INTERNATIONAL DEVICES & DIAGNOSTICS MONITOR

Vol. 4, No. 8
Feb. 19, 2018

IN THIS ISSUE

Gottlieb Details Plans for Allocating Administration's FY2019 Budget

FDA Commissioner Scott Gottlieb offered a closer look at initiatives and investments the agency would pursue in support of novel medical technologies using new funding requested in the Trump administration's budget for FY 2019.

Most of the proposed increase in the FDA's budget authority is targeted for expansion of the agency's capabilities for advancing innovative drugs and medical devices. The proposed budget would increase the FDA's discretionary budget authority by $663 million (13 percent) from the FY 2018 continuing resolution — including an increase of $473 in budget authority and $190 million more in user fees — for a total budget of $5.8 billion.

A total of $435 million would be invested in FDA infrastructure, including costs for modernizing its facilities, and another $486 million would be allocated to efforts to approve medical devices and drugs at a faster pace, as well as to reduce time and cost of manufacturers' market entry.

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China FDA to Issue Hundreds of Revised Device Standards Over Next Two Years

China's Food and Drug Administration plans to revise more than 300 standards by 2020, according to a new two-year plan for bringing the country's medical devices and in vitro diagnostics up to international standards.

The standards will cover technical requirements for development, risk management, quality control and clinical trials.

The revisions are part of ongoing reforms including more stringent medical device standards, improved quality system management and oversight as well as improved inspections. CFDA also wants to encourage innovation within the country, and the agency said it will identify priority areas for innovative device development to meet unmet needs.

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Budget, *from Page 1*

Gottlieb said the additional resources would help advance new and existing initiatives to promote innovation among manufacturers and broaden patient access through greater market competition.

The budget request also "provides the FDA with the resources to continue to fund our current programs at consistent levels" and harness the potential of continuous manufacturing platforms, Gottlieb said.

"These manufacturing platforms can bring more business back to the U.S., help lower drug and device development costs and reduce the risk of shortages," he said.

New funding under the proposed budget would boost efforts already underway within CDRH. These include establishing a voluntary program for device manufacturers that meet objective criteria to receive certification. CDRH launched the Case for Quality Voluntary Medical Device and Product Quality pilot program late last year and began looking to enroll nine participants last month (*IDDM*, Jan. 9).

For those manufacturers that receive certification under the program, the FDA intends to allow the use of third-party certifiers and to offer other regulatory incentives, Gottlieb said.

"These actions would increase manufacturing innovation, accelerate availability of high-quality devices to patients and foster a competitive marketplace around device quality…that would advance device innovations, reduce manufacturing costs and improve the quality and safety of medical devices," he said. Creating this kind of marketplace became crucial for devices not just because of their iterative nature, but because they are now more complex, he added.

CDRH also would use the new resources to create a new regulatory paradigm for digital health technologies and advance the use of real-world evidence in pre- and post-market regulatory decision-making — two efforts that are already underway.

The paradigm shift is taking place along with the launch of the digital health software Pre-Certification program, with nine participating companies ranging from diabetes startup Tidepool and wellness wearable company Fitbit to major tech companies like Apple and Samsung (*IDDM*, Feb. 5).

According to Gottlieb, the agency would also use the budget increase to create a Center for Excellence on Digital Health with a cybersecurity unit.

"Implementing these regulatory innovations and information technology improvements are essential for advancing software-based technologies…as the current regulatory framework is not well-suited for driving the development of safer, more effective software-based devices, including the use of machine learning and artificial intelligence," he said.

In addition, the National Evaluation System for health Technology Coordinating Center (NESTcc) launched 11 demonstration projects this month with a $3 million FDA grant to explore the use of robust RWE in support of the FDA's plan to increase the use of RWE. NESTcc said it chose projects, which involve participation from the FDA, Medtronic, Abbott, Me2Health, and many others for their "potential to provide proof of concept for innovative and scalable approaches to RWE generation across the medical device total product life cycle" (*IDDM*, Feb. 12).

Read the full budget request here: www.whitehouse.gov/wp-content/uploads/2018/02/msar-fy2019.pdf. — Ana Mulero

NPPA Extends Coronary Stent Caps Through 2019 With Modest Revisions

India's National Pharmaceutical Pricing Authority has extended its order imposing coronary stent price caps, with a slight increase for bare metal stents and a dip for drug eluting stents.

The new price caps came into effect on Feb. 13, a day after NPPA's initial decision to fix ceiling prices on stents was set to expire, and it will remain in place through March 31, 2019.

