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21st Century Cures Draft Bill Establishes Innovation Pathway

The House Energy and Commerce Committee has released a new, shorter draft of its 21st Century Cures legislation, setting in motion an expedited pathway to speed access to breakthrough medical technologies.

Under the proposed legislation, devicemakers developing advanced technologies that either have no alternative or offer a significant improvement over existing alternatives could apply for a priority review designation before submitting an application.

The legislation describes breakthrough technologies as offering significant advantages over existing approved or cleared alternatives, including the potential to reduce or eliminate the need for hospitalization, improve patient quality of life, facilitate patients' ability to manage their own care or establish long-term clinical efficiencies.

A team leader at the FDA would shepherd the product through a streamlined review process, including interactive communication and early agreement on clinical trial design. The draft calls for senior agency personnel to oversee these products and ensure a smooth development and review process.

HDE Criteria Expanded

The draft bill would also increase the use of humanitarian device exemptions by changing the definition of a rare disease from one with fewer than 4,000 diagnosed cases to one with not more than 8,000.

The bill would also allow devicemakers to rely more on observational studies, patient registries and real-life therapeutic use to demonstrate safety and effectiveness. The emphasis would be on reducing regulatory duplication and unnecessary delays and incorporating local considerations, community values and mechanisms to protect vulnerable populations into trial design.

The draft bill also calls for new guidance on the least-burdensome provision, which limits the amount of information the agency can request from devicemakers, and on the use of recognized standards in the device approval process.

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Certain types of medical software would be exempted from FDA regulation under the bill, including programs used in administrative, clinical or laboratory recordkeeping; programs that simply store, retrieve and transmit data; and apps to help people maintain a healthy lifestyle, such as fitness trackers. The FDA previously said it has no plans to regulate most of these products.

The Senate is developing a similar version of the bill, but it isn't publicly available.

Read the House draft here: www.fdanews.com/04-15-21stCenturyCures.pdf.
— Jonathon Shacat and Elizabeth Orr

Medtronic's SynchroMed Pain Pump Pulled Following FDA Consent Decree

Medtronic has reached a consent decree with the FDA that all but bars the company from selling its SynchroMed II drug infusion system.

The decree follows repeated flouting of FDA quality system regulations, including rules governing design controls and corrective and preventive actions. Medtronic's Columbia Heights, Minn., plant, where SynchroMed is made, has received three warning letters on similar violations since 2006. The problems could lead to over- or under-infusion or a delay in therapy for patients, the FDA says.

Medtronic met with the FDA to discuss concerns in January 2013 and said it was taking steps to address the violations. However, an April 2013 inspection found continued problems. The devicemaker's response to that inspection did not convince the FDA that the violations had been corrected.

Under the terms of the consent decree, Medtronic cannot manufacture or distribute SynchroMed II implantable Infusion Pump System units unless a physician deems the pump medically necessary. The company must also hire a third-party expert to help it develop plans to correct the various issues.

A pump remediation plan to correct the violations is due to the FDA within 20 days, and the consent decree will remain in effect until all violations are corrected, the agency says.

The remediation plan needs to include the following information:

- The identification of root causes or probable root causes of pump failures the firm plans to correct;
- A description of, and supporting documentation for, upgrades, modifications, or other actions needed to correct the failures;
- The testing planned to verify and validate the corrective actions;
- The schedule for implementing the pump remediation plan;
- How the upgrades and modifications will be made; and
- A statement regarding whether FDA approval will be required for the modifications.

Medtronic says it will focus corrective efforts on implementing SynchroMed pump design changes and enhancing the business unit's quality systems. The company is working with the FDA to address the violations as quickly as possible.

The consent decree names Medtronic CEO Omar Ishrak and Senior Vice President Thomas Tefft as defendants. View it at www.fdanews.com/05-04-15-medtronic.pdf. — Elizabeth Orr

Shuren: Most 510(k)s Now Clearing Refuse-to-Accept Bar with Ease

Devicemakers are doing a better job meeting FDA standards for 510(k) submissions, CDRH Director Jeffrey Shuren told an industry group Thursday.

