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IN THIS ISSUE

Final Guidance Updates, Clarifies Medical Device Reporting Requirements

Nineteen years after issuing final guidance on medical device reporting for manufacturers, the FDA has replaced that document with updated guidance providing new recommendations on reporting adverse events, requesting reporting exemptions, submitting five-day reports, and reporting remedial actions.

The guidance also makes two significant changes to draft guidance issued in July 2013. Specifically, it clarifies the draft's recommendations on manufacturer reporting requirements when a device malfunction causes or contributes to a death or serious injury, and on requirements for manufacturer employees who learn of a reportable event.

The final guidance provides that adverse events for a device that is lawfully marketed in the United States and is being studied under an Investigational Device Exemption (IDE) are subject to reporting under both the IDE and MDR regulations.

(See **Guidance**, *Page 2)*

Draft 510(k) Guidance Should Clarify 'Significant Change' Test, Commenters Say

Draft guidance on when to submit a 510(k) for significant changes to an existing device is more specific than previous guidance but needs to clarify the test for a significant change, manufacturers' groups said in public comments.

Ruey Dempsey, vice president of technology and regulatory affairs for the Advanced Medical Technology Association (AdvaMed), said the draft guidance conflates two different tests for determining whether a new 510(k) is needed.

He said that under current regulations on device modifications, the two tests include one for a technology change that could significantly affect safety or effectiveness, and one for a major change or modification in intended use. As a result, classification of a new

(See **510(k)**, *Page 4)*

Guidance, *from Page 1*

Adverse events occurring outside the United States must be reported under the MDR regulation if the device, or a similar device in the case of malfunctions, is marketed in the United States.

In addition, the guidance describes the process for a contract manufacturer to request an exemption from MDR reporting. It also describes the process for a foreign manufacturer to request an exemption from MDR reporting to allow the importer to file a single report that will satisfy both manufacturer and importer reporting requirements.

Another update to the 1997 guidance discusses procedures for submitting five-day reports and reporting remedial actions.

In particular, it states that only events that require remedial actions to prevent an unreasonable risk of substantial harm to the public, or events for which FDA requests such a report, must be submitted as five-day reports. Other reportable adverse events should be submitted as 30-day reports.

Lastly, for a malfunction that is "likely to" cause or contribute to a death or serious injury, a firm should document whether the malfunction has actually led to deaths or serious injuries and can use this information to support a request for exemption from further reporting of the malfunction.

Kotz said the final guidance also clarifies two points from the March 2013 draft guidance.

First, the draft guidance states that if a malfunction caused or contributed to a death or serious injury, the manufacturer must report the original malfunction and all further occurrences of the malfunction for a period of two years, even if the malfunction did not cause or contribute to additional deaths or serious injuries.

By contrast, the final guidance allows a manufacturer to request an exemption from further reporting of the malfunction if recurrences have not contributed to further deaths or serious injuries and are unlikely to do so.

Second, the final guidance describes reporting requirements for manufacturer employees who become aware of an MDR-reportable event. The final guidance clarifies that anyone, including contractors or consultants that work for or on behalf of the manufacturer to review and process complaints, is considered to be an "employee" for the purposes of MDR reporting, and their roles should be defined in the company's MDR procedure.

The final guidance can be read here: www.fdanews.com/11-07-16-deviceguidance.pdf.
— Jeff Kinney

FDA Issues Draft Guidance on Ultrasonic Surgical Aspirator Labeling

The FDA has released draft guidance on product labeling for ultrasonic surgical aspirator devices that it says will contribute to their safe and effective use.

The agency recommends that manufacturers of ultrasonic surgical aspirator devices with a general indication for use in general surgery, laparoscopy, or gynecologic surgery prominently include the following contraindication in their product labeling:

> CONTRAINDICATION: This ultrasonic surgical aspirator device is not indicated for and should not be used for the removal of uterine fibroids.

