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EU Device Regulations Advance, As Trilogue Members Agree to Updates

It's the final countdown for those long-awaited updates to regulations governing medical devices and in vitro diagnostics in Europe.

Last week, the Netherlands presidency of the Council and representatives of the European Parliament reached an agreement for the new rules that, among other things, seek to improve the quality of notified bodies.

Many in industry thought progress on the trilogue would be swifter after the European Council gave the green light to its MDR and IVD legislative proposals (*IDDM*, June 22, 2015). Now, however, industry has some clarity on a path forward.

While the updates are subject to the approval by the Council's Permanent Representatives Committee and Parliament's Environment, Public Health and Food Safety (ENVI) Committee, publication is expected this year.

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FDA Adcomm Gives Thumbs Up To St. Jude's Amplatzer

Despite clear data shortcomings, an FDA advisory committee half-heartedly recommended approval in an 11 to 5 vote for St. Jude Medical's heart closure device Amplatzer to treat stroke.

The panel homed in on the problems and limitations of the RESPECT trials, stating the eight year study was statistically underpowered and therefore clinically invalid. Specifically, the studies failed to show a reduced rate of strokes for patients implanted with the Amplatzer compared to antiplatelet therapy.

Panelists also highlighted the change in clinical trial design between 2000 and 2016, noting that the methods and procedures used underpowered the trial, and a new study with tighter parameters should be conducted.

But Bram Zuckerman, director of the Division of Cardiovascular Devices said the FDA was not going to "throw the baby out with the

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Gert Bos, executive director and partner at Qserve Group, told *IDDM* that the trilogue process should make for a smooth path for the regulations. "So, the anticipation is that besides some minor remarks, they [should] go through smoothly."

Notified bodies already have faced intense scrutiny, with many already exiting the arena. Bos said that there are unofficially fewer than 50 left. NANDO, the EU's database of Notified Bodies, lists 60, but experts in Brussels are saying there could be as few as 40 left by the end of the year, he added.

"Most of them will apply for the MDR, and as a first round of joint assessment has been done," with most expected to make the transition, he told *IDDM*. Initially, there will be an estimated 25 to 30 notified bodies under the MDR.

At last fall's Regulatory Affairs Professional Society Convergence Conference in Baltimore, Md., Bos told attendees that 25 percent of notified bodies have stopped operations ahead of the regulations. He added that it isn't outside the realm of possibility that another 25 percent could disappear (*IDDM*, Nov. 9, 2015).

Even after the next round of approvals, there could be further delay, as the regulations will need to be translated into all EU languages. That process could take some time, Bos told *IDDM*. If the ENVI committee approves it in August, it is likely to be published this year, he said. However, industry still could see a Q1 2017 publishing date.

Despite this potential delay, Bos had nothing but praise for the negotiators and Dutch presidency, particularly as there were some "fundamental debates" over IVD regarding genetic testing and counseling.

"Earlier in the year there still was a lot of ground to cover," Bos told *IDDM*. "The last two Trilogues in May were mainly focusing on transition and IVD, so generally people were anticipating at least the MDR to go through."

Serge Bernasconi, CEO of industry group MedTech Europe, acknowledged the importance of the updates, adding that the implementation will require "substantial resources from all stakeholders." However, he emphasized the importance of keeping "the overarching goals of patient safety and innovation in mind during the translation into implementable rules."

Senate Requests Performance Data from FDA on De Novo Devices

A Senate appropriations committee is requesting the FDA to provide documentation on *de novo* device approvals, classifications and postmarket surveillance standards.

The committee said it was concerned that the agency is not providing information on how it is meeting timelines established by Congress.

Under a manager's amendment to the 2017 Agriculture/FDA Appropriations bill, the Senate Appropriations Committee requested the FDA to report back to Congress in 90 days on:

- The number of *de novo* requests submitted to the FDA;
- The number of requests for 513(g) risk classifications of devices and the number the agency has met the 60-day requirement;
- The number of orders for postmarket device surveillance under Sec. 522 for which the agency has responded within 60 days.

Last year, during the MDUFA IV Session, the agency admitted to meeting its 120 day target for 40 percent of de novo applications (*IDDM*, Nov. 16, 2015).

Earlier this month the agency finalized guidance on its Section 522 surveillance program (*IDDM*, May 16).