In 2013 roughly 58 percent of device submissions were bounced back for failing to meet the detailed acceptance standards, Shuren told an FDA Town Hall session at the Medical Device Manufacturers Association's annual meeting in Washington, D.C.

That rate has since fallen to 30 percent, and CDRH is establishing a pilot program to let

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reviewers accept imperfect submissions at their discretion, Shuren said.

Even better, a full 90 percent of submissions are approved or classified as approvable after two cycles, Shuren said. The most common hold-ups are GMP inspections and labeling concerns, and CDRH is looking at moving inspections earlier in the device review cycle to avoid approval delays, he added.

The device center also has seen success with a program allowing manufacturers to submit questions and receive written answers before a formal presubmission meeting, Shuren said. In some cases, companies have cancelled the meetings because their questions had been fully addressed in writing.

Turning to staff training, Shuren said the experiential learning program, which sends CDRH employees into the field to meet with devicemakers, has seen more than 560 CDRH employees visit 57 locations. The agency is looking for more manufacturers to participate.

The center director also noted a priority of speeding device trial approvals, including allowing devicemakers to apply for investigational device exemptions earlier in the development process. The median IDE review time has dropped to 30 days in 2015, from 442 days in 2010. And the center has approved 17 IDEs since the first of the year versus 10 at this point a year ago.

The expedited process is allowing U.S. device approvals to catch up with the rest of the world, Shuren said, noting the previous delay between European and U.S. approval could be as long as five years.

CDRH also is focusing on quality, the center chief said. For example, the agency recently set up a CAPA system, known as Feedback CDRH, where stakeholder complaints are collected and reviewed in a standardized manner. The result, Shuren said, is a customer satisfaction rate of 88 percent — better than the center's target goal of 80 percent by June 2015.

The center has also been reviewing its traditional standards for evaluating device risk and is now placing a greater emphasis on patients' willingness to tolerate some risk if there is a true benefit from the device.

CDRH staff members are now allowed to approve devices posing a greater possibility of risk so long as patients accept that, Shuren said. For example, some devices may be approved with an indication for use only with patients willing to tolerate the different risk profile.

Shuren added that forthcoming guidance will clarify benefit-risk considerations in device clinical trials.

Shuren also discussed the agency's approach to regulating innovative technology, such as next-generation sequencing. Traditional diagnostics test for only one condition; modern DNA sequencing can check for as many as 3 million. To address that, CDRH is allowing manufacturers to submit results addressing the accuracy of next-generation sequencing tests based on only a subset of the data. One test for cystic fibrosis already has been approved in this way. — Elizabeth Orr

Experts: Don't Look to Congress For FDA LDT Guidance Fix

Legislation to overhaul the FDA probably won't touch the regulation of laboratory-developed tests, experts say.

Draft legislation now being circulated by the House Energy and Commerce Committee does not address the FDA's right to regulate the tests, but some still hope LDT provisions will be added to a final version of the bill *(see story, page 1).* LDT regulation has been addressed by both houses of Congress in larger 21st Century Cures hearings.

The FDA issued a risk-based LDT regulation proposal in 2014 to act on a perception that the increasingly complex nature of the tests and their proliferation in healthcare settings warrants stricter regulation than they currently get under the Clinical Laboratory

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Improvements Act, which is administered by the Centers for Medicare & Medicaid Services.

Speaking at a recent webinar hosted by the American Association for Clinical Chemistry, attorney Peter Kazon, with Alson & Bird, said he believes the FDA's draft guidance on LDTs will be finalized without congressional involvement. Absent congressional intervention, he expects the final guidance to be issued by the end of 2016 to avoid needing to restart in a new administration.

Kazon and Vanderbilt School of Medicine's James Nichols both expressed concern that the FDA's and CMS' oversight mechanisms will overlap, confusing labs and test equipment manufacturers. Nichols also wants the agencies to clarify how many times labs would be inspected and by which agency.

While a recently announced FDA-CMS task force on LDT regulation may help in that regard, it won't alleviate manufacturers' concerns completely, Kazon says. "The joint task force may look at the overlap between [quality system regulation] requirements and CLIA, but that doesn't solve many of the concerns that have been raised about the guidances in general," he tells *IDDM*.

