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IN THIS ISSUE

FDA Wrestles With Device Uncertainty In New Draft Guidance

The FDA may be willing to accept some uncertainty about a proposed medical device's safety if sponsors will carefully collect data after the device hits the market, the agency says in a new draft guidance.

The 21st Century Cures Act requires the FDA to fast-track approval for breakthrough devices when the approval is "in the best interest of patients." But fast-tracking breakthrough devices—or devices that target extremely rare diseases—may mean that regulators have to accept some unanswered safety questions.

The 22-page draft guidance is the FDA's attempt to wrestle with that uncertainty for breakthrough and rare-disease devices.

"The aim," Commissioner Scott Gottlieb said in a speech announcing the draft guidance, "is to support premarket decisions

(See **Uncertainties**, *Page 2)*

New FDA Pilot Program Will Speed 510(K) Reviews for Moderate-Risk Devices

The FDA announced a new pilot program that aims to streamline the review process for some moderate-risk medical devices.

The Quality in 510(k) (Quik) Review Program pilot will allow sponsors of the devices in question to submit their 510(k) applications using the FDA's eSubmitter software, with the option to fill out pre-existing fields. This will enable FDA staff to review the information in a more efficient, consistent manner, according to the agency.

The agency projects the program will reduce the maximum review-decision time for eligible sponsors a full third, from 90 to 60 days. All statutory and data requirements will remain unchanged, with sponsors still required to demonstrate the devices are substantially equivalent to a predicate device, according to the agency.

(See **510(k)**, *Page 2)*

510(k), *from Page 1*

About 40 product codes will be eligible for the pilot program, including products such as electronic stethoscopes, surgical wire and certain ophthalmological cameras.

The agency plans to assess whether to continue and expand the program after the pilot period ends in 2019.

FDA Commissioner Scott Gottlieb said the new process will allow the agency to put more time and resources into evaluating applications for devices that pose the highest potential risks to patients.

"Simplifying the process to submit applications is part of the FDA's ongoing effort to ensure that we're giving patients more efficient access to safe, effective, and high-quality medical devices," he said. — Zack Budryk

Uncertainties, *from Page 1*

that are based on the totality of scientific evidence available at the time of a device's market entry."

Though couched in careful language, the draft suggests that regulators might be willing to exchange unanswered pre-approval questions for solid, post-approval answers.

Sponsors can expect that they will have to abide by strict deadlines to report post-market safety, for instance, and they'll probably have to use real-world data for those reports. They may also have to agree to careful labeling about the open safety questions and be subject to post-market review by an FDA advisory council.

The draft guidance builds on a final guidance the agency issued in 2016, which laid out the ways regulators would analyze risk for new drugs or devices. That final guidance focused mostly on the potential harms caused by a proposed device; the new draft guidance suggests that regulators might be willing to accept some uncertainty if there are "probable" patient benefits from early access to the device and if:

- A disease or disorder is so rare that clinical data isn't available;
- Bringing a device to market will allow sponsors and regulators to gather safety data; and
- Post-market remedies, such as warning labels, are likely to mitigate any harm.

Read the draft guidance here: www.fdanews.com/09-07-18-BenefitRisk.pdf. — Bill Myers

FDA Urged to Tighten Requirements For Breakthrough Device Approvals

Researchers called on the FDA to beef up post-market requirements for its breakthrough devices program.

The call to tighten requirements was based on the results of a study by researchers from the University of California San Francisco School of Medicine and the Yale University School of Medicine, published in *JAMA Internal Medicine*, that evaluated clinical trials to assess the safety and efficacy of cardiovascular devices approved through the agency's priority review program.

The study notes that the breakthrough therapy designation under the 21st Century Act allows the FDA to accept "a greater degree of uncertainty of the benefit-risk profile for these devices if the uncertainty is sufficiently balanced by other factors … and adequate post-market controls to support premarket approval."

Researchers compared high-risk cardiovascular devices approved from Jan. 1, 2017 to Dec. 31, 2017 through the original pre-market process under the priority review program.

FDA advisory panels reviewed 10 of the devices, and two were reviewed a second time. Post market clinical studies were required for 13 of the 14 devices, and for these devices there have been two Class I and 13 Class II recalls for six of the 14 devices. Nearly half of the FDA expert advisory panels deemed the devices safe but not effective, the study authors said.

Read the study report here: https://bit.ly/2Njpl8Z.

