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IN THIS ISSUE

FDA Expands Inspections As Shutdown Persists

As the partial government shutdown entered a record-setting fourth week, the FDA expanded high-risk inspection activities by bringing back more unpaid staff.

The expanded activities include surveillance and response for serious recalls, and inspection activities beyond "for-cause" inspections, to include foreign and domestic surveillance inspections focused on the highest risk products and facilities.

"Many key functions aren't getting done. But we're focused on maintaining core activities that directly impact consumer safety and save lives," said Commissioner Scott Gottlieb.

Gottlieb announced that approximately 400 staff members would return to their posts, mostly for inspection-related tasks. "About 400 total staff are being engaged in this mobilization," he said. "The vast majority are inspectors and others are professionals who work in support of inspectors." Approximately 100 of those will focus

(See **Shutdown**, *Page 2)*

TGA Issues Draft Guidance On New UDI System

Australia's TGA is seeking stakeholder comment on draft guidance on implementing a unique device identification system.

The TGA is proposing that Australia follow the EU's transitional arrangements, which require UDIs on the label of the device and on all higher levels of packaging for:

- Implantable devices and Class III devices from May 26, 2021;
- Class IIa and Class IIb devices from May 26, 2023; and
- Class I devices from May 26, 2025.

The TGA plans on developing a UDI system that aligns with principles outlined in the International Medical Device Regulators Forum (IMDRF). IMDRF released guidance in October 2018 on a single, globally harmonized system to identify devices

(See **UDI**, *Page 2)*

Shutdown, *from Page 1*

on inspections of medical device manufacturing facilities, he said.

Democrats on the Senate Health, Education, Labor and Pensions Committee sent a Jan. 11 letter to Gottlieb calling for details of the shutdown's impact.

During the shutdown, the FDA is legally prohibited from accepting new submissions that require industry user fee payments, which support the review and approval of applications for medical devices, the lawmakers noted. As a result, the agency "will likely receive a large influx of applications from device makers following the conclusion of the shutdown, requiring the agency to triage review activities and probably causing a backlog in the approval process," they said.

The letter requests a full overview of the expected spike in application backlogs both currently and for each additional week the shutdown continues, including when the agency expects normal functions to resume.

Read the HELP Committee's letter here: www.fdanews.com/01-14-19-HELP.pdf. — Zack Budryk

UDI, *from Page 1*

internationally. Many countries have already implemented UDI systems, including Europe, the U.S., Japan, Brazil and China.

Sponsors of medical devices in Australia would be required to ensure their devices carry UDIs, and that relevant information be entered into an Australian UDI database (AusUDID), the draft guidance says. Sponsors that import or supply devices in Australia will be responsible for verifying that device manufacturers have assigned UDIs to their devices.

"Sponsors must have an agreement with the manufacturer authorizing the sponsor to include the key data elements and other relevant information in AusUDID," the TGA said.

The Australian UDI system will apply to all devices placed on the market in Australia except custom-made and certain other devices.

Australia would introduce the UDI system in stages. The guidance proposes amending legislation to enable the establishment of the UDI system and include provisions to:

- Allow the designation of issuing agencies and provide these with the power to issue unique device identifiers;
- Prescribe requirements for the placing of UDIs on a device, its labeling and packaging; and
- Establish the AusUDID and link it to the Australian Register of Therapeutic Goods (ARTG).

Australia's UDI system would include rules for specific categories of medical devices, including implantable devices, systems and procedure packs, software as a medical device and contact lenses.

The draft guidance includes core definitions, key data elements and main principles that are consistent with IMDRF UDI guidance, as well as FDA and EU regulations.

The guidance asks devicemakers whether the TGA should be responsible for establishing the Australian UDI database (AusUDID) or whether alternative organizations could establish and manage the database. It also asks for feedback on what core data elements and other relevant information should be included in the AusUDID.

Comments may be submitted on the draft guidance by Feb. 18. Read the guidance here: www.fdanews.com/01-18-19-UDI.pdf.

AdvaMed Suggests Health Canada Modify 3D Printing Guidance

AdvaMed called for Health Canada to revise and clarify its draft guidance on licensing requirements for implantable devices made through 3D printing.

Specifically, the association called for the agency to add clarifications and new information to the guidance, such as a revision to align the guidance with the agency's license applications guidance and to clarify the different expectations for Class III and IV devices.

"The license applications guidance asks for significantly less information on manufacturing and quality controls for Class III devices," AdvaMed said. "It is unclear in the 3D printing guidance if this expectation carries through to 3D-printed devices, or if there are higher expectations for Class III 3D-printed devices."

