INTERNATIONAL DEVICES & DIAGNOSTICS MONITOR

Vol. 2, No. 43
Oct. 31, 2016

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EU Medical Device Regulation Moves Toward Final Approval

Sweeping new medical device regulations in the European Union are expected to be finalized in December or early 2017, although medical device manufacturers will still have three to five years to comply.

The EU's new Medical Device Regulation will require risk management and quality management systems, the use of unique device identifiers, major changes to clinical evidence requirements and tighter control over distribution chains. It replaces EU Directives 90/385 (Active Implantable Medical Devices) and 93/42 (Directive Concerning Medical Devices).

Compliance for new devices will be optional when final and mandatory three years later, and existing medical devices will have five years to comply, said Paul Brooks, executive director of the Regulatory Affairs Professionals Society.

Substantive changes to the current draft are not expected at this point. It was approved by the European Parliament in May.

(See **EU MDR**, *Page 4)*

MDUFA IV Would Raise Fees, Reduce Time for Decisions

Two months after industry and the FDA approved an agreement on the MDUFA IV reauthorization, the agency on Oct. 25 released the document, under which it would use a $320 million increase in user fees to implement a host of process improvements sought by device manufacturers.

The FDA has agreed to cut time-to-decision goals for 510(k)s from 124 to 108 days, provide meaningful written feedback to companies at least five days before a scheduled pre-submission meeting and update its guidance on the pre-submission process as part of its efforts.

In addition, for the first time, the FDA would be required to document the scientific rationale for issuing a deficiency letter to a sponsor.

(See **MDUFA**, *Page 2)*

MDUFA, *from Page 1*

Funding for those commitments would come from $999.5 million in user fee revenue phased in over five years, compared with $679 million under MDUFA III.

The FDA is hosting a public meeting on the draft recommendations Nov. 2, after which comments will be accepted for 30 days.

The FDA is required to transmit its final recommendations, along with the explanation of any changes from the draft to the final version, to Congress by Jan. 15, 2017.

Under the draft agreement, the FDA would also commit to significant improvements in total review times.

For example, for premarket approvals, the average total time-to-decision goal is 290 days by FY 2022, a 25 percent decrease from the current benchmark.

First-time goals for de novo products call for the FDA to make a decision within 150 days for 70 percent of submissions by FY 2022.

Presubmission Metrics

Patrick Hope, executive director of the Medical Imaging and Technology Alliance, said MDUFA IV also includes performance metrics for the pre-submission process.

For example, within 15 calendar days of receipt of a pre-submission, the FDA would state whether the application had been accepted and, if applicable, schedule a meeting or teleconference. The FDA also would provide written feedback regarding issues raised in a pre-submission request within 70 calendar days or five calendar days before a scheduled meeting, whichever comes sooner, for a specified number of submissions in each of fiscal years 2018-2022.

MDUFA funding also will be used for a pilot project to assess whether real-world evidence can support premarket activities.

The three-year pilot will look at the use of real-world evidence for expanded indications for use, new clearances and approvals, and improved malfunction reporting. Manufacturers and other stakeholders will help oversee the coordinating center that will establish the pilot.

The agreement would increase patient input into the regulatory process by leveraging public-private partnerships and allowing for the voluntary use of publicly available and validated patient preference information (PPI) or patient reported outcomes (PRO) in device regulatory submissions.

In addition, user fee funds would be used to develop expertise within the FDA's device center to respond to submissions with PPI and PRO information.

Patient Input Provisions

"Industry strongly supports the expanded input and involvement the patient community will have in the device regulatory process under this agreement," AdvaMed President Scott Whitaker said in a statement. "Properly validated PPI and PRO information can play an enormous role in fostering medical technology innovation and improving patient care."

Eric Gaschow, vice president of government affairs at the National Health Council, which represents patients, also praised the patient input provisions.

"FDA is doing a really good job of moving patient engagement forward, but they've been doing it without user fees," he said. "And the fact that industry is willing to pay for this shows they think it's important as well."

"The problem with clinical trials is that often you don't get a full picture of what a device will do for a patient," he said. Real-world evidence will aid in the design of clinical trials and otherwise help "incorporate information developed in the post-market setting into the pre-market setting."

