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IN THIS ISSUE

FDA Aims to Help Sponsors Of Biodosimetry Devices

While exceedingly rare, radiological disasters — including the detonation of an improvised nuclear devices or a nuclear meltdown — do occur. To that end, the FDA has unveiled final guidance intended to help devicemakers develop products to help in mass casualty situations.

Dated April 18, a new guidance document applies to medical device systems that aim to measure biological responses to radiation absorption. It finalizes a draft guidance released Dec. 30, 2014; however, it isn't intended for radiation doses used in the course of therapy.

(See **Biodosimetry***, Page 6)*

FDA Funding Bill Clears House Subcommittee, Device User Fees Match Agency's Request

A fiscal 2017 agricultural appropriations bill that breezed through its first congressional hurdle Wednesday proposes a slight funding increase for the FDA, but is still well below the agency's funding request.

Under the funding bill, the FDA would receive $4.78 billion for the fiscal year starting Oct. 1, an increase of $97.4 million from the current budget year (*IDDM*, Dec. 21, 2015). However, that is $320 million less than the agency requested in its budget proposal (*IDDM*, Feb. 15).

The proposal provides $2.7 billion in discretionary funding, a bump of $33 million over the current fiscal year and in line with the agency's request, with the remainder coming from user fees.

The bill estimates roughly $145 million in medical device user fees, which falls in line with the agency's request. In addition, the bill would appropriate $439.2 million for CDRH and related field activities in the Office of Regulatory Affairs.

The House appropriations Agriculture, Rural Development, Food and Drug Administration and Related Agencies Subcommittee passed the appropriations bill with no amendments by voice vote. It now goes to the full Appropriations Committee. — Cameron Ayers

Firm Hit With 10 Observations Over Alleged Reporting Issues

The FDA is accusing a medical devicemaker of neglecting to report five cases of radiation leakage from its products and other reporting violations, according to a 10-observation Form 483.

The document details findings from a series of inspections of Spectranetics' facility in Colorado Springs, Colo., between Nov. 30, 2015 and Jan. 21. The inspector allegedly observed numerous paperwork and reporting issues — chief among them a determination that the company neglected to disclose five reports between 2013 and 2015 of patients and practitioners exposed to radiation after using damaged company products.

The 483 cites complaints related to use of GlideLight and SLS Laser Sheath devices used for pacemaker and defibrillator lead removal procedures. The company has received reports of cracks, splits, damage to the outer jacket and visible laser light through the outer jacket.

Minor Burns

According to the 483, the company received complaints of individuals receiving minor skin burns from using three of their products and of visible evidence that other products were damaged, such as sparks and burning odors. In one instance, a patient died during a procedure using a Spectranetics laser sheath ablation device that was damaged. The physician using the device also sustained hand burns.

The 483 also faulted the company for allegedly neglecting to validate certain processes. However, due to heavy redaction within the document, these processes could not be determined. The inspector cited nine apparent instances of unvalidated products, which the agency tied to reports that the devices obstructed patient catheters in five cases since 2014, one of which led to a patient dying.

The document also complained that Spectranetics failed to adequately document design inputs for two of its devices.

Another concern raised by in the 483 was that the company allegedly neglected to file a Medical Device Reporting notice with the agency within 30 days of learning about a patient death tied to the use of one of its products. The death is the same one cited for the unreported accidental radiation exposure.

The inspector also concluded that the company's risk analysis procedures are inadequate, with instances of patient deaths using the incorrect risk severity level rating, while complaint reports allegedly "do not always accurately reflect the actual severity and occurrence probabilities based on continual review."

The FDA inspector also concluded that the company's procedures for corrective and preventative action omit mandatory elements, such as "verifying and validating the corrective and preventative action to ensure that such action is effective and does not adversely affect the finished product."

She also contended that the company neglected to perform "quality reaudits," citing a postmarket surveillance report due in 2013.

Protective Housing

Additionally, the inspector observed that not every laser product receives protective housing to prevent human exposure to laser and collateral radiation. As evidence, the inspector cited five complaints the company received of visible cracks in the outer jacket of one device.

The 483 also complained that product certification was "not based upon a testing program in accordance with good manufacturing practices," referencing the aforementioned product defects that purportedly led to radiation exposure.

Finally, the 483 observed that the company neglected to notify the agency of reported product defects, citing the eight reports of product damage the company has received.

Check out the 483 here: www.fdanews.com/04-18-16-spectranetics.pdf. — Cameron Ayers

Dexcom Class I Recall Linked to Alarm Activation

San Diego-based Dexcom is conducting a Class 1 recall of glucose monitoring system receivers because of an alarm failure.

