INTERNATIONAL DEVICES & DIAGNOSTICS MONITOR

Vol. 4, No. 45
Nov. 12, 2018

IN THIS ISSUE

FDA Extends UDI Deadlines Another Two Years for Class I, Unclassified Devices

The FDA said it will allow device manufacturers of Class I and unclassified devices another two years to comply with its unique device identification system requirements, which are being phased in over seven years.

The agency said it decided to focus on addressing existing implementation challenges for higher-risk devices before focusing on implementing UDI for lower-risk devices.

In guidance released Nov. 2, the FDA said the new compliance dates for direct mark requirements for Class I and unclassified devices, other than implantable, life-supporting or life-sustaining devices are: Sept. 24, 2020. Even so, the agency said it does not intend to enforce direct mark requirements for these devices before Sept. 24, 2022.

Although Sept. 24, 2018 remains the deadline for standard data formatting, labeling and global unique device identification (GUDID)

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China Implements New Review Mechanism for Innovative Devices

China's State Drug Administration is implementing a new device review procedure to bring innovative devices to market faster and to encourage more innovation in China's supply chain.

The new Special Examination Procedure for Innovative Medical Devices, which becomes effective Dec. 1, aims to improve the efficiency of device reviews and inspections.

The new special examination procedure replaces the green channel special approval process launched in 2014. The document refines the application process, improves the initial review and prioritizes licensing requirements for innovative devices.

To be eligible for the innovative device review, applicants must have legal rights to the core patent technology inventions in

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

FDA Approves Reconfigured OTC Asthma Inhaler

FDA Commissioner Scott Gottlieb offered assurances about the agency's approval of an OTC asthma inhaler that was previously pulled from the U.S. market in 2011.

Amphastar Pharmaceuticals' new version of OTC Primatene Mist — the only OTC metered-dose inhaler approved in the U.S. — uses the same active ingredient, epinephrine, that was used in the 2011 product taken off the market because it contained CFC propellants that are known to deplete the ozone layer.

The new version contains hydrofluoroalkane propellants that are allowed under U.S. law, Gottlieb said in a joint statement on the combination product with CDER Director Janet Woodcock.

Making sure that patients can understand and apply the instructions for use was a critical consideration, they said. "For the right patient, our analysis of the data, including new information that was developed since this product was previously on the market, shows that there are no serious safety concerns when Primatene Mist is used as directed."

UDI, *from Page 1*

data submission, the agency said it would not enforce these requirements before Sept. 24, 2020 for Class I and unclassified devices.

For other device classes, established compliance dates remain as follows:

- Sept. 24, 2015 for life-sustaining devices;
- Sept. 24, 2016 for Class III devices; and
- Sept. 24, 2018 for Class II devices.

The FDA initially published its final rule establishing the UDI system on Sept. 24, 2013, and it established a series of compliance dates starting with Sept. 24, 2014 to Sept. 24, 2020 (*IDDM*, Sept. 5, 2016).

"Fully realizing the benefits of the unique device identification system depends on UDI being fully integrated into data sources throughout out the healthcare system, including in the supply chain, electronic health records, and registries," the guidance says. This requires UDI data of a high quality so that all stakeholders have confidence in the accuracy and completeness of the data.

During the implementation process, the FDA identified complex policy and technical issues that required resolution to ensure that UDI data would be high quality and available in standardized ways. Based on requests from devicemakers of Class II and Class III devices, the agency anticipates similar questions from Class I and unclassified device manufacturers.

The FDA acknowledged that the UDI direct mark requirements for devices has been a challenge for some devicemakers. The guidance describes a compliance policy for devices in inventory that don't comply with direct mark requirements when the device's UDI can be derived from other information directly marked on the device.

In determining whether a device's UDI can be derived from other information directly marked on the device, the agency will consider whether the labeler has developed a method for constructing the UDI from other information directly marked on the device, such as a catalog number, lot number or serial number, so that it is readily available at the point of use, and documented in the device master record and the GUDID.

Read the guidance here: www.fdanews.com/11-08-18-UDIGuidance.pdf.

Warning Letter Roundup: Three Firms Cited For Adulterated Devices

The FDA hit three foreign device manufacturers with warning letters, calling the firms out for quality system violations that led to adulterated products.

Leventon: Spanish devicemaker Leventon received a warning letter after the agency's March 19-22 inspection revealed the firm failed to confirm its device products conformed to specifications.