Read the MDUFA performance goals and procedures for FY 2018-2022 here: www.fdanews.com/10-27-16-goalsandprocedures.pdf

Read the draft recommended user fee changes here: www.fdanews.com/10-27-16-user fees.pdf. — Jeff Kinney

Guidance Should Clarify How FDA Will Use Real-World Evidence, Industry Says

The FDA guidance issued earlier this year on how it will use real-world evidence to make regulatory decisions is generally helpful but relies too heavily on registries and the pre-submission process and needs to be clarified, industry groups said in public comments.

In its comments, the Advanced Medical Technology Association said it is "optimistic about the potential benefits" of real-world evidence (RWE) and real-world data (RWD). However, it said the FDA needs to provide more information about how the agency will use the information.

In particular, it said the scope of the guidance should be expanded to include additional sources of RWE beyond registry data, clarify application of the guidance to Class II devices that are not subject to a registry, and explain how real-world evidence can support regulatory decision-making for Class II products in the pre-market phase of development.

The FDA issued guidance on July 26 on how it plans to evaluate RWE and RWD to determine when it could be used to support regulatory decisions for medical devices (*IDDM*, Aug. 1). The public comment period for the guidance closed Oct. 25.

AdvaMed also said the FDA should provide additional examples of how the agency can use RWE to bring products to market faster, better explain how it will weigh various data sources used to make regulatory decisions and clarify the application of informed consent to avoid conflating the use of RWE and RWD with the collection of research data when studying an investigational device.

In its comments, the Medical Imaging & Technology Alliance (MITA) urged the FDA to clarify that use of RWE and RWD is voluntary. The group also said the draft guidance should provide criteria for using RWE for regulatory decision-making.

In addition, the guidance asks manufacturers to notify the FDA through the pre-submission process when considering whether to use RWE to meet data requirements. MITA expressed several concerns about this requirement.

In particular, the guidance indicates that RWE can be used for a variety of regulatory decisions, including post-market controls. "MITA strongly believes that the use of the pre-submission process to discuss the use of RWE for post-market uses is inappropriate," the group said. It asked the FDA to provide another way to discuss RWE in the post-market process.

Economic Impact, Study Design Methods

The Small Biotechnology Business Coalition said the evidentiary burden placed on diagnostics developers is often comparable to that placed on drug companies, even though revenues for diagnostics developers are typically much smaller.

"Use of RWE in lieu of clinical trials has enormous potential to lower the barriers to diagnostics development without necessarily compromising safety or efficiency," the group said. "The draft guidance should elaborate on this point and stipulate that economic cost-benefit analysis should be given significant weight by the FDA when deciding whether to accept RWE in lieu of prospective data or traditional clinical trials."

The Biotechnology Innovation Organization (BIO) asked the FDA to provide guidance on "good study design methods, conduct or statistical methodology." In addition, BIO said the FDA should specify that there should be different types of studies required to inform different types of decisions, and it should provide additional clarity regarding how source data standards can be achieved while adhering to current privacy standards.

The 510(k) Coalition said the guidance should clarify the requirements for using different types of RWE and RWD. Most of the examples seem to focus on clinical-type data and do not consider data from sources such as engineering analysis and bench testing, which are often highly valuable in the device context, it said.

The guidance can be read here: www.fdanews.com/07-27-16-realworldevidence.pdf. — Jeff Kinney

EU MDR, *from Page 1*

But new guidelines published in June 2016—MEDDEV 2.7/1—which are meant to align with provisions in MDR and provide general principles for medical device clinical evaluations and introduce more thorough pre- and postmarket data collection standards, are already causing some frustration.

Ronald Boumans, senior global regulatory consultant at EMERGO's office in The Hague, said that some manufacturers are complaining that MEDDEV 2.7/1 is being applied as if it had the force of law.

Notified Bodies — organizations designated by an EU country to assess the conformity of certain products before they enter the market — are "already feeling the heat of the designation process required under the MDR, act with almost religious fanaticism" in enforcing the provisions of MEDDEV 2.7/1, he said.

"Suddenly manufacturers of devices that are on the market without serious safety issues may see their certificates suspended or not extended," Boumans said. That could mean devices that meet current legally binding safety regulations will no longer be available in Europe, he added.

Lincoln Tsang, a partner at Arnold & Porter, said that although guidelines like MEDDEV 2.7/1 have no legal force, the European Court of Justice has consistently held that they are useful for interpreting legal requirements and thus have a "quasi-legal status because a regulatory guidance document represents the agreed view of how the legal requirement can be workably applied in practice."

Under the new MDR, manufacturers will be required to place unique identifiers on their medical devices to ensure traceability.

