (PMSR) rule.

The FDA said it will not enforce recordkeeping requirements for combination product applicants who use the agency's Electronic Medical Device Reporting System (EMDRS) and the Adverse Event Reporting System (FAERS) before July 31, 2019.

The agency also will not enforce the rules on combination product applicants using the Vaccine Adverse Event Reporting System (VAERS) for individual case safety reports until Jan. 31, 2020.

(See **Combination**, *Page 2)*

India Issues Guidelines On Grouping Devices for Licensing

India's Ministry of Health and Family Welfare released guidelines for grouping medical devices into a single application for importing, manufacturing or distributing medical devices in India.

Applicants who want to license, import or manufacture a device may group similar devices in a single application. The ministry said the applications could include devices that have similar intended purposes or common technology.

A single medical device is one that that is sold as a distinct packaged entity and doesn't meet the criteria for a family of devices such as an in vitro diagnostic test kit, IVD cluster or a group. The device may be sold in a range of sizes, and it must be licensed separately. For example, condoms would be considered a single medical device application.

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Guidelines, *from Page 1*

The Ministry of Health said a medical device family is a collection of medical devices whereby each device is from the same license holder, is in the same risk classification class, has a common intended use, has the same design and manufacturing process, and could have variants "within the scope of permissible variants."

Under India's new medical device rules, a device may be considered a permissible variant if:

- The physical design and construction material are the same or very similar;
- The manufacturing processes, including sterilization method for the devices are the same or very similar;
- The intended purpose of the devices is the same; and
- The risk profile of the device is the same.

For example, spherical contact lenses with additional features of UV protection can be licensed as part of a family of devices, as this does not affect the basic design or manufacturing of the lens. However, contact lenses are available as either toric lenses that correct for astigmatism or spherical lenses, and because they have different intended purposes and performance and are designed and manufactured differently, they may not be considered as members of a family of devices.

A hip replacement system comprised of femoral and acetabular components may be licensed as a family because the combination of components achieves the intended purpose of a total hip replacement.

A medical device group is a collection of two or more medical devices supplied in a single package by the same license holder that are sold under the same brand name and are for a common intended purpose. For example, a first aid kit consisting of medical devices such as bandages, gauze, and thermometers, when assembled together as one package, can be licensed as a group.

Medical devices that comprise a system are from the same license holder, are used in combination to complete a common intended purpose, are compatible when used as a system, and are sold under a single proprietary name. For example, a glucose monitoring system composed of a glucose meter, test strips and control solution could be licensed as a system.

An IVD cluster would include a number of IVD reagents or articles that are from the same license holder, use a common methodology, are sold under a single proprietary name, and are compatible when used as a test kit.

Read the guidelines here: www.fdanews.com/03-20-18-Indiaguidelines.pdf.

Combination, *from Page 1*

In a separate draft guidance, titled Postmarketing Safety Reporting for Combination Products Guidance for Industry and FDA Staff, the agency detailed how to comply with the PMSR rule, noting the rule applies to both combination product applicants and constituent part applicants.

Both categories must meet the safety reporting requirements associated with the application type for which the product received the marketing authorization. Only combination product applicants, however, are subject to certain safety reporting requirements associated with the constituent parts of the product, the agency said.

Device applications or biologics license applications or for a product that contains a drug constituent part must also comply with field alert and fifteen-day reporting requirements.

Device applications or ANDA/NDA submissions for combination products containing a biological constituent part must comply with biological product deviation reporting requirements and fifteen-day reporting requirements.

For combination products featuring a device constituent part, the applicant must also comply with five-day, malfunction and correction or removal reporting requirements.

Read the two guidances here: www.fdanews.com/03-20-18-Guidance.pdf. — Zack Budryk

Vilex Warned for Manufacturing Adulterated Medical Devices

The FDA hit Vilex in Tennessee with a warning letter for producing adulterated medical device products at its McMinnville facility.

The company did not properly document design history files for multiple class II medical devices, including its Met-Head Implant, Vilex Bone Plate System, Dual Thread Bone Screw and Cannulated Hemi Toe Implant.

The firm stated in its response to a Form 483 report that some of the devices may have all of the documentation for a design history file in their 510(k) file, but the response was deemed inadequate because it did not indicate which devices it was referencing.

The agency noted the firm's failure to adequately establish design validation procedures — for example, engaging in validation activities two years before the validation protocol was approved. The agency found Vilex's response inadequate because it lacked updated procedures, evidence of training or reviews of previous and current design history files.