To address the uncertainty, the agency should clarify what it expects in an application versus what would be more appropriate for review during quality management system audits, AdvaMed said. The group also asked Health Canada to note when the information is in addition to the license applications guidance or when it is intended to clarify specific 3D-printed device expectations.

The trade group also urged the agency to replace the phrase "patient specific" with "patient matched" throughout the guidance, in order to align with the International Medical Regulators Forum (IMDRF)'s definitions for personalized medical devices and move closer to reaching a harmonized regulatory pathway for 3D-printed devices. "Patient-matched" is more descriptive of 3D-printed devices, the group said, because "patient specific" could be misunderstood as meaning "custom-made."

It also called for a restructuring of the document to better illustrate the manufacturing process flow of 3D-printed devices. 3D Printing is a manufacturing process — additive manufacturing — and manufacturers will follow design control and product realization processes, the group said. "The structure and flow of the guidance does not always follow this process and we believe it would be helpful to restructure the document accordingly."

Health Canada is represented on the IMDRF personalized devices working group and is currently participating in IMDRF's international harmonization effort.

Read AdvaMed's recommendations here: www.fdanews.com/01-17-19-Advamed.pdf.
— James Miessler

TGA Releases Draft Guidance On Device Cybersecurity

Australia's Therapeutic Goods Administration issued draft guidance for devicemakers on cybersecurity risks.

Effective cybersecurity requires steps by manufacturers, sponsors, clinicians and patients, the agency said. If the cybersecurity risk is not minimized throughout the life of the device, it can lead to a breach in the confidentiality, integrity and availability of medical device data, or malicious unauthorized access to the medical device and the network, TGA said.

The TGA pointed to the U.S. National Institute of Standards and Technology's cybersecurity framework as a model for addressing cybersecurity risks. Along each stage of the device lifecycle, devicemakers need to ensure compliance with essential principles, including risk management for cybersecurity.

The guidance recommends the following considerations for developing a risk management plan:

- Devices and associated networks can never be completely cyber secure, and device users themselves represent a potential threat;
- The evolving device cyber threat landscape requires constant monitoring and appropriate corrective and preventive action;
- Potential harm to patients from adverse events include physical harm and other consequences for patients could include psychological harm, breaches of privacy and financial consequences; and

(See **Cybersecurity**, *Page 4)*

Cybersecurity, *from Page 3*

- Clinical use of the device is often much longer than the expected lifespan of the technology, which means less frequent security patches over time as it becomes officially unsupported.

During the design and development stage, manufacturers should address cybersecurity risks, including general considerations such as standards and supply chain assessment. They should address technical considerations such as cybersecurity performance testing, modular design architecture, operating platform security, emerging software and trusted access and content provision.

One risk consideration the guidance highlights is the severity of patient harm if a vulnerability is exploited. It suggests using ISO 14971:2007 to determine the risk to patients. The guidance also lists the following standard that could help manufacturers meet regulatory requirements for cybersecurity:

- ISO 13485 - Quality management systems;
- IEC/EN 62304 - Software lifecycle requirements;
- IEC 60601-1 - Safety and essential performance of medical electrical equipment;
- UL 2900-1 - Cybersecurity for networks and connectable products;
- UL 2900-2-1 - Requirements for network connectable components;
- IEC 80001 - Application of risk management for IT networks incorporating medical devices;
- AAMU/UL 2800 - Safety and security requirements of interoperable medical systems;
- ISO 15408 - Evaluation criteria for IT security;
- IEC 82304 - Health software general requirements for product safety; and
- ISO/IEC 30111 - Resolve potential vulnerability information in a product.

The TGA pointed to the U.S. National Institute of Standards and Technology as a good framework to address cybersecurity risks throughout a product's lifecycle.

The agency is accepting comments until Feb. 14. Read the draft guidance here: www.fdanews.com/01-18-19-cybersecurity.pdf.

Special Risk Consideration: Cybersecurity

The FDA applies ISO 14971 risk management principles to its oversight of medical device cybersecurity, defined as the process of preventing unauthorized access, modification, misuse or denial of use, or the unauthorized use of information that is stored, accessed or transferred from a medical device to an external recipient. "Harm," according to ISO 14971, means physical injury or damage to the health of people, damage to property or damage to the environment, and "risk" is defined as the combination of the probability of occurrence of harm and the severity of that harm.