The FDA also recommends that manufacturers review and update other portions of their labeling to be consistent with this contraindication. For example, a manufacturer may revise the list of procedures in the labeling for which the ultrasonic surgical aspirator can be utilized.

Read the draft guidance here: www.fdanews.com/11-09-16-guidance.pdf.

FDA Asks Industry Where to Draw the Line on Off-Label Communication

Industry proposals to loosen regulations on off-label communication neglect to provide a comprehensive framework for the FDA to monitor unapproved uses, leaving the agency to wonder where boundaries should be drawn.

AdvaMed recommends the FDA expand the scope of scientific information devicemakers can share with healthcare professionals. Scientific findings on the use of a device should not be limited to data from randomized controlled trials, said Khatereh Calleja, AdvaMed's senior vice president of technology and regulatory affairs.

The FDA should also acknowledge the value of retrospective studies, registries, observational research and meta-analysis, she said at an FDA public hearing on off-label communication.

What constitutes scientifically sound analyses or evidence for off-label uses is unclear to the agency, said FDA Commissioner Robert Califf, asking industry to provide a "better description of valid scientific information" not available to the public.

Pragmatic trials, observational studies, cost-effectiveness and budget impact models are just a few of the sources industry would like to use to derive data to disseminate to prescribers and payers for unapproved indications, said Edith Perez, the vice president and head of the US BioOncology Medical Unit at Genentech Inc.

The countless sources of data raise concerns about the appropriate vetting of information.

"Are you proposing that there should be no requirement for peer review? That the company could go directly to physicians, for example, and show the results of observational studies and case studies and all that?" asked Califf.

"There is certainly absolutely value in peer review," said Calleja, but the agency should be open to lifting restrictions on sharing a broader range of information that is currently available.

The FDA is asking that device makers expand on their proposals to clarify whether industry is hoping for a specific pathway that would allow a "company to basically keep the information to itself and promote it without going through those steps of peer review, in a way that some people might regard as not being transparent with the information," said Califf.

The FDA will accept comments on off-label communication until Jan. 9. — José Vasquez

Circulatory Technology Hit With Form 483 for Improper Reporting, Evaluations

Circulatory Technology Inc. received a Form 483 for failing to submit a medical device report (MDR) in a timely manner, properly evaluate an MDR event, establish a design history file, establish adequate design plans, and properly investigate complaints.

First, the inspector said that Circulatory Technology failed to submit an MDR report within 30 days of becoming aware of information suggesting that a marketed device had malfunctioned and likely would cause or contribute to a death or serious injury if the malfunction recurred.

The Form 483 also states that the company did not evaluate MDR events in accordance with relevant regulations. Specifically, it was notified of two MDR reports for a device but did not open any complaint files or investigate the reported MDR events for the device.

Third, the inspector said that Circulatory Technology did not establish a design history file in accordance with regulatory requirements, including establishing design inputs, planning, risk analysis, transfer, and validation.

The inspector also found that design plans that describe or reference the design and development activities and define responsibility for implementation had not been adequately established.

Finally, the inspector said the company failed to investigate complaints involving the possible failure of a device to its specifications.

510(k), *from Page 1*

device turns on two distinct characteristics that are evaluated differently.

In its regulations, the FDA "clearly recognized that technology changes require a [safety and effectiveness] test to determine if such changes require a new premarket notification, and intended-use changes require a separate test to determine whether a change in intended use may result in a new device classification," he said. "In this draft guidance, it appears FDA is conflating two distinct regulatory concepts" by applying the "safety and effectiveness test" to the question of change in intended use.

The draft guidance issued Aug. 5 addresses the extent to which an existing 510(k) clearance covers labeling or product changes before a new notification is required. A companion document covers the same subject for software changes (*IDDM*, Aug. 8). FDA received 21 comments on the draft guidance by the time the comment period closed Nov. 7.

Ralph Hall of Leavitt Partners said on behalf of the 510(k) Coalition that the final version of the guidance should specify that a new 510(k) is likely needed — rather than absolutely needed, as the draft guidance states — if a modification is "a major change in intended use" or "a change that could significantly affect safety or effectiveness."

