International Devices & Diagnostics Monitor

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IN THIS ISSUE

Editor's Note: Due to the holidays, *International Devices & Diagnostics Monitor* will not be published Dec. 24 or Dec. 31. The next issue will be published Jan. 7, 2019.

Canada Issues Guidance on Premarket Requirements for Cybersecurity

Health Canada released guidance for devicemakers on how to comply with premarket cybersecurity requirements.

The agency noted the draft guidance reflects international moves to protect the healthcare sector from cyberattacks as increasing global interconnectedness and data exchange can leave devices particularly vulnerable.

"Health Canada considers the inclusion of cybersecurity measures an important consideration in issuing medical device licenses," the agency said. The guidance offers advice on practices, responses and mitigation measures that can improve device cybersecurity.

The agency calls for information to be submitted as part of a device license application or amendment to demonstrate that a device is sufficiently "secure from intentional or unintentional unauthorized access."

(See **Cybersecurity**, *Page 2)*

House Committee Introduces Five-Year Medical Device Tax Delay

A tax relief package introduced in the House Ways and Means Committee last week would delay the medical device excise tax another five years.

The 2.3 percent tax has been subject to several moratoria since its passage in the Affordable Care Act in 2010, including a two-year delay extension as part of a continuing resolution in early 2018. The new bill would extend the delay until December 31, 2024.

AdvaMed CEO Scott Whitaker called the tax "bad health policy and bad economic policy," and praised the committee for including the 5-year extension of the moratorium. He thanked congressional medtech champions Rep. Erik Paulsen (R-Minn.), Rep. Jackie Walorski (R-Ind.), and Chairman Kevin Brady (R-Texas) for "spearheading this piece of the bill."

(See **Tax** *Page 2)*

FDA Unveils Guidance On Diagnostic X-Ray Equipment

The FDA issued draft guidance to clarify radiation control regulations for diagnostic x-ray systems and their major components, including recordkeeping, reporting, manufacturing, importing and installation requirements for "electronic products."

The Food, Drug, and Cosmetic Act defines diagnostic x-ray systems as both a medical device and an electronic product, so the devices are subject to the FDCA's provisions that apply to medical devices as well as those that apply to electronic products, known as the Electronic Product Radiation Control (EPRC) regulations.

The draft guidance considers specific topics of importance to sponsors of diagnostic x-ray equipment, including certification, labeling, records, defects and specific components such as beam limiting devices.

The agency said manufacturers of diagnostic x-ray systems should be aware that CDRH intends to amend FDA's performance standards, to harmonize many of its requirements with those of the International Electrotechnical Commission standards because the agency acknowledges the importance of simplifying compliance for global manufacturers.

The draft guidance, when finalized, will supersede FDA's guidance, Clarification of Radiation Control Regulations for Diagnostic X-Ray Equipment, issued in March 1989.

Read the draft guidance here: www.fdanews.com/12-14-18-XRay.pdf.

Cybersecurity, *from Page 1*

Health Canada considers cybersecurity a component of a medical device's lifecycle that can impact safety and effectiveness. As such, it should be considered when designing the device.

For example, design inputs captured in a requirement specification should include those related to cybersecurity, and the cybersecurity requirements should be cross-referenced to specific device cybersecurity hazards if the requirements are mitigations to identified hazards.

Manufacturers should also consider design controls that allow the device to detect, resist, respond and recover from cybersecurity attacks. The design controls include secure communications, data security, user access, software maintenance, and reliability and availability.

Cybersecurity should be incorporated into the risk management process for every device that consists of or contains software, the agency says. Manufacturers should develop and maintain a framework for managing cybersecurity risks throughout their organizations. The following elements should be included to address cybersecurity risks:

- Secure design;
- Risk management;
- Verification and validation testing; and
- Planning for continued monitoring of and response to emerging risks and threats.

The agency recommends device-specific cybersecurity risk management processes be conducted in parallel with the safety risk management process.

The comment period closes on Feb. 5, 2019. Read the guidance here: www.fdanews.com/12-13-18-DraftGuidanceDoc.pdf.

Tax, *from Page 1*

"A 5-year moratorium will give companies greater confidence in planning long-term R&D — a component that is critical to maintaining the longevity of the industry and sustaining the innovation ecosystem. Future breakthroughs in patient care are undermined by the threat of the medical device tax," Whitaker said.