The CGM systems include a below-the-skin sensor that measures blood glucose readings, which are sent to a hand-held receiver. However, the audible alarm in the G4 Platinum and G5 Mobile CGM system may not be activated in the receiver when the system detects low or high glucose levels, according to the notice.

As a result, diabetes patients who rely on the system to alert them to low or high blood sugar could see serious adverse effects, including death.

Dexcom sent out notifications Feb. 23, informing customers of the problem. According to the company, it had received complaints about the speaker component failing to provide audible alerts and alarms.

However, William Blair analysts reviewed the FDA's MAUDE database and found several dozen patient reports about the issue over the past few months. They failed to find any instances of patient harm.

Further, they don't think it will have a major financial impact.

The analysts note it is a quality issue; however, company management has not detailed how it plans to resolve the problems.

According to the analysts, Dexcom "is not planning to proactively replace the handhelds in the field," and is simply notifying patients to test their devices periodically. "We believe it has been working with its supplier to resolve the issue and is replacing the defective devices when they fail," they write, adding that management "must have concluded that the rate and risk are both extremely low and manageable with this limited response."

The company did not respond to a request for comment by press time. — April Hollis

Report: Medical Device Startups Rake in More Than $500M in Q1

Private medical device companies are continuing to rake in the venture capital cash — more than half a billion dollars, according PricewaterhouseCoopers and the National Venture Capital Association.

During the quarter, medtech saw investments of $508.3 million, a big jump over Q1 2015's $480.3 million total. There were fewer deals this quarter, however, with 59 versus 76 in Q1, according to the "PwC/NVCA Money Tree Report, based on data from Thomson Reuters."

While the Q1 total is less than the final quarter of last year, which saw $648.5 million, the industry still is on track for its historic average, according to Greg Vlahos, a partner at PricewaterhouseCoopers. Typically, the industry brings in $2 billion to $3 billion annually, he added.

He tells *IDDM* that certain trends in terms of types of companies that received funding should continue this year, with drug delivery and cardiovascular startups proving popular. Vlahos adds that a wide spectrum of different technology should catch investors' eyes.

The big winner for Q1 2016 was Langhorne, Pa.-based Aprecia Pharmaceuticals, which raked in almost $79 million. The company has created a platform — known as ZipDose — that uses 3-D printing to produce a porous formulation that disintegrates with a sip of liquid.

Coming in second was Carlsbad, Calif.-based Acutus Medical, with $75 million. The company is focused on developing technology for the minimally invasive diagnosis of complex arrhythmias.

Menlo Park, Calif.-based Spirox raked in a bit less with $45 million. The company is developing solutions for nasal obstruction.
— Elizabeth Hollis

Improving Device Sustainability Boosts Reputation, Bottom-Line

For medical device manufacturers, taking sustainability into consideration during all stages of product development not only helps the environment, but also bolsters their reputation and bottom line.

Sustainable attributes should be considered at every stage — from product conception through end of life — according to a technical information report from the Association for the Advancement of Medical Instrumentation.

Joanna Schneider, a product engineer with 3M and co-chair of the AAMI committee that developed the TIR, says consumers are the impetus for the sustainability efforts. To meet these demands, the TIR recommends that manufacturers consider ways to extend their products' life to lower environmental impacts. "For example, manufacturers could offer an extended warranty or replacement parts after the product is discontinued," the report says.

In addition, manufacturers should design devices with simplicity in mind, particularly in terms of packaging. It recommends against using packaging made up of multiple materials or that include adhesives — both of which are a barrier to recycling.

Manufacturers should consider using recycled materials whenever possible; however, they should use high-quality materials that don't pose new environmental risks.

Committee Co-chair Ramé Hemstreet, vice president of operations and chief sustainable resources officer with National Facilities Services at Kaiser Permanente, tells *IDDM* that efficient use of energy and water during the manufacturing process also save devicemakers money.

The report stresses the use of renewable energy and recycled water during the manufacturing process. For example, manufacturers can use rainwater, storm water or process water to supplement freshwater, particularly in drought-affected areas.

Proper logistics planning can also have a significant effect on sustainability, as well as cost reductions. Logistics improvements can include no-idling policies for loading docks, updated business practices for distribution centers and warehouses, new modes of transportation and use of cleaner fuels for delivery vehicles.

This focus on sustainability can also translate to savings, with the report noting that resource management "is becoming a reliable indicator of improved economic performance" for companies, with assets in sustainability-focused managed funds exceeding $5 trillion.

The report recommends continuous improvement methodologies, such as Lean Manufacturing and Six Sigma, to evaluate waste-reduction efforts and improve efficiency. Additionally, life cycle assessments help analyze the environmental impacts of design, raw materials, manufacturing, distribution and disposal. Some devicemakers are using product category environmental LCAs to find the "hot spots," or aspects of the life cycle with the most environmental impact, the report says.