In addition, according to Hall, the final guidance should explicitly define "cumulative" device changes in a way that does not require every change to be separately documented and evaluated.

He said each time manufacturers make a change to a device, it should be compared to the most recently cleared device. "When the manufacturer compares the most recent proposed and validated modified device to the device in the last cleared 510(k), the manufacturer is in effect evaluating the cumulative impact of all changes since the last cleared 510(k)," he said.

Hall also said the Coalition supports the FDA's focus on using the Quality Systems Regulation processes "as a critical methodological tool" in determining whether a new 510(k) is needed. "We believe that risk assessments and the use of validation and verification processes are important for prioritizing whether a modification could significantly affect safety and effectiveness while not overburdening industry or the FDA with additional 510(k)s being submitted," he said.

Finally, the Medical Device Manufacturer's Association said the draft guidance inconsistently applies the concept of risk management in assessing the impact of a change to a device — or, in some cases, fails to apply it at all. "MDMA strongly believes that a risk-based assessment should be included consistently throughout the guidance, including the examples cited which outline the process companies should undertake to determine whether a new 510(k) is appropriate," the group said.

Commenters Suggest Changes To TGA Clinical Evidence Guidelines

Draft clinical evidence guidelines for medical devices published by Australia's Therapeutic Goods Administration (TGA) should deemphasize the use of literature reviews and equivalence determinations, and instead focus on clinical evidence specific to particular devices, commenters said.

Several comments also said the TGA should generally avoid interpreting its medical device regulations and guidelines — including the clinical evidence guidelines — to provide more stringent requirements than those in the European Union, which could make the Australian market less attractive to device manufacturers.

The TGA received 19 comments by the close of the comment period June 10.

Current Expectations

The draft guidelines outline current expectations for clinical evaluation reports and underlying evidence that must be supplied by manufacturers.

The document provides specific information on the clinical evidence requirements for total and partial joint prostheses; cardiovascular devices to promote patency or functional flow; electrical impulse generators; heart valve prostheses; supportive devices such as meshes, patches and tissue adhesives; and implantable medical devices in the magnetic resonance environment.

This evidence may be requested in support of applications for conformity assessment, inclusion in the Australian Register of Therapeutic Goods, and post-market monitoring.

The Bupa Group, which delivers a wide variety of medical services in Australia and New Zealand, criticized the draft guidelines for appearing "to accommodate the presentation of literature reviews and 'equivalence' as being appropriate clinical evidence for a device, even where there are modifications to the device that would necessarily differentiate it from prior iterations."

The group said the draft guidelines may provide too much flexibility for some devices to rely on literature reviews. It recommended that clinical evidence regarding the actual device under review be the primary focus, unless there are clear and compelling reasons for a lower benchmark.

The Medical Technology Association of Australia (MTAA) had a number of specific suggestions, such as clarifying which supporting documents are required with clinical evidence. In addition, the MTAA said that:

- Randomized controlled clinical trials are in most cases unsuitable for medical devices;
- Clinical quality registries, where available, can provide a high level of ongoing safety monitoring during the post-market phase, and the TGA could use the data from such registries to ensure that adverse event reporting aligns with actual experience; and
- Manufacturers of implantable medical devices should be able to decide the best way to provide essential product information, including magnetic resonance imaging safety status.

Medtronic Australasia Pty Ltd said although the draft guidelines resemble EU guidance for clinical evaluation in many respects, the TGA's interpretation of its medical device requirements "is often to the highest level possible."

Medtronic said the provisions of the draft guidelines might be similarly interpreted when they are finalized, which will make it more difficult to bring some products to the Australian market, which is only 2 percent of the global market.

The draft guidelines can be read here: www.fdanews.com/11-09-16-TGAGuidance.pdf.
— Jeff Kinney

Epimed Lands Form 483 For Inadequate Procedures

Epimed International Inc. was cited in a Form 483 for inadequate procedures for handling of complaints, design validation, design transfer, control over products, services and suppliers, and accepting incoming products at its Johnstown, N.Y. facility.

