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IN THIS ISSUE

Gottlieb Highlights Medical Device Initiatives in FY 2019 Budget Hearing

FDA Commissioner Scott Gottlieb featured new agency initiatives for medical devices in remarks to a Senate Appropriations subcommittee on the FDA's fiscal year 2019 budget request, flagging changes that could lower product development costs and boost safety.

"The investment you made in the FY 2018 Omnibus budget helps support programs that made 2017 the most successful in the FDA's history, with a record number of approvals of innovative and generic drugs and novel medical devices," Gottlieb said, adding that the FY 2019 budget request "builds on these goals."

Overall, the FY 2019 budget requests $5.8 billion in total resources for FDA, which includes an increase of $473 million in budget authority and $190 million in user fees.

The request includes $100 million to advance the use of real-world experience to inform patient care and provide potentially

(See **Budget**, *Page 2)*

FDA Spells Out Policy and Considerations For Multiple Function Devices

The FDA recommended factors to consider and precautions to take for premarket submissions of multiple function device products, noting there is no all-encompassing approach for the wide variety of multiple function devices.

The guidance defines the term "function" as a medical device product's distinct purpose, such as its intended use or a subset of its intended use. For example, a product whose intended use is to analyze data has a single function: analysis. A product with intended uses to store, transfer and analyze data has multiple functions: storage, transfer and analysis. A device's multiple functions could impact other functions and thus the device's safety and effectiveness.

The device function under review should be separated from other device functions "in its design and implementation," the agency said,

(See **Policy**, *Page 2)*

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lower cost ways to develop clinical data to expedite medical product development, he said.

The proposal would create the capability to conduct near-real-time evaluation down to the level of individual electronic health records for at least 10 million individuals from a broad range of healthcare settings.

The agency is taking steps to modernize its approach to the review of medical devices and assure their safety, he said, noting the budget proposal "builds upon our efforts as part of the [National Evaluation System for Health Technology], which is a public private partnership under the Medical Device Innovation Consortium."

With the new investment, FDA will be able to link across data sources, including electronic health records to evaluate broader sets of endpoints that are not easily accessible today. This will be a fundamental shift from passive to active device surveillance.

"These are transformative initiatives that can modernize the foundation of FDA oversight and improve patient safety," he said.

Read Gottlieb's remarks here: www.fdanews.com/04-24-18-Appropriations.pdf.

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noting it is easier to independently review the function's safety and effectiveness when it has higher degrees of separation from other functions.

"Architecture decisions early in the design cycle can facilitate optimal separation and support segregation necessary for risk control," it said.

When separation cannot be attained, connectivity between the reviewed function and other functions should be explained and appropriate controls should be made to reduce the adverse impact of other functions on the safety and effectiveness of the function under review.

The agency recommended that manufacturers consider the role other functions play in the performance of the function under review, as well as any limitations of using other functions with it, but noted that a relationship may not necessarily impact the safety or effectiveness of the reviewed function.

For example, it recommended that manufacturers consider if the device function under review relies on results from another function, or if they share the same output screen or code necessary for proper execution of the reviewed function.

In addition, manufacturers should develop multiple-function hardware and software specifications for the product to ensure the other functions perform when used with the function under review, and they should determine how to ensure appropriate actions are taken by the user when using the other functions with the function under review.

Read the guidance here: www.fdanews.com/04-26-18-DeviceProducts.pdf. — James Miessler

IMDRF Roundup: Working Groups Discuss Updates in Progress

The International Medical Device Regulators Forum released updates from its working groups on good regulatory review practices, unique device identifier harmonization, adverse event terminology and standards.

The Good Regulatory Review Practices Working Group reported on its efforts on harmonizing premarket requirements to improve efficiency in premarket reviews. The group is working on a proposed document on essential principles of safety and performance of medical devices and in vitro diagnostics.

The group is updating the document to reflect key changes of the EU Medical Device Regulations and ISO 16142. The work will streamline device and IVD requirements, update requirements for software as a medical device (SaMD), cybersecurity and performance characteristics of IVDs.

In addition, the working group is updating IMDRF's labeling and the instructions-for-use document based on global updates. It plans to submit a draft document in May.

Global Harmonization for UDI

The Unique Device Identifier Applications Guide Working Group is developing a globally harmonized approach to applying a UDI system. A preliminary draft is currently under review, covering responsibilities for establishing and maintaining a UDI, placement of UDI on all packaging and labeling, use of UDI in forms and databases, and general principles for implementing a UDI system and database.