Attorneys Urge Chinese Regulator To Engage More With Industry

The past year has seen a flurry of activity around China's medical device regulations and much of the reforms have been focused on encouraging innovation while at the same time beefing up post-market enforcement. But for the reforms to be successful, the regulators should consult more with industry, according to attorneys at Ropes & Gray.

China's National Medical Products Administration (NMPA) should take a step-wise approach by first exempting innovative or life-saving devices with urgent clinical needs from confirming to mandatory standards, the attorneys suggest.

China has 454 mandatory standards and many of them are not harmonized with ISO or IEC standards, they note in a white paper, adding that rigid conformance with the mandatory standards "may force a device manufacturer to change its product design specifically for the Chinese market."

Time to Market

Such design changes may not enhance product safety and effectiveness and could delay time to market and hinder access for patients, the attorneys said.

The law firm urged the regulatory authority to "regularly solicit and listen to the industry's concerns on mandatory standards." When a Chinese standard is inconsistent with the latest international standard, devicemakers should be able use the latest international standard, the law firm suggested.

When several manufacturers fail to comply with mandatory standards, the regulator should have discussions with the manufacturers to determine if the relevant standard is hindering technology development, it said.

Study authors Katherine Wang, a partner in Ropes & Gray's Shanghai practice, and Tina Wu, a senior associate in the Shanghai office, said they hoped to see the NMPA adopt a risk-based approach to review product technical requirements for all devices, "rather than mechanically applying mandatory standards to all devices."

Although the regulator has released a number of policies to improve clinical evaluation, the law firm said more guidance is needed as there are limited opportunities for pre-submission consultations (*IDDM*, Sept. 3).

User-friendly Approach Needed

Many devicemakers have been unable to take advantage of the lowered bar for clinical evaluation, the attorneys said. One of the barriers is establishing substantial equivalence in a manner acceptable to the Center for Medical Device Evaluation, the paper says, urging the regulator to adopt real-life examples and/or concrete assessment criteria. CMDE should regularly publish representative cases and explain how examiners drew their conclusions, the attorneys suggested.

The authority could rely on foreign real-world evidence when devices have been marketed in other countries for years but lack adequate premarket clinical data. It has made some pilot moves in this direction, but clear guidance on accepting real-world evidence is needed and is in line with global regulatory trends, the paper says (*IDDM*, April 9).

Positive outcomes have been achieved in the pharma industry by adding reviewers and expanding pre-submission communication with industry and the regulator, and the attorneys urged the CMDE to take similar steps in the medical device space.

Finally, the NMPA should adopt a more current approach to its device classification system. After discussions with stakeholders about IVD classifications, the regulator learned that many cases of noncompliance were due to conservative product classification. The attorneys urged the regulator to take a similar approach for medical devices and build on these types of successes.

Read the white paper here: bit.ly/2NPLOHy.

Health Canada Plans 3D Printing Guidance

Health Canada is developing guidance to help devicemakers seeking to license 3D-printed medical devices.

Also called additive manufacturing, 3D printing is increasingly being used by many hospitals to manufacture 3D-printed implanted medical devices. Hospitals that print such devices and distribute them beyond their institutions qualify as device manufacturers and as such must comply with the same regulatory obligations as other devicemakers, the regulator said.

Although 3D-printed devices are subject to the same pre- and post-market requirements as conventionally manufactured devices, there are additional considerations such as patient-specific devices and software.

The regulator said its draft guidance is intended to support pre-market Class III and Class IV applications for 3D implantable devices that fall under ISO 13485.

The guidance will largely be drawn from the definitions developed by the International Medical Device Regulators Forum, but will elaborate on pre-market licensing requirements and manufacturing processes such as material controls, device testing and labeling.

Guidance on stand-alone software, custom-made devices, patient-specific anatomical models, and devices with biological components will be developed later as the space matures and more is learned.

Pilot for Electronic Submissions

Health Canada is gearing up for a pilot program of its regulatory enrollment process using the common electronic submission gateway (CESG) for device applications. The program kicks off in December and will run until May 2019. It will cover all Class III and Class IV new and amendment applications.

By using a collection of web-based templates to capture information in a structured XML format, Health Canada will be able to receive information via the CESG and partially populate internal systems ahead of time and automate certain procedures when an application is received.

By having a common intake approach, the agency will expand the scope of the CESG to accept more transactions in various formats. Once fully implemented, the agency will re-engineer existing administrative processes to take advantage of electronic processing tools and reviews.

