International Devices & Diagnostics Monitor

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IN THIS ISSUE

Editor's Note: Due to summer breaks, *International Devices & Diagnostics Monitor* will not be published July 2. The next issue will be published July 9.

FDA Overhauls Manual on Inter-Center Consultations for Combination Products

The FDA updated its manual on handling inter-center consultation requests between CDRH, CDER and CBER for combination product reviews.

The agency overhauled the manual, the first update in 14 years, to include changes made to the process and piloted in 2016 in response to recommendations by the Combination Products Coalition (CPC), a group of leading drug, device and biologics companies. The revisions became effective June 11.

In 2014, the CPC issued recommendations for reforming combination product regulation to improve coordination among parties involved in combination product reviews, including sponsor communication and justifications for agency data requests. The coalition said the revisions would encourage innovation and "put combination product regulation on the right path."

(See **ICCR**, *Page 2)*

FDA Issues Draft Guidance On Coding for IVDs

The FDA called for consistent coding of in vitro diagnostic tests in a new draft guidance and urged devicemakers to use Logical Observation Identifiers Names and Codes.

The agency said LOINC coding is voluntary but it "strongly encourages the use of consensus standards for coding of IVD tests and specifically recognizes the utility of LOINC for this purpose."

LOINC is the IVD coding system that is most widely used by clinical laboratories and electronic health records.

The agency noted that LOINC codes are not the same as unique device identifiers. The LOINC coding system identifies the type of laboratory test being performed, while the UDI identifies a specific model and version of a device manufactured by a specific manufacturer.

(See **IVD**, *Page 2)*

ICCR, *from Page 1*

The process revisions include:

- Establishing center and submission-specific timelines for identifying products as combination products and issuing and completing consults needed for supporting the review;
- A tiered consult approach that streamlines interactions between centers and identifies the right experts for a consult;
- Defining clear roles and responsibilities for the lead center, consulted center(s), the Office of Combination Products and the Combination Product Council in reviews of combination product submissions; and
- Creating a semi-automated, user-friendly inter-center consultation request form that is handled electronically to ensure the form remains up to date and tracked through a single system.

Bradley Merrill Thompson, the CPC's general counsel, said the organization was pleased with the FDA's decision to adopt some of its recommendations, but the coalition hopes the agency will take further action to address more of its suggestions, such as specifying a required timing for consultations to allow for post-consultation communication among sponsors.

"All in all, this is a very positive step forward. The agency has been very responsive in addressing the issue of ensuring a mechanism for cross center input," Thompson told *FDAnews*.

But the coalition "identified many more issues than are addressed by this program, and we're hoping to see concrete steps taken to address the remaining issues," he said.

Read the manual here: www.fdanews.com/06-18-18-requestprocess.pdf. — James Miessler

IVD, *from Page 1*

The agency stressed the importance of interoperability for IVD tests, particularly in the context of aggregated data from multiple systems. It said that the use of LOINC codes would encourage interoperability for exchanging data with different information technology systems, software applications and networks.

"For instance, in the context of infectious diseases, semantically interoperable EHR systems can allow for more efficient tracking of outbreaks or significant public health threats by providing access to evaluable real-time IVD test information from multiple geographic locations," the agency said. "Consistent representation also allows EHR databases to be used to study diagnostic assays without having to adjust for different coding schemes at individual sites."

Being able to consistently identify IVD tests in EHRs can also minimize potential errors as information is transmitted across systems, the FDA said.

Devicemakers can include LOINC codes in labeling, or they may include a reference to an external location that lists LOINC codes for their IVD tests.

LOINC codes should be used for FDA-cleared devices, the agency said. It stressed that including a LOINC code on a device that suggests an unapproved indication for use "may be considered evidence of a new intended use and result in the device being considered adulterated and/or misbranded."

LOINC codes incorporated directly into devices may be subject to quality system requirements applicable to the device, the agency said.

Although the guidance does not recommend a specific format for distributing LOINC codes, it encourages using an FDA-recognized consensus standard. Standardized formats can facilitate a laboratory's ability to adopt new LOINC codes and incorporate updates or changes to existing codes.

The FDA urges manufacturers to follow developments in this area as standards for electronically transmitting LOINC codes are modified or expanded, or as new standards emerge.

Read the full guidance here: www.fdanews.com/06-19-18-IVDguidance.pdf.