The authority held three stakeholder meetings to revisit its February 2017 decision to introduce sharp decreases in prices, and it heard a lot of the pushback citing research showing that any cost saving resulting from price controls have not been passed on to patients in the past.

Industry groups such as AdvaMed argued the caps would negatively impact manufacturers' ability to pay for future R&D investments and job creation.

Wait-and-See Mode

AdvaMed's member companies in the India market have been in a "wait-and-see mode" since last year due to the uncertainty around viability of market success, Abby Pratt, vice president of global strategy and analysis, told *FDAnews*.

The trade association has about 30 members, including Abbott, Medtronic, Philips, and 3M, with a presence in India, but they have been holding off on expanding their market footprint, or are suspending future stent sales, he said.

Several stent manufacturers have applied to withdraw their brands from the market in India, the NPPA confirmed. Others "seem to have held up the process, probably waiting to see NPPA's decision," Pratt said.

NPPA considered allowing differential prices based on generational improvements to reward innovation. There was also a major push for drug eluting stent prices to be separated from those for bare metal stents, especially from U.S. manufacturers, to ensure future innovative growth in the sector.

But NPPA ultimately sided with domestic manufacturers who argued that there is no adequate clinical evidence of imported stents' superiority over theirs to support preferential prices, and that the previously set 8 percent trade margin for all coronary stents has led to the elimination of unethical market practices such as exploitative pricing.

NPPA reduced the DES price cap from Rs 30,180 (US$ 471) to Rs 27,890 (US$ 435), and increased the BMS cap from Rs 7,400 (US$ 116) vs. Rs 7,660 (US$ 120).

Same Bracket

The authority also decided to leave the stent types in the same bracket and the import duty capped at 8 percent as this "makes it imperative on Indian manufacturers to further improve the quality of their products so as to be able to compete" with stents that are U.S. FDA-approved and/or CE Marked.

Pratt said AdvaMed and its members are "deeply disappointed" by the decision because it "goes against patient interest by failing to reward innovative technologies thereby limiting patient choice for current and future medical device generations/innovations."

NPPA dismissed study findings showing that price controls have not provided the intended patient relief, contending that this was due to resistance at the hospital level to pass on the full benefits to their patients.

The authority directed coronary stents manufacturers in India to issue new price lists and ensure continued availability of all brands.

The authority imposed price caps on knee implants last year and has reportedly been considering controls on additional medical devices. — Ana Mulero

Standards, *from Page 1*

The policies are aimed at strengthening China's domestic device manufacturers, according to BMI Research.

"A growing number of hospital procurement initiatives giving priority to local products and government support for domestic innovation will enhance the competitiveness of Chinese medical devices, further increasing pricing pressures.

The drive to reduce dependence on imported products is gaining momentum under the 13th Five-Year Plan (2016 -2020)," the research group said, in a Feb. 13 report.

BMI noted that, in 2017, several Chinese provinces launched initiatives to boost uptake of domestic products. For example, Anhui province published an action plan stipulating that government-funded projects must purchase domestically produced medical devices.

In Guangdong province, the municipal government is giving priority to domestically produced equipment, as part of its public hospital reform program. The province has also set quotas for public hospital purchasing of domestically produced large scale medical equipment.

Similar initiatives are taking place in Liaoning province, Shangdong province, Sichuan, and Zhejiang.

The BMI report pointed to government support for device innovation under the 13th Five-Year Plan as another driver to increase the competitiveness of Chinese medical devices. "Local companies are starting to move into higher-end products to challenge the dominance of multinationals," the report said.

For example, EziSurg Medical, a Chinese developer of innovative endoscopic surgery products, whose easyEndo surgical stapler is already competing with Johnson & Johnson's stapling devices.

As more Chinese devicemakers enter the premium sector of the market, prices will be driven down, BMI said.

CFDA said it will continue to deepen international exchanges and cooperation in medical device standards to encourage its domestic sector to become more competitive.

The agency is also committing more staff resources to support a sustained and stable infrastructure. By 2020, the number of staff in the medical device standard management center will reach 70, and there will be an additional 200 full-time staffers for positions in technical committees and standard management.

China updated its good manufacturing practices in 2014, and the GMPs have been gradually phased in over the last four years. All device manufacturers were expected to be fully compliant with the GMP standards effective on Jan. 1, 2018.