TGA Allows Electronic Submissions Of Device Certificates

Australia's Therapeutic Goods Administration (TGA) has released a new method for device sponsors to apply for certificates of free sale and export electronically.

The new procedure — put in place because sponsors recently experienced problems in their efforts to get free sale and export certificates notarized and endorsed — streamlines the TGA's process for issuing the certificates, allowing them to submit their applications electronically. Sponsors may now select electronic delivery of their certificates on the application form as well.

Sponsors filing applications must be the sponsor of the device or a "recognized agent" of the product's sponsor and have a current inclusion on the Australian Register of Therapeutic Goods (ARTG) for the kind of device that covers their product. Sponsors must also "be exempt under Item 1.2, Part 1, Schedule 4 of the Therapeutic Goods (Medical Devices) Regulations 2002," the TGA said.

Applications must include, at a minimum, the ARTG number for the device type the sponsor wishes to export, as well as the global medical device nomenclature codes for the devices.

The agency said it intends to process applications within 10 business days, although it notes the process can take longer if "there appear to be discrepancies" between the application and information in the ARTG inclusion for your products" or the application is lengthy. — James Miessler

Switzerland's Bioptron Fails to Control Product, Racks Up 14-Item Form 483

Swiss medical light therapy manufacturer Bioptron failed to properly deal with products that didn't meet specifications and it lacked proper documentation, FDA investigators found in an inspection of the company's Wollerau facility.

The company lacked definitions for events that needed to be reported to the FDA. For example, there were no definitions for MDR reportable events, serious injuries, or malfunctions, and there were no reporting timeframes for MDRs.

The facility lacked documentation for design input requirements and procedures for design reviews. For example, investigators noted that no documentation identified verification testing for a software revision and the critical components at the time of testing.

Design validation results, including identification of the design and the individuals performing the validation were not properly documented. For example, the usability plan was dated as approved after the usability testing had been conducted.

The Form 483 from the agency's Oct. 30 to Nov. 2, 2017 inspection notes that there was no record of any product report for any of the Bioptron light therapy systems prior to marketing the models in the U.S.

Details were also lacking in the firm's CAPA procedures. Not all activities were documented,

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

If a Root Cause Can't Be Found

What if you can't determine the root cause of a problem in your manufacturing facility? Without a known root cause, it's difficult if not impossible to specify effective corrective actions. Corrective actions, meant to prevent (or in risk-management terms, reduce the likelihood of occurrence as low as possible) need to align with the root cause(s).

If a probable or likely root cause is not identified, the corrective actions identified may not be correct or specific enough. This is where training is often inappropriately used as a default corrective action; overuse of training as the primary corrective action is a strong clue that the investigation was inadequate.

Second, one needs to show diligence in the investigation. For example, the justification that shows that you really tried to find the cause could be examining each item on a fishbone diagram and giving a reasonable rationale for why that item was not a root cause – what evidence that does not support, for example, that there was not a correct procedure in place? This does take time, but it gives the auditor or inspector confidence that you really tried in your investigation.

Based on this approach, you may want to identify a "suspected" or "probable" root cause with some justification for why these have been selected.

There are two other points to consider if you do can't discover the root cause. These are based on the definition of risk used in the tool, Failure Mode & Effects Analysis (FMEA):

Risk = (Likelihood of occurrence) x (Severity of impact) x (Detectability [using an inverse scale]).

Since we are not able to reduce the likelihood of occurrence (that is, we do not know enough about the failure mechanism to "turn it off"), we can still decrease risk by reducing the impact's severity and by increasing the efficacy of detecting the unwanted event. For example, if you cannot identify the reason why a new microbial contaminant is showing up in your environmental monitoring, to reduce the severity you would want to be sure that if the microbe is present, it can be effectively killed in the sanitization program. You might also increase the monitoring i.e., detectability) for that organism, perhaps near entryways or using a more specific sampling strategy.

Excerpted from the FDAnews management report: *Quality Management Essentials – Expert Advice on Building a Compliant system*.

FDA Cites Alber for Lack Of Design Change Procedures

Lack of design change procedures and validation as well as inadequate complaint handling resulted in a 483 for German devicemaker Alber during an inspection of the firm's facility in Albstadt, Baden-Wurttemberg.

The firm's design change procedure for its mobility aids did not ensure that all changes were controlled or validated, the agency said. For example, design changes to the smart phone application used to control the cruise mode for the twion electric motor add-on were not controlled through the human factors engineering process, and design changes were released for production without adequate controls.

