INTERNATIONAL DEVICES & DIAGNOSTICS MONITOR

Vol. 4, No. 40
Oct. 8, 2018

IN THIS ISSUE

FDA Begins Pilot Of Special 510(k) Program

The FDA launched its Special 510(k) program pilot aimed at simplifying the process and expanding the types of product changes eligible for the program.

The launch of the program on Oct. 1 followed the release of draft guidance the previous week in which the agency requested feedback on a proposal to modify the rules of the Special 510(k) program, which forbade modifications to a device's intended use or labeling. The pilot will allow stakeholders and FDA staff a chance to test the proposed expansions.

As part of the pilot, certain design or labeling changes previously reviewed as traditional 510(k)s may be eligible for review under the Special 510(k) pathway.

The 510(k) should be for a proposed change to the applicant's own device, as the program uses FDA's previous reviews of information.

(See **510(k)**, *Page 2)*

Health Canada Details Investigational Testing Review Process

Health Canada released new guidance for device sponsors outlining the agency's review process for investigational testing authorizations for unlicensed Class I-IV medical devices that will be imported or sold in Canada for investigational testing involving humans.

The agency uses the reviews to assess whether the unlicensed device can be used without threatening patients' safety, if the study is contrary to the best interests of patients, and if the testing objectives are likely to be achieved. Reviews are not required if there is no sale of the medical device or a study uses a licensed device for its licensed indications.

Devicemakers' should submit information packages electronically with a proposed agenda and a summary of applicable data, including

(See **Testing**, *Page 6)*

FDA Guidance Revises Packaging Terms for Injectable Products

The FDA issued final guidance on "single-dose" and "multiple-dose" containers for injectable medical products — introducing a new term "single-patient use."

The containers may be part of a drug, a biological product, or a combination product assigned to CDER, CBER, or certain combination products assigned to CDRH.

The agency revised the terms after the improper use of single-dose containers led to the transmission of bacterial and viral infections in multiple patients.

The FDA defines a single-dose container — such as a vial, prefilled syringe or ampule — as "a container of a sterile medication for parenteral administration (injection or infusion) that is not required to meet the antimicrobial effectiveness testing requirements." The container, which should be labeled as a single-dose container when there's space and include appropriate discard statements, is intended for use with a single patient as a single injection or infusion, the agency said.

Multiple-dose containers, such as vials, hold sterile medication for parenteral administration that have met antimicrobial effectiveness testing requirements or are exempt from them, the agency said. They're meant to contain more than one dose of the product and should be labeled as such when there's room.

Generally, they contain 30 mL or less of medication, and their beyond-use dates when opened or entered — when punctured with a needle, for example — are 28 days unless otherwise noted by the manufacturer on the label.

The guidance introduces a new term — single-patient use container — and retires the term single-use due to past confusion, after it was wrongly interpreted as being interchangeable with single-dose.

The term single-use container was previously used by the FDA for package types that contained multiple doses but were intended to be used by a single patient. The new term is designed to make it even clearer that only one person should use it.

Sponsors should determine the proper package type term for the injectable medical product and use only that term in the labeling. The appropriate package type term should appear on all labeling components — including the container label and carton labeling, prescribing information, and labeling intended for the patient — to make it obvious to the user.

Multiple-dose containers typically don't require a discard statement because of their assumed beyond-use dates; however, if their beyond-use date exceeds 28 days, an appropriate discard statement should be placed on the container label, carton labeling and prescribing information.

Applicants should make the necessary labeling changes and identify any changes made in annual reports and supplements within two years of the guidance's publication, the agency said.

Read the guidance here: www.fdanews.com/10-02-18-Labeling.pdf. — James Miessler

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Additionally, performance data should not be needed — and if it is, well-established methods should be available to assess the change.

Lastly, all data required for supporting substantial equivalence must be reviewable in a summary or risk analysis format, the agency said.

Applicants should put together a Special 510(k) for participation in the pilot and be prepared to pay MDUFA user fees for their submission. — James Miessler

Webinar: Strategies for Getting Your De Novo Device Approved

Hogan Lovells attorney Kelliann Payne offered some best practices for getting de novo products through the FDA's review process, in a recent *FDAnews* webinar, noting the agency has streamlined its de novo pathway and made it more accessible for medical devices in the low-to-moderate risk category.