The FDA cited the manufacturer of pain management, radio frequency, and cryoanalgesia products for five observations.

The inspector's first observation found that the company failed to adequately establish procedures for receiving, reviewing, and evaluating complaints by a formally designated unit.

The 483 also cites Epimed for not adequately establishing procedures for design validation and design transfer. For example, the validation of a catheter was approved without a missing data point regarding catheter removal being identified or corrected, and the design validation did not follow the firm's procedures.

The inspector also found that the type and extent of control to be exercised over the firm's products, services, and suppliers were not clearly defined.

Specifically, the supplier of Epimed's bulk non-sterile RK epidural needles changed production to a new site and new contract manufacturer. However, Epimed had no documentation showing approval of this change and did not define the extent of control it had over the supplier.

Finally, the inspector found that the company had not established adequate procedures for accepting incoming products, including epidural needles. — Jeff Kinney

Usefulness of New Online Reporting Tool Questioned

The FDA's new online tool for reporting regulatory misconduct could subject industry to questionable allegations that disrupt business activities while producing little useful information for the agency, Hyman, Phelps, & McNamara attorney Jennifer Thomas said.

Although there is no guaranteed way to avoid becoming the subject of a regulatory misconduct allegation, device companies can reduce potential harm by implementing internal reporting systems and promptly addressing reports that come in. They also should respond quickly and completely to FDA requests pertaining to allegations submitted through the new portal, she said.

The FDA recently launched a website where anyone can file a complaint that a medical device is violating agency rules (*IDDM*, Oct. 31). 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.

Thomas said that while it is unclear exactly how the FDA will use reports of regulatory misconduct submitted through the site, many of these reports might contain misinformation, forcing companies to prepare for unnecessary investigations and the agency to track down false leads. This is primarily because the anonymous online tool is likely to be used by competitors, either as an alternative to a trade complaint or simply to disrupt a rival's business by initiating an FDA investigation.

She said that employee whistleblowers with well-documented allegations are likely to forgo using the online tool in favor of filing False Claims Act (FCA) lawsuits, which are potentially much more lucrative. Under the FCA, a whistleblower can collect 15 percent to 30 percent of any recovery that the government receives.

In addition, Thomas said the FDA probably will not be able to handle the likely flood of reports and will have to prioritize just a few of them — a decision that could backfire if the agency fails to act on what turns out to be a serious violation.

Finally, although the FDA has said that records will not be publicly released until an investigation is complete, companies could still receive bad press tied to baseless accusations.

For instance, the FDA may close an investigation after deciding that the allegation does not warrant an expenditure of its resources, but without reaching a conclusion about the merits. The allegation then might be subject to disclosure under the Freedom of Information Act, potentially damaging the company's reputation. — Jeff Kinney

Warning Letter Cites Valeant For Quality Systems Issues

A high-precision compounding and dispensing device used to mix two solutions together received a warning letter following an inspection that revealed a failure to maintain procedures for validating the device design.

Valeant stated that clinical testing of the ONSET Mixing Pen product was conducted as part of the initial device design prior to the product being acquired by the firm, however, there was no documentation of previous validation testing and/or documentation supporting why the design validation was no longer relevant.

Additionally, the firm failed to establish and maintain procedures for the identification, documentation, validation or verification, review and approval of design changes before their implementation. The ONSET Mixing Pen, for which Valeant is a distributor, underwent a design change; but design change procedures did not assure that design validation activities occurred for the product.

Investigators also noted corrective and preventive actions surrounding field action for the ONSET Mixing Pen were incomplete. They did not address or document how their actions affected existing product in inventory.

The firm responded to all the allegations but the agency found them to be inadequate despite the firm saying it will revise design control SOP and believes the issues were an isolated incident. — Derek Major

Biocompatibles Inc. Pleads Guilty To Misbranding Embolic Device

Biocompatibles Inc. has pleaded guilty to misbranding its embolic device called LC Bead and will pay more than $36 million in criminal and civil fines, the Justice Department announced.