Last week's move followed a letter to congressional leaders on Dec. 5 from a coalition of medtech groups and drugmakers, including AdvaMed, Bayer, Boston Scientific and Mallinckrodt. The signatories wrote that the tax applying specifically to revenues rather than profits is particularly burdensome to smaller companies that comprise the majority of the industry. The letter called on Congress to go even further and pass a permanent repeal by the end of 2018. — Zack Budryk

TGA Offers Guidance on Regulating Software as a Medical Device

Australia's Therapeutic Goods Administration is reviewing how it regulates software as a medical device (SaMD) and has issued guidance on its latest thinking.

TGA's regulatory scope does not include software that doesn't meet the definition of a medical device, including mobile apps that only serve as sources of information or tools that help a patient maintain a healthy lifestyle, the agency said.

Examples of SaMD include software that makes a diagnosis using patient information, X-ray image processing software and smart phone apps that calculate a patient's required insulin doses using their blood glucose levels, the guidance says, noting that the computers, mobile phones and tablets required to run various SaMD are not considered as devices.

The agency's medical devices regulations, which are risk-based, do not accurately classify all SaMD based on their risks, with many being categorized as low risk despite their potential for higher risks to users, TGA said, adding that it will be considering changes to the regulations to address this issue.

Mobile apps that can control medical devices, such as via Bluetooth or Wi-Fi, are considered to be SaMD as they "are accessories to the medical device" the guidance says. They share the same risk classification level as the medical device they control.

SaMD must be included on the Australian Register of Therapeutics Goods (ARTG). To be included on the register, manufacturers of any SaMD products higher than Class 1 — the lowest risk classification — must have conformity assessment certificates.

The agency says it recognizes that the existing regulatory framework for medical devices in Australia may not be well structured to address the potential public health risks posed by SaMD products. As part of its SaMD review, the agency is considering where it can harmonize with IMDRF technical documents.

Read the SaMD guidance here: www.fdanews.com/12-13-18-Regulation.pdf. — James Miessler

FDA Finalizes Guidance on User Fees And Refunds for Device BLAs, PMAs

The FDA issued final guidance on user fees and refunds for device biologics license and premarket approval applications with just minor changes from the October 2017 draft.

BLAs subject to user fees include original BLAs and BLA efficacy supplements. If an applicant requests withdrawal of an original BLA or efficacy supplement "at any time after FDA has taken its first action, regardless of when the action is taken, FDA will not refund any portion of the user fee," the guidance states. But if the applicant requests withdrawal of an original BLA or efficacy supplement before FDA makes the filing decision, the agency will refund 75 percent of the fee.

PMA applications subject to user fees include original and modular PMAs, premarket reports, licensing agreement PMAs, panel-track, 180-day and real-time supplements, 30-day notices and periodic reports. The FDA will not refund any portion of the user fee on an original PMA or panel-track supplement after the agency has taken its first action, regardless of when the action is taken.

The guidance also notes that an exemption for PMAs or BLAs intended solely for a pediatric population. The agency may, in certain curses, determine upon review of the device and its intended population, that the application qualifies for this exemption even though the applicant did not request a waiver.

Applicants are subject to the full user fee for traditional BLAs or PMAs if the applicant proposes usage conditions for adult populations after an original or modular PMA or BLA is approved for pediatric use.

(See **BLA**, *Page 4)*

Gottlieb Pledges Further Details About Precertification Program

FDA Commissioner Scott Gottlieb said the agency plans to release more details in the coming weeks about its precertification program for digital health technology, including details of the agency's testing plan for products in 2019.

Gottlieb made the announcement in the context of a new report last week by the agency on non-device software, which spells out the distinction between device and non-device software for regulatory purposes.

Unlike medical device software, health product software relates to maintaining or encouraging a healthy lifestyle.

"Moving forward, the FDA will continue to update this report to ensure the agency is striking the right balance in our approach to digital health," Gottlieb said.

Read the new report here: www.fdanews.com/12-13-18-SoftwareFunctions.pdf.
— Zack Budryk

J&J in $400 Million Settlement Over Faulty Hip Replacements

Johnson & Johnson agreed to settle consumer complaints of defective artificial hips for more than $400 million.

In a Dec. 9 court filing, a judge confirmed the company has settled or is currently settling about one third of the 10,000 lawsuits over its line of Pinnacle hip replacements.

Five more claims are set to go to trial in Dallas on Jan. 14. A jury ordered the company to pay multiple plaintiffs $1 billion in a similar case in 2016, although that amount was later reduced.