For example, the firm checked its Dosi Fuser product — a chemotherapy continuous infusion device — to ensure it provides an expected flow rate. However, it had no procedure in place explaining how to conduct the analysis, and did not tell the agency it planned to train employees on how to properly conduct it.

The company also didn't record all design changes properly. One of its change documents, which summarized a new product for the U.S. market, had a design verification record that showed the device didn't meet its required objective delivery time. To address this, the firm altered the tubing length of the product, but didn't document this in the change document.

Additionally, products the firm manufactured — the Dosi Flow elastomeric infusion pump and Dosi Flow administrative set devices — were determined to be misbranded, because the firm failed to provide required information about them.

For instance, Leventon didn't issue a report to the agency within 30 calendar days after it received information about the devices malfunctioning. A MedWatch report described events where up to 14 patients received early completion of infusion using the company's Dosi Fuser, a situation that could have been harmful to them.

Boule Medical: The FDA came down on Swedish manufacturer Boule Medical after the firm failed to investigate certain device complaints and maintain device history records.

The agency's May 7-11 inspection discovered that the firm hadn't investigated any of its U.S. service reports to determine why components failed, and chose to repair or replace the faulty components instead. While the firm revised its complaint procedure, it didn't provide evidence that staff members have been trained on the revamped procedures.

The firm also had inadequate device history records (DHRs) to show devices were made according to the device master record. Specifically, Boule had no written DHR procedure and DHRs for its Medonic M-series Hematology Analyzers were missing information, such as the location of their sub-assemblies and primary identification labels.

Cardiomed Supplies: Canadian devicemaker Cardiomed was hit with a warning letter for problems with procedures.

After a May 28-31 inspection, the agency called the firm out for failing to properly establish certain procedures. For example, while the firm performed validation activities, it lacked necessary procedures to explain how they would be performed, such as what testing methods, process parameters and acceptance criteria would be needed.

The company used Doboy sealers to seal pouches containing its phlebotomy bag products, but didn't establish specific sealing parameters — such as temperature, pressure and sealing time — and failed to monitor them during production.

It also sterilized samples in-house, but failed to confirm a Doboy sealer was adequately sealing certain pouches. Samples sealed "were originally sterilized prior to testing; and since the sterilization cycles were changed and brought in-house, no further testing of pouches has been performed," the agency said.

Read the Leventon warning letter here: www.fdanews.com/11-01-18-Leventon.pdf.

Read the Boule Medical warning letter here: www.fdanews.com/11-01-18-BouleMedical.pdf.

Read the Cardiomed Supplies warning letter here: www.fdanews.com/11-01-18-Cardiomed-Supplies.pdf. — James Miessler

EC Adds Four Devices to Manual On Borderline and Classification

The European Commission added four new products it considers devices to its Manual on Borderline and Classification in the Community Regulatory Framework for Medical Devices, including several related to contraception.

The manual helps devicemakers understand which products the commission considers to be medical devices, especially products and product categories that have previously been subject to doubt. The recommendations aren't legally binding.

The latest update — version 1.20 — adds trial hip prosthesis heads and stems, stand-alone software applications for conception and contraception purposes using patient-entered data, and products intended to facilitate contraception and enable contraception based on basal body temperature (BBT).

For example, the manual says that products intended to facilitate or enable contraception based on measuring BBT — which predicts ovulation by tracking the patient's body temperature and menstruation days — should be qualified as a medical device. Similarly, the stand-alone software intended to act as a natural method of birth control should also be qualified as a device.

Trial prosthesis heads and stems are surgically invasive devices but aren't reusable surgical tools, so they should be considered class IIa devices, according to the manual.

Read the updated manual here: www.fdanews.com/11-08-18-BorderlineManual.pdf.
— James Miessler

China, *from Page 1*

China. Manufacturers should submit applications no more than five years after a patent has been granted.

Another requirement is that the main working principle or mechanism of the product should be a first in China. The product performance or safety should be fundamentally better than current products on the market and it should be comparable to international standards and have significant clinical value.

Domestic companies will submit applications for an initial review to their provincial FDA, which will be reviewed within 20 working days. The provincial FDA will then submit the application materials and the preliminary examination opinion to the State Drug Administration for review.

Foreign applicants should submit applications directly to the State Drug Administration.

The SDA's Medical Device Technology Evaluation Center will establish a separate Innovative Medical Device Examination Office to review innovative medical device applications.

Sponsors will be able to participate and communicate with experts through video conferencing. The appraisal center has already carried out pilot projects in some provinces and cities, and has invited experts to hold special review meetings via remote video for innovative devices.

