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Gottlieb Answers Senate Questions On Upholding FDA Standards

FDA commissioner nominee Scott Gottlieb was grilled by a Senate panel Wednesday over his financial ties to the industry he would be charged with regulating.

The hearing marked Gottlieb's 19th time testifying before Congress on health care issues, and his experience showed.

Gottlieb said the agency should pursue alternative chronic pain treatments and look toward medical devices as therapy options.

That was a point of concern with Democratic senators, who said that during Gottlieb's time working for New Enterprise Associates, the venture capital firm invested in a company developing and marketing devices for treating chronic pain — one of 82 such companies that have products under FDA review.

Gottlieb told the Senate Health, Education, Labor and Pensions Committee he would be open to re-examining approval pathways for some combination products — either administratively at the FDA or

(See **Gottlieb**, *Page 2)*

IMDRF Recommends Principles for Using Global Device Registries, Qualifications for Reviewers

The International Medical Device Regulators Forum is seeking global coordination of medical device registries, and has recommended principles for evaluating data in a final document released following its March meeting in Vancouver.

By coordinating internationally on methodologies for collecting and evaluating clinical data, international stakeholders can begin to develop a minimum core dataset for evaluating device product life cycles to detect signals earlier. That is seen as a step toward establishing a National Evaluation System for health technology, which is one of the FDA's top priorities.

Under the IMDRF plan, international registry networks would agree on pre-specified analyses and collaborative sharing of

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Gottlieb, *from Page 1*

by working with Congress — noting that instructions for a generic drug-device combination need to be precisely the same as the reference product to go through the ANDA process.

He also spoke of his tendency to offer "unvarnished advice" to his superiors, and said that he would not allow political pressure to outweigh the agency's commitments.

Gottlieb has pledged to recuse himself from agency decisions related to companies where he previously had a financial interest, including global drugmakers GlaxoSmithKline, Daiichi Sankyo and Bristol-Myers Squibb (*IDDM*, April 3).

"I realize that someone could look at my background and have these questions," Gottlieb told the HELP committee, adding he would do nothing to reduce public confidence in the agency, and that his front office would develop processes to mitigate any conflicts.

The committee plans to take at least two weeks before voting to advance Gottlieb's nomination for consideration by the full Senate. — Conor Hale

IMDRF, *from Page 1*

outputs with each other and the regulators. A standing IMDRF registry working group would facilitate this and would focus on higher-risk implantable devices.

The registry working group notes that variations between countries would make pooling data tricky, but that by starting with the minimum necessary data for analysis, metrics could be applied based on similarities and differences. In addition, more could be learned about clinical variability across different populations, and from that data more objective performance criteria could be created.

IMDRF says registries could be used to apply comparative effectiveness data as well as root cause analyses. It calls for international methodology pilots to work out the practicalities of sharing international data.

Registries are an ideal infrastructure for initiating clinical trials, and regulators should reach consensus on an international set of principles for deciding when a randomized clinical trial should be required, the group says.

Another IMFDRF working group focused on good regulatory review practices. It provided recommendations for conduct, education, experience, and training for conformity assessment reviewers, whether conducted by regulatory authorities or Conformity Assessment Bodies (CABs). A common set of values would develop confidence in the consistency of reviews.

The working group stressed the importance of ensuring confidentiality of "professional secrecy" by regulatory reviewers in sharing information obtained in carrying out their tasks and it has developed a code of conduct for reviewers.

Read the IMDRF documents here: www.fdanews.com/04-05-17-IMDRFregistries.pdf and www.fdanews.com/04-05-17-IMDRFRegulatoryreviews.pdf.

European Parliament Adopts MDR And IVD Regs Without Amendment

The European Parliament adopted the medical device and in vitro diagnostic regulations without amendment April 5.

The regulations will create significant compliance headaches for manufacturers — including new harmonized standards, classification rules, and conformity assessment procedures (*IDDM*, April 3).

In addition, the updated rules improve traceability throughout the supply chain and set up a central database for products in the EU, which will be open to healthcare professionals, patients and the general public.

The new rules will apply three years after publication for medical devices and five years after publication for IVDs.

The European Council adopted the MDR and IVD regulations March 7 (*IDDM*, March 13).