FDA review times for de novo applications used to be longer than for premarketing applications, but that is beginning to change, Payne said. In terms of application volume, data requirements and FDA review time, the de novo pathway typically falls between the 510(k) and the PMA.

De Novo Applications

The de novo pathway is used when a device falls outside an existing classification regulation, if there isn't a predicate device, if the device has a new intended use, or if the device has different technological characteristics that raise questions of safety and efficacy that don't meet the 510(k) threshold.

"But when you get to the de novo, it's a little closer to a 510(k) in the fact that it doesn't require manufacturing information, typically," she said.

Most de novo applications require clinical data, but "typically it's not as robust as the clinical data that you see in a PMA," she said, noting that a PMA is "more like a regulatory patent," and requires the inclusion of manufacturing requirements that aren't needed in the de novo and 510(k).

However, now that the de novo process is being used more often, the FDA "is starting to get to weigh in on study designs earlier and so, you'll start to see some study designs that are pretty well thought out to support the indications for use."

Companies should file a pre-submission with the agency to discuss both the regulatory pathway and the data requirements, she said, noting that sponsors can save a lot of time by getting FDA feedback early in the process.

"In recent years," she said, "the de novo process had been unpredictable, but it's getting better, and the direct de novo option [introduced by the Food and Drug Administration Safety and Innovation Act of 2012] appears to have sped up the average review time," she said.

"I've probably filed about eight de novos in the past six months of varying lengths and varying clinical data requirements," and it is becoming more of a regular filing, she said.

Homework

Devicemakers should do their homework and look at the FDA's database to identify their market competitors and determine that there really is no 510(k) for their device, she advised.

"If you think you can make a decent 510(k) argument, at least summarize that argument in the alternative de novo language," she suggested. "Sometimes it's just a good strategy from a negotiation standpoint, because it's always a give-and-take, and if you give on the 510(k) argument and say you'll do de novo, then FDA is probably a little more willing to work with you on data requirements."

Payne noted there is no exclusivity when it comes to FDA marketing applications. "Once you get a de novo cleared, you become the predicate," so other devicemakers can write a 510(k) application off of your de novo. But making sure that the special controls are robust might buy some time by making it harder for another company to follow on, she said.

"The one thing that we try to do when we write de novos is make sure that the special controls are robust enough that maybe it does buy you a little bit of exclusivity if you conducted a decent-sized study," she said.

Access the webinar De Novo Strategies for Getting Your Medical Device Approved here: www.fdanews.com/products/56330.

Biodex Medical Fails to Establish Quality Control Procedures

Surgical instrument maker Biodex failed to report a medical device failure that resulted in a patient failing to the ground while being transported in an MRI stretcher that malfunctioned, according to a 483 that was issued following an April 24 to May 1 FDA inspection of the firm's Shirley, New York facility.

Biodex received the complaint on Feb. 29, 2016, but it did not report the incident to the FDA until May 25, 2016, falling beyond the required 30-day reporting window for MDR filing.

FDA inspectors said the firm had not established records that described quality control procedures to monitor aluminum equivalence attenuation within its surgical C-Arm tables. Device history records were not maintained, and required tests for the surgical tables were not documented.

Inspectors noted that Biodex lacked an evaluation process for contractors used to perform aluminum equivalence testing for its surgical tables. In addition, incoming acceptance procedures failed to identify specifications for acceptance of the table tops, and instructions were not developed to review the certificates of performance.

Read the Biodex Form 483 here: www.fdanews.com/10-03-18-biodexmedicalsystemsinc483.pdf.

Ensuring Quality Through Training

These four elements should be considered critical for a robust training program:

- Introductory training requirements for new employees with responsibilities for ensuring product quality and patient safety;
- Annual training requirements for all employees, regardless of function;
- Continuing education training for employees with responsibilities for ensuring product quality and patient safety; and
- Special training requirements that may be required for continuous quality and process improvements.

