INTERNATIONAL DEVICES & DIAGNOSTICS MONITOR

Vol. 2, No. 44
Nov. 7, 2016

IN THIS ISSUE

Industry Backs MDUFA IV, Will Closely Monitor FDA Time-to-Decision Performance

Industry representatives have endorsed measures that would streamline the FDA's premarket review process, but said they will be watching closely for tangible results in exchange for a $320 million increase in user fees.

They especially cited provisions in the draft agreement that would cut time-to-decision goals for 510(k) submissions from 124 to 108 days and for premarket approvals from 385 to 290 days by fiscal year 2022. The agreement also would make premarket reviews more consistent and transparent, increase funds for recruiting and retaining FDA staff, and set aside money for key information technology improvements.

The Nov. 2 public meeting was one step in the process of finalizing the draft recommendations. The FDA will accept public comments for 30 days following the meeting, incorporate any necessary changes, and transmit final recommendations to Congress by Jan.

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FDA Seeking Feedback on Patent And Care-Partner Connection

The FDA is asking for input on its new program, the Patient and Care-Partner Connection (P&CC), designed to allow CDRH staff to formally engage with patients and care partners to help develop, evaluate and monitor medical devices.

The P&CC will allow designated groups of patients and care partners to address specific questions about treatments, diagnoses and assessments by connecting patient organizations with CDRH staff.

The FDA has set a goal for 90 percent of CDRH employees to interact with patients as part of their job duties by December 2017. It expects to meet the goal by the first quarter of next year.

Read the notice here: www.fdanews.com/11-04-16-PCC.pdf.
— Jeff Kinney

MDUFA, *from Page 1*

15, 2017. Congressional passage of MDUFA IV is expected by the summer of 2017.

Under MDUFA IV, the FDA would collect $999.5 million in user fees over five years (up from $679 million under MDUFA III) for a host of process improvements long sought by industry.

FDA Associate Commissioner for Planning Malcolm J. Bertoni said at the meeting that the agreement includes a goal to provide written feedback on at least 1,950 pre-submissions within 70 days, or five calendar days prior to the scheduled meeting, whichever comes sooner, in FY 2022.

Additional Staff

The FDA also will hire additional staff to improve de novo submission procedures. In particular, the de novo performance goal would increase from 50 percent of submissions being reviewed within 150 days in FY 2018 to 70 percent in FY 2022. Currently, 40 percent of de novo submissions are reviewed within 150 days.

FDA funding needs were based on the most recent available annual cost data from fiscal year 2015. In addition, the "fifth-year fee offset" clause was eliminated to allow the agency to spend all the fees it collects — even if it collects more than expected — so it can take on additional work.

MDUFA IV lowers the 510(k) fee for small businesses by 5 percent compared to fiscal year 2016 despite making significant fee increases in other areas.

In addition, Bertoni said the agreement calls for a dedicated team to establish a quality management framework for the premarket submission process and to conduct routine quality audits. The framework will include infrastructure, senior management responsibility, resource management, lifecycle management and quality management system evaluations.

The FDA also plans to make IT improvements to facilitate new performance goals and reporting, enhance IT infrastructure to enable collection and reporting on structured data, develop and maintain a secure Web-based application that allows sponsors to view individual submission status in near-real time, and develop structured electronic submission templates as a tool to guide industry's preparation of premarket submissions.

Also under MDUFA IV, the agency will strengthen its Accredited Person Premarket Review Program by improving training for third-parties reviewers, redacting predicate review memos for use by third parties during their reviews, conducting audits of third-party review quality, and publishing assessments the performance of individual third parties. Bertoni said the goal of these measures is to eliminate routine re-review by FDA of third-party reviews.

'Reasonable Contribution from Industry'

Janet Trunzo, senior executive vice president for technology and regulatory affairs at AdvaMed, said her group fully supports MDUFA IV, which "builds on the success" of MDUFA III. She particularly cited the time-to-decision goals for 510(k) submissions and premarket approvals, as well as provisions calling for the FDA to specify the particular guidance, regulation, or standard that forms the basis of a deficiency letter.

Trunzo said the substantial fee increase from MDUFA III "represents a reasonable contribution from industry" in exchange for the process and efficiency improvements. "The end result of this agreement is a win for our patients, for FDA, and for innovation," she said.

