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IN THIS ISSUE

Editor's Note: Due to the holidays, *International Devices & Diagnostics Monitor* will not be published Dec. 28, 2015. The next issue will be published Jan. 4, 2016.

President Obama Signs Government Funding Bill Into Law

The U.S. House and Senate on Friday adopted a sweeping deal to keep the government running through next fall, under which the FDA would be awarded $4.68 billion in total funding for fiscal year 2016.

Part of that amount includes more than $2.7 billion in discretionary funding — a $132 million increase from the previous year — reflecting a 5 percent hike.

The amount is roughly $90 million to $100 million above the House and Senate committee bills passed earlier this year, and $14 million below President Barack Obama's budget request, according to an analysis by the Alliance for a Stronger FDA.

The bill passed easily, with a 316 to 113 vote in the House and a 65 to 33 vote in the Senate. Obama signed the year-end appropriatons bill late Friday.

(See **Appropriations**, *Page 2)*

A Look Back at 2015: Regulatory Reform, Safety, Inspections

2015 was a year of significant regulatory developments around the world. The Indian government began laying the groundwork for a complete overhaul of the country's medical device regulations. Meanwhile, EU officials have been unable to reach agreement for proposals on medical device and in vitro diagnostics regulation. The 21st Century Cures Act was blessed by the U.S. House of Representatives. The focus also was on inspections and audits. The EU signed on as a full observer to the International Medical Device Regulators Forum's single audit program. China's FDA warned that devicemakers can expect surprise inspections. In terms of safety, Ireland launched a medical device vigilance system. Meanwhile, concerns were raised over the risks of duodenoscopes, morcellators and cybersecurity. Finally, the FDA moved a step closer to new leadership, with Robert Califf getting nominated as commissioner.

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Appropriations, *from Page 1*

The Alliance for a Stronger FDA described the funding as a "victory," adding that the distribution of funds appears to largely mirror the priorities of the administration's request.

According to a review of the bill, the Center for Devices and Radiological Health will receive $430 million, up from the $421 million it received the previous year. Of the total, nearly $138 million will come from user fees, up from roughly $128 million.

The bill also contains a provision for a moratorium on the 2.3 percent medical device excise tax for 2016 and 2017 (s*ee story, page 3*).

Obama had promised to veto legislation that would repeal the tax. However, during a Wednesday press briefing, White House Press Secretary Josh Earnest said the President is willing to go along with the two-year suspension of the device tax, citing some important measures in the legislation.

Read the bill here: www.fdanews.com/12-16-15-Fiscal2016OmnibusBill.pdf. — Michael Cipriano

Year in Review, *from Page 1*

Regulatory Issues

India proposed an amendment to the country's Drugs & Cosmetics Act of 1940, although the measure has been tabled in the Parliament. Subsequently, the Health Ministry proposed changes to the Drugs & Cosmetics Rules to regulate medical devices separately from pharmaceuticals through the law ministry. The legal authority is greater with the statute versus the rules, but the Association of Indian Medical Device Industry still welcomed the proposal, saying it would pave the way for greater investment and R&D in the country.

In the U.S., Robert Califf was nominated as FDA commissioner, to fill a void left by Margaret Hamburg. AdvaMed applauded President Barack Obama's decision to nominate Califf, saying his background as one of the nation's preeminent cardiologists allows him to understand the value that medical technology brings to improving patient outcomes. However, the nominee faced disapproval from Democratic presidential nominee Sen. Bernie Sanders (I-Vt.), who cited Califf's so-called "cozy relationship with industry."

The House of Representatives passed the 21st Century Cures Act, which includes improvements to the FDA's premarket program for medical devices. The bill includes the establishment of an expedited pathway for breakthrough, innovative technologies, but also would apply Medicare rates for durable medical equipment to Medicaid. The measure has stalled in the Senate.

The FDA is planning to issue final guidance in 2016 on how it will enforce the regulation of laboratory-developed tests. Meanwhile, China's State Council unveiled guidelines intended to make the device approval process more science-based and efficient.

Brazil's president issued a decree implementing last year's anticorruption law, allowing for stiff fines and penalties to devicemakers involved in bribing government employees.

