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FDA Has Regulatory Options For LDTs Even Without Final Guidance

Manufacturers should probably expect some regulation of laboratory developed tests (LDTs) next year even though the FDA has said it will not finalize its draft LDT guidance, said attorney Jeffrey Gibbs, of Hyman, Phelps & McNamara P.C.

"While many in the lab community have been praising the announcement from FDA, in our view, this fight may not be over," he said. "It may now shift from a battle over sweeping guidelines to case-by-case challenges using ill-defined criteria."

On Nov. 18, the FDA announced that it will not release final guidance on LDTs, and instead will work with Congress and other stakeholders to determine how LDTs should be regulated (*IDDM*, Nov. 21). Although it is unclear exactly what form these regulations will take, there are a number of possibilities.

(See **LDT**, *Page 4)*

User Error, Other Provisions Of Reporting Guidance Draw Praise

Final FDA guidance updating device reporting requirements clarifies the obligations of contract manufacturers and makes other welcome changes to the March 2013 draft version.

Issued Nov. 8, the final guidance provides new recommendations on reporting adverse events, requesting reporting exemptions, submitting five-day reports, and reporting remedial actions (*IDDM*, Nov. 14).

Under the draft guidance, both contract manufacturers and specification developers for a given device must comply with MDR reporting obligations. The final guidance states that a contract manufacturer only needs to comply with reporting requirements if it also distributes or markets the device.

Hyman, Phelps, and McNamara attorney Jennifer Newberger praised this revision because it "means that contract manufacturers and specifications developers can continue doing what has been done

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for years – describe their reporting obligations via contract." However, she questioned how the FDA arrived at this conclusion, which is inconsistent with the MDR regulation (21 CFR 803), the draft guidance, and the position FDA has taken in warning letters issued prior to the draft guidance.

"Nevertheless, the language in the final guidance represents a good outcome for industry: contract manufacturers do not need to report and do not need to seek an exemption to avoid doing so," she said.

Newberger added that the FDA also "walked back" its position on devices that alarm before malfunctioning, which allow clinicians to intervene before an adverse event occurs.

Under the draft guidance, if a device malfunctions, but an alarm alerts the user before the patient is harmed, the event still should be reported as a malfunction because of the potential for harm if the malfunction recurs and either the alarm does not work or no one responds.

User Error

Newberger said this example was "one of the most egregious in the draft guidance" but was modified in the final version to remove any mention of alarms. "We hope that this modification means FDA agrees that an alarm sounding with no one to respond does not constitute a device malfunction," she said.

Finally, she said the final guidance clarifies the relationship between a user error and the obligation to report a user error as an MDR.

Both the draft and final guidance state that a user error could "reflect problems with device labeling, the user interface, or other aspects of device design," and should therefore "be reported in the same way as other adverse events which are caused or contributed to by the device." This raises the question of whether a user error should be considered a "malfunction" — in that a recurrence would likely cause or contribute to death or serious injury — and is therefore reportable.

The final guidance provides that if an event is solely the result of a user error with no other performance issue, and there has been no device-related death or serious injury, an MDR report is not required. "This implies that user error that results in a malfunction is not, on its own, likely to require MDR reporting, which is good news for device manufacturers," she said.

Hogan Lovells attorneys Edward Wilson, Michael Heyl, Jodi Scott, and Dennis Gucciardo praised the final guidance for clarifying several issues that often trigger questions from device manufacturers. In particular, the guidance states that:

- Delays in surgery are reportable if the manufacturer's awareness of the delay reasonably suggests that its device may have caused or contributed to a death or serious injury, or that its device has malfunctioned and the device or a similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction recurred;
- Complications associated with the use of a device addressed in the labeling are reportable if the device caused or contributed to a death or serious injury; and
- If a foreign manufacturer and importer decide they want the importer to submit the reports for adverse events involving a product for which they both have an MDR obligation, the foreign manufacturer must submit a request to us for an exemption from filing.

Keller & Heckman Partner Rick Stearns agreed with Newberger that the provision on contract manufacturers is a welcome change.

"You're making a device on behalf of someone else and being paid to produce something to someone else's specifications," he said. "You presumably have not agreed to take on the additional regulatory obligations that come with actually marketing the product, and it seems somewhat duplicative to have the contract manufacturer responsible for that as well as the named party."

However, he said that overall, he did not find the changes between the draft and final guidance "terribly shocking or surprising."

Australia Outlines System for Notified Bodies to Assess Devices, Diagnostics

Australia's Therapeutic Goods Administration is seeking industry comments on its proposed framework for establishing notified bodies in the country to assess devices and in vitro diagnostics.

The measures are part of the TGA's regulatory reforms that call for the government to develop measures to increase access for drugs and devices in the country. The proposed regulations will be rolled out over the next two years.

The TGA proposal for devices establishes a framework for designating assessment bodies to issue conformity assessment certifications under Australia's device regulatory framework. These certificates would only be recognized in Australia.