Appeals Court Re-Opens Stryker Lawsuit Over Kickbacks

A federal appeals court reversed a lower court decision and revived a lawsuit between device manufacturer Stryker and a Brazilian insurance association that is accusing the company of paying kickbacks to doctors for using its devices.

The Sixth Circuit Court of Appeals in Cincinnati ruled that the lower district court should not have ruled that the case be brought in Brazil rather than Michigan where Stryker is headquartered.

According to the Brazilian association, by offering kickbacks to doctors, "the improper influence Stryker allegedly brought to bear increased the cost of devices as well as the number of devices implanted and surgeries performed," which association members had to pay for, court documents said.

The association claims Stryker's alleged actions "not only injured its insurer members, but also the Brazilian public health system as a whole and patients throughout the country."

The district court had dismissed the case in June 2017 because the association had "minimal connection to the United States," court documents said. However, the federal appeals court ruled that a Brazilian court may not be able to "exercise jurisdiction over the defendant and offer a satisfactory remedy."

Read the court documents here: www.fdanews.com/06-20-18-Strykerlega.pdf.

Theranos Executives Could Face Up To 20 Years in Prison for Fraud

A federal grand jury indicted Theranos CEO Elizabeth Holmes and COO Ramesh Balwani on two counts of conspiracy to commit wire fraud and nine counts of fraud.

If convicted the two could face up to 20 years in prison and a fine of $250,000, plus restitution, for each count of wire fraud and for each conspiracy count, the Department of Justice said.

The charges stem from allegations Holmes and Balwani engaged in a multi-million dollar scheme to defraud investors and a separate scheme to defraud doctors and patients. Both schemes involved efforts to promote the Palo Alto, Calif.-based diagnostics firm founded by Holmes in 2003.

According to the indictment issued by the U.S. District Court of the Northern District of California, Holmes and Balwani used advertisements and solicitations to encourage and induce doctors and patients to use Theranos' blood testing lab services, even though they knew Theranos was not capable of consistently producing accurate and reliable results for certain blood tests.

The indictment alleges that the defendants used a combination of direct communications, marketing materials, statements to the media, financial statements, models, and other information to defraud potential investors.

The defendants claimed Theranos developed a revolutionary and proprietary analyzer able to perform a full range of clinical tests using small blood samples drawn from a finger stick. They claimed the analyzer could produce results that were more accurate and reliable than those yielded by conventional methods — and faster than was previously possible.

The indictment alleges Holmes and Balwani knew many of their representations about the analyzer were false. For example, they allegedly knew the analyzer had accuracy and reliability problems, performed a limited number of tests, was slower than some competing devices, and, in some respects, could not compete with existing, more conventional machines.

The DOJ, the FDA, the FBI and the U.S. Postal Service cooperated in the investigation.

(See **Theranos**, *Page 4)*

Theranos, *from Page 3*

"The conduct alleged in these charges erodes public trust in the safety and effectiveness of medical products, including diagnostics," said Catherine Hermsen, acting director of the FDA's Office of Criminal Investigations. "The FDA would like to extend our thanks to our federal law enforcement partners for sending a strong message to Theranos executives and others that these types of actions will not be tolerated."

FDA Inspections

Questions around Theranos' quality management practices first surfaced in 2015 during an Aug. 25 to Sept. 16 FDA inspection of the company's Newark, Calif. facility and the Palo Alto facility for which the FDA issued two Form 483s for documentation and QMS problems. Word of the 483s came days after news reports questioned whether Theranos' device, dubbed Edison, could be used in all of the tests the company claimed (*IDDM*, Nov. 2, 2015).

A year later, Theranos was hit with criminal investigations by the Securities and Exchange Commission, the U.S. Attorney's Office for the Northern District of California and the U.S. Department of Justice. That came after the Centers for Medicare and Medicaid Services cited the company's California facility for exposing patients to risk, failing to meet lab testing standards, employing unqualified staff and improperly reviewing patient test results (*IDDM*, April 25, 2016).

"The defendants knew Theranos was not capable of consistently producing accurate and reliable results for certain blood tests, including the tests for calcium, chloride, potassium, bicarbonate, HIV, Hba1C, hCG and sodium," the DOJ said.