One option the report floats is setting up a device take-back program when it can confer a reportable environmental benefit. Such programs close the loop on the product life cycle by controlling the movement of products to ensure the best possible usage, be it reuse, repair, remanufacturing or simply recycling.

Another to consider is emission reduction and emission capture strategies for handling medical gases, given that wasted anesthesia gas accounts for roughly 5 percent of a typical hospital's greenhouse gas emissions.

LCA-related resources include the 2013 AAMI White Paper "Elements of a Responsible Product Life Cycle," ISO 14040, "Environmental management — Life cycle assessment — Principles and framework" and ISO 14044, "Environmental management — Life cycle assessment — Requirements and guidelines."

To find out more about the TIR, visit www.aami.org. — April Hollis

Biodosimetry, *from Page 1*

While not providing specific study designs, the guidance gives an overview of the principles for studies to establish "reasonable assurance of the safety and effectiveness of biodosimetry devices." As the document notes, incorrect use of these devices could lead to inappropriate treatment for either a false positive reading or an overestimation of absorption.

Because existing methods to determine absorbed radiation take days to complete, the FDA is aiming to cut the amount of time it takes to develop a treatment strategy to patients.

To that end, sponsors should develop a validation plan to back up claims in the device's intended use statement and discuss their plans with the FDA before beginning their studies.

The agency up front acknowledges that it will be impossible to validate these devices before marketing them; therefore, they should include in their PMA submission a plan to conduct postmarket testing in the event of a real-world situation.

Unlike the draft guidance, the final document addresses the benefit of biodosimetry over physical dosimetry, which is more appropriate for measuring the actual radiation dose delivered. Biodosimetry, on the other hand, "takes into account the natural patient biological variability in radiation response," according to the document. That can prove helpful in differentiating between a patient who is radiation sensitive and one who is resistant.

Intended Use Statement

The final guidance also provides an overview of what an intended use statement should specify. It includes three items from the draft version — the nature of the analyte, specimen types for testing, for example, blood, urine or saliva, and the specific patient population — and adds a fourth: intended use setting.

In addition, the statement should include stage of response — that is, early field triage or during clinical evaluation. For the latter, "specific clinical indicators of health status should be part of the intended use statement," according to the document.

The statement also should address appropriate timeframes for testing and potential limitations, such as validation testing not being conducted in certain patient populations.

Sampling, Other Considerations

The document acknowledges that samples may be difficult to obtain during device validation. To address this problem, the agency says sponsors may use contrived samples — which are designed to mimic a patient sample — as a supplement to clinical samples. Examples include ex vivo irradiation of the appropriate matrix, spiking the analyte of interest into the appropriate matrix or using animal-derived specimens.

Other topics covered in the final document include instrumentation and software, animal study considerations, labeling and CLIA categorization.

Read the guidance here: www.fdanews.com/04-18-16-guidance.pdf. — Elizabeth Hollis

FDA Chides Florida Firm Over CAPA Procedures, Documentation

A Groveland, Fla.-based company has been taken to task by the FDA for a number of problems at its facility, including failure to identify actions to prevent recurrence of nonconforming products.

In a March 17 warning letter that followed an Oct. 13 to 15, 2015 inspection of the firm, the agency informed Miami Fat Supply — which makes Red Head, Red Head 2 and the Jordy Connection System to help with fat collection — that it failed to respond adequately to reports of faulty products. The company does not have premarket approval for the three devices, thereby making them misbranded, the letter adds.

The FDA cites instances in which the reuse of Red Head 2 has resulted in broken/cracked lids. Although the company plans to remove the product from the market until new lid material or mold is available it "will continue to distribute the Red Head 2 devices to existing customers who have not filed a complaint."

The letter also hits the company for a melted Jordy Cannula plastic connection. The device was not autoclaved properly; however, "no corrective action has been documented for the reported non-conformance."

A representative informed the FDA that the firm doesn't maintain certain records, including a CAPA request log.

In addition, the FDA alleges that the firm failed to validate sterilization processing of its Jordy Connections System and its Red Head 2 products. FDA stated that the company had not conducted or documented numerous design control procedures for Red Head 2, including documentation of design changes regarding gluing of canisters.

FDA also alleged that the company failed to adequately evaluate suppliers, contractors, and consultants in regard to the manufacture of lids, funnels, and Jordan adapters.

FDA noted that the company's October 28, 2015 response to receipt of a Form 483 inspection evaluation "did not provide adequate supporting evidence that the referenced corrections and planned course of action have been implemented." The company submitted an additional response in February for review by the agency.