Australia's medical device industry has long pushed for reform due to the time it takes to process applications. Currently, Australia uses European body conformity assessment certification as evidence to support marketing authorization, with the exception of high-risk devices, which require TGA conformity assessment certification.

Conformity assessment of high-risk devices requires significant expertise, which is in short supply in Australia, and developing conformity assessment bodies in the country could help establish a new industry, the proposal suggests.

Developing such bodies could add to the global body of expertise and could help expedite approval for devices. The TGA notes that two technical experts for each discipline are required to undertake assessments to provide effective oversight.

Should Assessment Bodies Certify All Devices?

The TGA asks industry to comment on whether designated Australian conformity assessment bodies should be able to provide conformity assessment certification for all medical device applications or if some device types should continue to require TGA conformity assessment certification.

The agency also wants input from device-makers on whether their organizations market devices to counties that rely on a "home market" regulatory approval, and if so, how the proposal would affect them.

Under the proposed framework, the TGA would remain the designating authority with the following main responsibilities:

- Ensure that certification bodies applying for designation meet the Australian regulatory requirements. This would mean that certification bodies would have the necessary technical, scientific and medical competence and facilities to carry out the assessments and would demonstrate the necessary level of "independence, impartiality and integrity" to act on the government's behalf;
- Monitor designated certification bodies to ensure they continue to comply with regulations; and
- Control and act on findings, including communicating to certification bodies about performance concerns, impose actions based on compliance and exercise enforcement powers where appropriate.

TGA Seeks Comments on Fees

Training assessment bodies and managing their activities will create an additional burden on the agency and will require additional funding. TGA's operations are cost recovered from industry, and these additional operations could also be cost recovered.

The agency wants comments from the industry on whether the costs of designation should be recovered directly as fees from conformity assessment bodies or whether some (or all) costs should be recovered via another mechanism such as direct charges to medical device sponsors.

The agency also asked whether there are other competitive neutrality concerns that the TGA should consider.

Conformity assessment bodies would be responsible for issuing conformity assessment

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LDT, *from Page 1*

First, the agency could step up enforcement of its October 2013 final guidance on research use and investigational use devices (RUOs and IUOs). Although there has been almost no public enforcement action in this area so far, "now that the LDT efforts are done — at least in their current incarnation — the FDA may turn its attention back to the marketing of RUOs and IUOs used in LDTs," Gibbs said.

Second, he noted that the FDA historically has tried to regulate certain LDTs by preventing distribution of collection devices needed to obtain patient samples, citing adulteration and/or misbranding. The agency could try to assert greater oversight of the lab test process by requiring premarket clearance or approval of collection devices for specific intended uses.

Third, the FDA could tell consumers and physicians that particular tests have safety risks — an approach the agency has taken before in other contexts. "As a practical matter, this kind of notice and the resulting publicity can kill a test, even though the company never got a chance to address FDA's concerns before publication," Gibbs said.

Gibbs said whatever the FDA does, it probably will not issue scaled-back LDT guidance, which industry is unlikely to accept at this point.

TGA, *from Page 3*

certifications, which would be based on full quality assurance procedures, including design examinations for high-risk devices, verification procedures, and clinical evaluation procedures among others. The bodies would also monitor and maintain conformity assessment certifications.

The assessment bodies would need to meet a range of requirements that would be based on European requirements for notified bodies.

The TGA also suggested that Australia has the option of adopting the current European designation framework. It notes that current regulations already closely parallel EU regulations. One big drawback, however, is that Australian-issued conformity assessment certificates would "still not be accepted for market authorization in Europe," and it is unclear whether Europe would recognize Australian designated certification bodes for European requirements.

The TGA asks medical device manufacturers to comment on whether the framework should be aligned to MDSAP requirements, European requirements or a hybrid. It also asked device-makers to comment on whether particular aspects of each system should be adopted.

The regulator further asked for comments on how alignment of the MDSAP and EU framework should be managed as international regulatory convergence develops further.

Read the TGA notice here: www.fdanews.com/11-22-16-TGAproposal.pdf. — Tamra Sami

Poor Supplier Evaluations Lead To Form 483 for CME America

A Colorado device maker received a Form 483 after investigators witnessed supplier observations and quality system issues. In total, six observations were listed

Investigators observed that CME America's procedures for design change were not adequately established and complaints involving the possible failure of a device were not reviewed, evaluated and investigated where necessary.

The inspection also pointed out that potential suppliers were not evaluated and selected based on their ability to meet specified requirements. The company has criteria to purchase goods and services, but lacked evidence that the criteria was met.

The company did not respond to a request for comment. The full 483 can be read here: www.fdanews.com/11-22-16-cmeamericallc483.pdf.

ANSM Issues Instructions For Clients of Denotified Bodies

French manufacturers that are clients of denotified bodies, or notified bodies that cease operation, can apply to the National Agency for the Safety of Medicines and Health Products (ANSM) to continue marketing their devices.

