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EU, UK Seek Agreement On Notified Bodies

The European Union and the UK have yet to finalize an agreement in their Brexit negotiations on how to handle notified bodies.

Under the draft agreement, EU member states and the UK would "transmit without delay any request" from the market surveillance authorities of the UK or the member states, to "a conformity assessment body established in their territory that concerns a conformity assessment carried out by that body in its capacity as notified body before the end of the transition period."

But the negotiators are still working out details for making available information held by notified bodies established in the UK or in EU member states.

The current draft states that the UK shall ensure that, upon request by the certificate holder, information held by a conformity assessment body established in the UK in relation to its activities as a notified body under EU law before the end of the transition period

(See **Agreement**, *Page 2)*

FDA Issues First Required Inspections Report, Covering 2017

In its first required inspection metrics report for 2017, the FDA found a median time of 35 days between inspection requests by the FDA to device manufacturing facilities and the beginning of inspections, and a median of five days between the beginning of a pre-approval inspection and the issuance of a Form 483.

The median times were longer for both the time between the issuance of a 483 and enforcement action (191 days) and between the issuance of a 483 and a regulatory meeting (169 days), according to the report.

The annual report is newly required under last year's reauthorization of the agency's user fees. The agency said it interprets the law

(See **Inspections**, *Page 2)*

China's FDA to Merge into National Market Supervision Administration

In a reshuffle of regulatory authorities in China, the FDA will split into separate units for medical products and foods, with medical devices handled by the State Drug Administration within the National Market Supervision Administration (NMSA).

CFDA's Medical Device Standardization Committee just released a two-year work plan for medical device standards, with plans to revise more than 300 standards by 2020.

The standards will cover technical requirements for development, risk management, quality control and clinical trials.

The Medical Device Standards Management Center will oversee the assessment work.

The revisions are part of ongoing reforms including more stringent medical device standards, improved quality system management and oversight as well as improved inspections (*IDDM*, Feb. 16).

Agreement, *from Page 1*

"is made available to a notified body established in a Member State indicated by the certificate holder without delay."

Similarly, EU member states shall ensure that, upon request by the certificate holder, information held by a notified body established in the member state concerned in relation to its activities before the end of the transition period is made available to a conformity assessment body established in the United Kingdom indicated by the certificate holder without delay.

The Association of British Healthcare Industries is pushing for regulatory stability regarding UK notified bodies and UK-based authorized representatives, but there is uncertainty over their status post-Brexit given the "intense pressure from a European Commission seemingly intent on sticking to its rigid set of negotiating objectives," according to BMI Research.

Points of disagreement between the Commission and the UK include intellectual property and registration procedures, restricted use of data and other matters related to judicial procedures and free movement of goods.

"Post-Brexit uncertainty will continue to impact the medical device market as companies face the prospect of increased business costs due to new border arrangements and regulatory divergence if the UK exits the single market," BMI said.

One UK-based notified body, BSI, has applied for notified body designation in the Netherlands, while Intertek has opted to close its UK AMTAC operations and focus on its notified body activities in Sweden.

Read the European Commission's update on the draft agreement here: www.fdanews.com/03-27-18-notifiedbodies.pdf.

Inspections, *from Page 1*

to require it to publish information with respect to pre-market approval submissions. The agency's interpretation limited the report to Official Action Indicated meetings, omitting those it classified as Voluntary Action Indicated.

The report found the FDA filed no resolutions for compliance actions for facilities issued a Form 483 resulting in a warning letter, regulatory meeting or import alert. The agency said it delayed five premarket approval application approvals from devicemakers due to the issuance of a Form 483.

PMA approvals can also be withheld when the agency performs a PMA inspection or a non-PMA inspection and issues a Form 483 resulting in a decision by CDRH to withhold approval until the issues are resolved.

Read the full report here: www.fdanews.com/03-28-18-FDARA.pdf. — Zack Budryk

GUDID Database Mostly Contains Class II and Implantable Devices

Nearly 80 percent of the 1.6 million medical devices registered in the FDA's Global Unique Identification Database are Class II medical devices and nearly half are implantable devices, the FDA reported.