The verdict is currently before the Fifth Circuit Court of Appeals, and the company may settle the remaining claims to improve its chances of winning the appeal.

The settlements would be the first in seven years of litigation over the devices, which were removed from the market in 2013 over allegations they were defective and caused problems such as metal poisoning. In August, DePuy Orthopedics, a J&J subsidiary, was ordered to pay $246 million in damages relating to Pinnacle implants to six plaintiffs, nearly a year after a jury found the patients did not receive adequate warning of the associated risks (*IDDM*, Nov. 27, 2017).

The company's strategy of seeking settlements in separate groupings rather than all at once repeats a similar approach it used to resolve lawsuits relating to its vaginal mesh inserts. Consumers whose devices were surgically removed would receive higher amounts than those who only needed minor adjustments to the inserts.
— Zack Budryk

BLA, *from Page 3*

The guidance also outlines certain PMA supplements that are not subject to user fees, including special PMA supplements, PMA supplements for manufacturing/sterilization site changes, supplements for trade name changes or post-approval study protocol, and post-approval study labeling updates.

In the case of modular PMAs, applicants must pay the full fee for an original PMA when submitting the first module. On receiving the last module, the modular PMA is converted to an original PMA review track, at which point the filing review for the PMA begins.

In cases where the first module was received between October 1, 2002 and September 30, 2007, the FDA will issue 75 percent refunds of the user fees for those withdrawn prior to the FDA's filing decision.

Those withdrawn after the filing decision are ineligible for refunds.

Read the final guidance here: www.fdanews.com/12-14-18-UserFees.pdf. — Zack Budryk

Surgical Instrument Maker Racks Up 11-item 483

Lax medical device reporting and CAPA procedures as well as a host of other quality issues were uncovered during a July 31 to Aug. 2 FDA inspection of LED Intellectual Properties' Irvine, Calif. facility.

Corrective and preventive action SOPs were found lacking because procedures didn't define requirements for dealing with existing or potential quality problems, the 11-item 483 said. The FDA inspector noted that the firm's CAPA procedures didn't require investigation to identify underlying causes for potential problems and a requirement to convey information to a responsible person.

The firm had no documentation for CAPA activities and complaints weren't handled in a timely manner. For example, at least five complaints were received but they were not fully investigated for at least six months.

LED's supplier controls were found to be lacking in that products were rejected for damage and flaws, but there were no CAPA investigations to determine the underlying cause of the nonconformances.

In addition, the inspector noted repeat observations related to inadequate device history records from a previous May 2016 inspection.

Read the LED Intellectual Properties Form 483 here: www.fdanews.com/12-13-18-ledintellectualpropertiesllc483.pdf.

Managing the Complaint Management System

Maintaining an effective complaint handling system requires attention to detail, robust internal audits and a solid training program.

There are a few steps that companies can take to ensure the regulatory success of their complaint handling systems. One is simply to check the procedures. A complaint handling system that meets all QSR requirements must include a large number of procedures, so a check to confirm that all of these are under document control, as laid out in 21 CFR 820.40 – Document Controls, can help catch any details that may have fallen by the wayside.

Likewise, a requirement-by-requirement review of each procedure against the pertinent regulations can help to ensure that the complaint handling and MDR procedures are fully compliant.

For every sentence in the regulations, you should have a place where it's addressed in your procedure. "If you have multiple procedures and work instructions, which often happens, make sure you review them together to make sure that everything is covered and that there are no inconsistencies," says quality expert Dan O'Leary, *president of Ombu Enterprises.*

Keeping up with training also can be a challenge. It's essential that everyone involved in the complaint handling process understands how those processes work and who is responsible for what. All employees who could potentially be involved in complaint handling must be trained in complaint procedures, and all training must be documented and training records maintained.

Sharing Data

Complaint data is an important resource for your CAPA department, so your complaint system should feed data into your CAPA system. Not all complaints will result in corrective action, but you should set clear criteria in your system to determine which complaints go on to that stage and how they will be handled.

Your complaint system also can feed data to the corporate management level to keep them informed. Managers are particularly interested in data on open complaints: how many; how long they have been open; what is their status. And for multisite corporations, managers can use complaint data to track problems by product line and facility.

Linking complaint data to other internal data sources in such areas as incoming acceptance, nonconforming materials, installation and servicing can help give management a broader view of corporate operations.

Ultimately, you can use your complaint data to evaluate the effectiveness of the complaint management system itself.