To apply for a marketing extension, a manufacturer must submit:

- A list of the references for all devices affected by the denotification decision;
- The sales volume and the European Union member states in which the devices are being marketed and/or distributed;
- A copy of the most current version of the CE compliance certificates identifying the devices covered by these certificates;
- A statement issued by the manufacturer certifying that its products continue to comply with fundamental requirements; and
- Identification of a new notified body, evidence that the certification process has been initiated and the anticipated date that it will be finalized.

In addition, a manufacturer must have a valid CE certificate at the time of its marketing extension application, with a date of validity subsequent to that of the denotification of the notified body.

A device may continue to be marketed while an application is pending. If the application is approved, the manufacturer may continue marketing the device until the end of the initial period of validity of the certificates, up to a maximum of 12 months following denotification of the notified body.

Finally, the manufacturer should send the audit report drafted by the new notified body and the new certificate to ANSM.

Complaint Evaluation Procedures Net Circle Prime Form 483

Circle Prime Manufacturing received a Form 483 after an FDA inspection revealed inadequate records, complaint procedures and a failure to describe its vendor rating criteria.

FDA inspectors visited Circle's Cuyahoga Falls, Ohio, facility in March and listed seven issues, including a lack of procedures for capturing, managing, and investigating complaints. Specifically, the firm had no way to capture potential complaints if a product was not returned.

The agency also determined that records of acceptable suppliers, contractors, and consultants were not being adequately established, and found that Circle lacked documentation and procedures to describe criteria for determining an approved supplier's rating or the potential ramifications of a "poor" rating.

Finally, a review of device history records for an insulation testing device showed multiple unaddressed discrepancies in the number of devices and components being manufactured and tested.

The full Form 483 can be read here: www.fdanews.com/11-22-16-circleprimemanufacturinginc483.pdf.

BRIEFS

SentreHeart Recalls Guidewire System Due to Coating Separation

SentreHeart has issued a recall for FindrWIRZ guidewire system because the PTFE coating may separate (e.g., peel, flake, shed, delaminate, slough off) from the packaging and potentially cause serious injuries to patients.

The guidewire system is used during minimally invasive procedures in the cerebrovascular, cardiovascular and peripheral vascular systems.

There are 98 systems recalled in the U.S. and they were manufactured between Jan. 4, 2016 to July 22, 2016.

FDA Confirms a 510(k) De Novo Path for EyeGate's Device

EyeGate has announced that it plans to pursue a marketing clearance of its EyeGate Ocular Bandage Gel (EyeGate OBG), via the de novo 510(k) pathway.

The ocular bandage gel is a synthetic biocompatible gel that coats the eye surface and is designed to resist degradation under conditions present in the eye.

"We look forward to announcing the top-line data from our PRK pilot study by the end of the year," the company said.

FDA's CDRH Creates Pact to Revamp Cybersecurity in Medical Devices

The FDA's CDRH has signed a memorandum of understanding with the National Health Information Sharing and Analysis Center and the Medical Device Innovation, Safety and Security Consortium to improve data sharing on cybersecurity measures.

The collaboration is intended to create a place for stakeholders to communicate and share information about cybersecurity vulnerabilities and their effects on healthcare IT infrastructure; develop an awareness framework for improving critical infrastructure cybersecurity; and encourage stakeholders to develop innovative strategies to employ measures to address vulnerabilities.

FDA Grants Xtant Medical Clearance for Allografts

The FDA cleared the Irix-C cervical cage for use with autograft and/or allograft and the expansion of the range of levels allowable from C3-T1 to C2-T1.

Their allografts, 3Demin and OsteoSponge, will be used with Irix-C due to their ability to compress, fill and expand in the device's graft chamber, allowing for ideal bone contact and fusion.

The Irix-C is a stand-alone cervical intervertebral fusion device intended for spinal fusion procedures at one level (C2-T1) in adult patients for treatment of degenerative disc disease.

These devices are available worldwide.

Allergan Receives FDA Clearance For the Xen Gel Stent

The FDA cleared the Xen glaucoma treatment system which consists of the Xen45 gel stent and the Xen injector, for use in the U.S.

The Xen glaucoma treatment system reduces inner eye pressure in patients, and is indicated for the management of refractory glaucoma, where previous surgical treatments have failed.

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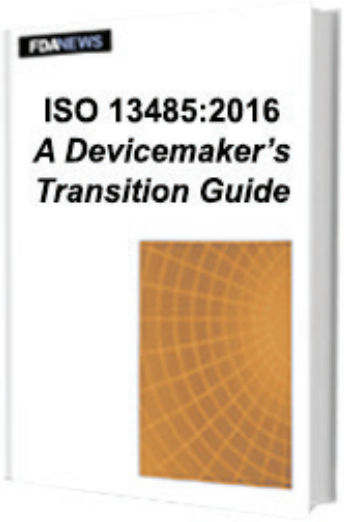

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