The firm also failed to confirm that all purchased products conformed to requirements. Its purchasing procedure was ruled inadequate because it did not ensure that suppliers of unverifiable critical processes were evaluated on their ability to meet specified requirements. The firm qualified its suppliers based only on ISO certifications.

The agency found the firm's response inadequate because it did not address training requirements related to updated forms and procedures.

The investigator also noted the firm's failure to rework and reevaluate entries in the device history record. The rework the firm claimed to have committed had no documentation in the DHR.

The agency said the facility's response was inadequate because it did not indicate a review of the system and of other potentially reworked products.

Read the Vilex in Tennessee warning letter here: www.fdanews.com/03-20-18-VilexinTennessee.pdf. — James Miessler

The Flow of Device-Specific Documentation

The FDA requires devicemakers to keep records of every step they take and every specification they set on the way to a finished, distributable device. And each device—or family of devices—they make must have its own set of three records or files that give a full picture of the device's life cycle, from design to production to distribution.

Documentation begins in the design phase, where all the details of the device's conception are recorded in the Design History File (DHF) and all the information needed to bring the design to life is included in the Device Master Record (DMR).

The DMR bridges the gap between theory and reality, translating the design specifications into the practical steps needed to produce a finished device: procurement of materials and services, production and labeling processes, installation requirements and service/maintenance details.

The third type of documentation, the Device History Record (DHR), wraps up all the information on what actually was done to create the device and shows how all of the requirements of the DMR were followed.

The Quality System Regulation (21 CFR Part 820) defines the Design History File as "a compilation of records which describes the design history of a finished device." According to the FDA, the DHF does not need to include every record produced in this phase as long as it contains sufficient information to give a clear picture of what went into developing the design. Records that the regulation requires the DHF to contain include:

- Design reviews;
- Design verification;
- Design validation; and
- Design changes.

Excerpted from the *FDAnews* management report: *Device Documentation: A Guide to Managing Four Critical Production Files*.

China FDA Releases Draft Guidance On UDIs

China's Food and Drug Administration asked for additional feedback on its draft guidance covering its unique device identification system.

The CFDA wants to strengthen the supervision and management of medical devices sold in the country. It plans to use the international GS1 standard and will likely introduce a separate national standard, according to consultancy Global Regulatory Partners. The CFDA may act as the issuing agency for the national code.

China is taking a similar approach to that of the U.S. FDA for its UDI database. It plans on using a global medical device nomenclature (GMDN) and a national nomenclature. The China Medical Device Nomenclature (CMDN) has already assigned codes to about 20 percent of domestic devices.

There is currently no global definition of what constitutes a UDI system, and differences across jurisdictions are causing a fair amount of confusion. The International Medical Device Regulators Forum (IMDRF) released UDI guidance in December 2013 to provide a framework for regulators that intend to develop a UDI system that achieves a globally harmonized approach.

Unique Identifier

China's UDI system follows the IMDRF guidelines with a few differences such as the CMDN. China's system will include a medical device unique identifier, a unique identification data carrier and a unique identification database. Under the GS1 standard, the UDI system includes a global trade item number to identify the device (UDI-DI), and a production identifier code for each unit (UDI-PI).

China is introducing the UDI system as part of step-wise reforms. In 2006, Shanghai FDA launched a pilot project for retrospective coding of implantable medical devices. In 2012, the State Council issued the "Twelfth Five-Year National Drug Safety Plan," which required national uniform codes for high-risk medical devices. In 2016, the State Council issued the "13th Five-Year Plan for National Drug Safety Plan," which requires establishing a medical device coding system and medical device coding rules.

The CFDA will first develop rules to guide the coding process. Standards and guidelines will be developed separately for unique identifiers, data carriers, and databases.

The CFDA draft guidance lays out the purpose of the rules, the definition of UDI, and clarifies that the system will apply to all devices distributed in China. The guidance includes UDI requirements for labeling as well as the database. It notes that applicants will need to upload product identification and relevant data to the national database within 30 days after a device has been registered.

Continuous Lifecycle

China's UDI will identify the filer of the device and the model specifications and packaging of the device. The production identification code identifies details related to production processes, including the serial number, lot number, manufacturing date and expiration date.

The UDI system is intended to provide information on the continuous lifecycle of a medical device, the CFDA said, and if changes to a product affect the identification, traceability or regulatory requirements of the device, a new UDI should be created. When a device ceases to be sold, its UDI may not be used for other medical devices.