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

BRIEFS

China Releases Checklist to Guide Inspections of Device Trials

China's National Medical Products Administration released a checklist for sponsors of device trials that places data integrity at the top of the list.

The authority said it developed the checklist in response to recurring problems seen during inspections.

The agency lists red flags that would indicate a problem with data authenticity, such as clinical trial data that is not traceable, failure to report serious adverse events, or clinical trial data submitted with the application that is inconsistent with data reported by the clinical trial institution.

The checklist covers quality management standards as well as device registration and good clinical practices. It includes on-site inspection elements that should be checked. Other topics covered include preparation for a clinical trial, informed consent, ethical reviews, clinical trial protocols, clinical trial reports and processes, recording clinical trial data and medical device test management.

India to Regulate Gowns, Drapes as Devices

The Indian government proposes to include surgical gowns and drapes as medical devices and the Medical Technology Association of India says it welcomes the change.

The group says the proposal by the Central Drugs Standard Control Organization (CDSCO) would ensure uniformity of quality in the products that were previously not regulated.

The association's Director General, Pavan Choudary. says the group will work with its member companies to ensure compliance and to streamline the transition to the new requirements.

EU Member States to Work Together to Boost AI

The European Commission and EU member states agreed on a coordinated plan to foster the development and use of artificial intelligence in Europe, including for precision healthcare applications.

In 2019, member states will map out national AI research excellence centers and their core competencies to support EU-wide cooperation and networking.

The Commission will fund networks of AI research excellence centers with 50 million Euro ($56.5 million) in 2020, and it will make 390 million Euro ($441 million) available for developing platforms and large-scale pilots.

Beyond 2020, under the Digital Europe Program, the Commission will establish testing sites for AI-powered products and services throughout Europe.

Two big projects are expected to begin building a database of 1 million sequenced genomes accessible in the EU by 2022 and to develop a common database of health images initially dedicated to the most common forms of cancer.

FDA Issues Final Rule On Reclassification of Devices

The FDA issued a final rule streamlining its classification procedures for medical devices and allowing for changing classifications by administrative orders rather than the rulemaking process.

The final rule follows up on a proposal issued in 2014 that uses authority granted under Food and Drug Administration Safety and Innovation Act of 2012. The agency makes clear it can reclassify any higher-risk class III device to either class I or class II.

In the case of reclassification proceedings based on new information and proceedings calling for PMAs for a pre-FDASIA class II device, the agency must convene a classification panel and obtain panel recommendations on classifications. For FDA-initiated reclassification proceedings, however, the agency has the option to choose whether to consult with a panel, according to the final rule.

"We believe the process in this final rule providing for a proposed order, panel consultation as appropriate, consideration of comments, and final order provides sufficient opportunity for participation and review of reclassification of transitional devices," the agency says.

The final rule further simplifies the reclassification process by eliminating the requirement to provide two forms as part of a device reclassification petition — the General Device Classification Questionnaire and the Supplemental Data Sheet.

Read the final rule here: www.fdanews.com/12-13-18-Finalrule.pdf. — Zack Budryk

FDA Guidance Outlines Rules For Site Change Supplements

Final guidance issued by the FDA on Friday outlines what devicemakers should know about manufacturing site changes and when they should submit supplements.

Applicants should submit a 180-day premarket approval (PMA) supplement for using a different site if the change affects the device's safety or effectiveness. Humanitarian device exemption (HDE) holders, meanwhile, are required to submit a 75-day supplement.

All site change supplements should clearly identify any changes to manufacturing locations and associated changes to the manufacturing process that result, such as requirements for alterations to the water filtration for manufacturing. If activities being moved are not already conducted at the new manufacturing site, a full supplement is required.

The FDA does not require a PMA supplement in cases where a new facility is used for the manufacture, processing or packaging of a component for a finished device. Companies that manufacture components but not finished devices are not subject to the QS regulation requirements but are "encouraged to use appropriate provisions" of 21 CFR, the agency says.

Applicants should submit 30-day notices for use of new suppliers of any components critical to the finished device's function, operation or specifications, as those changes may affect the finished device's effectiveness or safety.

"Manufacturing changes to components that are not critical to the device's function, operation or specifications do not require firms to submit a site change supplement or a 30-day notice; however, these changes must be reported in the Annual Report," the guidance states.