The working group intends to consider the draft at its June teleconference and a final document could be available by December 2018.

The IMDRF's Adverse Event Terminology and Coding Working Group released updated IMDRF terminologies for categorized AERs in September 2017, but three additional annexes are now at the consultation stage, covering health effects terms and conditions that are based on FDA terms and refer to MedDRA.

The move aligns with the FDA's plans to update its adverse event codes this spring and to deploy CDRH's electronic medical device reporting system and eSubmitter software.

Code hierarchies posted on FDA.gov are linked to IMDRF codes as the agency ultimately plans to harmonize all other adverse event codes with IMDRF terminologies.

IMDRF's Standards Working Group released a consultation document on optimizing standards for regulatory use which the forum believes can help harmonize international standards. The document covers essential principles of safety and performance, as well as the use of consensus standards.

The Patient Registries Working Group issued a final document on tools for assessing the usability of registries in support of regulatory decision making. The document provides guidance to regulators for using patient registries to make decisions on device approvals, expanded indications, and post-marketing surveillance, as well as on performance criteria (*IDDM*, April 16).

FDA to Host Software Precertification Pilot Program Interactive Session

The FDA plans to host a May 10 interactive session to discuss its progress on the Software Precertification Pilot Program.

The aim of the program is to help the agency to develop regulatory models to better analyze software's safety and effectiveness without restricting patient access.

The program is currently limited to FDA-regulated software as a medical device (SaMD), which the agency defines as software intended for use for at least one medical purpose that functions without being part of a hardware medical device.

In the upcoming session, the agency will discuss the program working model and seek feedback on potential next steps for the program. — Zack Budryk

Symantec Warns of Cyber Threat From 'Orangeworm' Group

Symantec has identified a group conducting cyberattacks that target computers used to control high-tech imaging devices.

The Orangeworm group conducted targeted attacks on organizations across the supply chain but almost 40 percent of the group's targets were in the healthcare sector, including hospitals, drugmakers and IT solution providers.

The Kwampirs malware was found on machines that use software to control imaging devices such as X-ray and MRI machines.

The hackers gain access using a "backdoor" method that is better-suited to older operating systems such as Windows XP. Symantec believes the healthcare industry is particularly vulnerable due to the common use of such older systems within the sector.

The largest group of victims is U.S.-based, but the number of victims who operate large international corporations have led to cyber infections in multiple countries, including India, Saudi Arabia and the Philippines. The hacker group collects information about compromised computers and then uses the data to determine whether the victim is a high-value target.

"We believe that these industries have also been targeted as part of a larger supply-chain attack in order for Orangeworm to get access to their intended victims related to healthcare," Symantec said.

"Orangeworm's secondary targets include manufacturing, information technology, agriculture, and logistics. While these industries may appear to be unrelated, we found them to have multiple links to healthcare, such as large manufacturers that produce medical imaging devices sold directly into healthcare firms, IT organizations that provide support services to medical clinics, and logistical organizations that deliver healthcare products."

Symantec believes Orangeworm is not state-sponsored but likely an individual or a small group of individuals and notes there are currently "no technical or operational indicators" to identify the group's origin. — Zack Budryk

Huestis Machine Corp Racks Up 11-Item 483 for GMP Failures

Bristol, Rhode Island-based devicemaker Huestis Machine Corp. was cited for numerous GMP failures in an 11-item Form 483 following a September 2017 inspection.

Certification of the company's collimators was not based on a testing program in accordance with good manufacturing practices, the FDA said.

There were numerous discrepancies between documented X-ray peak energy values in the collimator leakage test procedure and the production log, and the firm could not provide a documented justification. Similar discrepancies were noted for values listed in the collimator aluminum equivalence procedure and production log with no written documentation.

Moreover, collimators returned by customers for repair weren't tested to performance requirements before they were released, and no justification was provided. The FDA found that the firm failed to evaluate the impact of a design change, and it didn't document results of incoming, in-process and finished device tests.

Other GMP deficiencies uncovered included inadequate corrective and preventive action procedures and failure to establish procedures that ensure nonconforming products were controlled.

(See **483***, Page 6)*

Types of Data to Examine for Verification and Validation

When devicemakers conduct validation and verification testing, they will look at two general types of data — continuous and discrete. Continuous or typical data essentially apply to performance requirements.