Once an application is submitted, manufacturers can check the progress of the review by logging in to the website of the National Bureau of Testing. Paper notices will no longer be printed after the new procedures are implemented.

After receiving the application, the Innovative Medical Device Examination Office will issue a review opinion within 60 working days.

Before the product registration application is accepted and during the technical review process, the inspection center will designate a person to promptly communicate and provide guidance to the applicant on technical issues.

The SDA will conduct good clinical practice inspections to review the clinical trial plan, use method, specification model, intended use, scope of application or adjustment of population, and safety and effectiveness of the device.

China's inspection agencies will give priority to inspections for innovative devices.

Read the SDA notice here: www.fdanews.com/11-08-18-ChinaInspections.pdf.

483 Roundup: FDA Cites Firms For Quality, Risk Analysis and SOPs

Three devicemakers drew 483s for quality system and other failures observed during FDA inspections.

Hospira: A number of quality system deficiencies resulted in Hospira test devices failing to meet specifications, according to a Form 483 to the Pfizer subsidiary's Rocky Mount, North Carolina facility following a Jan. 29 to Feb. 2 FDA inspection.

Routine inspection of mechanical equipment was not performed according to a written program designed to assure proper performance, the four-item 483 said.

Although deviations were reported, all possible root causes were not identified to ensure that corrective actions would prevent reoccurrence, the FDA said. For example, the corrective action for one deviation was limited to retraining the equipment operator.

The quality laboratory continued to use a certain wash that is known to deteriorate and discolor devices and affect the accuracy of at least one trace metal test method used for finished product testing, the agency said.

Investigations were incomplete in that although devices were washed and reused with various combinations of solutions, the investigators didn't consider the possibility of the solutions influencing other quantitative test results by absorbing and leaching other metals, for example.

The agency also cited the firm for failing to justify deviations from written production and process control procedures. It noted that historical searches showed repeated occurrences of production processing events with a possible impact on product quality that were not identified and properly trended.

The firm was also flagged for failure to document CAPA activities. The inspectors noted four separate examples where the firm failed to conduct CAPA effectiveness checks.

Innovative Medical Equipment: Failure to conduct adequate risk analysis for its

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

Manufacturing Equipment Audits

Internal quality audits are important tools to ensuring QSR compliance, and they should include a review of manufacturing process equipment. When identifying which equipment to include in such an audit, devicemakers need to remember that while major production equipment may be obvious, they should also include all support equipment — for example, air handling, air compressors, input/output filters and backup generators. Any equipment used to assist something leaving or entering production equipment needs to be included as well.

Inspection, measuring and test equipment (IM&TE) also are covered under QSR's equipment section, so devicemakers need to review SOPs and work instructions to determine which pieces of IM&TE are associated with manufacturing equipment.

To ensure that all equipment the FDA might examine is included in an internal audit, O'Leary recommends thinking about less obvious things, such as supporting equipment that may sit in back rooms or separate from manufacturing areas but is still attached to and/or affecting production equipment.

For any new equipment being audited for the first time, devicemakers need to include steps to verify that design and construction of that equipment meet requirements and specifications. Likewise, companies must verify during audits that the installation of new equipment does, in fact, facilitate maintenance, adjustment, cleaning and use, which will require review of installation records.

This part of the audit will not have to be done more than once for each piece of equipment because once it is installed and in operation, it's unlikely that any of those things will change unless the devicemaker should relocate the equipment, in which case, it would need to be treated as new equipment for auditing purposes.

Excerpted from the *FDAnews* management report: *Three Phases of QSR-Compliant Equipment Control*.

483s, *from Page 5*

Thermazone heating and cooling device landed Innovative Medical Equipment a Form 483 following a July 10 to July 17 FDA inspection of its Lyndhurst, Ohio facility.

The firm's risk analysis documents didn't capture all potential hazards, the FDA said. The company submitted a medical device report of a serious injury when a patient fell asleep with the ThermaZone device on and sustained serious burns and blisters and permanent scarring.

The firm's risk analysis listed the hazards associated with excessive time as "safe," the FDA said, noting that the firm had not adequately assessed and mitigated the potential risk.

"Your instructions for use warn of the risk of fire and injury — including death for failure to follow the instructions/safety manual," the 483 says. "None of the hazards in your risk document are assigned with your highest potential severity rating."