"The defendants nevertheless used interstate electronic wires to purchase advertisements intended to induce individuals to purchase Theranos blood tests at Walgreens stores in California and Arizona. Through these advertisements, the defendants explicitly represented to individuals that Theranos's blood tests were cheaper than blood tests from conventional laboratories to induce individuals to purchase Theranos's blood tests."

The indictment alleges that based on the defendants' misrepresentations and omissions, patients and their insurance providers paid Theranos, or Walgreens acting on behalf of Theranos, for blood tests and test results, sometimes following referrals from their defrauded doctors. The defendants delivered to doctors and patients blood results that were inaccurate, unreliable, and improperly validated. The defendants also delivered to doctors and patients blood test results from which critical results were improperly removed.

The indictment describes a number of schemes the two executives allegedly engaged in to mislead investors, doctors, and patients. For example, they allegedly purchased and used commercially available analyzers to test patient blood, while representing to investors that Theranos conducted the tests using its manufactured analyzers.

FDA Hits Vital Connections For Validation Procedures

The FDA issued a Form 483 to Vital Connections, citing the medical device manufacturer on process and design validation procedures.

The FDA issued the form after a March 2018 inspection of the firm's Tipp City, Ohio, facility. Investigators found the facility did not maintain process validation procedures and had not conducted validation activities for any of its production processes, including mold press operations used to manufacture plastic connectors and snaps.

Investigators found the company's design control validation procedure did not ensure that the validation followed pre-established protocols. In July 2015, the company sent product not yet available for sale to several local hospitals without developing a protocol to ensure that design validation activities were adequately completed or setting parameters to be tested.

The company also failed to ensure all specifications were met, with three assembly processes reviewed during the inspection failing to meet the established setting.

The agency also faulted the company on its corrective and preventive action procedures, noting that the company standard operating procedures for CAPAs did not ensure problems were adequately handled.

The FDA also hit the firm on its document control procedures. Its SOPs did not properly ensure all documents used in the manufacturing areas are controlled.

On one occasion, investigators observed a Post-It Note with handwritten manufacturing steps attached to a printed procedure.

Read the Vital Connections Form 483 here: www.fdanews.com/06-22-18-vitalconnectionsinc483.pdf. — Zack Budryk

Failure Investigations and Root Cause Analysis

Q: *For lower priority CAPA issues, would it be better to employ some type of continuous quality improvement process to allow the engineers to go ahead with engineering change orders based on their own understanding of what's coming in terms of complaints and management reviews?*

A: Yes. It is important to make sure that constant ongoing processes, like continuous improvement processes, continue. Companies should not ignore so-called minor issues or small kinds of problems that don't occur frequently. Sometimes those things have a tendency to be the biggest issues in the long run. The key is to do good root cause analysis so that the engineers have something to base it on so that they can make the right decisions. The company's process, like most continuous improvement processes, would then go back and make sure that the correction has been successful.

The key is to be able to prioritize these things effectively. Companies should look for commonality across causes. Look for problems that are occurring in a number of places. Don't let CAPA drive everything. Good business practice needs to drive what companies do, and CAPA should be treated as an exception that companies have to address outside of their normal business practice. Build in good systems, good operations and good processes.

Q: *What happens if a company has a deviation related to a microbiological out of specification? How can it confirm the root causes?*

A: The company will probably have to do separate studies to confirm the cause of whatever excursion it found. If it was contamination, it can prove that by testing for whatever the contamination was and prove that it was the root cause. If it was environmental, the company may have to shut the area down and do some tests to confirm that it was, for instance, a problem with a bad filter in the HEPA filter system. But once the company establishes the root cause, if it doesn't really take the time to confirm it, it might not lead to the right corrective action.

Excerpted from the *FDAnews* management report: *Creating QSR-Compliant CAPA Systems: A Practical Guide for Devicemakers*.

FDA Updates Software Precertification Pilot Program

The FDA released version 0.2 of its Developing Software Precertification Program intended to allow the agency to more efficiently approve software as a medical device (SaMD) without risking patient health and safety.

The agency announced a pilot program in July 2017 and in September 2017 named nine participants selected for the pilot, including Apple, Fitbit, Johnson & Johnson, Pear Therapeutics, Phosphorus, Roche, Samsung, Tidepool and Alphabet's Verily (*IDDM*, Oct. 2, 2017).