Pennsylvania-based Biocompatibles combined LC Bead with prescription drugs for use as a drug-delivery device or "drug-eluting" bead even though the FDA has not approved LC Bead as a drug-device combination product or for drug delivery.

In addition, the Justice Department said Biocompatibles marketed the device for drug delivery against express FDA wishes and told healthcare providers that LC Bead provided a superior therapy for certain types of cancer, despite a lack of evidence to support those claims.

Under the terms of the plea agreement before the U.S. District Court for the District of Columbia, Biocompatibles pleaded guilty to a misdemeanor charge in violation of the Food, Drug and Cosmetic Act. It also will pay an $8.75 million criminal fine for misbranding LC Bead and a criminal forfeiture of $2.25 million.

In addition, Biocompatibles will pay $25 million to resolve civil allegations under the False Claims Act that the company submitted false claims to government healthcare programs for procedures in which LC Bead was loaded with chemotherapy drugs and used as a drug-delivery device.

LC Bead is used to treat liver cancer and other diseases. It was cleared by the FDA as an embolization device that can be placed in blood vessels to block or reduce blood flow to certain types of tumors and arteriovenous malformations.

BRIEFS

DeGette, Brooks Ask FDA For Specifics on Device Cybersecurity

House Energy and Commerce Committee members Diana DeGette (D-Colo.) and Susan Brooks (R-Ind.) have asked the FDA to explain how it is addressing cybersecurity vulnerabilities in medical devices.

In a letter to FDA Commissioner Dr. Robert M. Califf and Director of the Center for Devices and Radiological Health Jeffrey Shuren, DeGette and Brooks inquired about the agency's plans to further reduce risks of hacking, unauthorized access, and use of malware in medical devices.

The representatives requested a response by Dec. 16.

Kator Receives FDA Clearance For Knotless Suture Anchor System

Kator, subsidiary to Surgical Frontiers, has gained its second FDA 510(k) clearance for its Kator Suture Anchor System.

This new FDA clearance expands the system for use with 2mm wide high strength suture tape. Made from PEEK material, a single Kator Suture Anchor is FDA-cleared for use with up to 4 strands of #2 suture or up to 2 strands of 2mm wide suture tape.

EOS Imaging Receives FDA 510(k) Clearance For kneeEOS 3D Surgical Planning Software

EOS Imaging has received a 510(k) clearance to market kneeEOS software the U.S.

The kneeEOS online 3D planning software utilizes weight-bearing 3D images and data from the EOS system to provide an optimized surgical plan for Total Knee Arthroplasty.

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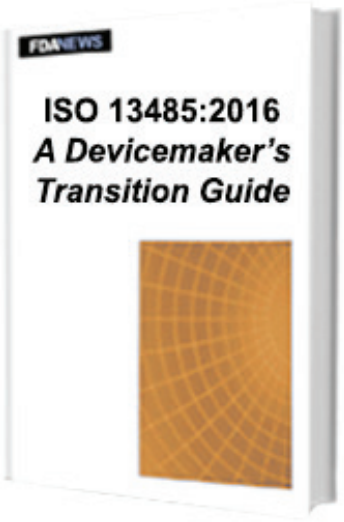

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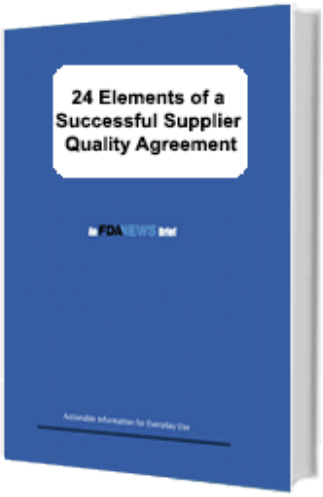

24 Elements of a Successful Supplier Quality Agreement

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