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IN THIS ISSUE

FDA Wants to Further NGS, IVD Development To Foster Oncology Innovation

FDA Commissioner Scott Gottlieb elaborated on FDA initiatives aimed at developing next generation sequencing platforms and in vitro diagnostics to improve cancer treatment and research productivity and encourage innovation.

Speaking at the 2018 Community Oncology Conference in Oxon Hill, Maryland on Apr. 12, Gottlieb stressed the potential of NGS diagnostic technologies to target cancer with precision guided treatments and develop new treatments and highlighted the FDA's efforts to keep pace with NGS technologies.

"We're developing a policy approach…that give[s] patients and clinicians confidence in these panels' analytical and clinical validity, while still allowing these sequencing systems to be efficiently updated as new genes, or gene variants, or improved algorithms come online," he said.

(See **Development***, Page 2)*

FDA Guidance Proposes Expanding 510(k) Pathway for Moderate Risk Devices

The FDA issued draft guidance proposing an expanded abbreviated 510(k) clearance program that would allow companies to show a new product's substantial equivalence to an existing device using performance criteria rather than directly comparing the device's performance to a predicate device.

The FDA reasoned that substantial equivalence based on a legally marketed device that has the same intended use and suitable technological similarities can mean basing clearances on predicate devices that are many years old.

Under the expanded abbreviated 510(k) program, if a device meets performance criteria relevant characteristics for safety and effectiveness and a new device meets or exceeds the same levels, the agency could deem the device as safe and effective as the predicate instead of requiring a direct comparison.

(See **510(k)***, Page 2)*

Japan Raises Medical Device Registration Fees

Japan's Pharmaceuticals and Medical Devices Agency raised its registration fees for most medical devices effective April 1.

The new fees for pre-market approval for Class II, III and IV devices represent an increase of about 8 percent to 15 percent.

The updated fees range from $147,012 for registering a new Class IV device, $107,998 for a Class II/III device and $86,114 for a reprocessed single-use Class IV device.

The PMDA also increased fees for devices changes, charging roughly half of the fee for a new PMA registration for devices in the same class.

New Class II (medium risk), Class III (high-risk) and Class IV (implantable devices) require pre-market approval, can take from 6 to 36 months depending on classification and clinical requirements. Lower-risk Class I devices are generally considered accepted upon submission, according to the consultancy AsiaActual.

The PMDA outsources quality system conformity assessments to registered notified bodies. There are 14 notified bodies registered in Japan, seven of which are international companies.

Development, *from Page 1*

He announced the release of two final guidances and one draft guidance on NGS and in vitro diagnostic development, stating the policies are designed to further the development of the platforms by allowing for more efficient regulatory review.

The first guidance discusses the FDA's considerations for validating NGS-based tests designed to diagnose germline diseases, while the second describes the FDA's thoughts on scientific evidence from accessible genetic variant databases being used to support clinical validity during premarket review.

A third draft guidance describes an optional streamlined submission process to determine the risks or non-risks of using investigational in vitro diagnostics in a clinical trial of investigational cancer drug or biological products.

"These new policies will improve the FDA's ability to protect public health by ensuring these tests provide accurate and meaningful results, while at the same time speeding patient access to NGS assays by lowering barriers to innovation," he said.

"The actions we're taking today will encourage greater innovation and accelerate the adoption of tools that can increase the productivity of clinical research and improve the delivery of cancer care." — James Miessler

510(k), *from Page 1*

Individual submissions for the expanded abbreviated 510(k) program will still require the identification of predicate devices for the technological characteristics and intended use portions of evaluating substantial equivalence.

The agency said the finalized guidance "could reduce regulatory burdens while maintaining standards for safety and effectiveness and providing patients and healthcare professionals with greater confidence that the device meets modern performance standards."

The FDA plans to offer information about device types to which the performance criteria would apply, including appropriate intended uses and indications for use, technological characteristic expectations and the relevant product code.

Read the guidance here: www.fdanews.com/04-12-18-510k.pdf. — James Miessler

FDA Issues New Guidance on IVDs Using Next Generation Sequencing

The FDA issued two new guidances on development of in vitro diagnostics that use next generation sequencing (NGS) technology to create individualized, genetic-based medical plans tailored to specific patients.

The first guidance, Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics, encourages developers to use clinical evidence found in FDA-recognized public databases to support clinical claims for their tests. The agency said this will ensure accurate clinical evaluation while providing developers with an efficient means of gaining marketing clearance or approval for new tests.

The guidance describes the FDA's considerations for recognizing publicly accessible genetic variant databases as sources of valid scientific evidence during premarket review.