This is a bit different from most risk management, which addresses harm to a patient or to a healthcare professional using a device. In its 2005 guidance on pre-market software devices — entitled *Content of Pre-market Submissions for Software Contained in Medical Devices* — the FDA clearly defines level of concern in terms of injury to a patient or user.

In the case of cybersecurity, however, the FDA and other regulators extend concern beyond the individuals to property and the environment. While physical injury or damage to the health of people remains a top concern for medical device cybersecurity risk management, cybersecurity breaches in general are more likely to involve damage to property.

A particular concern for devicemakers is unauthorized use of information that involves intellectual property. For patients and healthcare providers, unauthorized access to patient health data, which certain medical device software generates and/or stores, is also a major concern. Property damage is in scope for ISO 14971, so the FDA has adopted that standard's approach for its oversight of device software cybersecurity.

The framework for medical device cybersecurity mirrors that for other risk assessment and mitigation. The FDA also plans to implement an existing National Institutes of Standards and Technology (NIST) cybersecurity framework. Under this framework, which echoes existing pre- and postmarket risk management principles for medical devices, companies must identify cybersecurity risks, take steps to protect their devices from those risks, establish methods for detecting breaches, discover those breaches and respond effectively to them.

Excerpted from the FDAnews management report: *Device Software Development — A Guide to Risk Management Requirements*.

483 Roundup: FDA Flags Three Firms for MDRs, Other Violations

The FDA cited three device companies for medical device reporting, corrective and preventive actions and other violations found during inspections.

Alba Bioscience: Alba Bioscience did not properly implement medical device reporting procedures or document control procedures, the FDA said following a September 2018 inspection.

The FDA issued a Form 483 following its inspection of the firm's Edinburgh, Scotland facility and found it had not implemented medical device reporting procedures for several licensed in vitro diagnostic devices, including blood grouping reagents, reagent red blood cells and anti-human globulin. The inspection also determined the facility had not established controls for electronic data acquisition systems and found a failure to prevent unauthorized access of changes to data. The company also did not establish procedures for issuing and reconciling batch manufacturing records or QC test record forms used to document device production and testing.

Moreover, the company's procedures for non-viable particle monitoring during filling operating did not ensure meaningful data were collected and the required sample collection was not clearly defined in either written procedures or the sample map.

Thermogram Assessment Services: The FDA cited Thermogram Assessment Services for problems with its CAPA, complaint-handling and MDR procedures.

The agency inspected Thermogram's Dallas facility in October 2018 and found it lacked a CAPA procedure or complaint handling procedure, according to the Form 483. The inspection also determined the facility lacked compliant process control procedures to ensure conformance to specifications.

In addition, the company lacked procedures for medical device reporting and for purchasing controls to ensure all received products and services met specified requirements.

OCCK: The FDA issued device manufacturer OCCK a Form 483 for issues with its Salina, Kansas facility's quality system management and device history records.

The investigator, who inspected the firm from Aug. 8-9, 2018, found that the facility had not documented the appointment of a management representative to ensure that quality system requirements are fulfilled.

The firm was also called out for device history records, which lacked identification labels and labeling, such as batch numbers.

OCCK was also cited for its document control procedures, which lacked evidence that a designated individual reviewed and approved them. These included manufacturing, packaging and sub-contract work corrective action plan, medical products complaint process, quality management system and management review of quality system for medical device product procedures.

Additionally, the firm's CAPA standard operating procedure lacked certain requirements. Specifically, it didn't require the analysis of quality data to pinpoint existing and potential causes of nonconforming product and didn't require investigating the cause of nonconformities, identifying actions to correct and prevent repeated nonconformance, and other quality issues.

Read the Alba Bioscience Form 483 here: www.fdanews.com/01-18-19-albabiosciencetd483.pdf.

Read the Thermogram Form 483 here: www.fdanews.com/01-18-19-thermogram483.pdf.

Read the OCCK Form 483 here: www.fdanews.com/01-17-19-occkinc483.pdf.

IMDRF Mulls Device Single Review Program

The International Medical Device Regulators Forum is making progress in developing a medical device single review program (MDSRP).

Members of the IMDRF Good Regulatory Review Practices Working Group gathered in Tokyo following the full IMDRF meeting in

(See **IMDRF***, Page 6)*

IMDRF, *from Page 5*

Beijing in September and agreed to basic principles for a single review program.