The company could not be reached for comment. — Michael Levin-Epstein

FDA Creates Combination Products Policy Council to Combat Criticism

The FDA unveiled the new Combination Products Policy Council, which will have decision-making authority on issues relating to combination products, cross-labeled products and medical product classification.

Under the current regulatory scheme, the Office of Combination Products determines the lead center for the investigation of a combination product by what's called the primary mode of action of the medical product. In most cases, the type of investigational application is that typically required by the lead center. For example, if the device is the PMOA, the lead center would be CDRH, and the investigation would be under an IDE that includes the drug information.

But this system has met with increasing criticism as the number of combination products in development have escalated. Although OCP is charged with coordinating pre- and post-market review of combination products to ensure consistency, critics have asserted that this effort often has fallen short.

In making its announcement, FDA specifically noted that the council was being formed to resolve differences and inconsistencies "in statutory and regulatory requirements for different application types, including evidentiary standards, data requirements and review limitations."

The council will be housed in the Office of the Commissioner as part of a concerted effort to develop a unified FDA position on combination products. In addition to serving as a communications hub, the council will be involved in developing agency-wide and external communications, such as draft guidances and publications. — Michael Levin-Epstein

BRIEFS

FDA Clears Next-Gen Enroute TNS

Silk Road Medical has gained FDA clearance for its next-generation Enroute transcarotid neuroprotection system, indicated for transcarotid artery revascularization. The system allows for direct access to the carotid artery to target blockages that could cause a stroke. The first procedures with the device have been performed across the country.

IsoRay Cans GliaSite Due to Low Sales

IsoRay has bid adieu to its GliaSite radiation therapy system and certain ancillary products, following "marginal sales" since its introduction, the company announced in a regulatory filing. IsoRay has issued notices to end licensing agreements with Dr. Reddy's Laboratories and Hologic and has slashed a distribution agreement with Karlheinz Goehl-Medizintechnik Goehl. The system is designed to deliver brachytherapy radiation to treat brain cancer.

FDA Clears FilmArray Torch for 3 More Panels

BioMérieux subsidiary BioFire Diagnostics has garnered FDA clearance for its FilmArray Torch for use in conjunction with the FilmArray blood culture identification panel, gastrointestinal panel, and meningitis/encephalitis panel. Additionally, the system received the CE Mark.

The PCR system offers up to "six times more sample throughput per square foot of benchtop space," according to the company. The system was previously FDA cleared for use with the FilmArray respiratory panel in February.

Halyard Health to Acquire Corpak MedSystems

Halyard Health, a developer of infection prevention solutions, has entered an agreement to acquire Corpak MedSystems. Under the agreement, Halyard will pay $174 million in cash consisting of current cash and Halyard's credit facility, according to a prepared statement. Completion of the transaction is expected during the second quarter and is subject to customary conditions.

RTI Surgical Adds Solution to Streamline TL System

RTI Surgical has unveiled its Streamline TL spinal fixation system with deformity instrumentation for use in adult deformities or curvatures. The system allows for the creation of a rigid construct within the thoracolumbar spine using pedicle screws, set screws, rods and crosslinks, according to the Alachua, Fla.-based company. The device first launched in 2011, and the company has continued to expand the system's offerings over time.

Predictive Technology Group Acquires ReNovo

Predictive Technology Group has finalized its acquisition of ReNovo Biotech, which will now be called Predictive Biotech, the Salt Lake City, Utah-based company announced Tuesday. PRED will gain access to ReNovo's cellular, tissue, biomaterial and regenerative products and candidates, in addiction to distribution channels. The buy advances PRED's expansion strategy of acquiring complementary diagnostic and therapeutic companies. Financial terms were not disclosed.

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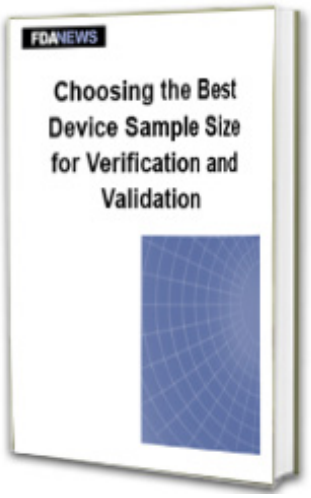

Choosing the Best Device Sample Size for Verification and Validation

If you're like many manufacturers, you understand the essence of the *21 CFR 820.30* requirement: you must run enough test samples of a product so its test results can be successfully applied to full-scale production runs. And, like many manufacturers, you've probably had trouble for years determining exactly how many units of a product you should test to satisfy the FDA.

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