Mark Leahey, president and CEO of the Medical Device Manufacturers Association,

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Begin Form 483 Response by Analyzing Symptoms of Quality System Failure

A response to a Form 483 is not a routine or informal communication and should be given the same attention and care you would give to defending your company from a federal indictment — because that's what a 483 actually is.

Essentially, a 483 is a written indictment issued by a federal law enforcement officer (the FDA investigator) informing a company that it is in violation of the law. It's the warning that comes before enforcement action, and a company's response to the observations listed in a 483 is its chance to head off the FDA before the agency takes that action.

The purpose of the response is to make your case to the FDA: Convince the agency that you take its warnings seriously, are committed to improvement and have a solid, detailed plan for fixing your deficiencies. Unfortunately, the FDA provides no guidance on what it expects to see in a response. Even worse, the agency gives you only 15 days to deliver it.

Report on Effective 483 Responses

FDAnews has recently published a report — *Effective 483 Responses: Focus on CAPA Violations* — that provides the advice the agency does not: from the 15-day deadline to the audience the response should address to such practical matters as proofreading your draft.

The report explains that the most important step in developing a response is analyzing the observations in the 483. Most of the time, 483 observations reflect symptoms or signals of a quality system failure. Look at every aspect of the quality system, including training, oversight, recordkeeping and auditing. You need to make sure the plan you present in your response is fully corrective and preventive. And make sure to consider short-term actions or controls to maintain a state of control until the fully corrective actions are in place.

Following through on commitments is another critical part of the response. The FDA will review and verify whether all of those commitments made in the response have actually been met. It's important to operate in a very coordinated, open-communication mode so everyone involved understands the commitments and progress toward meeting them.

While enforcement of quality system regulations is not cookie-cutter, and outcomes vary by the unique circumstance of the particular case, there are some common truths to be found in any collection of 483 responses:

- Respond on time
- Get upper management involved
- Strike the right tone
- Describe the immediate response
- Cover each CAPA cited in the observation
- List the root cause of each cited CAPA mistake
- List corrective and preventive actions for each cause
- Address cited mistakes on a systemic level
- Consider the potential impact on non-CAPA quality subsystems
- Describe training and other implementation actions
- Specify implementation dates or timetables
- Describe verification efforts
- Provide documentation
- Invite feedback
- Provide regular implementation updates

The 479-page FDAnews report provides full explanations of the best practices listed above and provides expert evaluation of the responses to 28 Form 483s.

The full report can be purchased here: www.fdanews.com/products/52827.

Second Circuit Upholds Injunction On Imported Glucose Test Strips

A federal appeals court has upheld an injunction against wholesalers' U.S. sales of Abbott Laboratories' "FreeStyle" blood glucose test strips that were bought overseas at discount prices.

Abbott Laboratories claimed that the defendants illegally imported the test strips that Abbott had sold overseas, repackaged them and sold them in competition with the Abbott product. Abbott sells the test strips at lower prices overseas than it does in the U.S. market.

"We find no abuse of discretion in the district court's thorough and well-reasoned order," the U.S. Court of Appeals for the Second Circuit said.

H&H Wholesale Services, Matrix Distributors and others had appealed a ruling by the U.S. District Court for the Eastern District of New York granting Abbott's motion for a preliminary injunction.

U.S. District Judge Carol Bagley Amon agreed with Abbott and granted the injunction. H&H and Matrix appealed, arguing that the district court abused its discretion in finding that Abbott was likely to succeed on the merits of its claims.

In addition, both H&H and Matrix argued that the district court abused its discretion in finding a likelihood of irreparable harm in the absence of preliminary relief. The Second Circuit disagreed.

Read the Second Circuit's order here: www.fdanews.com/11-04-16-SecondCircuit.pdf.
— Jeff Kinney

MDUFA, *from Page 2*

also praised MDUFA IV, but said that industry expects a real return on its investment of user fees. "If the FDA can execute on their commitments, it will benefit all parties," he said.

Like Trunzo, Leahey said the process improvements for deficiency letters will help industry respond appropriately, because the exact nature of alleged deficiencies was not always clear in the past. Specifying which standard was allegedly violated will show manufacturers "where they might have fallen short," but also "provide a check for FDA" when it claims something went wrong, he said.