A review of CAPA procedures during the May 2017 inspection showed that at least three complaints for non-conforming products were marked "closed" but not all effectiveness checks were completed. Another CAPA was opened due to complaints that the wheel did not move following a design change, and CAPAs that were considered "minor" were not added to the CAPA database.

Read the Alber Form 483 here: www.fdanews.com/09-06-18-albergmbh483.pdf.

483, *from Page 5*

and procedures didn't require validation of corrective actions to ensure devices were not adversely affected. Repair activities were also not documented.

The FDA said that the firm's nonconformity process procedures didn't ensure that nonconforming products are documented appropriately. In addition, the type and extent of control to be exercised over supplies and contractors was not clearly defined. For example, steps to take when supplier performance was inadequate were not defined, and requirements for evaluating and monitoring non-conforming incoming product were lacking. The firm also fell short on its procedures for quality audits.

Read the Bioptron Form 483 here: www.fdanews.com/09-06-18-bioptronag483.pdf.

FDA Releases Guidance on Treatments For Hay Fever, Non-Allergic Rhinitis

The FDA issued two new guidances for sponsors of products designed to treat hay fever as well as other cold-like symptoms that aren't caused by allergies — and said it considers the delivery system for a topical drug as part of its review, so the whole product is evaluated as a hybrid drug/device.

Sponsors should enroll seasonal-allergy sufferers with at least a two-year history of hay fever—and participants shouldn't start an immunotherapy or change their regular treatment or dose within at least a month of the trial. Patients with acute or chronic sinusitis, chronic asthma and/or a history of using corticosteroids, leukotriene modifiers (asthma drugs like Singulair) or long-acting antihistamines should probably be excluded from trials, the agency said.

The FDA recommends that "all key trials in the development program, including dose-ranging trials and confirmatory efficacy and safety trials, be conducted with the to-be-marketed product," the guidance says. "Depending on the nature and extent of the changes, the altered product may be viewed as a new product, necessitating a separate development program with efficacy and safety trials."

Read the hay fever guidance here: www.fdanews.com/09-05-18-AllergicRhinitis.pdf.

Read the non-allergic rhinitis guidance here: www.fdanews.com/09-05-18-NonallergicRhinitis.pdf. — Bill Myers

German Devicemaker Meluna Falls Short on Quality Standards

German menstrual cup maker Meluna fell short on medical device reporting, complaint handling, and CAPA procedures, the FDA said in a six-item Form 483 following an inspection of the firm's Haundorf facility.

The firm's MDR procedure didn't include an internal system for timely and effective identification and evaluation of events. For example, the firm's device reporting SOP didn't include adequate definitions and timelines to ensure timely submission of events subject to MDR requirements, the agency said.

The facility's procedures for handling complaints were found lacking because they didn't require information such as the name, address and phone number of the complainant, the date the complaint was received, the lot or serial number of the device and dates and results of investigations. During a review of complaint files, FDA inspectors noted that none of the complaints included any documentation of the MDR evaluation or any reply to the complainant.

CAPA procedures didn't include appropriate statistical methodology to detect recurring quality problems, and the company did not investigate the cause of nonconformities. Complaints related to a chip on the rim of a menstrual cup were not correctly documented, investigators noted. For example, there was no record verifying the corrective action of increasing the time in the mold.

Process validation procedures were also not established, and the 483 noted that there were no records of the installation qualification, operational qualification or process qualification. In addition, the facility did not ensure equipment was routinely calibrated.

Read the Meluna Form 483 here: www.fdanews.com/09-06-18-meluna483.pdf.

APPROVALS

Parker Labs Gains CE Mark For UltraDrape Dressing

Parker Laboratories' UltraDrape barrier and securement dressing was granted the CE Mark for use in ultrasound-guided peripheral intravenous (UGPIV) insertions.

The device addresses challenges that clinicians face when conducting UGPIV insertions, such as cross contamination, long procedure times, increased risk of infection and securement failure from inadequate gel removal. It also eliminates the need for additional dressings, gel and probe covers.

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

Approvals, *from Page 7*

The product allows clinicians to apply ultrasound gel to a removable film layer that keeps the sterile puncture area dry and gel-free.

FDA Clears Eden Spine's Lumbar Spine Locking Plate

The FDA granted 510(k) approval to Eden Spine's Sphynx, a thoraco lumbar spine locking plate used for spine instabilities.

The device, which is made titanium, is implanted via the antero-lateral approach and is used to treat instabilities in the thoraco-lumbar regions of the spine.