Participants in the pilot program agreed to provide information on how they develop, test and maintain their software products and on their quality management systems. They also committed to being available for site visits from agency officials.

The FDA released its first working model of the program in April and it flagged the changes in the revised version. The agency plans to review the public docket every two weeks and to further refine the program to reflect the comments in future versions.

SaMD Definition

Version 0.2 clarifies the definition of SaMD as "software intended to be used for one or more medical purposes that performs these purposes without being part of a hardware medical device." A SaMD is "capable of running on general purpose (non-medical purpose) computing platforms," to include smart phones and watches, laptops, glucose meters and infusion pumps. The category includes in-vitro diagnostic (IVD) devices.

Software that is necessary for a hardware medical device to fulfill its intended medical purpose is not considered a SaMD, the agency said. Rather, a SaMD is "software that acts on data for a medical purpose." Medical devices such as MRI and ECG machines and general wellness devices collect data that can be used as input into a SaMD. Mobile apps that meet these definitions are also considered to be SaMD.

Version 0.2 distinguishes between organizations that have successfully marketed medical products and those that have not. The original version of the program proposed to include only companies that had already successfully marketed and maintained medical devices. However, version 0.2 states that the FDA's current thinking "reflects the belief that an organization of any size without a medical device or SaMD currently on the market should have the opportunity to deliver products for medical purposes as a pre-certified organization."

Despite this new thinking, no new companies have been added to the original nine that were selected to take part in the pilot project, FDA spokesperson Stephanie Caccomo told *FDAnews*.

Version 0.2 also adds new proposed elements for demonstrating excellence in order to obtain program precertification, including new performance indicators.

The FDA is seeking further comments from stakeholders on which elements of the program are likely to "provide confidence that an organization makes high quality products" and how to "provide a least burdensome approach for software organizations to identify their processes/activities and outcomes."

The agency expects to release version 1.0 of the program by December 2018.

See version 0.2 of the precertification program here: www.fdanews.com/06-21-18-Precertification.pdf. — Donna Scaramastra Gorman

BRIEFS

Saudi Arabia Changes Policies For Imported Devices, IVDs

Saudi Arabia's Food and Drug Authority eased import requirements for lower-risk devices in a move expected to reduce the time devices and IVDs may be held at ports.

The authority issued new guidance noting that lower-risk medical devices that are non-sterile no longer require formal registration.

The new requirements address labeling, shelf life and temperature requirements as well as general requirements for registering devices and IVDs in Saudi Arabia. The guidance says shipments that meet certain criteria relating to the importers' past compliance history may be cleared faster and without inspection.

Mexico Updates Electronic Advertising Recommendations

Mexico's Federal Commission for Protection Against Sanitary Risks (COFEPRIS) has revised some of its guidelines for advertising medical devices via social media.

Device manufacturers should submit proposed advertising to the agency before it is launched online. The regulatory authority recommended that companies designate digital experts to help manage in-house and third-party content.

Earlier this year, COFEPRIS announced it would deregulate many of its lower-risk devices, enabling earlier market access. The move also allows the regulator to focus on enabling earlier access for innovative devices (*IDDM*, Feb. 23).

APPROVALS

CleanCision System Earns CE Mark Approval

Prescient Surgical received CE mark approval for its CleanCision system designed to prevent surgical site infections.

The approval means that the system is now available to European hospitals that face high rates of surgical site infections in colorectal and other abdominal surgeries.

CleanCision uses both wound protection and irrigation in its retraction system, allowing it to actively clear harmful bacteria that invade incisions made during surgery.

MicroVention Gains Expanded Indications for Sofia Catheter

The FDA cleared an expanded indication for MicroVention's Sofia catheter designed for intracranial access.

The Sofia catheter is designed for precise delivery of multiple neurovascular therapies and is used for distal navigation, allowing it to provide support close to the site of treatment.

The device is now cleared for contact aspiration procedures to treat astute ischemic stroke. It received a CE Mark in the EU for the same indication in 2015.

AMG Receives CE Mark Approval For Biodegradable Stent

German-based medical device company AMG received a CE Mark for its Archimedes biodegradable biliary and pancreatic stent.

AMG's product is a fully biodegradable stent used for obstructed biliary or pancreatic ducts. It can potentially reduce complications that may arise from plastic stents and removal procedures.