Roughly 43 percent of medical devices fall under this category and include devices such as powered wheelchairs and pregnancy test kits.

Approximately half of the devices in the database are implantable devices, the FDA said in a new report.

Of the implantable devices in the database, more than 35 percent are orthopedic devices, followed by dental devices, general and plastic surgery devices, cardiovascular, and general hospital devices.

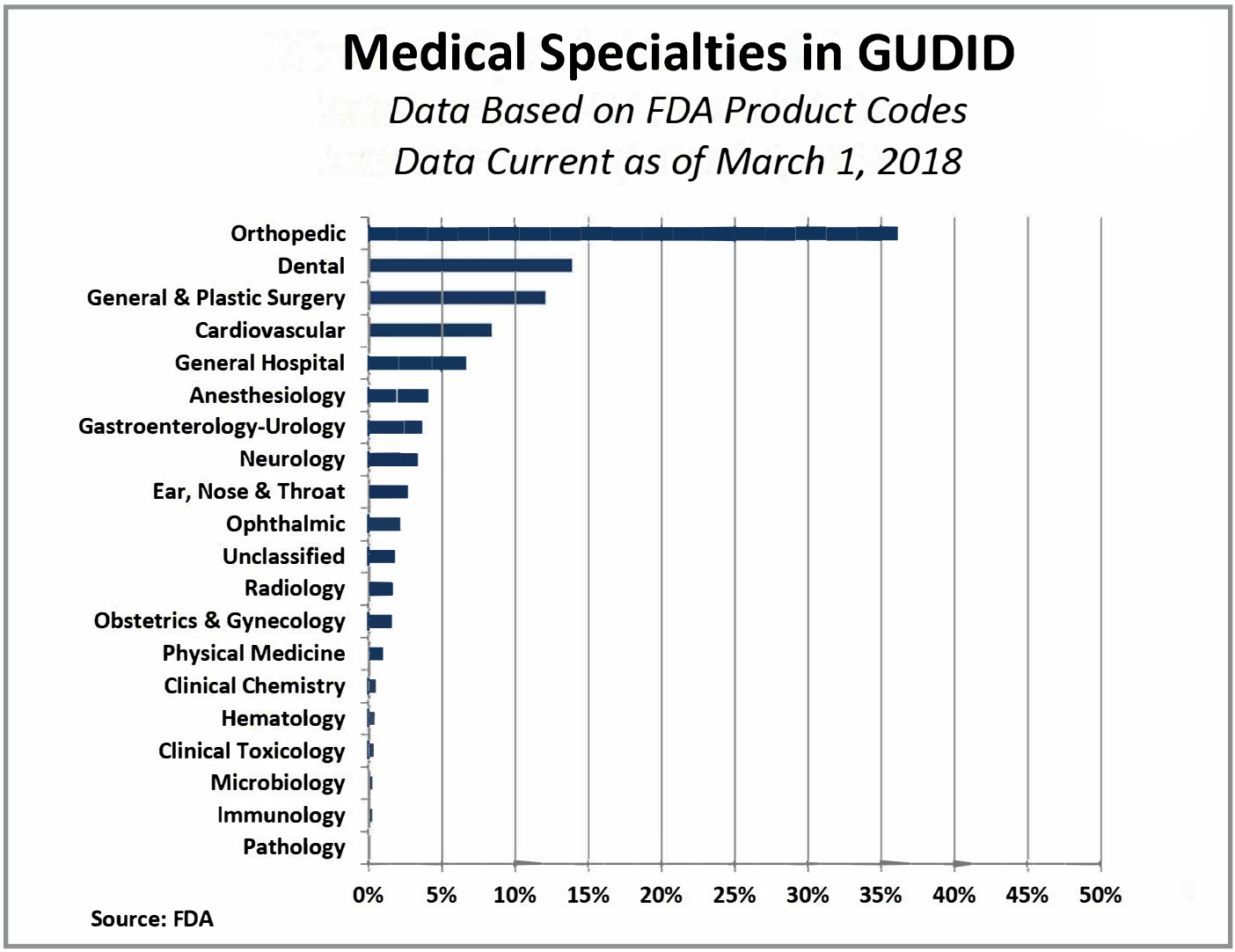
Devicemakers are required to submit data to the Global Unique Device Identification Database under the unique device identification (UDI) system requirements to better identify and track medical devices.