Industry Reps Cite Tight Timeline for MDUFA IV

The FDA will have to issue potential layoff notices to about 500 reviewers of medical devices if lawmakers fail to reauthorize user fees by the end of July, industry representatives told the Senate's health committee.

Scott Whitaker, president and CEO of AdvaMed, praised "ground-breaking" process improvements in the MDUFA III agreement, which he said allowed the FDA to reduce its total time to decision for product submissions while maintaining strong safety and effectiveness standards.

He said MDUFA IV will build on those improvements by making the device review process more predictable, consistent, accountable, and timely.

However, Whitaker and representatives from BIO, the Association for Accessible Medicines, and the Alliance for Aging Research expressed concern over the limited time left for Congress to act on user fees.

The committee hopes to move user fee reauthorization to the Senate floor by the end of April, and the current user fee programs expire at the end of September.

The FDA will be required to issue potential layoff notices to the approximately 3,000 reviewers for devices and drugs whose jobs are funded by industry dollars if Congress does not reauthorize the programs on time, witnesses said.

MDUFA IV would aim to collect $183 million in fiscal 2018, increasing annually to $213 million through fiscal 2022.

The fees were previously negotiated by the FDA and regulated industry, to cover medical product reviews through fiscal 2022.

Last month, the directors of CDRH, CDER and CBER implored the committee to pass the reauthorization package on time (*IDDM*, March 27).

CDRH Director Jeffrey Shuren said reauthorization of user fees would expedite the availability of innovative products, cut approval times, improve the agency's use of real-world evidence, and make regulatory decisions more consistent, transparent, and predictable.

FDA Extends UDI Compliance Date for Soft Contact Lenses

The FDA is delaying UDI rule requirements for soft contact lenses until one year after it resolves a technical problem — and the agency has granted a third extension for labelers of the lenses.

The FDA granted the extensions because, based on the current industry practice of assigning a different device identifier to each prescription, submission of soft contact lens information would produce a large number of virtually identical records.

Read the FDA's extension letter here: www.fdanews.com/04-04-17-contactlensletter.pdf.

FDA Grants Marketing Approval for First Direct-to-Consumer Genetic Tests

The FDA has issued marketing approval for the first direct-to-consumer genetic tests to assess inherited risks for 10 diseases.

The tests were approved through the de novo premarket review pathway.

The 23andMe Personal Genome Service Genetic Health Risk (GHR) tests identify risks for Parkinson's disease, late-onset Alzheimer's disease, Celiac disease, Alpha-1 antitrypsin deficiency, early-onset primary dystonia, Factor XI deficiency, Gaucher disease type 1, glucose-6-phosphate dehydrogenase deficiency, hereditary hemochromatosis; and hereditary thrombophilia.

The tests isolate DNA from a saliva sample, and test for more than 500,000 genetic variants. The presence or absence of some of the variants is associated with an increased risk for developing any one of the 10 diseases.

The FDA is requiring special controls for accuracy, reliability and clinical relevance, to provide reasonable assurance of safety and effectiveness for these and similar GHR tests.

The agency intends to exempt additional 23andMe GHR tests from premarket review, and GHR tests from other makers may be exempt after submitting their first premarket notification.

MHRA Issues Guidance on Device Manufacturer Registration

The UK's Medicines and Health products Regulatory Agency (MHRA) has issued new guidance on how to register a device manufacturer or authorized representative with the agency in order to sell devices and IVDs.

Entities seeking to register must inform the MHRA if they intend to sell, lease, lend, or gift:

- A class I device it has manufactured;
- A class I device it refurbished or re-labelled;
- Any system or procedure pack containing at least one medical device;
- Custom-made devices;
- An IVD the entity has manufactured; or
- An IVD undergoing a performance evaluation.

The manufacturer must ensure that all Class I devices comply with the relevant requirements of the EU Medical Device Directive and obtain CE markings.

The MHRA does not register Class IIa, IIb, III, or active implantable devices. For these, the manufacturer must follow the appropriate conformity assessment route, which includes being assessed by a notified body.

Manufacturers without a place of business in the EU must appoint an authorized representative in the EU before marketing a device.