The bill can be found here: www.fdanews.com/05-26-16-2017AgricultureAppropriations-Bill.pdf. — Joya Patel

Industry, FDA Hammer Out MDUFA IV Programs

Devicemakers and FDA are inching towards an agreement over MDUFA IV goals, but industry says additional resources and infrastructure are needed to achieve those goals.

AdvaMed, MDMA and MITA presented proposals that would provide FDA with $680 million including inflation to meet FDA's current performance goals, plus an additional $131 million spread over five years to support the 91 FTE's needed.

FDA acknowledged that industry's proposals were a step in the right direction but the agency didn't address additional resources or staffing, according to MDUFA meeting minutes posted on the FDA's website May 26.

Industry's proposal lies in bulking up FDA's workforce to improve on the time it takes the agency to reach decisions on 510(k) and PMA applications by the end of 2022.

The proposal included resource estimates for several areas, including pre-submissions, quality management, total product life cycle, *de novo*, CLIA waivers, independent assessments, IT improvements, recruitment, third-party review programs, digital health, and standards.

Industry did not address real world evidence, patient engagement and manager incentive pay proposals, and stakeholders said they needed more information to address these topics, meeting minutes indicated.

Furthermore, industry proposed an additional $6 million for an "independent assessment" of the review process; $4.5 million for development of a "myDevices" portal for device sponsors as proposed by ACLA; $2.5 million to improve FDA's recruiting processes through external recruiters; and $4 million to boost the agency's third-party premarket review program.

FDA stressed that industry's proposal was incomplete based on the agency's estimated analysis of prior program performance and trends.

The agency also said that industry did not include IT operating dollars in their resource estimates. FDA said that without user fee support for the necessary changes to legacy IT systems, FDA would not be able to implement IT changes for the review program to reflect MDUFA IV processes and performance goals.

View the meeting notes here: www.fdanews.com/05-27-16-427MDUFAIVMeetingNotes.pdf. — Joya Patel

J&J Hit With Lawsuits Over Alleged Pelvic Mesh Injuries

Johnson & Johnson is facing lawsuits in two states that allege the company engaged in deceptive marketing claims for "new and revolutionary" surgical mesh used to treat women with pelvic organ prolapse.

Attorneys general in California and Washington announced the separate suits last week that hit the company and its Ethicon unit for distributing deceptive informational and marketing materials to consumers and doctors.

These materials included consumer brochures and radio and television ads, Washington State AG Bob Ferguson said during a press conference.

The products in question are the Prolene Mesh/Prolene Soft Mesh, Gynemesh, Gynemesh PS, TVT, TVT- 19 Obturator, TVT-SECUR , TVT Exact, TVT Abbrevo, Prolift, Prolift+M, 20 Prosima, Artisyn and other polypropylene mesh products.

Washington State's Allegations

In their lawsuit, filed in the King County Superior Court, Washington officials maintain that the company was aware that the polypropylene threads that make up the mesh — coupled with the process of implanting mesh through the vagina — could lead to "unavoidable

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bath water," and nullify all the work done in the RESPECT trials. Instead, the agency would coax out what was learned from the trial about individualized risk-factors, he said.

"There is no single standard of care antithrombotic medical therapy to reduce the risk of recurrent stroke in patients with cryptogenic stroke," the FDA said in briefing documents.

The agency added that the use of multiple combinations of anti-thrombotic agents also presented challenges in "defining the probable benefits of the device versus medical therapy."

The patent foramen ovale (PFO) occluder is intended to put a stopper on blood shunting across the PFO, which can potentially lead to recurrent ischemic strokes.

In spite of heated debate over the indication and patient population, the committee ultimately agreed that the Amplatzer should be restricted to percutaneous, transcatheter closure of a PFO to prevent recurrent ischemic stroke in patients who have had a cryptogenic stroke due to presumed paradoxical embolism.

Members of the agency's Circulatory Systems Devices Panel of the Medical Devices Advisory Committee also voted on the safety, effectiveness and risk to benefit ratio for the device. The panel voted 15 to 1 on the safety, 9 to 7 on the effectiveness and 11 to 5 stating the benefits outweighed the risks.

The FDA identified several major problems with the Amplatzer study, stating "missing data is more influential than the data presented."

The panel said its approval should be contingent upon the FDA and sponsors conducting additional work to identify the selective group of patients who would benefit most. The group also recommended adding rigorous criteria on the proposed label as well as further postmarket analysis.