The Archimedes stent degrades completely via hydrolysis in approximately 12, 20 or 77 days depending on its composition.

PerkinElmer's EuroImmun Cleared by FDA

The FDA gave 510(k) clearance to PerkinElmer's EuroImmun Crithidia luciliae immunofluorescence test (CLIFT) and CLIFT sensitive assays.

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

Approvals, *from Page 7*

CLIFT testing is important in detecting anti-double stranded DNA, one of the markers for the severe rheumatic autoimmune disease known as Lupus.

The EuroImmun's sensitivity helps reduce false negative results and improve confidence in lupus diagnoses.

Tilak Gains CE Mark Approval For Mobile Medical Videogame

Tilak received CE Mark approval for its therapeutic mobile videogame, Odysight, which triggers medical tests for follow-up of patients with chronic eye diseases.

The game, which is only available via prescription, monitors the evolution of visual parameters, such as near visual acuity, contrast sensitivity and the presence of scotomas or metamorphosis.

Using the medical mobile game app, the ophthalmologist can follow the patient in real time or during the consultation to track changes in the patient's visual parameters through an online dashboard.

B. Braun Receives 510(k) Clearance For Space Syringe Pump

B. Braun gained 510(k) clearance from the FDA for its Perfusor space syringe pump, a wireless device that offers interoperability in various care and transportation settings.

The pump is cleared for use with air and road transportation and has an integrated piston brake to help prevent unintentional delivery of medication when changing the syringe.

The device includes a microprocessor to allow for independent modular use, which helps prevent catastrophic pump failures and channel confusion.

BayLabs' Automated Ejection Fraction Software Cleared by FDA

The FDA granted 510(k) clearance to BayLabs' EchoMD AutoEF software for fully automated AI echocardiogram analysis used in cardiovascular imaging.

The software features fully automated clip selection and calculation for left ventricular ejection fraction — a calculation widely used for measuring cardiac function such as the heart's pumping efficiency that forms the basis for many clinical decisions.

The EchoMD AutoEF's algorithms remove the need to manually select clips and views, automatically manipulating them for quantification.

Neural Analytics Obtains CE Mark For Robotic Ultrasound System

Medical Robotics Company Neural Analytics secured CE Mark certification for its NeuralBot robotic ultrasound system.

The device can regulate its position and orientation with professional guidance, and can help physicians diagnose brain disorders, possibly without the need for more invasive testing.

It can be used with the Lucid M1 Transcranial Doppler Ultrasound System, a device that provides a platform for analyzing brain waveforms, to observe a patient's blood flow characteristics, which can be used to diagnose multiple neurological disorders.

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FDANEWS

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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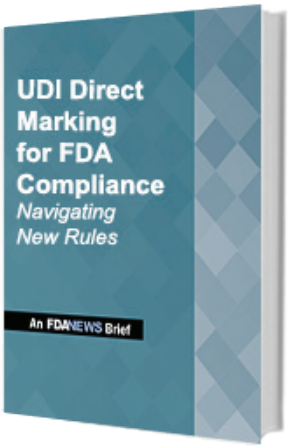

UDI Direct Marking for FDA Compliance: *Navigating New Rules*

Confused by the FDA's UDI direct marking regulations? What information should go on the label and the device itself? What methods of marking are acceptable? What's the difference between a device identifier and a production identifier? What additional requirements are placed on reprocessed devices?

The FDA's final guidance on UDI (unique device identification) raises as many questions as it answers. With full compliance for Class I, II and unclassified devices looming, lawyers are hard at work parsing the FDA's language.

Jay Crowley was the architect of UDI while at the FDA. Now a consultant advising devicemakers, he remains the go-to expert on UDI compliance. In the FDAnewsBrief, **UDI Direct Marking for FDA Compliance**, Crowley lays out a path to compliance. He explains:

- The technology necessary for creating and verifying bar codes
- The difference between direct marking and direct part marking
- How the rules apply to device components and accessories
- Exceptions to the direct marking requirements
- Record-keeping requirements
- Testing to make sure any direct mark doesn't affect the safety or performance of the device
- UDI requirements in the premarket submission stage.

Order your copy of the **UDI Direct Marking for FDA Compliance: *Navigating New Rules*** and receive guidance from the man who wrote the FDA's Unique Device Identification rules.

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