In addition, requirements similar to those currently in place for postmarket monitoring the effects of drugs will be introduced with respect to medical devices.

The MDR also will describe in detail how manufacturers should plan, continuously conduct, and document premarket clinical evaluations. For example, it requires manufacturers to establish a system to review existing data, identify gaps in the data, and identify how those gaps can be addressed to fully document the safety and effectiveness of a medical device.

Regarding health-related mobile apps, it is uncertain which will be covered by the MDR. However, certain categories of apps will not be covered, including clinical decision support tools for diagnosis and treatment recommendations and point-of-care diagnosis, monitoring, or treatment aids.

Tsang noted that the MDR provides more detailed requirements than the guidelines for pre-market clinical evaluations and post-market clinical follow-ups. These provisions provide a regulatory framework for continuous evaluation throughout a product's lifecycle.

Read the draft MDR here: www.fdanews.com/10-25-16-MDR.pdf.

Read the guidelines here: www.fdanews.com/10-25-16-guidance.pdf. — Jeff Kinney

Manufacturers Need Cyber Risk Assessment Team, Framework

Protecting medical devices against cyber threats will require manufacturers to assemble an assessment team with a broad understanding of each device's design, intended use and data functions.

Manufacturers also need to develop a comprehensive risk assessment framework to help identify assets and cybersecurity risks, link those risks to appropriate cybersecurity controls, assess the impact of cyber vulnerabilities on device functionality and users, assess whether vulnerabilities can be exploited, and determine mitigation strategies, says Nick Sikorski, senior consultant with Deloitte & Touche.

To make the framework successful, the assessment team needs to understand how the product being assessed works, including the software it uses, network characteristics, the type of information the device collects and uses, and any physical security features it has, Sikorski told an FDAnews webinar.

Nine-Part Framework

Overall, Deloitte recommends the framework look like this:

- Gather information on the product, threats, and vulnerabilities;
- Identify applicable device profiles;
- Develop a component register;
- Perform a security controls analysis;
- Conduct threat modeling;
- Pair identified vulnerabilities with threats;
- Calculate the risk rating of vulnerabilities;
- Identify mitigating controls; and
- Calculate the residual risk rating after those controls are implemented.

Identifying applicable device profiles allows the assessment team to understand the environment the product operates in, including its architecture, operational design, specific uses, and the data it stores and transmits. "This information will assist in the identification of vulnerabilities and in building out the threat matrix," Sikorski said.

A component register for the product is needed to determine threats and vulnerabilities. Top-level components might include a user interface, printer, and analyzer. A component register also can help determine threats to similar devices.

An analysis of selected medical device security controls will help document the current state of these controls, which is required before needed improvements are determined. Security controls can include protecting data in transit, protecting against data leaks, managing access permissions, and protecting network integrity.

Threat Landscape

Sikorski said conducting threat modeling is "one of the most important steps" in the framework and involves understanding "the threat landscape of the product." That includes identifying the threat agent; the agent's motivation, skill level, and goals; and the affected assets that are associated with the product.

Pairing vulnerabilities with threats is important for several reasons, such as identifying whether a given vulnerability actually has a specific threat to exploit it. Similarly, there might be a cyber threat that does not have an associated vulnerability.

Calculating the risk of a particular vulnerability involves assessing an attacker's ability to exploit it, as well as the impact on confidentiality, integrity, and availability of the data at risk.

The final steps in the framework involve identifying mitigating controls and calculating residual risk. Based on the calculated risk scores, additional mitigating controls need to be identified to reduce the risk to an acceptable level. Once these mitigations have been put in place, the residual risk associated with the vulnerability should be calculated. — Jeff Kinney

FDA Launches Website for Reporting Medical Device Regulatory Violations

Medical device manufacturers have yet another database to worry about, since the FDA launched a website where anyone can file a complaint that a medical device is violating agency rules.

Allegations of "regulatory misconduct" can include failing to register and list a medical device, marketing unapproved products, failing to follow quality system requirements, or engaging in misleading promotions. Examples of the kinds of allegations include:

- A company promotes or advertises a device outside the approved indications for use.
- A device manufacturer fails to submit required reports for device-related safety concerns and/or is not conducting required follow-up investigations.
- A company's medical devices or manufacturing processes do not meet their design and manufacturing responsibilities.
- A manufacturer markets a medical device without a 510(k) or premarket approval.
- A manufacturer imports medical devices into the U.S. that do not meet U.S. legal requirements.
- A third party outside the medical device company forges or falsifies an export certificate to bring medical devices into the U.S.
- A company fails to register and list its medical device products with the FDA.
- A manufacturer knowingly deceives the FDA, for example by hiding information or falsifying documents.