Megan Hayes, director of regulatory and standards strategy for the Medical Imaging & Technology Alliance, said in an interview after the meeting that MDUFA IV's provisions — although welcome in principle — need to be "carefully evaluated" to see if they really do make the premarket review program faster, more transparent and more accountable.

"We understand that FDA's overall mission is larger than that, but we really believe MDUFA should provide additive funds to improve the premarket process" above all other considerations, she said. — Jeff Kinney

Western Enterprises Hit With Form 483 Over Handling of Complaints

Western Enterprises was cited in a Form 483 for inadequate investigations of and responses to complaints at its Westlake, Ohio, facility.

The FDA cited the manufacturer of oxygen tanks, gauges and fittings for five observations.

The inspector's first observation found that Western failed to document an investigation of complaints involving the possible failure of a suction regulator to meet its specifications. For example, a complaint reported that the device malfunctioned, but Western did not have the device analyzed.

The 483 also cites Western for failing to completely document all corrective and preventive actions taken in response to a complaint that a production unit had leaked.

The inspector also found that Western failed to adequately establish procedures for receiving, reviewing, and evaluating complaints by a formally designated unit; and procedures to ensure that all purchased or otherwise received products and services conformed to specified requirements.

Finally, the inspector said that Western had not validated certain processes and product lines according to established procedures.

Read the Form 483 here: www.fdanews.com/11-02-16-Western483.pdf.

FDA Announces Unchanged Final Guidance for IDEs for Neurological Diseases

Seven months after releasing draft guidance, the FDA has issued virtually unchanged final guidance to assist sponsors who intend to submit an IDE to conduct clinical trials on medical devices targeting neurological disease progression.

The guidance aims to help weigh the risks of medical devices that target either the cause or progression — rather than the symptoms — of neurological conditions such as Alzheimer's disease and Parkinson's disease.

For each planned clinical study, sponsors should include proposed indications for use and target population; study type (i.e., pivotal, feasibility); study design; total time planned; sample size; number of investigational sites; safety and effectiveness endpoints; details on tests and testing methodologies; and participating investigators.

The guidance says IDE applications should also include plans for clinical outcome assessments, which should consist of direct quantitative assessments of the effect of the treatment on disease progress and effect on the patient.

Another essential element is use of a risk-benefit framework that is capable of incorporating evidence and information from different domains — clinical, non-clinical and patient perspective. The FDA said it may approve applications in which only a subset of the subject population is willing to accept the risks as weighed against the benefits, provided there is an adequate informed consent process in place.

The few comments filed on the draft guidance were generally supportive.

Read the guidance, "Clinical Considerations for Investigational Device Exemptions (IDEs) for Neurological Devices Targeting Disease Progression and Clinical Outcomes," here: www.fdanews.com/11-04-16-investigational.pdf. — Jeff Kinney

Health Canada Issues New Guide on Device Recalls; No Substantive Changes

Health Canada has issued a new, simpler guide on regulations governing device recalls that replaces a five-year-old document but makes no substantive changes.

The new guide has improved the graphic display of information it contains and provides links to definitions, laws and regulations. It also adds several appendices with information on recall stages, roles and responsibilities, checklists for distribution records and recalls, and writing guidelines.

The new guide can be read here: www.fdanews.com/11-04-16-Canadarecalls.pdf.

New ISO Standard Updates Luer Connector Design

The International Organization for Standardization has released a standard that specifies design and performance requirements of small-bore Luer connectors used in intravascular applications or hypodermic connections in medical devices and accessories.

According to an analysis by the Association for the Advancement of Medical Instrumentation (AAMI), the new ISO standard provides needed updates on the Luer, a type of tapered small-bore connector that has been implicated in numerous patient safety problems.

AAMI said manufacturers have long used the Luer to attach tubing, catheters, and syringes to their devices because of its universal design, low cost, and simplicity.

However, it said patients today — especially in intensive care units, cardiac care, and emergency rooms — may be hooked up to dozens of devices at once, all of which use the same Luer connectors. This increases the risk that unrelated systems can be mistakenly connected, which can cause injury or death.