"The UDI will function as the key that can be used to obtain critical information from the GUDID about the medical product," the FDA said. The database only includes information that is important to identify devices and not information that would identify patients.

The FDA is updating the database so UDI labelers will have the ability to unlock their device identification records to make error corrections.

In summer, the FDA will release premarket submission and supplement numbers into the database.

(See **GUDID**, *Page 4)*



Alere Settles False Claims Suit for $33.2 Million

Massachusetts-based medical device manufacturer Alere and its subsidiary Alere San Diego agreed to pay the United States more than $33 million to resolve False Claims Act allegations that Alere knowingly sold unreliable point-of-care diagnostic testing devices to hospitals.

According to lawyers for the Department of Justice, Alere sold the Triage testing devices between 2006 and 2012 despite customer complaints that the devices produced erroneous results. The devices were frequently used by emergency departments to conduct blood and urine tests to aid in the diagnosis of acute coronary syndromes, heart failure and drug overdose.

The DOJ contended that Alere knew some of its devices produced faulty results, adversely affecting clinical decision making and leading to unnecessary medical interventions, but the company failed to take corrective measures until an FDA inspection in 2012 prompted a nationwide product recall.

In that 2012 inspection, the FDA found statistically significant disparities between the actual device specifications and the specifications listed on the product labeling. Inspectors also found a high degree of variability when conducting quality control testing of the devices and changes to manufacturing that resulted in the release to market of some product lots with significantly decreased precision.

"Physicians who work to treat patients with suspected myocardial infarctions rely upon devices such as Alere's Triage Cardiac products for quick and accurate readings," said Stephen Schenning, acting U.S. attorney for the District of Maryland. "When manufacturers such as Alere make changes to the specifications that affect the product's reliability without informing physicians or the FDA, patient care is put at substantial risk."

The lawsuit was filed in 2011 under the whistleblower provision of the False Claims Act of 1863, which permits private parties to file suit on behalf of the United States for false claims. Successful whistleblowers can receive 15 to 30 percent of the government's recovery.

The suit was filed by Amanda Wu, formerly a senior quality control analyst at Alere San Diego. As part of the settlement, she will receive approximately $5.6 million.

Alere was acquired by Abbott Laboratories in 2017. Abbott disclaimed any liability, stating that Alere had already agreed to settle the case prior to its acquisition last year.

The DOJ noted that the claims resolved by the settlement are allegations only, and there was no determination of liability.
— Donna Scaramastra Gorman

GUDID, *from Page 3*

Higher-risk Class III devices are already required to comply with the new UDI requirements as are most Class II devices. The compliance deadline for some Class II devices was pushed back to September 2018.

The FDA issued guidance for manufacturers of Class I and unclassified medical devices in January on compliance dates for meeting UDI requirements. For the standard date formatting, labeling and GUDID data submission requirements, the compliance date is Sept. 24. For UDI direct mark requirements, the compliance date is Sept. 24, 2020.

These differ from the agency's enforcement dates, however. The FDA does not intend to enforce UDI labeling, GUDID data submission or standard date format requirements for Class I and unclassified devices manufactured or labeled on or after Sept. 24, 2018 until Sept. 24, 2020.

For devices manufactured or labeled before the compliance date, the enforcement date for these requirements is set for Sept. 24, 2021, as the FDA is required to provide a three-year transition period for finished devices (*IDDM*, Jan. 8).

Read the FDA report here: www.fdanews.com/03-27-18-GUDID.pdf.