Companies making sterile devices, particularly implantable devices, are being closely watched in China, and quite a few multinational devicemakers have had their overseas plants inspected.

PEOPLE ON THE MOVE

Medtronic appointed **Alex Gu** as senior vice president and president for its greater China region, including mainland China, Hong Kong, and Taiwan. Gu was previously vice president of regional growth initiatives for Greater China, and leader of Medtronic's minimally invasive therapies group in the region. Gu brings nearly 20 years of experience in the China healthcare market. He joined Medtronic as part of the Covidien acquisition in 2015. Previously, he served at McKinsey & Company, General Electric, and Sabic in China and in the U.S. He was one of AdvaMed China Council's founding steering committee members.

Cardiovascular Systems named **Rhonda Robb** as new chief operating officer. Robb formerly served as vice president and general manager for heart valve therapies at Medtronic. In that role, she was responsible for the transcatheter and surgical valve franchises. Previously, she held leadership positions in Medtronic's coronary, peripheral and cardiac rhythm businesses.

FDA Warns German Device Firm Over Lack of Procedures

A four-day FDA inspection of Curasan's manufacturing facility in Frankfurt, Germany revealed a lack of manufacturing and adverse event reporting procedures.

At the time of the agency's visit last May, the firm lacked documented design validation in the design history file — completed in July 2009 — for its Osbone Dental device. It also had failed to establish a procedure for the manufacturing of its IngeniOs HA-Synthetic Bone Particles, according to an FDA warning letter.

The firm's July 2017 response to these GMP violations, first noted as Form 483 observations, described corrections such as revising documentation and personal training. But it did not specify whether the effectiveness of the corrective actions had been verified, and did not include reviews of all existing products and potential adverse events.

The FDA also flagged nonconformities in the firm's complaint handling procedures. Curasan had failed to establish a requirement for evaluating complaints to determine whether they should be reported to the FDA under the medical device reporting regulations.

None of the 11 complaints that were reviewed by the FDA during the inspection had been evaluated for MDR reportability, and the firm also admitted to having no written MDR procedures.

The firm submitted an MDR procedure for review as part of its response to the 483. But the FDA deemed the identified corrective action to be inadequate. The procedure lacked definitions for certain key terms. — Ana Mulero

Stages of Complaint Management

Warning letters that mention problems in complaint handling typically say that a company has either failed to document a procedure or failed to implement it. Both of these are critical to establishing a robust complaint handling process, which includes four broad stages:

Stage One: Receipt and Documentation

Creation of a complaint file is triggered by receipt of a comment that alleges a deficiency matching the FDA definition of a complaint.

Stage Two: Evaluation

The complaint management unit must then characterize the complaint in accordance with the attributes included in the FDA definition—quality, durability, reliability, safety, effectiveness or performance. A single complaint may involve more than one of these attributes.

Stage Three: Investigation

Once a complaint has been deemed potentially reportable as an MDR under 820.198, a designated individual within the complaint handling unit must promptly begin an investigation.

Stage Four: Remediation

Reporting requirements are governed by 21 CFR 806 – Reports of Corrections and Removals, which explains that any action taken to correct or prevent a potential "risk to health" must generate a report. The regulations define that risk as "a reasonable probability that use of or exposure to the device:

1. Will cause serious adverse health consequences or death; or
2. May cause temporary or medically reversible adverse health consequences, or an outcome where the probability of serious adverse health consequences is remote."

The challenge manufacturers face is determining which situations fall under the second part of the risk-to-health definition and require a corrections and removals report rather than an MDR or do not need to be reported at all. Some companies decide to take the conservative approach and file both reports just to cover all the bases.

Excerpted from the *FDAnews* management report: *Complaint Management for Devicemakers: From Receiving and Investigating to Analyzing Trends*.

FDA Clarifies How to Get Feedback Prior to Marketing Submissions

The FDA used a Q&A format to issue final guidance on an informal, non-binding process for sponsors to obtain preliminary feedback before submitting marketing applications.

Sponsors of medical products have the option of obtaining preliminary assessments using the Pre-Request for Designation (Pre-RFD) process — available through the Office of Combination Products (OCP) — with regard to the "regulatory identity or classification of a human medical product as a drug, device, biological product, or combination product," the FDA said.

The process also lets sponsors know which center within the FDA — CDER, CDRH, or CBER — will regulate a non-combination product, or will have the primary jurisdiction over the premarket review and regulation of a combination product. Information on both the product classification and appropriate center can also be received as a formal, binding determination with an RFD.