According to the FDA, device misconnections can occur for many reasons, including:

- The similar design of many connectors and widespread use of connectors with similar sizes and shapes.
- Human error, arising from conditions such as multiple connections on one patient, poor lighting, lack of training, time pressure, fatigue or high-stress environments.

The FDA provides an example of a child in a pediatric intensive care unit who had both an IV line and a trach tube. The IV tubing was mistakenly connected to the trach cuff port, which resulted in the IV fluid over-expanding the trach cuff to the point of breaking, and IV fluids entered the child's lungs. As a result, the child died.

The new ISO 80369-7 attempts to address situations like this by defining certain parameters that will ensure that Luer connectors cannot be attached to other types of connectors. ISO 80369-7 does not call for a complete redesign of Luer connectors.

Part of Larger Effort

ISO 80369-7 is part of a series of standards being developed by the FDA, ISO, other members of the standards community, and industry to make device misconnections less likely.

Two standards recognized by the FDA provide overarching recommendations for small-bore connectors:

- ISO 80369-1:2010, "Small-bore connectors for liquids and gases in healthcare applications" – Part 1: General requirements – specifies general provisions for small-bore connectors and methodology for assessing design characteristics to reduce the risk of misconnections between medical devices or accessories.
- ISO 80369-20:2015, "Small-bore connectors for liquids and gases in healthcare applications" – Part 20: Common test methods – specifies test methods to support small-bore connectors' functional requirements.

Current standards recognized by the FDA for specific small-bore connector applications include:

- Blood pressure cuffs (IEC 80369-5:2016);
- Enteral devices such as feeding tubes (ISO 80369-3:2016);
- Neuraxial devices such as epidural catheters (ISO 80369-6:2016).

The FDA said it anticipates recognizing additional standards for specific small-bore connector applications as they are developed. For example, work is underway on the international standard for breathing or respiratory devices such as anesthesia machines and ventilators.

Read the ISO announcement here: www.fdanews.com/11-04-16-ISO.pdf. — Jeff Kinney

BRIEFS

Arterys Receives 510(k) Clearance For Arterys Software

Arterys has received 510(k) clearance from the FDA for its software for cloud-based medical image visualization and quantification.

This clearance allows the Arterys product to be used in clinical settings for the quantification of cardiac flow, which includes 4D flow and 2D Phase Contrast workflows, and cardiac function measurements.

Arterys now plans on launching the product in the U.S. through a partnership with GE Healthcare as the ViosWorks 4D product.

Onkos Surgical Receives FDA 510(k) Clearance for Eleos Limb Salvage System

Onkos Surgical has received clearance from the FDA to market the Eleos Limb Salvage System to treat patients with significant bone loss due to cancer, trauma, or previous surgical procedures.

The Eleos system is a long-term reconstructive option for oncology patients.

Tyto Care Receives FDA Clearance

The FDA has granted 510(k) clearance for its digital stethoscope, a device that will be part of the company's advanced set of digital examination tools.

TytoCare's modular exam tools and telehealth platform enable a remote examination of the heart, lungs, heart rate, temperature, throat, skin and ears. Examinations can be done in real time as part of a live video telehealth visit, or in advance of a telehealth exam.

Tyto Care has presented two new products: TytoPro for clinicians to capture and share remote examination data, conduct a specialist consultation, or get a second opinion and Tyto-Home for consumers to use at home to connect with a clinician.

Neural Analytics Receives 510(k) Clearance For Transcranial Ultrasound System

Neural Analytics has received 510(k) clearance from the FDA for its next-generation ultrasound device, the Lucid M1 Transcranial Doppler Ultrasound System.

The device system is a battery-operated medical-grade tablet device designed to be moved easily throughout a medical facility in a range of settings that require the rapid assessment of blood flow in the brain to expedite treatment for conditions such as traumatic brain injury.

There are 2.5 million people affected by TBI each year in the U.S. and 14.8 million people affected globally.

FDA Approves IDE for Balloon Angioplasty Clinical Study

The FDA has granted staged approval for Intact Vascular's investigational device exemption application to begin its Tack Optimized Balloon Angioplasty II BTK clinical study.

The study will examine the safety and efficacy of the tack endovascular system when used to repair dissections in the arteries below the knee following percutaneous transluminal angioplasty as a treatment for critical limb ischemia.