Earlier this month, panel chair Richard Page was granted a waiver to participate in the advisory committee meeting as a non-voting participant (*IDDM*, May 16). Page said he would have voted in favor of the safety of the device, but would have voted no for effectiveness and risk versus benefits.

The RESPECT study began in 2003, enrolling 980 patients who were randomized to either PFO closure or medical therapy alone. The patients were followed up for 2.5 years, and showed a 51 percent reduced risk of recurrent stroke in the device group.

St. Jude inherited the device when it acquired AGA Medical in 2010. There is little doubt the news will be greeted by Abbott, which agreed to acquire St. Jude Medical for $25 billion in a cardiovascular device market megamerger earlier this month (*IDDM*, May 2). — Joya Patel

Renovis Surgical Warned Over Quality System Violations

Renovis Surgical Technologies received a strong warning from the FDA over its failure to conform to quality system regulations covering design verification, process validation, product development requirements and risk analysis.

The Redlands, Calif.-based company is an original equipment manufacturer of spinal implants, hip and knee replacements and surgical instruments.

The May 5 warning letter cites the OEM for failing to confirm that design output meets design input requirements during design verification. The firm's titanium stand-alone anterior lumbar fusion cage did not contain documentation to support the firm's design verification conclusions.

Specifically, there was no documentation to confirm that the contract manufacturer performed validation activities, and documentation covering sterilization validation was inadequate.

The warning letter notes similar examples of failure to document testing to confirm that design outputs met design inputs.

Risk analysis was also found lacking for the lumbar device because the firm did not reference cleaning and sterilization validation studies even though the design history file requires risk activities due to potential risk of infection.

FDA Warns German Diagnostics Maker Qiagen For TB Test Failures

The FDA issued a scathing warning letter to Germany-based Qiagen for numerous quality system failures related to its QuantiFeron TB test.

During an inspection at the firm's Hilden, Germany plant Feb. 26 to April 8, inspectors noted that multiple CAPAs were opened due to repeated complaints for high false positive readings for the TB test.

The firm implemented corrective actions but they weren't effective because the contract manufacturer wasn't able to meet the new specifications, and there was no endotoxin specification change, the May 16 warning letter notes.

It also notes that another CAPA was opened due to endotoxin contamination found in two lots of blood collection tubes, which could lead to false-positive results.

The agency also chided the firm for not establishing adequate controls for suppliers and contractors, noting that the firm's contract manufacturer did not have adequate process validation procedures in place. The firm's response was also deemed inadequate because it did not address any updated quality requirements with the contract manufacturer to ensure that appropriate endotoxin levels could be met.

Inspectors also found fault with the firm's design change procedures in that design output for the TB test was changed but a design change was not opened and the specification was not verified. There also was no verification for the Nil blood collection tube.

The warning letter also slammed the company for not adequately investigating complaints. It notes that despite numerous complaints over the false-positive tests, tube lot information was obtained for only 12 of the complaints.

Qiagen also failed to submit medical device reports to the FDA within 30 days as required by 21 CFR 803.50. The agency also dinged the firm for failing to submit a written report to the FDA of a correction or removal of a device. — Tamra Sami

WHO Creates Device Regulatory Blueprint for Developing Nations

The World Health Organization has published a model regulatory guidance for medical devices and IVDs intended to support developing nations that have yet to develop regulations covering medical devices.

The model counsels on basic regulatory requirements such as registration of medical devices, listing of medical devices and postmarket controls; it is geared towards a country's regulatory authority and does not detail responsibilities of other stakeholders.

Importantly, it provides groundwork for principles, harmonized definitions, regulatory authority and fundamental elements for regulating medical devices.

The framework draws from guidance documents developed by the Global Harmonization Task Force (GHTF) and its successor, the International Medical Device Regulators Forum (IMDRF) (*IDDM*, Oct. 26, 2015).

The model consists of five chapters that address the following premarket and postmarket areas, including:

- Using the guidance in conjunction with current regulations;
- Distinguishing risk classes and principles of design, manufacturing, and performance for a medical device regulator;
- Setting up methods for effective GMPs;
- Detailing a stepwise approach to implementing and enforcing regulatory controls and practice through a trusted regulatory system; and
- Providing a list of things to consider and how to address these topics when developing and implementing regulations.