The medical device label may take the form of one-dimensional code, two-dimensional codes, or radio frequency tags. It should meet the requirements of automatic identification, data acquisition technology and human reading, CFDA said.

About 4,000 device manufacturers in China will be affected by the UDI requirements.

Malaysia Introduces Registration for OEMs

Malaysia's Ministry of Health and Medical Device Authority will start to enforce licenses for original equipment manufacturers for devices sold in Malaysia.

In the past, OEMs were allowed to sell their products to other companies without a license. The regulator said no device may be imported, exported or placed on the market unless it is registered and provides evidence of establishment license.

Moreover, companies may not import, export or place devices in the market unless they hold an establishment license.

The ministry is changing its policy to facilitate OEMs obtaining licenses to market their products globally. Previously OEMs were not regulated under the country's Medical Devices Act because they didn't fit the definition of establishments or authorized representatives.

The Medical Device Authority said local manufacturers that perform activities as OEMs will be licensed as the manufacturer and will need to register their devices under their own brand. They also must declare that the listed brand is the same as the registered medical device brand in terms of manufacturing processes and specifications.

OEMs that do not have their own brands will need to be licensed as authorized representatives and register their products. They must submit a declaration letter with the application stating that they are not the brand owner of the device and only act as the manufacturing facility.

Hong Kong Recalls Eurogine IUDs Due to Breakage Issues

Hong Kong's Department of Health recalled five lots of Eurogine SL intrauterine devices, citing an increased risk of breakage when the IUDs are extracted. About 1,400 of the affected IUDs were distributed in Hong Kong.

According to Eurogine, the issue was caused by defective manufacturing of the raw material. It said the efficacy of the IUD is not affected, and premature removal is not recommended.

The recall affects the Ancora 375 Cu Normal and the Novaplus Cu Normal models.

Health Canada Reclassifies Sterilant Solutions, Disinfectants as Devices

Health Canada announced that sterilant solutions and disinfectants to be used with medical devices are now classified as medical devices.

Medical device disinfectants and sterilants that don't meet the definition of an antimicrobial agent are no longer regulated under Canada's Food and Drug Regulations and are now subject to requirements of the Medical Device Regulations (MDR), the regulator explained.

The reclassification of high-level disinfectants and sterilant solutions falls under the Canada-United States Regulatory Cooperation Council (RCC) Work Plan for Medical Devices, and it is intended to better align regulatory requirements between the two countries.

At this time, these products are considered Class II devices, but Health Canada plans on reclassifying them as Class III devices.

The regulator said it is allowing an 18-month transition for manufacturers to obtain quality management system certificates.

China's CMDE Releases Guidance For 3D-Printed Device Registration

China's Center for Medical Device Evaluation issued draft guidance for the registration of 3D-printed medical devices including bone, joint and dental implants.

Registration applications should include the device's chemical composition, including ratios of materials, and device designs be appropriately validated. Product specifications, such as structural characteristics and dimensional parameters, should also be included, CMDE said.

Sponsors should list the product's intended uses, the user base and potential impact on the environment, as well as any skills, knowledge or training needed to properly use the device.

Product sponsors should include a risk management report to prove a risk management plan was properly undertaken. — James Miessler

Maitland Flagged for Inadequate Test Validations, Rework Protocols

The FDA rapped Maitland Engineering for numerous deficiencies including a lack of validation for testing, inadequate process controls and protocols for rework of nonconforming product.

The agency issued a Form 483 after a September 2017 inspection of the company's South Bend, Indiana facility. Investigators observed problems with one of the facility's cleaning processes that did not meet the company's own definition of operational qualification, failing to identify all operating parameters, operation ranges or acceptance criteria.

The firm's process for cleaner validation also did not include a performance qualification section as required under Maitland's process validation SOP, according to the FDA.

The agency also found Maitland's process control procedures for a device component featured conflicting requirements for cleaning the device, with different documents disagreeing on whether there was a cleaning process prior to certain steps in the production process.

The investigator also flagged the company's procedures for rework of nonconforming product. Of 11 nonconformity reports the agency reviewed, one re-inspection did not include all aspects of the device that might have been affected during the rework operation.

In addition, the inspection found problems with Maitland's corrective and preventive action procedures. The firm's corrective action SOP called for all reviews to include verification and validation of corrective actions that involved follow-up actions.