Read the guidance here: www.fdanews.com/04-05-17-MHRAguidance.pdf.

PEOPLE ON THE MOVE

Tyme Technologies has appointed **Ben Taylor** as president and chief financial officer. He has joined Tyme Technologies from Barclays Capital Inc., where he has been the head of commercial pharma since February 2016. Prior to Barclays, Mr. Taylor spent 10 years at Goldman, Sachs & Co. in various positions of increasing responsibility, most recently as head of emerging pharma.

Ehave has recruited **Dave Goyette** as chief technology officer. Prior to joining Ehave, Mr. Goyette, together with Ehave CEO Prateek Dwivedi, developed a cancer informatics program at Princess Margaret Hospital at the University Health Network in Toronto.

Titan Medical has hired **Curtis R. Jensen** as vice president of quality and regulatory affairs. Prior to joining Titan, he served as senior regulatory affairs associate at EKOS. Prior to EKOS, he held positions of increasing responsibility at Domain Surgical.

David A. Jonas joined **Minnesota Medical** as chief financial officer/director. He has joined Minnesota Medical from Rochester Medical Corp where he served in a variety of roles since 1998.

Witnesses Call for Cooperation On Cybersecurity

Device industry representatives discussed cybersecurity with lawmakers last week and offered some suggestions for how to improve it.

Michael McNeil, global product security and services officer at Philips, who spoke on behalf AdvaMed, told the House Energy and Commerce Committee security risks should be tackled via recognized standards and reference documents. He said the device industry is committed to developing a strong security framework that encompasses pre- and postmarket management of medical technologies.

Device cybersecurity is a "shared responsibility" among manufacturers, providers, and all other stakeholders in the healthcare community, he said. Engineers and other individuals outside device companies who discover vulnerabilities should have a way to let manufacturers and the FDA know about them, and manufacturers should "judiciously" share threat and vulnerability information, he said.

Terry Rice, vice president of IT risk management and chief information security officer at Merck, who serves on the board of the National Health Information Sharing and Analysis Center, said his group and other ISACs help the public and private sectors address cyber threats to the nation's critical infrastructures.

Participation rates in ISACs are low, however, in part because companies are wary of disclosing confidential information. Rice said participation in ISACs could be encouraged through tax breaks and by appointing a cybersecurity specialist at the Department of Health and Human Services to act as a single point of contact for industry.

Read materials from the hearing here: www.fdanews.com/04-05-17-cybersecurityhearing.pdf.

China Ramps Up Device Inspections, Fast-Track Approvals

China's Food and Drug Administration boosted device approvals by 20 percent in 2016.

Overall, the agency approved 5,751 device applications, according to CFDA's annual progress report for 2016. Eight applications were rejected for data integrity issues.

CFDA conducted more than 30 overseas inspections in 2016 and plans to inspect 30 to 40 foreign companies every year for the next five years.

The authority accepted 1,690 applications for Class II imported devices and 1,405 applications for imported Class II in vitro diagnostic devices, according to the agency's 2016 report. It accepted 2,331 applications for imported Class III devices and 487 imported IVD Class III applications.

The agency has revised its review process, so all imported devices will be reviewed by CFDA, as well as Class III domestic products. Class I and II devices from domestic manufacturers will be reviewed by provincial FDAs.

CFDA's device review process is faster than that of the U.S., Dan Zhang, CEO of Beijing-based CRO Fountain Medical Development, told *IDDM*. In 2016, the CFDA approved 45 innovative devices via its fast-track pathway. Similar to the U.S. FDA's breakthrough pathway, the innovative pathway can shorten development time by 18 months.

Katherine Wang, Shanghai-based partner in the law firm Ropes & Gray, said the assessment of risk by China's regulators is usually more conservative than that of the U.S. FDA. For example, a product that is qualified for the 510(k) application pathway in the U.S. would be considered a Class III product in China.

There are significant delays in updating Chinese standards to reflect the latest ISO standards, so device makers seeking to introduce new technology to the Chinese market need to be sure the product complies with the Chinese standards.

"This requires companies to really think about the Chinese standards and its complications during the product development stage," she said.

TGA Proposes to Reclassify Low-Risk Products

Australia's Therapeutic Goods Administration (TGA) is proposing to review products currently classified as Class I medical devices to see if they should be reclassified as consumer goods.