What companies must examine is part-to-part variability, a factor that is very important to a device's risk profile. In choosing a sample size for testing, companies must consider sources of variation, which can increase a device's risk.

For example, a tongue depressor represents a simple, low-risk medical device used frequently in doctors' offices. If a design requirement calls for the depressor to be flat, and not bowed, the company making this product must determine how much variability exists as part of its determining a sample size.

"But ultimately the question is: 'What is the risk to the patient if the physician was to get a slightly bowed tongue depressor?'" according to Steven Walfish, president of Statistical Outsourcing Services. "It's probably a very low risk. So I'm not going to spend a lot of time in sample size and in the risk for this product."

However, a high-risk product, such as an implantable pacemaker, is another matter. If voltage is the specification to be tested, for instance, part-to-part variation in batteries and wiring, among other parts, can have an effect. The manufacturer has to take into account how those tolerances will affect the pacemaker's performance. And that in turn will affect the sample size for validation and verification testing.

Both verification and validation may require physical samples across lots, batches and operators to demonstrate that the specified requirements have been fulfilled. This must occur any time a product has a high lot-to-lot variability.

The second type of data that devicemakers may need to consider is discrete data, which typically involve functional requirements. As with continuous data, companies must consider sources of variation and risk in discrete data when determining sample size. However, individual parts or a process generally are not the sources of variation seen in discrete data. Rather, the variation stems from such things as interactions, timing, initial conditions, workflow, prior events, configurations, options and accessories.

In some situations, Walfish explained, a company must test whether something works or not; he compared it to flicking a light switch: "If I turn on the switch in a room and the light goes on, I don't have to test that 100 times. If it works once, it's always going to work."

Excerpted from the FDAnews management report: *Choosing the Best Device Sample Size for Verification and Validation.*

Florida's Oculus Surgical Lands 483 For Failing to Document Complaints

FDA inspectors found Oculus Surgical's procedures for receiving, reviewing and evaluating complaints to be lacking following a December 2017 inspection of the firm's Stuart, Florida manufacturing facility.

The firm released defective devices to customers, and although defects were identified by sales representatives at the customer site, they were not documented as complaints, the agency found. An investigation was not launched because a previous investigation was performed for similar complaints. However, there was no documentation of the investigations or a corrective and preventive action plan.

The FDA said Oculus had not determined the probable root cause of the recurrence of these types of complaints.

Read the Oculus Surgical Form 483 here: www.fdanews.com/04-25-18-oculussurgicalinc483.pdf.

Validation Failures Plague Italian Devicemaker Gallini

Numerous validation issues and CAPA failures were uncovered during a 2017 inspection of Gallini's Mirandola, Italy manufacturing plant.

Validation failures cited in the Form 483 included inadequate test validation and process validation procedures and an inadequate validation master plan. The FDA inspector pointed to missing critical parameters for testing, failure to indicate sample sizes or to select random samples, and missing packaging validation procedures.

FDA investigators found "no protocols, sample size rationale, worst product/package evaluation operational qualification, performance qualification, and batch records for test batches."

The firm that makes surgical equipment had not established adequate CAPA procedures, the agency said. In one example, actions were taken in response to a complaint on March 30, 2016, but a CAPA was not initiated until Nov. 14, 2016.

The FDA determined that process control procedures were lacking, and the firm failed to establish adequate procedures to control nonconforming products.

The FDA said the firm did not properly evaluate design changes to be sure changes didn't adversely affect the safety, efficacy or performance specification of products.

Read the Gallini Form 483 here: www.fdanews.com/04-25-18-galinisrl483.pdf.

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The firm did not evaluate or document nonconforming products identified during processing and manufacturing. When asked about rework activity, the firm could not locate information on the disposition of several nonconforming products.

The agency noted that procedures for receiving, reviewing and evaluating complaints by a formally designated unit had not been established, and medical device reporting procedures had not been developed. Finally, software used as part of the quality system had not been validated.

Read the Huestis Machine Corp Form 483 here: www.fdanews.com/04-25-18-huestismachinecorp483.pdf.

PEOPLE ON THE MOVE

Toronto-based **Profound Medical** appointed **Ian Heynen** as its senior vice-president of sales and marketing. Heynen most recently served as acting president — international at Hologic, with responsibility for all regions outside of the United States. He joined Hologic in 2010 on the company's acquisition of Sentinelle Medical, a breast MR imaging company for which he served in the dual role of chief financial officer and chief operating officer.