Reports may be submitted anonymously, but the FDA requests contact information in case follow-up is needed. Identity and contact information of those submitting reports will not be shared with anyone outside the FDA unless it is legally required.

More information is available here: www.fdanews.com/10-28-16-RegMisconduct.pdf.

China FDA Priority Review Procedure to Take Effect Jan. 1

Manufacturers will be able to request priority review and approval of Class II and III devices exported to China under a new procedure that will take effect Jan. 1, the China Food and Drug Administration announced.

According to the law firm Ropes & Gray, an applicant with a Class II device (limited to import applications) or a Class III device (both domestic and import applications) can request priority review when submitting a device application, if (1) the device has been enrolled in the National Science and Technology Major Project or National Key Research and Development Plan, or (2) the device can:

- diagnose or treat rare diseases and has significant advantages in clinical practice;
- diagnose or treat malignant tumors and has significant advantages in clinical practice;
- diagnose or treat specific and frequently occurring diseases in the elderly, and where there is no effective way to diagnose or cure such disease;
- diagnose or treat specific and frequently occurring diseases in children, and where there is no effective way to diagnose or cure such disease; or
- address an urgent clinical need, and the same type of device has not yet been marketed in China.

Regulators will determine whether a device is eligible for priority review and which priority review designation applies before conducting a technical review.

The CFDA press release can be read here: www.fdanews.com/10-28-16-CFDArelease.pdf

The priority review and approval procedure (in Chinese) can be read here: www.fdanews.com/10-28-16-procedure.pdf.

BRIEFS

FDA Approves Device For Prevention of Recurrent Strokes

The FDA has approved the Amplatzer PFO Occluder device, which reduces the risk of a stroke in patients who previously had a stroke believed to be caused by a blood clot passing through a small hole in the heart, called a patent foramen ovale, and then traveling to the brain.

The Amplatzer PFO Occluder is inserted through a catheter that is placed in a leg vein and advanced to the heart. It is then implanted close to the hole in the heart between the top right chamber and the top left chamber.

The safety and efficacy was assessed study with 499 participants aged 18 to 60 years old who were treated with the Amplatzer PFO Occluder plus blood-thinning medications compared to 481 participants who were treated with blood-thinning medications alone. The study found a 50 percent reduction in the rate of new strokes in participants.

FDA Delays Phase III Trial of Inovio's DNA Vaccine, Delivery Device

The FDA has placed a clinical hold on a proposed Phase III trial of Inovio Pharmaceuticals' VGX-3100, a synthetic DNA vaccine being studied in cervical dysplasia because of questions on the delivery device for the drug. The Cellectra 5PSP immunotherapy delivery device is designed to administer DNA immunotherapies directly into muscle tissue.

Inovio estimated that the start of the Phase III trial could be delayed until at least the first half of 2017, pending a resolution, and expects a full formal letter from the FDA within the next 30 days.

FDA Wants Input on PMA Information Collection

The FDA asked for public comments on the burden imposed by information collection requirements for premarket approval of Class III medical devices.

The FDA estimates the annual reporting burden to be 350,562 total hours, involving 4,846 respondents.

Comments are due 60 days from the publication of the Federal Register announcement, which is available at www.fdanews.com/10-18-16-premarketapproval.pdf.

Amniox Announces Improved Outcomes With Clarix Regenerative Matrix Treatment

Amniox published the results of a prospective randomized clinical study of its proprietary cryopreserved Amniotic Membrane (AM) as an adjunct to lumbar discectomy.

The study included 80 patients, with half of the patients receiving Clarix 100 in the disc space following removal of the disc herniation and half receiving the standard of care, which involved removal of the herniation alone.

"These results indicate that the application of Clarix can influence the healing response to significantly improve post-surgical outcomes. Patients experience reduced pain and a faster and sustained return to activities of daily living," the company said.

FDA Grants Four Emergency Use Authorizations for Zika Diagnostics

The FDA has issued Emergency Use Authorizations for four in vitro diagnostic devices for detection and/or diagnosis of Zika virus in response to outbreaks in the Americas.

Authorizations were granted for Siemens Healthcare Diagnostics, Luminex, InBios International and Roche Molecular Systems.