Device sponsors include a significant number of products as Class I devices in the Australian Register of Therapeutic Goods (ARTG) that should be classified as consumer products because they pose little or no risk to health or safety, according to TGA.

TGA is inviting comments from stakeholders by May 12 on several options, including:

- Working with procurement branches of state and territory health departments to eliminate incentives for including products that are not therapeutic goods in the ARTG;
- Explicitly excluding certain devices, such as devices that claim to admit or absorb vibrations or waves but have not been validated, from the ARTG; and
- Implementing additional verification procedures to prevent non-therapeutic goods or misclassified products being included in the ARTG.

Read the consultation document here: www.fdanews.com/04-03-17-TGAguidance.pdf.

South Africa's MCC Issues Draft Guideline on Quality Manuals

South Africa's Medicines Control Council (MCC) released a draft guideline listing minimum requirements for quality manuals that medical device importers, manufacturers, distributers, exporters, and wholesalers must maintain.

MCC says quality manuals must include information about the facilities, personnel, and quality assurance policies and procedures that demonstrate an organization's ability to meet the MCC's regulatory requirements for medical devices.

The manuals must include:

- Company information such as registered name, address, and MCC license details;
- A description of the company's QMS, including quality control procedures, personnel roles and responsibilities, adverse event reporting requirements, and third-party service providers; and
- Information about each site where medical devices are manufactured or stored, including address, key personnel, security measures, environmental controls, and equipment lists.

For each item to be included in a quality manual, the guideline provides a reference to the corresponding ISO 13485 standard.

MCC is inviting comment s on the draft guideline by April 28.

Read the guideline here: www.fdanews.com/04-03-17-MCCguideline.pdf.

Understanding When An Accessory is a Device

When is an accessory a device for which an application needs to be submitted to the FDA, and how is the accessory classified?

The answer to that question can be a bit muddy, and although the FDA released final guidance on device accessories and how to classify them earlier this year, the answers are not so clear cut.

An accessory to a medical device is in itself a medical device and is regulated as such with all the same quality system regulations as the parent device, explained Dan O'Leary, president of Ombu Enterprises during a recent FDAnews webinar.

Two New Definitions

The FDA offers two new definitions to determine whether an accessory is a device: "A parent device is a finished device whose performance is supported, supplemented and/or augmented by one or more accessories." And, an accessory "is a finished device that's intended to support, supplement or augment the performance of one or more parent devices" (*IDDM*, Jan. 2).

Previously, the FDA didn't say a lot about accessories, but the issue arose when the unique device identification regulations came into effect, and people began to question how UDIs would affect accessories and whether they would require a UDI.

O'Leary said the company should first conduct an analysis to answer the question: "Does this accessory enable the intended use of the parent device, or does it facilitate the intended use of the parent device?" A device can also supplement or augment the performance if it adds a new function or a new way of using the device without changing the intended use of the parent.

For example, an infusion pump stand supports the intended use of an infusion pump, because it holds liquids or medications firmly at an appropriate height and in a convenient reach. The infusion pump can do its work — its intended use — without the stand, but the stand facilitates the infusion pump's use. Therefore, it's an accessory to the infusion pump and is a medical device.

Many people would argue that the risk associated with the stand is not the same as the risk associated with the infusion pump. That's why this accessory might want to be in a different class than the infusion pump, O'Leary advised.

Once the manufacturer has decided the article is an accessory, then it needs to be classified according to its risk profile.

O'Leary suggests using a decision tree to analyze all the ways in which a medical device could harm the patient or user. That means an analysis of performance and intended use.

To figure that out, the manufacturer needs to look at the labeling and promotional materials of the accessory, not the parent device. This is important because it might be a case in which the parent device is in a higher risk class.

De Novo Pathway

If the accessory is a new type of product and has not been classified before and there is no comparable predicate device on the market, the sponsor should use the de novo classification pathway, O'Leary said.

"It may turn out that the accessory is already classified, but historically, it's in the wrong classification because the accessory does not have the same risk as its parent device, which means that you could ask FDA to reclassify it," O'Leary said.