But the "more flexible option" has become "increasingly customary with sponsors, and for some, even preferable to the formal RFD process," according to the FDA. As such, the new guidance provides some clarifications and recommendations on the process used by FDA staff to review a Pre-RFD, the general timeframes for sponsors to receive feedback, the types of information that should be included in a Pre-RFD, and the process for sponsors to request a meeting with OCP.

The office intends to provide feedback on the two-part process — preliminary classification and jurisdictional asessment — within 60 calendar days or "communicate the need for more review time…in a timely manner." Pre-RFDs should be clear and concise to receive timely reviews.

Sponsors are encouraged to "pay particular attention" to five sections of a Pre-RFD, which can be submitted at any point throughout a product's development. These include the complete product description, its intended use; how it works; and any previously made or planned claims about the product. If it may be a combination product, the submission should also include any available information that relates to the "relative contribution of each of its components to the overall intended therapeutic/diagnostic effects of the combination product," the agency said.

Considering a teleconference rather than an in-person meeting with OCP, and contacting the agency to present any additional information to the submitted Pre-RFD if a sponsor disagrees with the preliminary assessment are among the other recommendations in the guidance.

The submissions are not required of any sponsors, and are not needed for every product, as some already have well-established classifications and jurisdictional assignments. But for those that don't, using this process to better understand how these products will be regulated by the FDA "will help lead to better decision-making for your company," the FDA said.

Read the final guidance here: www.fdanews.com/02-15-18-PreRFDGuidance.pdf. — Ana Mulero

MDSAP Accepts NSF Health Sciences as Auditing Body

The Medical Device Single Audit Program Regulatory Authority Council authorized NSF Health Sciences as an official auditing organization.

The MDSAP program continues to gain momentum as a cornerstone of the International Medical Device Regulators Forum (IMDRF) initiative for aligning international medical device regulations. MDSAP auditing organizations help ensure manufacturers across all participating jurisdictions are meeting the quality management system requirements of ISO 13485.

IMDRF gained its 10th member, South Korea, late last year, joining the U.S., Europe, Canada, Australia, Japan, Brazil, China, Russia, and Singapore (*IDDM*, Dec. 29, 2017).

The way MDSAP audit reports will be used varies among the different jurisdictions. For example, the U.S. FDA intends to substitute them for routine medical device inspections whereas Health Canada will use them as part of marketing clearances, making the audit certificates a requirement for high-risk devices, beginning Jan. 1, 2019.

Kim Trautman, executive vice president of medical device international services at NSF International says the benefits of MDSAP participation are "two-fold in that government resources can be focused on high-risk or problematic medical devices and manufacturers that are not in compliance with the regulations, and manufactures will be able to have one audit satisfy the requirements of all participating regulatory jurisdictions." — Ana Mulero

APPROVALS

FDA Clears Smart Watch For Epilepsy Management

Massachusetts-based devicemaker Empatica obtained FDA 510(k) clearance for its Embrace smart watch intended to aid patients with epilepsy management.

The wearable device uses machine learning technology to monitor patients to detect dangerous, convulsive seizures and alert caregivers. It also monitors sleep, rest, and physical activity.

Masimo Gets CE Mark for Heart Disease Screening App

Masimo, a Switzerland-based global developer of health monitoring technologies, received a CE Mark for its critical congenital heart disease newborn screening application called Eve.

The new mark allows for Eve to be used in the EU with the company's Rad-97 Pulse CO-Oximeter device.

The application features an automated synchronization algorithm designed to reduce calculation errors and it provides visual instructions, animations, and an easy-to interpret display of screening results.

Orthofix Snags FDA Nod For Expandable Spine Fusion System

The FDA cleared Orthofix International's Forza XP expandable spacer spinal fusion system.

The system is indicated for posterior or transforaminal lumbar interbody fusion procedures for patients with degenerative disc disease. It enables surgeons to place bone graft material inside the device after implantation.

FDA Approves RadioGenix System for Key Medical Isotope in Diagnostic Imaging

NorthStar Medical Radioisotopes received FDA approval for its RadioGenix System indicated for producing technetium-99m, the most widely used radioisotope in medical imaging.

The Tc-99m diagnostic agent is intended to aid clinicians in diagnosing ailments, such as coronary artery disease and cancer, by producing images of internal organs and evaluating their function.