WHO intends to finalize the plan by the end of the year; public comments can be submitted until June 20.

Read the guide here: www.fdanews.com/05-26-16-WHODraftMedicalDeviceRegulatoryFramework.pdf. — Joya Patel

J&J, *from Page 3*

complications," including loss of sexual function and painful intercourse.

"For more than a decade, Johnson & Johnson misrepresented the risks associated with [its] products," said Washington State AG Bob Ferguson during a press conference. "This is an important consumer protection case because of how harmful these misrepresentations were."

State Seeks Penalties

He told reporters that the state was alleging tens of thousands of violations. The state is asking the court to prohibit J&J from using the misleading marketing and seeking the maximum penalty of $2,000 for each violation.

The defendants sold roughly 12,000 such devices in Washington between 2005 and 2015, according to the lawsuit.

While there are no hard figures on the number of women who suffered complications from the mesh, Assistant AG Lisa Erwin said there was a complication rate of 30 percent.

She acknowledged that California was considering suit and that other states "are considering their options in terms of litigating."

Ferguson said J&J was aware that the state had been conducting an investigation and tried to resolve the dispute. However, Ferguson said he wasn't satisfied with J&J's offer to resolve the claims.

California AG Kamala D. Harris made a similar allegation against the company, saying it denied women the chance to make a well-informed choice about their health.

That suit has been filed in the Superior Court of the State of California for the County of San Diego. According to California AG Kamala D. Harris, 42,000 were sold in California between 2008 and 2014.

Read the California lawsuit here: www.fdanews.com/05-30-16-calif.pdf and the Washington lawsuit here: www.fdanews.com/05-30-16-washington.pdf.

FDA Reclassifies Cardiovascular Compressor Devices

The FDA is reclassifying external cardiac compressors from Class III, which requires premarket approval, to Class II devices.

Cardiopulmonary resuscitation (CPR) aids, will also be reclassified from Class III to Class II, according to a final order issued May 25.

Reclassification of both devices is supported by their safe history of use and the need for such devices in situations with inadequate access to professionally trained rescuers.

The FDA also revised the device labeling special controls section to clarify intended use as an addition to manual CPR.

The agency proposed a reclassification of the devices in January 2013, requesting comments from industry stakeholders. In September 2013, the Circulatory System Devices panel recommended the devices be reclassified into Class II. The committee recommended CPR aid devices without feedback be reclassified into Class I because general controls were sufficient.

FDA refined special controls by adding requirements for automated ECC devices, including performance testing of the time necessary to deploy the device and additional labeling requirements.

Manufacturers of ECC devices and CPR aid devices with feedback that have not been legally marketed prior to the effective date of the final order, or models that have been legally marketed but are required to submit a new 510(k) must demonstrate compliance with the special controls included in the final order, before marketing the new or changed device.

The final order can be found here: www.fdanews.com/05-25-16-ReclassificationCardiovascularDevices.pdf. — Joya Patel

Edwards Lifesciences Victorious In CardiAQ Spat with Neovasc

A U.S. district court awarded CardiAQ $70 million in its suit against former service providers Neovasc, for allegedly stealing the company's technology.

Originally filed in June 2014, the lawsuit accused Neovasc of using CardiAQ's technology to develop its Tiara transcatheter mitral valve replacement (TMVR).

CardiAQ hired Neovasc in 2009 to provide tissue processing and valve assembly services for its TMVR program, and Neovasc signed a non-disclosure agreement covering the technology.

During the contract period, Neovasc began developing its own TMVR program without disclosing its actions to CardiAQ, court records from the U.S. District Court for the District of Massachusetts show.

In response, CardiAQ sued the company in late 2011, after it discovered that Neovasc filed a patent for its technology. The suit accused Neovasc of deceitful business practices and theft of proprietary technology.

The jury found Neovasc guilty of breaching the non-disclosure agreement, misappropriating CardiAQ's trade secrets, intentionally using deceptive trade practices, fraud and breaching its partnership with CardiAQ, according to court documents.

A judge is expected to decide whether CardiAQ founders should be added as inventors to Neovasc's TMVR patent.

If the founders are added to the patent, Neovasc will have to create a license agreement with Edwards to commercialize the device. This could potentially result in Neovasc paying 25 percent royalties to CardiAQ. Neovasc is seeking an appeal.