"Moreover, while it may clarify where the line is between QSR and CLIA, it doesn't answer the questions that many laboratories will have concerning how to comply with the QSR requirements themselves," Kazon says.

FDA manufacturing standards also could hurt LDT makers, the lawyer says. While laboratories already follow common international standards to ensure safety, these aren't used when sourcing solvents, salts and other raw materials used in making diagnostics under the FDA's quality management systems rules. The draft guidance also leaves questions about how LDTs will be classified, Kazon says.

Moreover, clinical lab resources already are strained due to low reimbursement levels, Nichols notes. Investing toward research required for FDA approval, as well as any user fees the FDA imposes, could squeeze some labs out of the business, he says. — Elizabeth Orr

CDRH on Target to Complete PMA Code Review This Year

CDRH has reviewed 69 percent of PMA products approved before 2010 — exceeding its 2014 target — as it works to implement a goal of speeding new technologies to patients without compromising safety.

Under its 2014-2015 strategic goal of balancing premarket and postmarket data collection during the premarket application review, CDRH aimed to review half of those product codes by the end of last year. PMA codes created since 2010 weren't included because the device center needs more information on postmarket performance of these devices before evaluating them for a change in classification or data collection requirements, CDRH says.

In a retrospective review published April 29, CDRH listed 42 product codes identified as

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candidates for reclassification, three that were reclassified in 2014 and 96 expected to remain unchanged.

The list includes 21 codes for products considered candidates for reclassification into Class II, such as cervical dilators, certain laser and testicular hypothermia devices. Codes were placed in this category if it was determined that special controls would suffice to provide reasonable assurance of safety, CDRH says.

Another 21 codes were determined to be candidates for reduced premarket data and greater reliance on postmarket controls or data collection.

Products under these codes include silicone gel-filled breast prostheses, cervical cytology slide processors and radionuclide microspheres.

Ninety-six codes — including pacemakers and heart valves, intraspinal catheters, cochlear implants, multifocal intraocular lenses, hip prostheses and glucose sensors — should remain in Class III with no changes to data collection, CDRH says.

CDRH is working to have 75 percent of product codes reviewed by June 30 and 100 percent by the end of the year. Once that is done, the FDA will prioritize candidates for reclassification and for change in data collection to determine how to ensure the greatest impact, the review says.

The review follows the release of two guidances by CDRH and the Center for Biologics Evaluation and Research last month on balancing premarket and postmarket data collection for devices and expedited access to devices for patients with life-threatening or irreversibly debilitating conditions.

CDRH seeks public comment until June 29 on the product codes it has reviewed. Read the guidance at www.fdanews.com/04-28-15-Premarket.pdf. — Charlotte Astor

TGA Updates Guideline on Reducing Medical Device Assessment Fees

Australia's Therapeutic Goods Administration has updated the procedures for determining when fees can be reduced for audits and conformity assessments of medical devices.

Under the guidance, issued April 24, the TGA may reduce the fee by 70 percent if an applicant can show there is a public health need for the device or that it would not be commercially viable for the devicemaker to pay the full amount.

Application fees also may be lowered based on the amount of regulatory assessment already undertaken by the TGA or a recognized conformity assessment body, such as a European notified body, the agency says.

The revised guidance doesn't include exact reduced fee amounts for the various circumstances that allow for a shortened conformity assessment, but rather describes scenarios for shortening the assessment and provides a description of how to determine the reduced fee.

Read the guidance, which replaces a 2011 version, at www.fdanews.com/4-15-TGA-Fees.pdf. — Jonathon Shacat

NuVasive Agrees to Pay $13.8M Over FCA Allegations

NuVasive announced Wednesday that it will pay nearly $14 million to settle a U.S. government investigation.

The tentative settlement with HHS' Office of the Inspector General will see NuVasive paying $13.8 million, including fees, to resolve the concerns, which involved possible false or improper claims submitted to Medicare and Medicaid. The company does not anticipate a corporate integrity agreement as part of the settlement.