However, in 4 of 11 CAPAs reviewed during the inspection, the "verification" performed by the firm only documented the implementation of the corrective action and did not assess whether or not the corrective action was effective.

Read the Form 483 here: www.fdanews.com/03-23-18-maitlandengineeringinc483.pdf.
— Zack Budryk

Easyscan Cited for CAPA, Complaint Handling Deficiencies

The FDA issued a Form 483 to Easyscan for deficiencies in its complaint-handling and CAPA procedures.

The agency issued the form following a May-June 2017 inspection of Easyscan's facility in The Hague, Netherlands.

Investigators found the firm's complaint-handling procedures did not adequately ensure complaints were processed in a timely manner or evaluated for MDR reportability. The procedures, investigators wrote, did not include adequate requirements to "ensure that when a decision is made not to investigate a complaint that the reason is documented and the individual making the determination to not investigate is recorded."

None of the complaints investigators reviewed included sufficient documentation of the MDR evaluation identifying whether the device was being used for a patient at the time of the failure or whether it was being used for diagnosis. Not all of the complaints were properly dated or included the results of the subsequent investigation, nor did all of them include any reply to the complainant.

Investigators also found the firm's design output procedures did not include adequate requirements for defining output or make reference to acceptance criteria. Procedures for design review did not feature adequate requirements to ensure participants at each review properly represented all functions in the design stage.

The FDA also cited the company for its CAPA procedures, finding it did not verify or validate all corrective and preventive actions to ensure they did not adversely affect the devices or include requirements to document all activities. Two of three CAPA files reviewed did not fully document all activities including verification and validation.

The company also lacked acceptable rework instructions for nonconforming devices and did not require retesting and re-evaluation of nonconforming products after reworking, including a full determination of any adverse effects.

Read the full Form 483 here: www.fdanews.com/03-23-18-easyscanbv483.pdf. — Zack Budryk

APPROVALS

United Health Products Granted CE Mark for Hemostatic Gauze

United Health Products received a CE Mark for its product, HemoStyp, in the European Economic Area, for internal surgical procedures.

HemoStyp is a patented, hemostatic gauze intended for use in the healthcare and wound care sectors. It is effective in immediate homeostasis, accelerating healing for trauma and post operational wounds and defending the wound site.

The product is created with regenerated oxidized cellulose and designed to control bleeding and absorb exudate and drainage from superficial wounds.

Exactec Cleared to Market Equinoxe Shoulder Prosthesis Product

The FDA issued Exactec 501(k) clearance for its Equinoxe stemless shoulder prosthesis.

The device incorporates a bone cage for bone through-growth to increase the chances of biological fixation and uses a three-dimensional porous structure.

The product is designed for anatomic total shoulder arthroplasty.

CereMetrix's Brain Imaging Device Receives 510(k) Clearance

CereMetrix received 510(k) clearance from the FDA for its neuroimaging analytics and quantification platform, CereMetrix Silver, an image viewer for brain imaging analysis that can detect, quantify and evaluate brain function.

The device, which serves as a tool to aid in the evaluation and information management of

(See **Approvals**, *Page 9)*

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digital medical images, can analyze PET, SPECT, MRI and CT scans.

Accuray's Data Management System Upgrade Gets 510(k) Clearance

Accuray's iDMS data management system, which was upgraded for use with the company's TomoTherapy platform, received 510(k) clearance from the FDA.

The system is designed to integrate with different systems, including TomoTherapy, Radixact, Accuray Precision and CyberKnife, as well as third-party treatment planning and oncology information systems.

Qiagen's T. vaginalis Detection Kit Gains CE Mark

Qiagen's new artus assay for detection of the sexually transmitted infection Trichomonas vaginalis received a CE Mark.

The kit detects the infection from DNA collected from vaginal swabs, endocervical swabs and urine samples. The diagnostic test is designed for use with the company's QIAsymphony SP/AS and Rotor-Gene Q instruments.

T. vaginalis is the most common curable STI and it can cause adverse pregnancy outcomes, infertility and postoperative infections.

Philips Gets Go Ahead To Market ProxiDiagnost N90

The FDA issued a 510(k) clearance for Philips' ProxiDiagnost N90, a digital radiography and nearby fluoroscopy system.

The dual-use device provides low-dose, high quality images, eliminating the need for several frames to produce a useable image for diagnosis. It also features an open overhead area and table which allows closer proximity to the patient during procedures.

The device is able to perform both nearby fluoroscopy and digital X-rays.