The authorizations follow a Feb. 26 determination by the HHS secretary that there is a significant potential for a public health emergency involving the Zika virus.

RTI Surgical Gains Additional 510(k) Clearance for Streamline OCT System

RTI Surgical has received 510(k) clearance for the Streamline OCT Occipito-Cervico-Thoracic System.

(See **Briefs**, *Page 8)*

Briefs, *from Page 7*

This clearance expands the indication for polyaxial screw placement to include the cervical spine, and also includes clearance for a dual-diameter transition rod.

In addition, levels of fixation can be accomplished by connecting to other RTI pedicle screw systems through the newly cleared transition rod or currently available rod-to-rod connectors.

FDA Releases Labeling Guidance On Tubal Implant Devices

New FDA guidance identifies the content and format for certain labeling components for permanent, hysteroscopically placed tubal implant devices intended for female sterilization.

The guidance applies to all devices of this type, regardless of the insert material composition, location of intended implantation, or exact method of delivery. It specifies inclusion of a boxed warning and patient decision checklist.

The guidance can be read here: www.fdanews.com/10-28-16-guidance.pdf.

Quidel Receives FDA Clearance For Solana(R) Strep Complete Assay

Quidel has received 510(k) clearance from the FDA to market Quidel's new Solana Strep Complete Assay for the rapid and qualitative detection and differentiation of Streptococcus pyogenes (Group A beta-hemolytic Streptococcus) and Streptococcus dysgalactiae (pyogenic Group C and G beta-hemolytic Streptococcus) nucleic acids isolated from throat swab specimens obtained from symptomatic patients.

The device can process up to 12 patient samples in each 25-minute run.

Spineology Gains FDA Clearance Of Rampart Duo Interbody Fusion System

Spineology has received FDA clearance for the Rampart Duo Interbody Fusion system.

The device design includes PEEK spacer blocks that are positioned at each end of the device and a flexible porous graft containment mesh that creates a central graft cavity.

After implanting, the porous graft containment mesh is filled with bone graft to release the device in the anterior-posterior direction and in the superior-inferior direction to provide conforming apposition with the vertebral endplates.

"The implant design allows for decreased retraction requirements when compared to current interbody systems. The minimized tissue retraction may reduce the potential for nerve damage and resultant leg pain associated with the lateral approach," the company said.

FDA Issues Form 483s to Hospitals For Failing to Report Adverse Device Events

The FDA has issued Form 483s to 11 hospitals for failing to report adverse events related to the use of morcellators and contaminated duodenoscopes.

The FDA will hold a public workshop Dec. 5 to solicit input and advice on improving hospital-based surveillance systems and the broader role of using hospitals to evaluate how well devices work in the clinical setting.

A summary of the inspections and links to the Form 483 are available here: www.fdanews.com/10-27-16-hospitalinspections.pdf.

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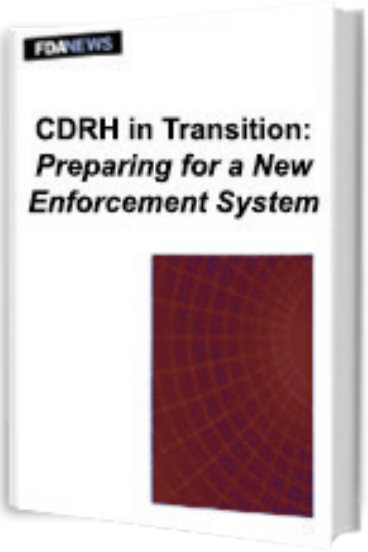

CDRH in Transition: *Preparing for a New Enforcement System*

The looming realignment of CDRH's programs and retooling of inspection procedures have raised many questions among devicemakers trying to prepare for future inspections.

Currently, devicemakers are used to seeing one "generic" investigator at their inspections and they are used to investigators following the approach set out in the FDA's Investigations Manual and Quality Systems Inspection Technique.

But that's all about to change, creating a "perfect storm" that will leave devicemakers drowning in unfamiliar waters. Now is the time to make preparations to weather that storm, and **CDRH in Transition: *Preparing for a New Enforcement System*** is the place to start. In this report, noted industry expert John Avellanet gives his well-informed perspective on where CDRH enforcement is headed and what adjustments devicemakers will need to survive.

CDRH in Transition: *Preparing for a New Enforcement System* outlines how — and when — CDRH plans to update its programs in the coming years and how devicemakers should respond. Think of it as your to-do list for the next 18 months.

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