The FDA said a review of verification testing found that design outputs "did not appear to meet design input requirements" for IME's new heat exchanger. The agency said that testing results didn't document the pressure used for testing, and leak failures were found for some of the pads but there was no evidence of retesting before the products were released.

Vector R&D: Failure to establish adequate procedures for receiving, reviewing and evaluating complaints landed devicemaker Vector Research and Development in hot water with the FDA during a July 5 to July 8 inspection of its University Place, Washington plant.

Vector R&D is an initial importer of dental equipment and repair parts. The firm's Class II devices include the Victor LED Turbo curing light, the Little Beaver ultrasonic scaler and the MAXRAY mobile X-ray system.

The firm was unable to provide evidence of an investigation of non-conforming product or an evaluation for medical device reporting for four complaint files reviewed, the Form 483 said.

Corrective and preventive action procedures were also lacking, the FDA said. Instructions for performing servicing activities and verifying that servicing met specified requirements also fell short and the facility was not able to provide documentation for device servicing and testing.

In addition, the 483 said the firm had not established document control procedures, and there was no corrective action report.

Read the Hospira Form 483 here: www.fdanews.com/11-08-18-hospiraapfizerco483.pdf.

Read the Innovative Medical Equipment Form 483 here: www.fdanews.com/11-08-18-innovativemedicalquipment483.pdf.

Read the Vector R&D Form 483 here: www.fdanews.com/11-08-18-vectorrandd483.pdf.

FDA Issues Updates on Overheating Problems in MR-Guided Lasers

The FDA announced that Monteris is releasing a new version of its NeuroBlate probe to address a problem with overheating of its magnetic resonance-guided laser thermal therapy device. The new probe is equipped with a nonmetallic fiber optic sensor.

In a Nov. 8 update, the FDA recommended that users of the probe — a component of the NeuroBlate system that is used in the removal of brain lesions — weigh the risk and benefits of using it on a patient-to-patient basis until the new model is available and consider alternative treatments.

The agency also summarized recommendations from Monteris on the NeuroBlate system and from Medtronic on its Visualase thermal therapy system.

Users should keep the cooling system on throughout thermal monitoring, including while the laser is on and after it is turned off. This will return the tissue next to the fiber to baseline temperature within two minutes after laser delivery, the agency said.

The agency also cleared a premarket submission for the redesigned NeuroBlate system that includes updated labeling regarding the use of MR thermometry to help predict thermal damage.

APPROVALS

FDA Clearance Combines Invisalign With Mandibular Advancement

The FDA has given 510(k) clearance to Align Technology's Invisalign treatment with mandibular advancement, allowing the two technologies to be used together.

The agency's clearance allows the clear-aligner treatment to be used with mandibular advancement to simultaneously reposition the jaw and align the teeth of teenage patients aged 12 to 13.

Invisalign treatment combined with mandibular advancement can replace Class II elastics and appliances and reduce costs and time for adjustments and repairs.

Zimmer Biomet's Revision Knee System Cleared by FDA

The FDA granted 510(k) clearance for Zimmer Biomet's Persona revision knee system for use in revision knee replacement procedures.

The knee system enables surgeons to perform simple and complex revision procedures using their preferred approach.

It is matched according to a patient's anatomy to achieve a personal fit.

PlexBio's Lung Cancer Panel Gains CE Mark

Taiwanese diagnostics manufacturer PlexBio has received the CE Mark for its IntelliPlex lung cancer panel, used for identifying DNA mutations.

The assay can recognize 36 DNA mutations, including ones in the KRAS, NRAS, PIK3CA, BRAF and EGFR genes, and 19 gene rearrangements of ALK, ROS1, RET, NTRK1 and MET genes.

It can use Plexbio's πCode technology, a circular disk that can create more than 16,000 image patterns for use in multiplexing.

FDA Clears ELITechGroup's Herpes Assays

ELITechGroup's real-time PCR assays for detecting herpes simplex viruses 1 and 2 was granted 510(k) clearance by the FDA.

The assays, used with the company's InGenius sample-to-result device, can detect and differentiate between herpes simplex viruses 1 and 2.

The assays analyze nucleic acid obtained from the patient's lesions on the skin, genitals, lips or mouth.

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

Approvals, *from Page 7*

Focal Healthcare Gets FDA's OK For Prostate Fusion Biopsy Device

The FDA cleared Focal Healthcare's Fusion Bx 2.0, the second generation of the prostate fusion biopsy device.

The device, which uses an MRI to mark potential lesions and ties it to live ultrasound images, makes a 3D model of the patient's prostate.