Melissa Torres, associate director for international affairs at CDRH, is chair of the working group. Torres noted that the development of a MDSRP program would allow for a single regulatory premarket review to satisfy multiple regulatory jurisdictions. The program will be modeled after the Medical Device Single Audit Program (MDSAP) and aimed at promoting a harmonized approach to assessing safety and performance.

The working group agreed on recognition requirements and procedures for pre-market evaluations of devices. The move marks the first step in developing a MDSRP program among member countries that take different approaches to premarket evaluations.

The U.S. FDA first proposed a MDSRP program in 2015. At the time, the FDA proposed strengthening its third-party premarket review program by offering training to third party review entities, conducting audits and publishing performance reports of individual third-party entities.

The FDA said it would evaluate the feasibility of harmonizing the third-party review program with international review programs like the MDSRP program.

Issues that need to be resolved to develop a program would include:

- Training and competency requirements for the reviewer performing the assessment;
- Types of submissions or device categories that are to be covered by the program and establishment of specific criteria for each of those;
- Legislative framework of each jurisdiction (such as timeframes, flexibility and specific requirements);
- Harmonization of submission requirements;
- Harmonization of the review process;
- Accreditation of entities that would perform, the assessments of premarket submissions; and
- Programmatic implementation.

One of the first steps was the IMDRF Regulated Product Submission Table of Contents pilot program, which evaluated the agreed upon structure that would allow submissions to work for multiple regulators. Australia, Brazil, Canada, China, the EU and the U.S. are participating in the current pilot. A previous pilot used historical submissions for products, but there were no guidelines at that time for building a regulated product submission (*IDDM*, Aug. 7, 2015).

Following the Beijing meeting, IMDRF's Good Regulatory Review Practices Group released final guidance on the Essential Principles of Safety and Performance of Medical Devices and IVDs, with harmonized principles for designing and manufacturing devices. The document is for regulatory authorities, conformity assessment bodies, industry and other stakeholders (*IDDM*, Nov. 16, 2018).

FDA Revises Antimicrobial Drug/Device Guidance

The FDA released revised draft guidance on coordinated development of antimicrobial drugs and antimicrobial susceptibility test (AST) devices.

The agency says antimicrobial sponsors and AST device manufacturers should coordinate development wherever possible and should begin discussions early during new antimicrobial drug development to allow generation of data helpful during clinical trials for developing AST devices.

When AST sponsors who have not coordinated development with a drugmaker as part of an NDA seek to submit a 510(k) application, they can get device development feedback through CDRH's Q-Submission program, the agency says.

Device sponsors should use the program to submit a coordinated development plan to CDRH for review and feedback shortly after the NDA submission at the latest. The plan should identify the antimicrobial drug under development and include letters of authorization from both sponsors that allow the FDA to reference information from any relevant NDAs or INDs.

After the initial Q-Submission is sent, sponsors may also submit supplements as necessary, both after NDA submission and during NDA review to aid future 510(k) submissions. The FDA specifically suggests additional Q-Submissions if the device under development will be used in phase 2 or 3 clinical trials. An investigational device exemption may also be required in certain circumstances.

Applications for 510(k) clearance for AST devices should be submitted four to six weeks before anticipated drug approval, according to the guidance. "The submission may be based on provisional susceptibility test interpretive criteria (breakpoints) and updated as needed when final breakpoints are identified or recognized by CDER," the guidance states.

If appropriate documentation is provided giving FDA permission to share information from the NDA with the AST device sponsor, the FDA can share information such as indicated organisms with the AST device sponsor. In cases where such agreements do not exist, the final breakpoints and indicated organisms will become publicly available upon drug approval.

CDRH's review of 510(k) submissions can begin during the NDA review process regardless, which will improve the odds that the sponsors can clear the AST device either shortly after or at the same time as drug approval, the agency said.

Read the guidance here: www.fdanews.com/01-18-19-AST.pdf. — Zack Budryk

APPROVALS

FDA Approves Abbott's Premie Heart Opening Treatment

The FDA approved Abbott's Amplatzer Piccolo occlude, a device that can be implanted in babies weighing as little as two pounds to treat patent ductus arteriosus.

The minimally-invasive device, which is smaller than a pea, is able to treat the life-threatening opening between two blood vessels leading from the heart that can occur, most often in babies born prematurely.

The self-expanding, wire mesh device is inserted in the baby via a small insertion in the leg and directed through vessels to the heart, where it is placed to seal the opening.

Gramercy's Nitinol Staple System Cleared by FDA

Gramercy Extremity Orthopedics received FDA clearance for its Nitinol staple system for treating bone-related conditions.