New employees with responsibilities in the quality assurance, quality control and manufacturing departments should be trained on good manufacturing practices requirements for the type of product they are producing. These procedures should include proper gowning technique, cleanroom behavior, and introduction to contamination control and good documentation practices.

This initial training may consist of participating in an interactive training session followed by some type of test for comprehension. A minimum grade of correct answers must be achieved before the employee is considered to have a basic knowledge of various topics. If the required minimum grade is not achieved, the hiring supervisor and the training team should meet to determine what additional retraining should be provided to the employee or if there needs to be changes made to the training because the concepts being communicated were not clear. If after retraining, the required minimum level of comprehension is not achieved, quality assurance staff will inform the hiring manager and indicate the new employee may not suitable for the intended position.

Once new employees have passed the minimum understanding requirements on the quizzes, they should be required to read and discuss general SOPs.

Some new employees targeted for special functions, such as a visual matter inspector for injectable products, should receive additional hands-on training from the hiring manager and quality assurance staff. This training should focus on their ability to perform the special function.

All employees should be trained annually on the following topics:

- cGMPs;
- Conducting investigations and root cause analysis;
- Microbiological control in manufacturing; and
- Good documentation practices.

Quality assurance and quality control personnel should assess the comprehension of the training and note this assessment on the training records.

Excerpted from the FDAnews management report: *Quality Management Essentials – Expert Advice on Building a Compliant System.*

Sleep Apnea Devicemaker Respire Fails to Report Recall

Failure to report a voluntary recall to the FDA landed Respire Medical an FDA Form 483 following an April 24 to May 2 inspection at its Brooklyn, New York facility.

The firm issued a recall for its Respire Pink oral sleep apnea device on Sept. 6, 2017, because of a risk of device failure where the arm broke off while in use. Respire issued a recall letter to customers regarding the device failure, but did not report the recall to the FDA.

The firm was also cited for failing to submit a medical device report within 30 days of becoming aware of information that "reasonably suggests that a marketed device has malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur."

The FDA said the firm did not adequately investigate complaints involving the possible failure of the device. The investigator said the firm documented the failure but "did not properly investigate to determine why the device broke while in use."

Respire Medical failed to validate the sleep apnea device under defined operating conditions, the FDA said. The firm's design history file indicated supporting documents for various tasks performed such as design verification, mechanical safety and stability, but the firm was unable to provide any of the supporting documents during the inspection.

Read the Respire Medical Form 483 here: www.fdanews.com/10-03-18-respiremedical483.pdf.

PEOPLE ON THE MOVE

Terry Ransbury is joining **LuxCath** as chief technology officer. In his role, Ransbury will lead development and commercialization of the company's proprietary OmniView light-guided catheter ablation system. He is a co-founder and former president at medical device development company Nocturnal Product Development, LuxCath's product development partner.

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all completed pre-clinical and clinical studies, the standards used in design and manufacturing, observed adverse events and a rundown of any potential safety issues, along with the specifications for the device and preclinical testing.

The submission package should also include a proposed global clinical plan for the current stage of device development that includes the device's regulatory status in other countries and the details of the proposed clinical investigation to be conducted in Canada within the scope of the ITA.

The details should include the trial protocol design, a study hypothesis, the condition the device is intended to treat, proposed procedures and/or criteria for patient monitoring, and any statistical considerations, the agency said.

Read the full guidance here: www.fdanews.com/10-04-18-GuidanceDocument.pdf.
— Zack Budryk

Beverly Hills Breast Implant Practice Lands 15-Item 483 for QS Failures

Failure to establish a design history file for its Pocket Protector breast implant pouch, landed the Beverly Hills practice of breast augmentation surgeon Mark Berman a 15-item 483 following a July 7 to July 13 FDA inspection.

The firm lacked a design plan documenting design requirements to address the intended use of the device. It had not conducted any risk analysis and no records were maintained to verify or validate design changes.

The breast implant is manufactured in a sterile room, but the firm had not implemented procedures to control environmental conditions to ensure sterility. Inspectors observed contaminated surgical equipment and contaminated device components in the sterile room and said personnel entered the room freely without any restriction or gowning procedures. In addition, there were supply/return air vents above the manufacturing area and air supplied to the room was not filtered.