The new technology was "the result of a broad collaboration across the federal

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government and industry, and has the potential to benefit many patients as well as restore the U.S. ability to domestically supply a critical medical diagnostic tool for the first time in 30 years," said FDA Commissioner Scott Gottlieb.

"Because the imaging agent has a limited shelf life, a stable supply chain is critical," he said.

Canon Medical Imaging System Snags Expanded Clearance

Canon Medical Systems received expanded 510(k) clearance for new neuro and cardiac MR imaging capabilities on its Vantage Galan 3T XGO Edition.

The system's expanded capabilities were designed to provide higher resolution brain diffusion weighted imaging with "up to 30 percent improved signal-to-noise ratio," the device-maker said.

It is also features the company's MultiBanD SPEEDER technology for faster image sampling.

Naviswiss Miniature Hip Navigation Unit Snags CE Mark

Switzerland-based medical technology company Naviswiss received a CE Mark for its Total Hip Replacement THR miniaturized handheld navigation unit.

The navigation system is designed to aid orthopedic surgeons in implanting artificial joints with greater accuracy to reduce time and costs of surgical procedures.

According to Naviswiss, the system provides surgeons "cup alignment, leg length and offset."

FDA Approves Expanded IDE Program for Skin Regeneration Device

Regenerative Medicine Company AVITA Medical received FDA approval to increase the number of patients by 20 who can receive treatment with its skin regeneration medical device under the agency's Compassionate Use Investigational Device Exemption program.

This is the fifth expansion the FDA has approved for this program, bringing the total number of patients who may be treated with the RECELL Autologous Cell Harvesting Device to 88.

FDA Approves Becton Dickinson HPV Assay

The FDA granted premarket approval to Becton Dickinson for its BD Onclarity HPV assay.

The assay is performed on the company's molecular platform for automated sample processing for the detection of high-risk HPV using samples from cervical cancer screening using the BD SurePath liquid-based cytology vial.

Viz.AI Scores FDA Nod For Stroke Care App

San Francisco-based healthcare company Viz.AI received FDA marketing authorization for its stroke care ContactCT application.

The software device provides clinical decision support using deep learning algorithms to automatically analyze CT neuro images for the detection of indicators associated with stroke.

It also notifies clinicians when a potential stroke is identified in their patients, enabling direct-to-intervention care. The company obtained a CE Mark for ContactCT just last month.

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Risk-Based Monitoring of Clinical Trials 2017: *New Trends and Best Practices*

The biggest driving factor behind implementing risk-based monitoring (RBM) of clinical trials is savings. Centralized monitoring of trial sites based on risk profile is cheaper, less resource-intensive and, ultimately, more efficient.

But consider this: trials that are using RBM have found that it increases the effectiveness of quality control as well as data accuracy, according to a recent survey by QuintilesIMS. Here are some other key findings:

- The top therapeutic areas using RMB are dermatology, oncology, biologics and immunology;
- Use of RBM in Phase 2 through Phase 4 studies is increasing; and
- RBM users are increasingly shifting from 100 percent on-site monitoring to some degree of remote monitoring.

Most telling of all is that more than half of survey respondents not currently using RBM plan to implement it within the next two years.

The new FDAnews management report **Risk-Based Monitoring of Clinical Trials 2017: *New Trends and Best Practices*** will show you, step-by-step, how to properly design and implement your risk-based clinical trial monitoring program to fully satisfy the FDA's requirements.

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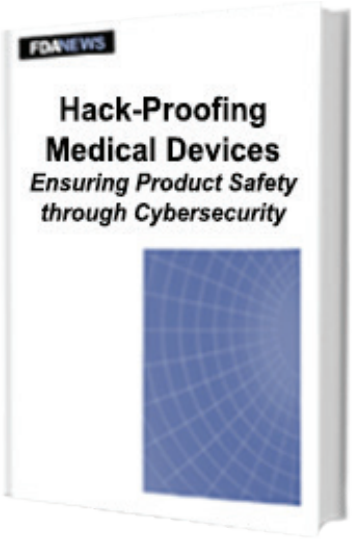

Hack-Proofing Medical Devices: *Ensuring Product Safety through Cybersecurity*

How does the FDA expect you to fight cyber incursions?

With the recent release of the final guidance on postmarket management of cybersecurity, you now have advice from the agency.

The key is awareness — of product vulnerabilities, current threats, developments in cybersecurity protection, how to defend your company from disastrous liability litigation… and the list goes on.

Hack-Proofing Medical Devices will show you how to get — and keep — control of your devices' networked operations. The management report covers:

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