FDA Commissioner Scott Gottlieb said the agency "recognizes the tremendous potential of NGS technology to guide and improve patient outcomes:" and said the agency is "developing a policy approach to keep pace with fast-moving NGS technologies that give patients and clinicians confidence in these panels' analytical and clinical validity, while still allowing these sequencing systems to be efficiently updated as new genes, or gene variants, or improved algorithms come online."

The second guidance, "Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing (NGS)–Based In Vitro Diagnostics (IVDs) Intended to Aid in the Diagnosis of Suspected Germline Diseases," provides recommendations for designing, developing and validating NGS-based tests used to diagnose individuals with suspected genetic diseases. The guidance describes how the FDA evaluates premarket submissions to determine how accurate a test is at detecting a particular genomic change.

The FDA developed the guidelines because current regulatory approaches are "appropriate for conventional diagnostics" that measure a limited number of chemical substances, while new sequencing technologies can examine millions of DNA variants at a time, and require a more "flexible approach to oversight that is adapted to the novel and evolving nature of these tests."

Read the draft guidance on databases here: www.fdanews.com/04-13-18-Databases.pdf.

Read the draft guidance on design considerations here: www.fdanews.com/04-13-18-Guidance.pdf. — Donna Scaramastra Gorman

FDA Proposes Optional Process for Oncology IVD Risk Factors in Trials

The FDA announced draft guidance introducing an optional submission process for determining the risks or non-risks of using an investigational in vitro diagnostic in a clinical trial involving an oncology investigational drug.

The submission process determines whether the use of an investigational IVD in a clinical trial for an oncology therapeutic is a significant risk, nonsignificant risk or exempt. The trial may require an investigational device exemption (IDE) approval if it is found to be a significant risk, the guidance stated, in addition to an investigational new drug (IND) application.

A single sponsor should be prepared to hold communications with the FDA about the IND, the guidance said, and should submit information about the oncology development program to either CBER or CDER, who will consult CDRH to determine its risk factor.

That information includes how the sponsor will apply investigational IVD results to the clinical trial, what they know about the prevalence of the biomarker in the patient population, and the specimen type that will be collected for investigational IVD testing, the guidance stated. In addition, if a biopsy is required for the IIVD testing, the sponsor should note any potential risks.

Read the draft guidance here: www.fdanews.com/04-13-18-InVitro.pdf. — James Miessler

FDA Halts Distribution of Essure To Establish Additional Safeguards

The FDA ordered a restriction on marketing and distribution of Bayer's permanent birth control device Essure amid fears that patients were not given enough risk information to make informed decisions about the product.

Some patients implanted with Essure reported adverse events such as perforation of the uterus and fallopian tubes, persistent pain or hypersensitivity or allergic reactions. In addition, some reported hair loss, depression and mood changes, among other side effects, the agency said.

The agency implemented a unique restriction by freezing the sale and distribution of the device in order to require additional information on the device's safety. The agency chose to step in after it became aware that some women were not being adequately informed about the device's risks before implantation, the FDA said.

The agency stated that after reviewing the device's use, it felt that the product "requires additional, meaningful safeguards to ensure women are able to make informed decisions about risk when considering this option," FDA Commissioner Scott Gottlieb said.

The product's new labeling, which is now legally required when the product is offered to a patient, restricts its sale and distribution solely to health care providers and facilities that provide information about its risks and benefits to patients.

A risk and informed decision acknowledgement checklist must now be reviewed with the patient by the health care provider, and both the patient and the physician implanting the device must sign it.

Lawmakers previously questioned the FDA on Bayer's Essure device, calling it "a prime example of systemic medical device oversight shortfalls and insufficient enforcement to ensure the safety and efficacy of medical devices" (*IDDM,* Nov. 6, 2017). — James Miessler

Endotec Cited for Validation Issues, CAPA Deficiencies

The FDA handed Endotec a Form 483 after a December inspection of its Santa Fe Springs, California facility brought to light validation failures and corrective and preventive action shortcomings.

The firm produced hip, knee and shoulder orthopedic implants that were sterilized by a contract sterilizer since March 2017. However, no records were provided showing that the sterilization process was validated although devices processed by the sterilizer were released for distribution.

Although the firm had a validation protocol for its B-P Knee Replacement System device, there were no records to show the protocol had been followed. It was also deficient, as it did not include a physical performance qualification and did not address its applicability to other firm products.

In addition, all three of the firm's CAPA records opened and closed since October 2016 lacked verifications that the corrective actions were successful.

Procedures were also not established to identify products that do not conform to requirements. For example, although the firm required investigation of nonconformities and their causes, eight out of 13 nonconformance reports the agency reviewed did not have investigations or justifications for why one was not needed.

Read the Endotec Form 483 here: www.fdanews.com/04-12-18-endotecinc483.pdf. — James Miessler

Danmar Flagged for CAPA Records, Equipment Calibration

The FDA cited Danmar Products over inadequate calibration of equipment and procedures for accepting incoming products.