UroViu's Uro-V System Gets 510(k) Clearance

The FDA granted 510(k) clearance to UroViu's Uro-V system, a single-use, handheld diagnostic cystoscope designed for female diagnostic cystoscopy.

The battery-operated device uses a disposable cannula with a reusable handle that includes a video processor, touch panel interface and LCD display. The tube is equipped with a 140-degree-field-of-view camera and an LED illumination module and a shared single channel for fluid infusion.

Trice Medical Earns CE Mark and Health Canada Approval for mi-eye 2

Trice Medical received a CE Mark and Health Canada approval for its mi-eye 2, a camera-equipped throwaway needle intended to help diagnose joint injuries.

The updated device includes enhanced resolution, field of view and depth of field. The product is designed for diagnostic and operative arthroscopic and endoscopic procedures to provide visualization of interior cavities of the body through natural or surgical openings. It also allows physicians to inject or aspirate under direct visualization.

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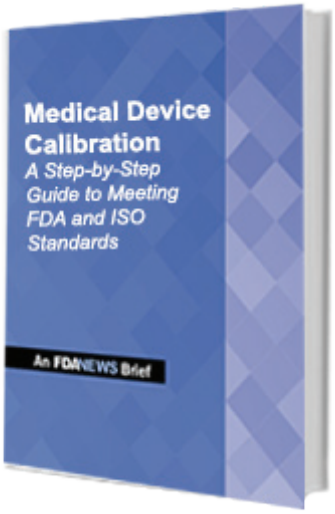

Medical Device Calibration: *A Step-by-Step Guide to Meeting FDA and ISO Standards*

Warning letter citing calibration failures are on the rise — indicating that the FDA is paying more attention to the issue.

Both the FDA and ISO have specific requirements for calibrating medical devices. And — they don't always line up. So devicemakers doing business in the US and abroad need a clear path to compliance if they want to avoid penalties.

Medical Device Calibration: *A Step-by-Step Guide to Meeting FDA and ISO Standards* provides a roadmap that walks devicemakers through each aspect of calibration requirements — showing where the FDA and ISO differ and where they match up — and explains how to combine them to endure full compliance.

You will learn:

- The role of monitoring and measuring in a medical device Quality Management System (QMS)
- Requirements for calibration in FDA's Quality System Regulation
- How to distinguish between accuracy and precision
- The role of traceability in a calibration program
- The audit requirements in both QSIT and MDSAP

The report defines key terms and concepts involved in calibration including proving that calibration practices can be traced back to recognized national and international standards.

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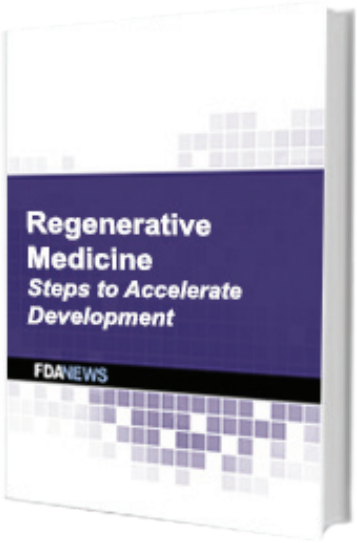

Regenerative Medicine: *Steps to Accelerate Development*

With the 21st Century Cures Act, attention is being focused on the use of human cells and tissue to treat serious and underserved conditions.

The FDA created a new regulatory paradigm in November 2017 when it issued four guidances — 2 final and 2 draft — aimed at explaining, streamlining and accelerating development of regenerative therapies.

Key among these developments is the creation of a new Regenerative Medicine Advanced Therapy (RMAT) designation that offers applicants an abbreviated pathway to approval, working closely with the FDA throughout the process.

Regenerative Medicine outlines the RMAT pathway and breaks down requirements regenerative medicine developers must meet to qualify. The FDA granted RMAT designation to 12 organizations in 2017 — the first year of the program. Now is the time to get in the mix, work with the FDA to develop the program and improve your chance of being one of the next RMAT designees.

You will learn:

- Key definitions the FDA uses in evaluating regenerative medicine applications
- Requirements to be eligible for RMAT designation
- How to apply for RMAT designation
- How the final versions of the Same Surgical Procedure and Minimal Manipulation guidances differ from their drafts

Order your copy of **Regenerative Medicine: *Steps to Accelerate Development*** and learn what it takes to get in on the ground floor of the new approval pathway and use it to accelerate your road to market.

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