483 Roundup: FDA Cites Devicemakers For Inadequate CAPAs, Investigations

The FDA flagged two U.S. facilities and one in Germany for a variety of deficiencies including CAPA failures and investigations of nonconforming products.

HQ: Inadequate CAPA procedures and failure to investigate failures of the CorTemp ingestible core body temperature sensor devices landed devicemaker HQ a Form 483 following a September 2017 FDA inspection of its Palmetto, Florida facility.

The FDA inspector noted that the firm failed to initiate corrective and preventive actions on at least four occasions for high numbers of nonconforming products.

Nonconforming products were not discussed in meetings and the facility had no records of an investigation of environmental control conditions that may have affected electrostatic discharge. Records didn't indicate whether there was an investigation to determine if component suppliers made changes to the product or whether they failed to control their production processes.

At least six of 11 complaint records failed to document a complete investigation into the malfunctioning CoreTemp devices. In a few cases the investigation was limited to a review of the device history records, and a few potential causes for the failures were listed but apparently were not followed up. This was a repeat observation from a July 2012 inspection.

The firm was cited for failing to develop written procedures for medical device reporting as well as failing to control products that didn't conform to specifications. The FDA inspector said the firm was not taking measures to prevent damage to sensitive electronic components from electrostatic discharge, and the acceptance status of products was not identified to indicate conformance or nonconformance with acceptance criteria.

The inspector observed documents in the production workflow that had not been approved. The 483 noted that a production employee said the procedure had not been formally approved yet but it was being used for current work

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

Gathering Information on Complaints

Since frontline employees often field the initial complaint, they should receive training in how to gather information for the investigation that will follow.

The following questions are important when investigating a complaint:

- Who is providing the information?
- What happened?
- Did the device malfunction?
- Was the patient injured?
- Was the event (or clinical study) related to the device?
- What was the severity of the injury?
- How was the issue resolved?
- What was the device lot or batch number?
- Was the device reprocessed?
- Had the device reached the end of its life? and
- Is the device available for analysis?

The more information employees can dig out, the better the company will be able to resolve the issue. If the problem is the result of user error or misuse of the device, the whole picture can change.

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

483s, *from Page 5*

instruction. This was also a repeat observation from the 2012 inspection.

Maico Diagnostics: Maico Diagnostics received a Form 483 following an October 2017 inspection for its failure to have a formally designated unit to handle complaints, quality audits and procedures for design review.

Complaints involving possible failure of devices to meet any of their specifications were not reviewed, evaluated or investigated, the 483 said. For example, a number of failures were noted and closed without any investigation or analysis of service records.

The firm's complaint handling procedures didn't require that complaints be handled in a uniform and timely manner, and they didn't require information on whether the device is used for treatment or diagnosis. Complaint procedures didn't require a unique device identifier or universal product code.

In addition, the written medical device reporting procedures didn't include an internal system for identifying events that may be subject to MDR requirements.

Finally, the firm had not established procedures to conduct quality audits to be sure it was in compliance with quality system regulations. The 483 noted that Maico had "an extensive backlog of unresolved complaints and servicing records from 2016 to 2017."

Unique Instruments: Mississippi's Unique Instruments racked up a nine-item Form 483 for numerous quality system failures observed at its Bridgeport facility during an October 2017 inspection.

The sterile packaging process was not properly validated for the company's Paradigm Spine Coflex Interlaminar devices. For example, during the installation qualification conducted in 2015, not all preventive maintenance requirements were completed. Inspectors noted that during the operational qualification the temperature range was limited, and the firm was unable to provide objective evidence that packages were sealed at the parameter settings defined in the protocol.

The 483 said the firm failed to establish procedures for monitoring and controlling process parameters for a validated process, procedures to control environmental conditions and corrective and preventive actions.

One of the firm's operators told inspectors that when an in-process inspection failed to meet specifications, the initial failed result and the reason for scrapping devices were not documented.

Read the HQ Form 483 here: www.fdanews.com/03-29-18-hqinc483.pdf.