NIST Issues Cybersecurity Framework With New Focus on Supply Chain Risk

The National Institute for Standards and Technology released a new cybersecurity framework that focuses on supply chain risks and risk management.

Version 1.1 of the Framework for Improving Critical Infrastructure Cybersecurity "should be every company's first line of defense," and adopting the new version is a "must do for all CEOs," said Commerce Secretary Wilbur Ross.

The voluntary framework consists of standards, guidelines and best practices. The updated document includes a new section on self-assessment; how to use the framework for cyber supply chain risk management purposes; refinements to better account for authentication, authorization, and identity proofing; and coordinated vulnerability disclosure.

Cyber supply chain risk management activities may include:

- Determining cybersecurity requirements for suppliers;
- Enacting cybersecurity requirements through formal agreements;
- Communicating to suppliers how cybersecurity requirements will be verified and validated; and
- Verifying that cybersecurity requirements are met through a variety of assessment activities.

The core of the NIST framework consists of five functions — identify, protect, detect, respond and recover. Considered together these functions provide a high-level, strategic view of the lifecycle of an organization's management of cybersecurity risk.

Devicemakers can use their existing processes and leverage the framework to identify opportunities to strengthen and communicate cybersecurity risks while aligning with industry practices.

"Organizations will continue to have unique risks — different threats, different vulnerabilities, different risk tolerances," NIST said. "They also will vary in how they customize practices described in the Framework."

Cyber supply chain risk management addresses both the "cybersecurity effect an organization has on external parties and the cybersecurity effect external parties have on an organization," NIST says. A primary objective of cyber supply chain risk management is to identify, assess, and mitigate "products and services that may contain potentially malicious functionality, are counterfeit, or are vulnerable due to poor manufacturing and development practices within the cyber supply chain."

Read the NIST framework here: www.fdanews.com/04-24-18-NISTframework.pdf.

APPROVALS

LivaNova Receives CE Mark For Nerve Stimulation Device

LivaNova received a CE Mark for its vagus nerve stimulation therapy system SenTiva generator for treating drug-resistant epilepsy.

The implantable device can detect seizures and automatically deliver an extra dose of therapy. The generator is also designed to log events including a patient's body position and heart rate fluctuations. The system includes a tablet and a wireless programming wand.

The product received FDA clearance in October 2017.

CE Mark Granted for Hematology Analyzer

Beckman Coulter Diagnostics received a CE Mark for its DxH 520 hematology analyzer.

The company used its flagship DxH 800 analyzer as the predicate product for the DxH 520. The system uses just two reagents and includes on onboard cleaner.

The analyzer is pending clearance by the FDA, so it not yet available for in vitro diagnostic use in the United States.

(See **Approvals**, *Page 8)*

Approvals, *from Page 7*

Cantel Medical Earns 510(k) Clearance for Endoscope Reprocessor

Cantel Medical received FDA 510(k) clearance to market its automated endoscope reprocessor, which helps prevent infections from endoscopic procedures.

The Advantage Plus Pass-Thru automated endoscope reprocessor can disinfect commonly used endoscopes, including duodenoscopes, and it features a one way workflow.

The hands free operation reduces scope handling and allows reprocessing of four to five scopes in an hour. The device has been validated for use with Cantel's Rapicide PA disinfectant.

FDA Clears Arthrosurface's Shoulder Arthroplasty System

Arthrosurface's Ovomotion shoulder arthroplasty system received 510(k) clearance from the FDA for marketing and is cleared for use with the novel Arthrosurface Inlay Glenoid System.

It is designed for patients with painful or severely disabled shoulder joints caused by arthritis, traumatic events or avascular necrosis.

The stemless total shoulder system enables surgeons to minimize bone removal.

FDA Authorizes First Test For Candida Auris

The FDA authorized the first test for identifying *Candida auris,* a multidrug resistant pathogen that can cause serious infections in hospitalized patients.

The agency approved a new use of the Bruker Maldi Biotyper CA system for identifying the pathogen, expanding the system's uses to 424 clinically relevant bacteria and yeast species.

The system uses mass spectrometry in combination with a reference organism database.

Lumendi Receives 510(k) Clearance For Endoscopic Accessory

The FDA gave Lumendi 510(k) clearance for its DiLumen C2 device, an endoscopic accessory used to ensure complete positioning of an endoscope in the large intestine.

The DiLumen C2 uses two 6mm diameter tool channels which accommodate two flexible articulating hand instruments.