Alternately, if it's a 510(k) device and a company doesn't believe that those controls are necessary to make the device safe, it can ask for an exemption.

Read the final guidance here: www.fdanews.com/12-29-16-Accessories.pdf.

Access the webinar CD/Transcript here: www.fdanews.com/products/53946.

BRIEFS

Singulex Gains CE Mark For Sgx Clarity System

California–based Singulex received a CE mark for its Sgx Clarity system, an automated, in vitro diagnostics platform that can count single molecules of biomarkers and distinguish individuals who have disease from those who do not, before symptoms are apparent, leading to improved outcomes.

Singulex will submit data for regulatory clearance of the Sgx Clarity system in the United States, and it anticipates FDA clearance in 2018.

NICO Wins CE Mark For BrainPath Cranial Access Tech

Indianapolis–based Nico has been awarded a CE mark for BrainPath — a technology that provides non-disruptive access to the brain by using both a parafascicular and trans-sulcal surgical approach.

BrainPath uses the folds of the brain as a path to the surgical site. It displaces brain tissue to create a corridor to a tumor or hemorrhage site, through an opening the size of a dime.

ETS Wound Care Wins FDA Clearance for Mirragen

Montana–based ETS Wound Care received FDA clearance for its Mirragen advanced wound matrix for treatment of acute and chronic wounds.

The device consists of a resorbable borate glass matrix comprised of fibers and beads. Mirragen is designed to be packed into wounds to control wound fluids.

The company plans to make the device commercially available via a controlled domestic market release in early second quarter of 2017 and to release it to the broader domestic market in 2018.

Australia Clears Milestone's Epidural And Intra-Articular Instruments

New Jersey–based Milestone Scientific has received marketing clearance in Australia for its CompuFlo epidural and intra-articular instruments.

CompuFlo's dynamic pressure sensing provides feedback that allows anesthesiologists to identify the epidural space.

The DPS technology is also incorporated into the CompuFlo intra-articular instrument to provide computerized drug injections into intra-articular joint spaces in osteoarthritis patients.

AirXpanders Receives FDA Clearance For AeroForm Tissue Expander

The company has received FDA marketing clearance for an enhanced film material used to contain carbon dioxide within the device.

AeroForm is activated by a handheld wireless controller that administers small amounts of CO2 up to three times a day, to gradually stretch the tissue to prepare for a breast implant.

AeroForm received de novo clearance from the FDA in December 2016.

Occlutech Obtains CE Mark For its PmVSD Occluder

Swiss device maker Occlutech has gained a CE mark for its perimembranous ventricular septal defect (PmVSD) occluder used in treating the congenital heart condition.

The implantable device is indicated for minimally invasive closure of perimembranous ventricular septal defects. The occluder consists of a flexible nitinol wire mesh with "shape-memory" properties.

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Customer Service
(888) 838-5578 • +1 (703) 538-7600
customerservice@fdanews.com

Editorial: Declan Conroy
+1 (703) 538-7644
dconroy@fdanews.com

Ad Sales: Jim Desborough
+1 (703) 538-7647
jdesborough@fdanews.com

Multi-User Sales: Jeff Grizzel
+1 (703) 538-7669
jgrizzel@fdanews.com

300 N. Washington St., Suite 200 • Falls Church, VA 22046-3431 • Phone: (888) 838-5578 • +1 (703) 538-7600 • www.fdanews.com

Reporters: Cynthia Jessup, Conor Hale, Zack Budryk

President: Cynthia Carter

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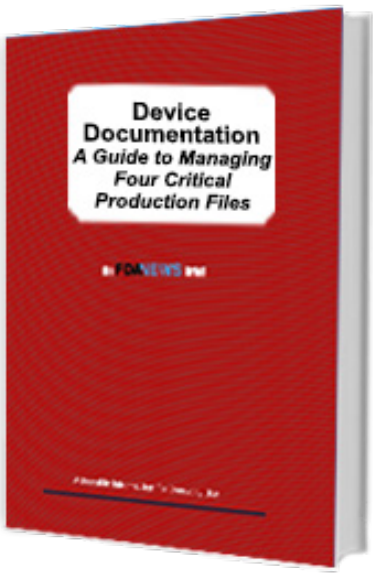

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