Read the Maico Diagnostics Form 483 here: www.fdanews.com/03-29-18-maicodiagnosticgmbh483.pdf.

Read the Unique Instruments Form 483 here: www.fdanews.com/03-29-18-uniqueinstrumentsinc483.pdf.

IMDRF Undertakes New Clinical Evaluation Project Proposed By China

China's Food and Drug Administration reported that International Medical Device Regulators Forum (IMDRF) members unanimously supported China's proposal for a new work item on clinical evaluation of medical devices — presented during the March 20-22 IMDRF meeting in Shanghai.

The proposal calls for international collaborative research on basic requirements for clinical trial decisionmaking, requirements for clinical evaluation and accepting data from overseas clinical trials. It is the first proposed project China has submitted to IMDRF.

Read the CFDA notice here: www.fdanews.com/03-27-18-China.pdf.

APPROVALS

Edwards Lifesciences Granted De Novo Request for Acumen HPI Software

The FDA granted Edwards Lifesciences its De Novo request for the company's Acumen hypotension prediction index (HPI) software, technology that uses predictive analytics to indicate the presence of potential low blood pressure before it occurs in surgical patients.

The Acumen HPI uses software algorithms to assess cardiovascular vital signs and predict future cardiovascular status. The HPI feature is part of the Edwards Accumen intelligent decision-support software suite and is used with the minimally invasive FloTrac IQ sensor.

Harmonus' ProBx Software Granted 510(k) Clearance

The FDA gave Harmonus' ProBx software 510(k) clearance for use in MRI-guided prostate interventions.

The software targets and confirms suspicious lesions and creates a detailed record of sampling locations, allowing the doctor to monitor the lesions and treat them.

It is attached to an MRI console and receives digital images that can be displayed in 2D and 3D.

Iridex Probe Earns CE Mark

Iridex's G-Probe Illuminate was cleared for marketing in Europe, offering both transillumination and laser fiber for targeted transscleral cyclophotocoagulation (CPC).

It is the company's third probe powered by the CYCLO G6 glaucoma laser system, and features built-in transillumination that optimizes the probe's placement. The device helps physicians deliver more targeted laser treatment.

Advantis' Cloud-Based Neuroimaging Software Receives CE Mark

Advantis received a CE Mark for its Brainance MD cloud-based neuroimaging software used for advanced processing of brain magnetic resonance images.

The software analyzes various types of images including diffusion tensor imaging, dynamic susceptibility contrast perfusion and functional MRI, in an integrated user environment.

Brainance is accessible from a web browser and supports collaborative analysis. It is compatible with picture archiving and communication (PAC) systems and the digital imaging and communications in medicine (DICOM) standard.

FDA Gives Life Spine Clearance for Plateau-Lo

Life Spine received 510(k) clearance for its Plateau-Lo insert and rotate spacer system, used for micro-invasive lumbar interbody fusions.

The product combines with the company's AVATAR percutaneous screw system and its CENTRIC-T pedicle-based retractor system for use in micro-invasive procedures.

Plateau-Lo features an aggressive tooth pattern that prevents graft migration, a bullet tip for simple insertion, and large, open graft windows to contain bone grafts and maximize visibility.

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

Approvals, *from Page 7*

Balt USA's Optima Coil System Granted 510(k) Clearance

The FDA granted Balt USA 510(k) clearance for its Optima coil system, a product used in the treatment of aneurysms.

The system consists of a coil, pusher and instantaneous thermal detachment system, and has moved to full market release in Europe and a limited market release in the U.S.

The Optima provides physicians a soft coiling and rapid detachment system to help treat complex aneurysms.

Additional Clearance Awarded to Cook Medical Endomicroscopy System

The FDA granted further 510(k) clearance to Cook Medical's Cellvizio confocal laser endomicroscopy (CLE).

The probe-based CLE system uses laser scanning technology to create real-time images of internal tissue microstructure.