In Europe, a trialogue has been under way between the EU Council, Parliament and Commission for proposals on medical device and in vitro diagnostics regulation. It appeared the parties would not be able to reach an agreement by the end of this year, due to too many outstanding political issues, Erik Vollebregt, an attorney with Axon Lawyers in the Netherlands, tells *IDDM*. Still, experts anticipated a further reduction in notified bodies, and advised devicemakers to choose their notified bodies carefully.

Risks & Safety

In the EU, the debate over device regulations on reprocessing was compounded by reports of outbreaks of antibiotic-resistant superbugs in the U.S. linked to the use of reprocessed duodenoscopes.

(See **Year in Review**, *Page 4)*

U.S. House, Senate Funding Bill Includes Device Tax Suspension

Devicemakers may get a reprieve as part of a bill passed by the U.S. House and Senate on Friday that included a provision to suspend the 2.3 percent medical device excise tax for 2016 and 2017. President Barack Obama signed the year-end omnibus appropriations bill late Friday.

Obama had promised to veto legislation that would repeal the tax. However, during a Wednesday press briefing, White House Press Secretary Josh Earnest said that although the temporary suspension of the tax is not supported by the administration, "we're willing to go along with it because of the important measures that are included in this legislation."

Industry has been pushing for an outright repeal of the medical device tax. Although the suspension is a compromise, it also represents an important positive for the industry, says Lawrence Biegelsen, a senior analyst with Wells Fargo Securities.

"A two-year delay lays the groundwork for future delays or an outright repeal in our view," he says.

AdvaMed, the Medical Imaging & Technology Alliance and the Medical Device Manufacturers Association applauded passage of the legislation.

The tax has been a drain on the economy and has halted investment in research and development for advanced imaging and other life-saving technologies, says MITA Board Chairman Nelson Mendes, president and CEO of Ziehm Imaging.

Earlier this month, the Senate voted 52 to 47 in favor of H.R. 3762, also known as the Restoring Americans' Healthcare Freedom Reconciliation Act of 2015, which contains a provision to repeal the device tax. That vote followed an Oct. 23 House vote of 240 to 189 to pass the measure. (*IDDM*, Dec. 4).

Read the text on the device tax moratorium here, under Section 174: www.fdanews.com/12-15-HouseBill.pdf. — Jonathon Shacat

FDA Issues Final Guidance on Minimally Invasive Glaucoma Surgical Devices

The FDA has given its final word on how sponsors of implantable minimally invasive glaucoma surgical devices should conduct clinical and nonclinical studies to support a premarket approval.

Sponsors should follow patients during clinical studies for at least 12 months prior to submitting a premarket application for MIGS devices, according to the final guidance. If follow-up will be less than 24 months, sponsors should provide justification based on a benefit-risk analysis.

The endpoint for primary effectiveness should be the percentage of subjects with a reduction of at least 20 percent in mean diurnal intraocular pressure from baseline. The secondary endpoint should be the mean diurnal IOP change from baseline.

Also, the FDA recommends nonclinical testing, saying it should be performed on the finished sterilized product that is intended to be marketed. Biocompatibility testing should consider factors such as cytotoxicity, sensitization, ocular irritation, genotoxicity and carcinogenicity.

Bioabsorbable materials should be tested for toxicity, with assessments continuing until the polymer is no longer present in the tissue, or until the biological tissue response is demonstrated to be stable, the guidance says.

The final guidance, issued last week, is largely similar to a draft version released earlier this year (*IDDM*, Feb. 6).

Twelve comments were submitted, including some addressing the inclusion of pre-perimetric glaucoma — optical coherence tomography changes and optic nerve changes without any field abnormalities. But, the FDA does not believe pre-perimetric glaucoma should be included in interventional studies because there are differing expert opinions about whether the condition warrants surgical treatment.

Read the final guidance on *Premarket Studies of Implantable Minimally Invasive Glaucoma Surgical Devices* here: www.fdanews.com/12-15-FDA-MIGS.pdf. — Jonathon Shacat

Year in Review, *from Page 2*

Indeed, the FDA tightened reprocessing rules in response to an outbreak of antibiotic-resistant bacteria linked to duodenoscopes.