The site change supplement should include a description of the device, its intended use, and the nature and purpose of the site change, including a full description of what manufacturing activities will take place at the proposed site. It should also feature a diagram of the proposed new site or sites and a flow diagram laying out the steps involved in the manufacture, processing, packaging or distribution of the device under review at the proposed site.

Read the full guidance here: www.fdanews.com/12-14-18-SiteChangeSupplements.pdf. — Zack Budryk

APPROVALS

Subtle Medical Cleared For AI-Powered Imaging Tech

Subtle Medical's SubtlePET, a positron emission tomography (PET) imaging system driven by AI technology, was granted 510(k) clearance by the FDA. The device recently received a CE Mark in Europe.

The device can be used by hospitals and imaging centers to enhance images and speed up scanning times for PET scans.

Because the technology is able to reduce scanning times, it is capable of increasing the number of scans health care professionals can run each day.

FDA Clears Bausch + Lomb's Multifocal Toric Lens

Bausch + Lomb's ULTRA Multifocal for Astigmatism contact lenses received the FDA's go-ahead in a 510(k) clearance.

The monthly silicone hydrogel lens were developed to help patients correct astigmatisms without needing custom lenses or glasses.

Patients can be immediately fitted by eye care professionals with a diagnostic version of the newly approved contact lenses.

SpeeDx Gains CE Mark For Gonorrhea Test

SpeeDx's ResistancePlus GC gonorrhea assay has earned the CE Mark.

The polymerase chain reaction test detects gonorrhea and allows doctors to assess the disease's susceptibility to the antibiotic ciprofloxacin before prescribing.

The assay is the first commercially available molecular test in the EU that provides information on the disease's antibiotic susceptibility.

FDA Clears Edwards Lifesciences's Hemodynamic Monitoring Platform

Edwards Lifesciences' latest HemoSphere advanced hemodynamic monitoring platform received 510(k) clearance from the FDA.

The device includes solutions that enable predictive monitoring of moderate- to high-risk surgical patients, such as its Acumen hypotension prediction index software, which uses AI to determine the likelihood of a low blood pressure event.

HemoSphere also includes a minimally-invasive sensor that automatically updates advanced hemodynamic parameters every 20 seconds.

Contego Medical Cleared For Angioplasty System

The FDA granted 510(k) clearance for Contego Medical's Vanguard IEP peripheral balloon angioplasty system.

The device is designed to protect patients that are vulnerable to embolization — the passage and lodging of an object, such as a blood clot, in the blood stream — during peripheral angioplasties, in which a surgeon repairs or unblocks blood vessels.

The system, which has an over-the-wire design, can protect the patient's lower limbs during angioplasty and requires no additional devices or exchanges.

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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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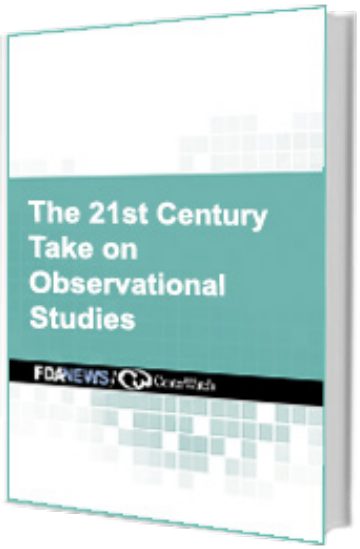

The 21st Century Take on Observational Studies: *Using Real-World Evidence in the New Millennium*

Many companies have taken their first steps in the frontier of real-world evidence and what they have learned may surprise you.

This new edition of **The 21st Century Take on Observational Studies** presents new information on the encouraging results those pioneers have found. New to this edition are the results of a groundbreaking study from Tufts University's Center for the Study of Drug Development. Learn how your colleagues — and competitors — are using real-world data to advance their products.

The management report walks you through everything you need to know about the opportunities and pitfalls observational studies can offer. The report looks at the growing trend toward observational research and how provisions in the 21st Century Cures Act create even more incentives to rely on real-world evidence in the development of medical products. The report covers:

- How observational studies can be used in the preapproval and postmarket stages
- New data sources that make observational studies a viable alternative to clinical trials
- How drug- and devicemakers view observational research and how they are using it
- The potential for saving time and money
- The evolution of patient-focused research

Order your copy of **The 21st Century Take on Observational Studies: *Using Real-World Evidence in the New Millennium*** and learn effective uses of observational studies in both the preapproval and postmarket phases; how to identify stakeholders and determine what kind of data they needed, and how the FDA's view on observational research is evolving.

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