In July 2013, HHS subpoenaed NuVasive for claims records from January 2007 to April 2013,

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with the request focused on interbody quantitative and biologic, Osteocel bone graft and thermograph devices.

The move comes several weeks after NuVasive announced a new CEO, Greg Lucier. He replaces former CEO and founder Alex Lukianov, who was asked to step down over noncompliance with expense reimbursement and personnel policies.

Spokeswoman Stacy Roughan says the staff change is unrelated to the settlement.

The agreement should be a boon for the company, says Leerink Research analyst Richard Newitter, who notes the ongoing investigation lowered stock prices and distracted company management.

He expects the cost of the settlement to be relatively minor as compared to NuVasive's $400 million cash on hand.

The company will release its first-quarter earnings on May 4. — Elizabeth Orr

Quality Electrodynamics warned Over CAPA, Complaint Handling

The FDA handed Quality Electrodynamics a warning letter for poor complaint handling, CAPA and validation practices, including failure to adequately validate suppliers.

The April 10 letter says that MRI body coils returned for repairs aren't properly evaluated to see if they meet the criteria for complaints. A database search of complaints received during the past two years revealed 10 reports of burns and 28 reports of heat that weren't documented, evaluated or investigated as complaints.

Although the Mayfield Village, Ohio, company has added additional key words to generate complaints from the repair database, its procedure doesn't require a retrospective review of repairs to determine which stem from complaints and should be evaluated or investigated, the FDA says.

The letter also cites CAPA procedures — specifically the company's engineering change orders for designs of printed circuit boards.

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According to the investigator, the validation of the surface mount technology process completed in January 2014 identified design issues related to the parts for the circuit boards which are components of the MRI coils. But despite updating its CAPA procedures, the system doesn't address whether a corrective action will be taken for circuit board issues identified during the SMT validation.

The FDA also dinged the company for failing to implement quality requirements for suppliers — specifically, to validate that suppliers properly use processes such as oxide coating used in manufacture of circuit boards and electrical assemblies.

Quality Electrodynamics says it has updated its procedures and that suppliers whose processes require validation have been added to its audit schedule. The company takes the observations in the warning letter seriously, President and CEO Hiroyuki Fujita tells *IDDM*.

The warning letter followed a Feb. 10 to March 9 inspection. Read it at www.fdanews.com/04-21-15-Coils.pdf. — Charlotte Astor

FDA Bans Infant Evacuation Chair Due to GMP Violations

The FDA has banned imports of Doro's Evacu B wheeled stretchers for infants, after a Nov. 10-13, 2014, inspection found serious GMP violations related to the device.

An FDA spokesman confirmed that all devices from Ottawa, Canada-based Doro have been placed under detention without examination, which prohibits devices that have not met GMPs from entering the U.S.

Doro manufactures security devices and wheeled stretchers for infants and adults. The company's website says the Evacu B is the only neonatal hospital evacuation chair that requires only one nurse to move six babies from a neonatal intensive care unit.

The violations were noted in the November inspection and Form 483. The company must provide a written response describing corrections planned or undertaken within 15 days to lift the ban.

The investigator cited Doro for not including specifications for the device or its production process, including production methods, procedures and environment specifications, in its device master record. The DMR also lacked quality assurance procedures and specifications, including acceptance criteria, a March 9 warning letter says.

Also missing from the DMR were packaging and labeling specifications and procedures for installation, servicing and maintenance.

Doro also lacked records on evaluations of custom component suppliers. Although the firm revised its evaluation procedures, the process still lacks requirements for evaluating suppliers for quality and removing them when necessary and doesn't provide for ongoing supplier evaluation, the warning letter says.

Doro's design control procedures also came in for a hit. According to the investigator, the design history file for the Evacu B lacks records for reviewed or approved design inputs or verification. Requirements for addressing ambiguous or conflicting design input requirements also are missing.

The company further failed to ensure that equipment is routinely calibrated and checked. Doro's procedures say that special devices are calibrated before each use, but don't define how the calibration is performed.

The FDA also found that tools used for in-process and finished device testing were in use before the inspection, but were not calibrated until the last day of the inspection. Doro also has no record of nonconforming product or rework activities and no requirement for investigation of nonconforming product, the warning letter says.