Issues surrounding the risks of power morcellators remained a hot topic, following an FDA safety alert issued last year saying the instrument's blades could spread unsuspected cancers in as many as one in 352 cases. The Federal Bureau of Investigation launched an investigation into whether major devicemakers and their customers routinely broke the law by failing to report adverse events related to uterine morcellation.

Ireland launched a national eALert system intended for healthcare facilities to help prevent recurrences of medical device-related adverse events. Implementation of the system coincided with the launch of a tool that provides opportunities for service areas to gain an informed picture of the quality of services and practices in relation to device equipment.

Elsewhere, New Zealand finalized an update to the code for executing medical device recalls, while Malaysia issued new rules on incident reporting. South Africa proposed guidelines on recalls and withdrawals.

Cyberattacks were highlighted as a risk, with the U.S. Inspector General of HHS saying networked devices pose a security threat. A report by Forrester Research predicted that hackers will target medical devices for cyber extortion as early as next year.

Inspections & Audits

FDA investigators were busy conducting quality system inspections at international facilities, with inspections at foreign manufacturers jumping by more than 29 percent between 2013 and 2014 — from 460 to 594.

China's FDA issued guidance warning that devicemakers could expect surprise inspections.

The EU signed on as a full observer to the International Medical Device Regulators Forum's single audit program. MDSAP pilot full members are the U.S., Australia, Brazil, Canada and Japan. — Jonathon Shacat

FDA, Industry Make Progress On MDUFA IV Negotiations

Negotiations continue to move forward for the fourth installment of the Medical Device User Fee Act, with FDA and industry representatives focusing attention on improving performance of the review process.

The FDA is proposing to introduce new user fees to increase review capacity for *de novo* requests and pre-submissions, according to Nov. 18 meeting minutes released earlier this month.

The FDA says there has been an upward trend in the number of *de novo* requests, thus increasing the agency's workload. That additional work — coupled with limited resources — means the FDA is meeting the 120-day target for about 40 percent of *de novo* requests.

"FDA proposed that user fees be provided to increase review capacity such that 70 percent of *de novos* can be completed within 120 days by the end of MDUFA IV," the meeting minutes say.

The Medical Device Manufacturers Association, Medical Imaging Technology Alliance and AdvaMed want more and are pushing for 90 percent of direct *de novos* to receive a decision in 120 days, while 90 percent of post-not-substantially-equivalent decision *de novos* would receive a decision in 90 days.

Meanwhile, the third-party 510(k) program has experienced increasing review times and a sharp decline in use. The FDA believes that "a course correction is needed," following a recent survey of agency staff who assessed 510(k)s reviewed by third parties. According to survey results, 80 percent of submissions had major issues in five key areas, including not providing a substantial equivalence rationale, not providing a summary of the review and not providing a comparison to the predicate device.

As a result, the FDA has proposed a multi-pronged approach by training and auditing third parties, providing redacted example reviews, tracking the scientific quality of the review memos, removing incompetent third parties and tailoring the program for specific, targeted areas.

"With dedicated resources to correct and maintain oversight of the program, FDA proposed to make a decision on 85 percent of third party 510(k)s within 30 days by the end of MDUFA IV," say the meeting minutes.

During the previous MDUFA IV meeting, which took place Oct. 26, stakeholders and FDA officials nominated priorities for reauthorization of the program, including incorporating patient perspectives in FDA reviews, using data from device and patient registries more efficiently for pre- and postmarket purposes and coordinating the FDA's work in areas such as combination products and companion diagnostics to ensure adequate user fee funding (*IDDM*, Nov. 13).

Read the Nov. 18 meeting minutes here: www.fdanews.com/12-15-MDUFA-Minutes.pdf. — Jonathon Shacat

bioMerieux Recalls Etest Kits Due to Performance Shift

Ireland's Health Products Regulatory Authority issued a safety notice last week advising patients to stop using Etest kits that include piperacillin/tazobactam antibiotic, following a recall initiated last month by bioMerieux SA.