The firm fell short on process control procedures during manufacturing and it had not established procedures for evaluating and selecting suppliers and contractors. For example, it did not maintain records to demonstrate that the supplier of the polytetrafluroethylene sheets used to manufacture the implants were evaluated to ensure they met specifications.

The FDA cited the firm for other quality control lapses such as procedures for acceptance of incoming products, control of storage areas, and for receiving and reviewing complaints.

Read the Mark Berman Form 483 here: www.fdanews.com/10-03-18-markhberman483.pdf.

APPROVALS

Baxter's Altapore Bioactive Bone Graft Receives Extended 510(k) Clearance

Baxter received an extended 510(k) clearance for its Altapore bioactive bone graft, a bioactive and osteoconductive bone graft substitute.

The additional clearance allows the bone graft to be used as an autograft extender in posterolateral spinal fusion.

The bone graft received previous 510(k) clearance for use in orthopedic surgery in the pelvis and the extremities.

Stryker Receives 510(k) Clearance For Implantable Fracture Reduction Device

The FDA granted Stryker's SpineJack implantable fracture reduction system 510(k) clearance for use in reducing osteoporotic vertebral compression fractures.

The SpineJack system had better results versus balloon kyphoplasty during the Sakos clinical study.

After the titanium implant is inserted and expanded, the restored vertebral body is stabilized by adding bone cement at low pressure. It is available in three sizes to adapt to different vertebral body sizes.

Abbott Earns CE Mark for Blood Test to Predict Cardiac Events

Abbott's Troponin-I blood test has received CE Mark approval for predicting a patient's chance of heart attack or other cardiac event.

The blood test can predict, potentially within months to years in advance, if patients who otherwise seem healthy may experience heart attacks or cardiac events.

Because the test can detect levels of troponin — even if they are very low — it can be used to determine cardiac risks in patients who exhibit no symptoms.

Sensile Medical Micropump Gains CE Mark

Sensile Medical's wearable micropump received a CE Mark for treatment of Parkinson's disease.

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

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The device includes an automatic filling feature designed for use with liquid medicines, as well as a color display, charging unit and leather bag to attach the device to the user's belt.

The micropump also has a programmable feature that can deliver a bolus with the press of a button.

TransEnterix's Ultrasonic Instrument Cleared in EU

TransEnterix's received the CE Mark for its Senhance Ultrasonic Instrument System, a device used in minimally invasive surgeries.

The ultrasonic device delivers controlled energy to seal and cut tissue while minimizing thermal injury to the body and it can be used to manage complex surgeries.

The device is particularly useful to laparoscopic surgeons because it can be used for a wide range of procedures.

Abbott's Sensor-Based Glucose Monitor Gains CE Mark

Abbott's Freestyle Libre 2, a sensor-based continuous glucose monitoring device, has received the CE Mark.

The device allows patients to self-monitor their blood glucose levels without the use of finger sticks.

The glucose monitor uses Bluetooth technology with its new alarm feature to alert patients when they have low or high glucose levels.

Kheiron's Breast Cancer Screening Software Receives CE Mark

Kheiron Medical Technologies has been granted the CE Mark for its deep learning-based breast cancer screening software, making it the first UK company to receive the mark for deep learning radiology software.

The CE approval means that European healthcare providers can use the software as secondary analyzers of mammographic images in breast cancer screenings.

In a clinical study, the software performed better than the average national standards for breast cancer screening. It uses artificial neural networks and high performance computing to evaluate the medical images.

The company is currently seeking FDA approval for the software.

Xtreem Pulse's Rapid Pulse Compressor Gains CE Mark

Xtreem Pulse's PureFlow device received the CE Mark for its rapid pulse compression device, for use by athletes and individuals looking to improve their cardiovascular health.

The device promotes optimal performance and recovery, increasing oxygenation, circulation and detoxification by optimizing blood flow.

The increased blood flow caused by the device's pumping action helps to send oxygen and nutrients into cells.