Sphynx's indications include spinal fractures, vertebral tumors, secondary instabilities of the thoracic and thoraco-lumbar spine, and other indications requiring an anterior stabilization low profile.

Meccellis Biotech Granted CE Mark For Breast Reconstruction Products

Meccellis Biotech received the CE Mark for its range of biological matrix products used in abdominal wall and breast reconstruction surgery.

The CE Mark for the products was previously withdrawn. The renewal allows its client, Surgical Innovations, to resume selling the Cellis product range.

The CE Mark covers a range of products that are due to be launched in the UK next year.

Quidel's Lyme Fluorescent Immunoassay Cleared by FDA

Quidel received FDA clearance for its Sofia 2 lyme fluorescent immunoassay, used in conjunction with its fluorescent immunoassay analyzer to detect human IgM and IgG antibodies.

The assay is used to rapidly diagnose Borrelia burgdorferi — lyme disease — from finger-stick whole blood specimens.

The device integrates wireless connectivity with an updated graphical user interface and optic system.

Embolx Earns CE Mark For Sniper Microcatheters

Silicon Valley-based Embolx earned a CE Mark for its next generation Sniper balloon occlusion microcatheters for the treatment of cancerous tumors, enlarged prostate and uterine fibroids.

The microcatheters are available in 110 cm, 130 cm and 150 cm lengths, enabling physicians to access through femoral or radial arterial sites.

The microcatheters increase therapeutic agent delivery to target areas, while protecting surrounding healthy tissues, by controlling pressure to alter blood flow. Advancements in the balloon and tip designs allow larger vessels to be occluded and improve the ability to track inside vessels.

The Sniper devices received 510(k) clearance from the FDA in June.

Cancer Screening Capsule Cleared for Marketing in Israel

Israel's Ministry of Health granted CheckCap marketing approval for its C-Scan capsule for colorectal cancer (CRC) screening.

The ingestible capsule, which received the CE Mark in January, gives physicians structural information about the endoluminal surface of the patient's colon.

The product can be used for screening CRC in patients at average risk for the disease who cannot or do not wish to receive a colonoscopy.

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FDANEWS

EU MDR Compliance: *A Checklist for Meeting Manufacturing, Safety and Performance Requirements*

The new EU Medical Device Regulation is massive… complex… and confusing… and you must be ready to comply by May 26, 2020.

When the European Union revised its system of rules for medical device manufacturers in 2017, it replaced a longstanding set of directives on specific topics with one large document that covers all aspects of making devices in EU countries.

Not only did they consolidate all the rules, they gave them greater weight. Previously, medical device directives provided guidance but did not have the force of law. The new MDR, however, contains mandates that are legally enforceable by EU member countries.

The FDAnews report **EU MDR Compliance** can help. Our editors have combed through the regulations, picking out the most minute compliance points and building them into a checklist of 200+ requirements you can use to confirm that you are satisfying all the EU mandates for device manufacturing. The report provides:

- Definitions of key terms in the EU MDR
- Knowing where to find specific requirements in the 150+ page regulation
- Checklists that walk you through every aspect of manufacturing, safety and performance requirements
- A training tool for employees new to the regulations

EU MDR Compliance: *A Checklist for Meeting Manufacturing, Safety and Performance Requirements* is the tool that collects all the requirements, explains them and itemized them in an easy-to-use form to ensure compliance.

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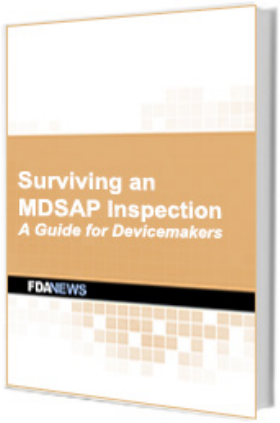

Surviving an MDSAP Inspection: *A Guide for Devicemakers*

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

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The prescriptive nature of the MDSAP model makes it relatively easy to prepare for an audit — if you know what to expect. **Surviving an MDSAP Inspection** provides all the information you'll need to understand the MDSAP model. You'll learn:

- The standard schedule for and duration of audits
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- How to create a checklist to make sure all your bases are covered
- The MDSAP grading system and how nonconformance issues can be escalated — and consequences of getting a bad grade

The management report also includes a copy of the MDSAP Companion document — the official guide — auditors will follow.

Order your copy of **Surviving an MDSAP Inspection: *A Guide for Devicemakers*** and know what to expect from an MDSAP audit and how to prepare for it.

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