The manufacturer received reports from customers of low minimum inhibitory concentrations. Data analysis showed the performance of the test has shifted when compared with the published characteristics, bioMerieux says in a field safety notice.

The Etest potentially could report false susceptibility results for piperacillin/tazobactam, the company says. "This risk may lead to medical intervention for the patient because the erroneous result could negatively influence the selection of antibiotic therapy," it adds.

bioMerieux did not respond to a request for comment by press time.

Read the safety notice and field safety notice here: www.fdanews.com/12-15-Etest-Notice.pdf and here: www.fdanews.com/12-15-Etest-Letter.pdf, respectively. — Jonathon Shacat

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FDA Launches precisionFDA Online Portal for NGS Analysis

The FDA is hoping to improve the quality and accuracy of genomic tests, through the launch of a new online portal that will allow for collaboration on developing the science behind next-generation sequencing.

Users of precisionFDA will have access to a reference sample of DNA for validating human genome sequences developed by the National Institute of Standards and Technology. The platform also provides a private area to conduct genome analysis and comparison against reference material, as well as a community area to publish and share results.

Launched last week, the initiative could one day enable doctors to diagnose, treat or cure patients based on their genes, say director of the FDA's office of health informatics Taha Kass-Hout and precisionFDA project manager Elaine Johanson in an *FDAVoice* blog post.

The FDA sits on a vast mountain of data that potentially could be useful in the future of new drug development, repurposing existing products and resurrecting molecules currently on the shelf, says Peter Pitts, president of the Center for Medicine in the Public Interest.

"If the agency database can indeed be made available, it's a step in the right direction. We'll never know unless we try — and that's precisely what the FDA is facilitating," he tells *IDDM*.

More information is here: https://precision.fda.gov/. — Jonathon Shacat

EMA Issues Q&A on Consultation For Ancillary Products in Devices

Devicemakers should submit a letter of intent to the European Medicines Agency at least six months in advance before they plan to seek an initial consultation on an ancillary medical substance or ancillary human blood derivative incorporated in a device, according to a new question & answer guidance.

The initial application should be submitted to the EMA using the eSubmission Gateway or the eSubmission Web Client. It also should be submitted in parallel to the appointed rapporteur, co-rapporteur and peer reviewer, using the Common European Submission Platform.

Following the consultation, devicemakers should submit Type IA, IB or Type II variations to the EMA, as well as the appointed rapporteur and co-rapporteur. Submissions should include the application, a cover letter, the procedure number and relevant documentation.

Read the Q&A here: www.fdanews.com/12-15-EMA-QA.pdf. — Jonathon Shacat

FDA Goes After More Companies For Selling Unapproved DTC Tests

The FDA has taken Genomic and Healthspek to task for marketing direct-to-consumer tests that appear to meet the criteria of medical devices, but have not been cleared by the agency.

In separate letters to the companies, the FDA highlighted Genomic's tests for Plavix (clopidogrel) response, Coumadin (warfarin) sensitivity and Nolvadex (tamoxifen) response, as well as Healthspek's drug metabolism test, which is known as Healthspek PGT.

The agency directs the companies either to provide the FDA clearance numbers for the tests, or explain why they don't believe that they are required to obtain clearance.

The letters follow similar correspondence sent by the FDA to Kalios Genetics, Harmonyx, DNA-Cardiocheck, DNA4Life and Interleukin Genetics.

The FDA has shrugged off complaints that its efforts are hindering innovation, maintaining it is contacting the companies to make sure the tests are safe and effective (*IDDM*, Nov. 25).

Genomic tells *IDDM* the company is preparing a response to the FDA letter, but declined to elaborate because it does not comment publicly on ongoing discussions with regulatory agencies. Healthspek could not be reached for comment by press time.