SurModics Gets FDA Clearance For Balloon Dilation Catheter

The FDA granted SurModics 510(k) clearance for its 0.18" low-profile percutaneous transluminal angioplasty balloon dilation catheter.

The device is indicated for use in peripheral vascular applications ranging from 2mm to 10mm diameter.

FDA Clears Viz.ai's CTP Image Processor

The FDA gave Viz.ai 510(k) marketing clearance for its automated CT perfusion image processor Viz CTP.

The processor allows the user to view dynamic CT perfusion images and offers automated large vessel occlusion (LVO) stroke identification and notification.

In addition, the Viz.ai system offers patient selection, HIPAA compliant communication, transport coordination and mobile medical image viewing.

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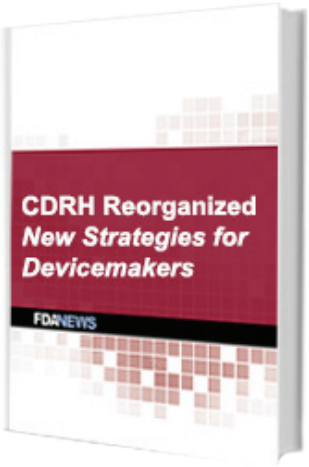

CDRH Reorganized: *New Strategies for Devicemakers*

Device regulation is about to change in ways large and small, as the CDRH moves toward a total reorganization.

CDRH's reorganization plan — to be carried out over the next two years — aims to replace current siloes of responsibility with a team approach that follows a device from development to application to premarket planning and ultimately to postmarket surveillance, with the same people working together at each stage.

CDRH Reorganized lays out all of the moving pieces and lets you know what to expect, how to take advantage of new opportunities and how to influence the direction of the new system. And you'll hear it from one of the people most qualified to interpret the changes, former CDRH Associate Director of Policy Paul Gadiock.

Gadiock recommends devicemakers get in on the ground floor of this reorganization. "Disruption can be unsettling," he says, "but if you're attentive, it also presents opportunity for new ideas because there's less inertia standing in your way."

You will learn:

- The planned structure of CDRH's regulatory and clinical evidence offices
- The most effective strategies for communicating with the FDA post-reorganization
- How the center's new focus on total product life cycle will drive premarket and postmarket data collection
- How the new CDRH Digital Health unit will help streamline the review process for digital health devices
- And More…

Order your copy of **CDRH Reorganized: *New Strategies for Devicemakers*** and learn how to deal with the new CDRH structure at each stage of your device's life cycle.

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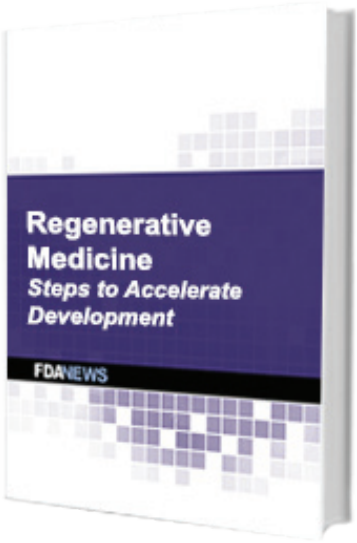

Regenerative Medicine: *Steps to Accelerate Development*

With the 21st Century Cures Act, attention is being focused on the use of human cells and tissue to treat serious and underserved conditions.

The FDA created a new regulatory paradigm in November 2017 when it issued four guidances — 2 final and 2 draft — aimed at explaining, streamlining and accelerating development of regenerative therapies.

Key among these developments is the creation of a new Regenerative Medicine Advanced Therapy (RMAT) designation that offers applicants an abbreviated pathway to approval, working closely with the FDA throughout the process.

Regenerative Medicine outlines the RMAT pathway and breaks down requirements regenerative medicine developers must meet to qualify. The FDA granted RMAT designation to 12 organizations in 2017 — the first year of the program. Now is the time to get in the mix, work with the FDA to develop the program and improve your chance of being one of the next RMAT designees.

You will learn:

- Key definitions the FDA uses in evaluating regenerative medicine applications
- Requirements to be eligible for RMAT designation
- How to apply for RMAT designation
- How the final versions of the Same Surgical Procedure and Minimal Manipulation guidances differ from their drafts

Order your copy of **Regenerative Medicine: *Steps to Accelerate Development*** and learn what it takes to get in on the ground floor of the new approval pathway and use it to accelerate your road to market.

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