Applied BioCode Cleared To Market New Diagnostic Device

The FDA granted 510(k) clearance to Applied BioCode's MDx3000 high-volume molecular diagnostic device that can detect 17 types of gastrointestinal pathogens, bacteria, parasites and viruses.

The system is based on Applied BioCode's barcoded magnetic beads technology which offers up to 4,096 different barcoded patterns. Up to 100 different barcodes per assay can be run on the device.

Up to 94 patient samples can be completed on the system in less than five hours.

Acessa Health Cleared For Uterine Fibroid Ablation Device

The FDA granted 510(k) clearance to Acessa Health's ProVu System, a device used to treat women with symptomatic uterine fibroids who don't want to undergo a hysterectomy.

The system combines radiofrequency ablation, guidance mapping and ultrasound visualization to target and ablate the fibroid. The ablated fibroid is then absorbed harmlessly by the body over time.

CDRH Issues Guidance Wish Lists for Next Fiscal Year

The FDA released three lists of guidance documents it will or may issue in the next fiscal year — including an "A-list" of those the agency plans to publish, a "B-list" of guidance it hopes to issue, and a list of existing final guidances that it plans to review.

The planned final guidances on the A-list include guidance for sponsors on the humanitarian device exemption, the breakthrough devices program, the Special 510(k) program, and on the agency's least burdensome regulatory approach.

Draft guidances on the A-list include labeling recommendations for surgical staplers and staples; recommendations for dual 510(k) and clinical laboratory improvement amendments waiver by application studies; and guidance for nonbinding feedback after certain FDA inspections of device establishments.

Read the full lists here: www.fdanews.com/10-04-18-CDRH.pdf. — Zack Budryk

A-list Final Guidance

- Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device Premarket Approvals, De Novo Classifications, and Humanitarian Device Exemptions;
- Unique Device Identification: Policy Regarding Compliance Dates for Class I and Unclassified Devices and Direct Marking of Inventory;
- Breakthrough Devices Program;
- Expansion of the Abbreviated 510(k) Program: Demonstrating Substantial Equivalence through Performance Criteria;
- The Least Burdensome Provisions: Concept and Principles;
- Changes to Existing Medical Software Policies Resulting from Section 3060 of the 21st Century Cures Act;
- Clinical and Patient Decision Support Software;
- Multiple Function Device Products: Policy and Considerations;
- Humanitarian Device Exemption Program;
- Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program; and
- The Special 510(k) Program.

A-list Draft Guidance

- Content of Premarket Submissions for Cybersecurity of Medical Devices of Moderate and Major Level of Concern;
- Surgical Staplers and Staples – Labeling Recommendations;
- Nonbinding Feedback After Certain FDA Inspections of Device Establishments;
- Select Updates for Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices;
- Recommendations for Dual 510(k) and Clinical Laboratory Improvement Amendments Waiver by Application Studies;
- Computer Software Assurance for Manufacturing, Operations, and Quality System Software;
- Patient Engagement in Clinical Trials; and
- Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices.

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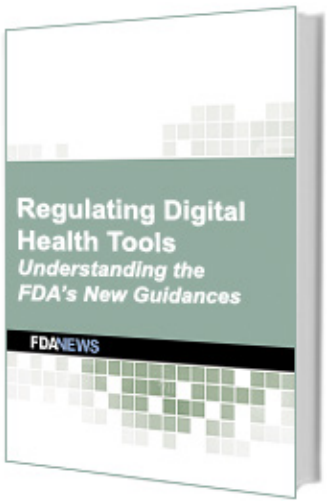

Regulating Digital Health Tools: *Understanding the FDA's New Guidances*

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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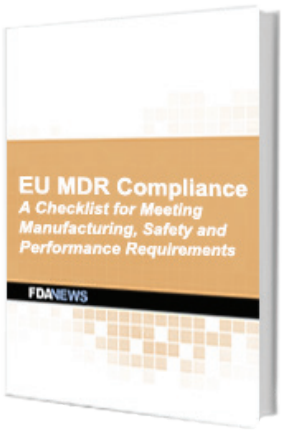

EU MDR Compliance: *A Checklist for Meeting Manufacturing, Safety and Performance Requirements*

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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