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Customer Service
(888) 838-5578 • +1 (703) 538-7600
customerservice@fdanews.com

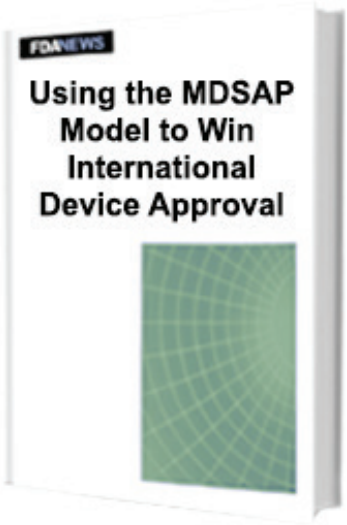
Editor: Jeff Kinney
+1 (703) 538-7634
jkinney@fdanews.com

Ad Sales: Jim Desborough
+1 (703) 538-7647
jdesborough@fdanews.com

Multi-User Sales: Jeff Grizzel
+1 (703) 538-7669
jgrizzel@fdanews.com

300 N. Washington St., Suite 200 • Falls Church, VA 22046-3431 • Phone: (888) 838-5578 • +1 (703) 538-7600 • www.fdanews.com

Reporters: José Vasquez, Cynthia Jessup, Derek Major, Conor Hale **Managing Editor:** Jim Stimson **President:** Cynthia Carter



Using the MDSAP Model to Win International Device Approval

Are you one of the 75% of device manufacturers who conduct internal audits solely "because you have to — because the FDA and ISO regs say so?"

Instead of cringing at the idea of conducting an internal audit, consider implementing the Medical Device Single Audit Program (MDSAP) model. It's a single audit of your quality management system and satisfies medical device regulatory authorities.

Currently, Australia, Brazil, Canada, Japan and the United States are participating in the program. If you pass one MDSAP inspection then you will be ready to pursue marketing authorization in five separate countries.

The **Using the MDSAP Model to Win International Device Approval** management report explains what MDSAP auditors will focus on and teaches you how to build an internal audit program that will get your quality system in state-of-the-art shape for international inspections.

You will learn:

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- How to identify and understand the requirements as interpreted by the various regulatory authorities
- How to determine gaps in your current documentation
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- How to report the audit findings using a standard report template
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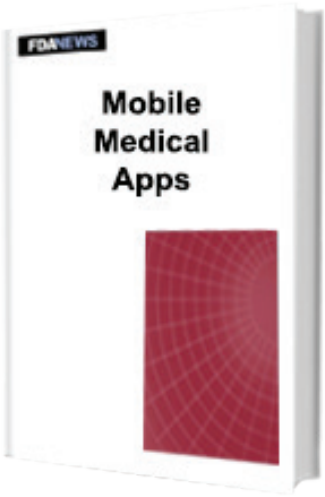

Mobile Medical Apps: *Keeping Up with the FDA's Evolving Requirements*

Just because an app is running on an unregulated phone or tablet doesn't mean that the app itself isn't a medical device in the FDA's eyes.

Where does the agency draw the line between unregulated products and those it must approve?

The final guidance for *Mobile Medical Applications* helps clarify the FDA's position on regulating mobile apps, but leaves several areas open to interpretation.

You need to know:

- How the FDA categorizes mobile apps and decides how — or whether — to regulate them as medical devices.
- How the FDA evaluates an app's "intended use."
- How to interpret the FDA's promise of "enforcement discretion" for certain types of apps.
- Who can be considered a mobile medical app developer and what regulations affect them.

This management report interprets the FDA's evolving stance on mobile apps and explains how the FDA sorts mobile apps into three categories:

1. **Administrative health information technology** (e.g, billing, claims processing, general communication and scheduling): This is not a medical device and not regulated by the agency.
2. **Health management information technology** (e.g., medication management, data capture, electronic access to clinical results, provider order entry): This is under FDA jurisdiction but generally so low risk that the agency can exercise enforcement discretion and not apply regulations.
3. **Medical device health information technology** (e.g., computer-aided detection and diagnosis, robotic surgical planning, remote display of bedside alarms, radiation treatment planning): This is actively regulated under Class I, Class II and Class III medical device rules.

Mobile Medical Apps explains what the FDA means by enforcement discretion and how it considers an app's intended use in category assignment.