Doro President Douglas Gervais tells *IDDM* the company has hired outside consultants to address the administrative issues in the warning letter. Read it at www.fdanews.com/04-21-15-Doro.pdf. — Charlotte Astor

IN BRIEF

BSX Settles Transvaginal Mesh Lawsuits

Boston Scientific has settled part of a series of lawsuits alleging the devicemaker's transvaginal mesh product for urinary incontinence is defective and causes complications, the Marlborough, Mass., company said. Boston Scientific plans to pay an estimated $119 million to resolve 2,970 cases, a fraction of the more than 25,000 mesh claims it is contending with in U.S. federal and state courts. The agreement is tied to a $35 million verdict in a Dallas County, Texas, district court case that is subject to appeal. The company lost two federal trials, in West Virginia and Miami, and was ordered to pay $18.5 million and $26.7 million, respectively. Women complained of suffering pain, bleeding, infection and injury while using the Pinnacle device. The devicemaker denied allegations the product was to blame for plaintiffs' complications and won its first two mesh cases in Massachusetts state court.

Uterine Balloon Tamponade Developed

Cambridge Design Partnership is seeking funding for its Uterine Balloon Tamponade designed to help medical professionals treat life-threatening postpartum hemorrhage, specifically in developing countries, the UK devicemaker said. Current UBTs cost as much as $200 and have to be inserted by trained clinicians, which limits their use in developing countries. Cambridge's UBT is meant to bridge the gap between commercial and condom catheters, lowering costs and allowing for patient safety when administered by minimally trained birth assistants. The devicemaker is seeking partners and funding to continue the UBT's development process.

Stent Graft System Clinical Trial Starts

Medtronic has launched a clinical study to evaluate the efficacy of the Endurant Evo abdominal aortic aneurysm treatment stent graft system, the Ireland-based devicemaker announced. The company recently conducted the first implant of the device. The multicenter clinical trial will enroll 140 patients at up to 30 sites in the U.S. and Europe. The study's primary safety endpoint has been designated as the proportion of patients experiencing a major adverse event within 30 days of implantation. The FDA has designated the device for investigational use only.

Abbott Pregnancy Test Gets FDA Nod

Abbott's i-Stat Total β-hCG pregnancy blood test has won FDA regulatory approval, the Abbott Park, Ill., devicemaker announced Thursday. The first-of-its-kind blood test rapidly and accurately detects the hormone commonly associated with pregnancy, the company says. By measuring very low hormone levels in the blood, the test can determine if a woman is in the early stages of pregnancy within 10 minutes. Previously, medical professionals had to rely on urine-based testing, which can be difficult if a woman in an emergency setting is dehydrated, experiencing pain or unconscious. By displaying results that specify the amount of the hormone present, the i-Stat test could potentially cut down on false-negative readings.

The i-Stat blood test is currently available in Canada, Europe, the Middle East, South Africa, Australia and New Zealand.

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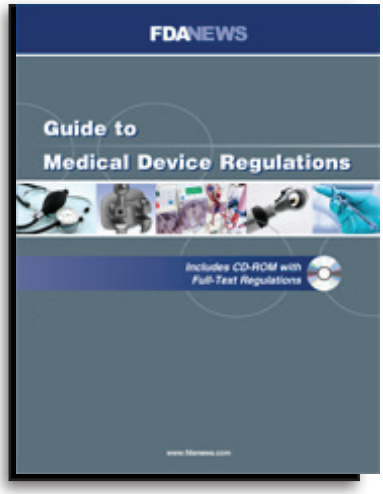

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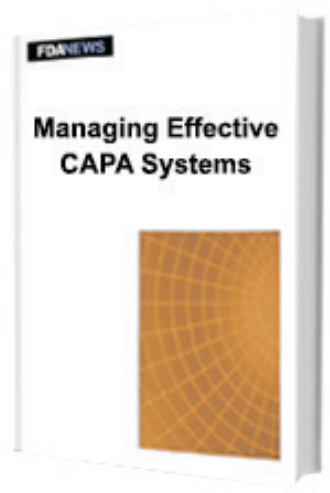

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