Read the letters to Healthspek and Genomic here: www.fdanews.com/12-15-FDA-Healthspek.pdf and www.fdanews.com/12-15-FDA-Genomic.pdf. — Jonathon Shacat

BRIEFS

FDA Panel to Discuss Leadless Pacemaker

An FDA advisory committee will discuss clinical trials, postapproval study design and physician training requirements for leadless cardiac pacemaker device technology during a meeting in February. The Circulatory System Devices Panel will make recommendations on topics such as the acceptability of adverse event rates in acute and chronic timeframes as well as indications for use. The meeting is scheduled for Feb. 18. Read the *Federal Register* notice here: www.fdanews.com/12-15-FDA-CSD.pdf.

Medtronic to Open Ireland Facility

Medical device giant Medtronic has unveiled plans to open a new facility in Galway, Ireland to manufacture its IN.PACT Admiral drug-coated balloon for the treatment of peripheral artery disease. The decision to open the new facility was based on the existing high-tech capability and expertise at the site in drug-device combination products for the company's coronary business, according to the Irish devicemaker. The facility — which will have 20,000 square feet of space with 8,000 square feet for manufacturing — will cost about $14.3 million.

Avita Scores FDA EAP Designation for ReCell

The FDA has granted Avita Medical's ReCell expedited access pathway designation. ReCell enables a clinician to quickly create regenerative epithelial suspension — an autologous suspension comprising the cells and wound healing factors necessary to regenerate skin — with a small sample of the patient's skin, in approximately 30 minutes. Avita has recruited 26 of the target 30 patients for the trial of the device that will take place at seven burn centers. The company estimates that ReCell will receive regulatory approval in the third quarter of 2017. It is currently CE marked in Europe, TGA-registered in Australia and CFDA-cleared in China.

Hoang Long to Distribute CytoSorb in Vietnam

Medical distributer Hoang Long Pharma has reached a multi-year agreement to distribute CytoSorbents' CytoSorb extracorporeal cytokine adsorber in Vietnam. Financial terms of the agreement were not disclosed. Using blood purification to control deadly inflammation, CytoSorb works to reduce the "cytokine storm" that could cause massive inflammation, organ failure and death in critical illnesses such as sepsis, burn injury and trauma. The device is approved in the EU with distribution in 32 countries around the world.

Alimera Inks Pact With MEAgate

An Alimera Sciences unit has entered an agreement that will allow MEAgate International to distribute the ILUVIEN implant throughout the Middle East. Under the agreement, MEAgate will open a scientific office for Alimera in the Middle East to support regulatory, medical affairs, sales and marketing operations. The ILUVIEN implant — which has U.S. regulatory sign off for the treatment of diabetic macular edema — is designed to release submicrogram levels of fluocinolone acetonide for 36 months. Countries included in the agreement are Bahrain, Egypt, Iraq, Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia, the United Arab Emirates and Yemen. An estimated 16 million people are living with diabetes in these countries, according to Alimera.

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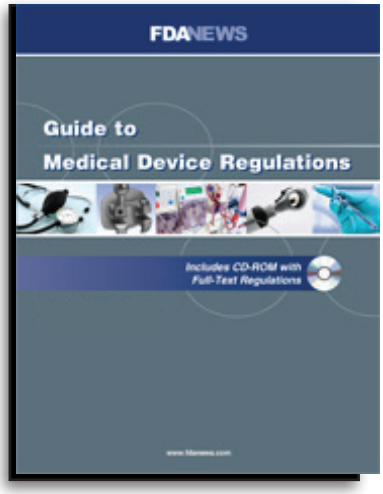

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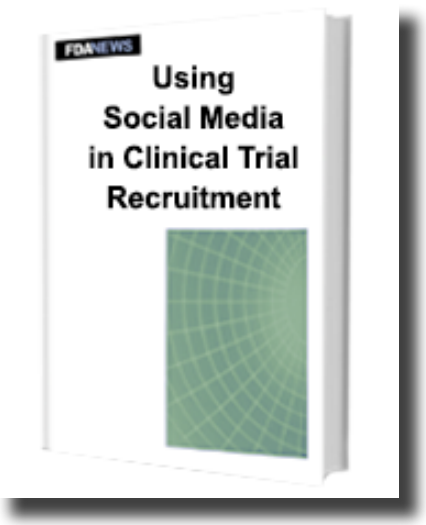

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