The prostate model is used by urologists to target specific regions for biopsy, enabling more accurate and effective prostate cancer diagnoses.

Blue Spark's Temperature Monitor Receives CE Mark

Blue Spark may now market its TempTraq wearable temperature monitor in Europe after gaining the CE Mark.

The Bluetooth-enabled monitor is a disposable patch that provides caregivers with wireless, continuous temperature data.

TempTraq can send alerts to mobile devices when temperature reaches either pre-determined or user-set levels.

Shoulder Innovations' Humeral System Cleared by FDA

The FDA granted 510(k) clearance to Shoulder Innovations' InSet humeral short stem system for use in shoulder arthroplasty.

The system includes products used in partial or total shoulder arthroplasty, a surgical procedure that uses a prosthetic implant to treat degenerative, rheumatoid or traumatic arthritis in the shoulder.

InSet includes coating technology for implant fixation while preserving the humerus bone.

EU Approves Micro Medical's Microstent

Micro Medical Solutions received CE Mark approval for its 4Fr.-compatible Microstent 120 cm delivery catheter, as well as approval for Microstent devices in five lengths and diameters.

The devicemaker's newly approved Microstents — which are intended to reduce amputations below-the-knee caused by peripheral artery disease and resulting critical limb ischemia — offer physicians a longer access system and a greater selection of stent sizes.

The technology's new approvals apply to the 8mm, 15mm, 25mm, 40mm and 60mm sizes, allowing for customized use by the physician.

FDA Clears NinePoint Medical's Imaging System Upgrade

The FDA cleared an upgrade to NinePoint Medical's Nvision volumetric laser endomicroscopy (VLE) imaging system.

The Intelligent Real-time Image Segmentation (IRIS) software upgrade is an AI-based platform used for image feature segmentation — dividing a digital image into multiple segments for improved analysis.

The Nvision VLE imaging system is used to allow for VLE procedures that generate real-time, high-resolution, cross-sectioned images. These images are used to evaluate esophageal tissue surface and sub-surface for potential diseases that can't be seen through traditional technology.

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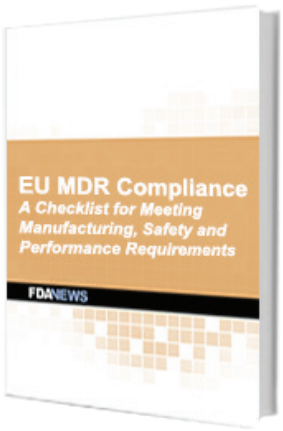

EU MDR Compliance: *A Checklist for Meeting Manufacturing, Safety and Performance Requirements*

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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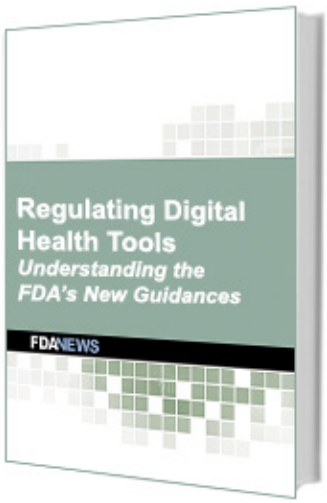

Regulating Digital Health Tools: *Understanding the FDA's New Guidances*

Clinical decision support software … software as a medical device … artificial intelligence and machine learning – rapid developments in digital technology are blurring the line between FDA-regulated medical devices and unregulated "lifestyle apps."

To keep pace, the FDA has issued a slew of guidances to explain what and how it will regulate software-driven devices. The final guidance *Software as a Medical Device* and two draft guidances, *Clinical and Patient Decision Support Software* and *Multiple Function Device Products*, aim to clear up the confusion, but devicemakers still need a map for navigating the regulatory maze.

Regulating Digital Health Tools — based on a presentation by noted regulatory expert Bradley Merrill Thompson — combs through the guidances and sets out the rules devicemakers must follow. You'll learn:

- How the FDA's new policy allows sponsors to comply with postmarket surveillance requirements
- How the FDA is working with industry to promote innovation in the development of digital health functions, as well as how these novel products can be integrated into advanced therapeutic options for patients
- The status of the FDA's precertification pilot program and how it may determine future regulation
- Industry reaction to the FDA's efforts

Regulating Digital Health Tools: *Understanding the FDA's New Guidances* gives readers a complete understanding of how the FDA is regulating software applications and digital health devices — and where a device falls on the spectrum from unregulated "lifestyle" apps to high-risk regulated medical devices.

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