The staple system is cleared to fixate osteotomies and small bone fragments. It's also cleared for joint fusion surgery.

The device provides an array of sterile symmetric and asymmetric, barbed and smooth nitinol staples that come in various widths and lengths.

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

Approvals, *from Page 7*

IschemaView Gains Expanded Clearance for Neuroimager

The FDA handed medical imaging developer IschemaView expanded clearance for its Rapid neuroimaging platform.

The imaging platform is intended for use in selecting stroke patients that are expected to benefit from endovascular thrombectomy, which treats strokes by pulling blood clots out of arteries.

FDA Clears Immuno Concepts' Rodent Tissue Slides

The FDA granted 510(k) clearance for Immuno Concepts' Histofluor rodent liver, kidney and spleen tissue slides.

The rodent tissue slides are available in both mouse and rat substrates, and all components come ready-to-use.

The slides can be used manually or with Immuno Concepts' Image Navigator device, an automated microscope that can capture multiple images and assemble them into a panoramic view.

FDA Approves Teva's Digital Inhaler

Teva's ProAir Digihale, a digital inhaler device that works in conjunction with a mobile app, has been approved by the FDA.

The device, which has sensors built in that detect device use and measure respiratory flow, connects to a mobile application and provides inhaler use information for patients with asthma and COPD.

The inhaler is indicated to treat or prevent bronchospasms in patients aged four years or older with obstructive airway disease, and to prevent exercise-induced bronchospasms in patients of the same age.

Edwards Lifesciences' Heart Valve Approved

The FDA approved Edwards Lifesciences' SAPIEN 3 Ultra, a heart valve used in transcatheter aortic valve replacements.

The system is intended for severe, symptomatic aortic stenosis patients found to be at intermediate or greater risk of needing open-heart surgery.

The valve includes technological enhancements and a new delivery system that builds on the previous SAPIEN 3 units.

Japan Clears Foundation Medicine's Genomic Profiling Assay

Japan's Ministry of Health, Labor and Welfare approved Foundation Medicine's FoundationOne CDx genomic profiling assay.

The sequencing-based assay can detect substitutions, insertion and deletion alterations and copy number alterations in 324 genes, and is able to detect genomic signatures such as the tumor mutations in DNA.

The assay, which received FDA approval in 2017, can also select gene rearrangements that have been found to spur cancer growth.

Bedsore Scanner Receives Marketing Authorization From FDA

The FDA granted Bruin Biometrics marketing clearance for its SEM Scanner, a wireless device for assessing patients at higher risk of pressure ulcers.

The scanner can identify specific areas of the patient's body that are at increased risk of pressure damage.

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Device Software Development: *A Guide to Risk Management Requirements*

Medical device risk management — specifically device *software* risk management — calls for a solid understanding of a myriad of requirements.

The FDA Quality Systems Regulation, ISO 14971, the new EU Medical Device Regulation all stress the importance of building risk management into the development process of software that will be used in or as a medical device.

Device Software Development — based on a presentation by quality systems expert Dan O'Leary — is a comprehensive, point-by-point guide to developing software that meets all FDA and international standards for successful market clearance. You'll learn:

- Which ISO standards touch on software development and risk management and what guidance is available
- What requirements the new EU MDR places on software development
- How to assess the level of a hazard's severity
- How to identify software's safety classification
- Pre- and postmarket risk management considerations

In addition to outlining effective risk management factors, the report includes the following downloadable tools:

- 510(k) Change Analysis Decision Flowcharts
- Level of Concern Calculator
- Software Safety Classification Guide

Device Software Development: ***A Guide to Risk Management Requirements*** shows you know what risk management methods and requirements you need to follow to get approval to market your device.

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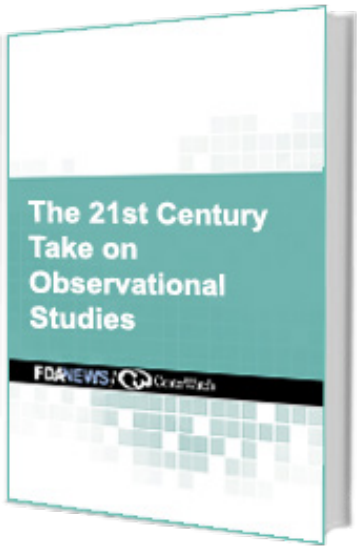

The 21st Century Take on Observational Studies: *Using Real-World Evidence in the New Millennium*

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.

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- 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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