The new indication allows the product to be used for *in vivo* imaging of the internal microstructure of tissues, helping urologists identify cells, vessels and their architectures during endoscopic procedures.

Agendia's MammaPrint BluePrint Kit Obtains CE Mark

Irvine, California-based Agendia received a CE Mark for its next-generation sequencing-based MammaPrint BluePrint breast cancer recurrence and molecular subtyping kit.

MammaPrint analyzes 70 genes most connected with breast cancer recurrence to determine a low or high risk of cancer recurrence result, while BluePrint analyzes 80 genes which classify a patient's breast cancer into functional molecular subtypes.

The device can aid physicians in personalizing treatment management for patients by identifying early-stage breast cancer in women that is at a genomic low or high risk for distant metastasis within five years.

Longhorn Vaccines and Diagnostics' PrimeStore Cleared by FDA

The FDA granted 510(k) clearance for Longhorn Vaccine's PrimeStore molecular transport medium, designed to inactivate pathogens and stabilize RNA and DNA for downstream molecular testing and characterization.

PrimeStore is used for stabilization, transportation and inactivation of infectious unprocessed nasal washes thought to contain influenza A virus RNA. It is also intended to do the same for infectious unprocessed sputum samples thought to contain Mycobacterium tuberculosis DNA from human samples.

The molecular transport device can accelerate efforts to identify and control seasonal, pandemic and endemic diseases like influenza and M. tuberculosis.

Orthofix Wins 510(k) Clearance For G-Beam Fusion Beaming System

The FDA gave Orthofix's G-Beam fusion beaming system clearance for the treatment of the debilitating condition Charcot foot where bones in the foot weaken and collapse.

The G-Beam devices can be implanted in the affected foot's medial and lateral columns to give alignment, stabilization and fixation.

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Medical Device Calibration: *A Step-by-Step Guide to Meeting FDA and ISO Standards*

Warning letter citing calibration failures are on the rise — indicating that the FDA is paying more attention to the issue.

Both the FDA and ISO have specific requirements for calibrating medical devices. And — they don't always line up. So devicemakers doing business in the US and abroad need a clear path to compliance if they want to avoid penalties.

Medical Device Calibration: *A Step-by-Step Guide to Meeting FDA and ISO Standards* provides a roadmap that walks devicemakers through each aspect of calibration requirements — showing where the FDA and ISO differ and where they match up — and explains how to combine them to endure full compliance.

You will learn:

- The role of monitoring and measuring in a medical device Quality Management System (QMS)
- Requirements for calibration in FDA's Quality System Regulation
- How to distinguish between accuracy and precision
- The role of traceability in a calibration program
- The audit requirements in both QSIT and MDSAP

The report defines key terms and concepts involved in calibration including proving that calibration practices can be traced back to recognized national and international standards.

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Regenerative Medicine: *Steps to Accelerate Development*

With the 21st Century Cures Act, attention is being focused on the use of human cells and tissue to treat serious and underserved conditions.

The FDA created a new regulatory paradigm in November 2017 when it issued four guidances — 2 final and 2 draft — aimed at explaining, streamlining and accelerating development of regenerative therapies.

Key among these developments is the creation of a new Regenerative Medicine Advanced Therapy (RMAT) designation that offers applicants an abbreviated pathway to approval, working closely with the FDA throughout the process.

Regenerative Medicine outlines the RMAT pathway and breaks down requirements regenerative medicine developers must meet to qualify. The FDA granted RMAT designation to 12 organizations in 2017 — the first year of the program. Now is the time to get in the mix, work with the FDA to develop the program and improve your chance of being one of the next RMAT designees.

You will learn:

- Key definitions the FDA uses in evaluating regenerative medicine applications
- Requirements to be eligible for RMAT designation
- How to apply for RMAT designation
- How the final versions of the Same Surgical Procedure and Minimal Manipulation guidances differ from their drafts

Order your copy of **Regenerative Medicine: *Steps to Accelerate Development*** and learn what it takes to get in on the ground floor of the new approval pathway and use it to accelerate your road to market.

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