The lawsuit was inherited by Edwards when it acquired CardiAQ Valve in August 2014 (*IDDM*, Sept. 5, 2015).

Read the case file here: www.fdanews.com/05-25-16-CardiAQCase.pdf. The jury's verdict can be found here: www.fdanews.com/05-25-16-CardiAQCaseVerdictForm.pdf. — Joya Patel

BRIEFS

Health Canada Updates Essure Labels

Health Canada is working with Bayer to update labels and increase monitoring of its Essure birth control implant.

In the U.S., more than 25,000 women reported symptoms — including extreme pelvic and abdominal pain, migraines, loss of teeth and hair, and the coil cutting into the uterus and other organs in the abdominal cavity — and 10,000 have filed formal complaints with the FDA.

In February, the FDA completed its investigation of Essure, ordering Bayer to conduct a 2,000 patient postmarketing study, requiring a black box warning label for the device and guidance on proposed language for labeling. (*IDDM*, March 7).

Health Canada is working with Bayer to implement risk communication strategies to better community adverse events reported and publicize risks associated to patients and healthcare professionals. The safety review can be found here: www.fdanews.com/05-25-16-EssureHealthCanada.pdf.

Titan Scores Approval for Opioid Implant

The FDA has approved Titan Pharmaceuticals' Probuphine implant for treating opioid dependence.

A buprenorphine implant, Probuphine is designed to provide a constant, low dose of the drug for six months in patients who already take low-to-moderate doses of buprenorphine.

In a clinical trials, 63 percent of patients treated with Probuphine had no evidence of illicit opioid use throughout the six months of treatment. Buprenorphine was previously approved only as a pill or a film placed under the tongue or on the inside of the cheek.

A Titan spokeswoman said details about pricing and launch plans will be available next week.

Comment Period on ESDs Extended

Industry will have until July 25 to comment on FDA's proposed rule to ban electrical stimulation devices published on April 25.

The agency announced a proposal to ban ESDs used for self-injurious or aggressive behavior because they present a substantial risk to public health that cannot be corrected or eliminated through changes to the labeling (*IDDM*, May 2).

According to the FDA, there is evidence of a number of risks associated with these devices that make it necessary to ban the product.

The agency extended the comment period due to numerous requests for extensions.

FDA's Lerner Moves on to Hogan Lovells

After 13 years at the FDA, Herbert Lerner, deputy director of the FDA's Division of Reproductive, Gastro-Renal and Urological Devices will leave the agency to join Hogan Lovells as senior director of Medical and Regulatory Affairs in its Medical Device Practice Group in Washington.

At the FDA, Lerner oversaw medical device reviews in connection with premarket approval applications, 510(k) notices, *de novo* petitions, and investigational device exemption applications for reproductive, gastro-renal, and urological devices.

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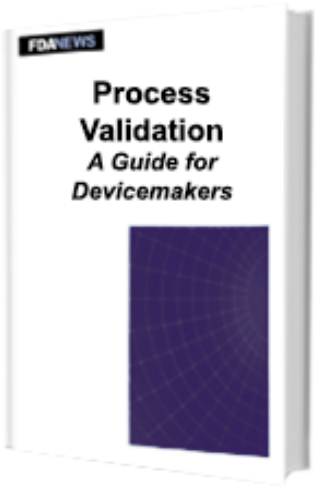

Process Validation
A Guide for Devicemakers

When must a process be validated? That is the first crucial question devicemakers must answer. But with no clear guidance from the CDRH, finding the answer can be difficult.

The new FDAnews management report — **Process Validation: *A Guide for Devicemakers*** provides you with the answers. This report will walk you through each point in the decision-making process, including how to determine if a product can be "fully verified," and how FDA inspectors define that term.

In it, you'll also find a valuable in-depth overview of all of the currently applicable regulatory guidelines that have an impact on process validation for devices, including those from three key sources: the FDA, the International Organization for Standardization (ISO) and the Global Harmonization Task Force (GHTF).

Process Validation: *A Guide for Devicemakers* teaches the proper application of the regulatory requirements that lead to successful process validation, and also offers advice on the practical issues confronting validation compliance by using real-life anecdotes and scenarios.

You also get invaluable extras, such as checklists for IQ, OQ and PQ — and hundreds of pages of appendices, including the invaluable *Medical Device Quality Systems Manual: A Small Entity Compliance Guide*, which is no longer available from the FDA.

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