The agency issued a Form 483 after a November 2017 inspection of the company's Ann Arbor, Mich., facility. Investigators found during a walkthrough that several products were past their

(See **CAPA**, *Page 6)*

Enteromedics Slammed For Validation Issues

Enteromedics drew a Form 483 from the FDA for producing printed circuit boards using a non-validated process, not identifying defective circuits and incorporating the nonconforming boards into its devices.

After inspecting Enteromedics' Saint Paul, Minnesota facility from November to December 2017, the agency found that its correct and preventive actions did not properly address the issue of its Rechargeable Neuro-Regulator (RNR) devices containing circuit boards manufactured by the firm with a non-validated process.

The firm issued a recall for non-implanted devices but no actions were taken for devices already implanted in patients, the agency found.

In addition, a medical device report was not submitted for a complaint regarding a malfunctioning RNR device that caused a delay after implantation. The company also failed to submit an MDR for a patient who developed an infection at the incision site for the device.

The firm's purchasing procedure also required process validation requirements to be explained in a statement of work and communicated with a supplier, but this was not done for the validation failures.

Read the Form 483 here: www.fdanews.com/04-12-18-enteromedicsinc483.pdf. — James Miessler

CAPA, *from Page 5*

calibration due dates. Moreover, the firm did not follow its procedures for evaluating and approving suppliers and monitoring their performance.

Danmar did not sample enough products per lot to fulfill the requirements of its sampling plan for two of nine receiving reports the agency reviewed.

The agency also faulted the company on its CAPA handling, writing that in at least six nonconformance investigation reports, it did not justify its lack of corrective action as required by company's standard operating procedures.

The company also did not adequately document its CAPA enforcement. Investigators found a CAPA the company opened on July 29, 2015 was closed in May 2016 without documenting the effectiveness of the actions taken. The firm's quality control engineer said he reviewed the production data while performing the acceptance process but provided no documentation.

The company also did not adequately document acceptance activities. Of 17 device history records and nine receiving reports the FDA reviewed, none identified the equipment used in acceptance activities. Lastly, the firm maintained no records of a correction or removal that justified not reporting it to the FDA.

Read the Form 483 here: www.fdanews.com/04-12-18-danmarproductsinc483.pdf. — Zack Budryk

Australia Will Introduce Patient Cards for Implantable Devices

Australia's Therapeutic Goods Administration is getting ready to introduce patient cards and consumer device information for all permanently implanted medical devices.

The TGA will introduce the cards in a staged approach beginning with urogynecological mesh devices on Dec. 1.

The move to require patient cards came in response to consumer concerns about the limited information provided with devices implanted during surgery. The agency said devicemakers must:

- Identify hazards and associated risks arising from the use of their device for its intended purpose and foreseeable misuse of the device;
- Eliminate or reduce risks as much as possible by adopting a policy of safe design and construction;
- If appropriate, ensure that adequate protection measures are taken, including alarms for risks that cannot be eliminated; and
- Inform users of any residual risks that may arise due to shortcomings of the protective measures adopted.

FDA Clears First Device to Use AI for Diabetic Retinopathy

The FDA cleared the first medical device to use artificial intelligence to measure eye disease diabetic retinopathy in diabetic adults.

The condition, caused by high blood sugar levels damaging retinal blood vessels, is the most common cause of vision loss among diabetics and the leading cause of blindness among working-age adults.

The device uses AI software to analyze images of users' eyes taken with retinal cameras. A doctor uploads the photos to a cloud server, after which the software can diagnose diabetic retinopathy.

It is the first FDA-authorized device that provides a screening decision without the need for a clinician's opinion, so doctors who do not normally provide eye care could potentially use it.

The clearance "permits the marketing of a novel artificial intelligence technology that can be used in a primary care doctor's office," said Malvina Eydelman, director of CDRH's Division of Ophthalmic and Ear, Nose and Throat Devices.

The FDA based its clearance on a clinical study of 900 patients at 10 primary care sites that found the device correctly identified the presence of retinopathy 87.4 percent of the time. — Zack Budryk

APPROVALS

FDA Clears Acuvue's Oasys Contact Lenses

The FDA granted clearance for Acuvue's Oasys contact lenses, indicated for daily use to correct vision impairments caused by myopia and hyperopia in patients with non-diseased eyes.

The contacts contain a photochromic additive that adjusts visible light filtered to the patient's eye based on the amount of UV light they are exposed to, slightly darkening the lenses in bright sunlight and reverting to a regular tint in normal or darker light.

The lenses can also be used by individuals with certain degrees of astigmatism.

Ortho Connect V2.0 Wins Marketing Clearance

The FDA issued 510(k) marketing clearance for Ortho Clinical Diagnostics' Ortho Connect V2.0, a middleware system that centralizes laboratory operations and workflow across networks and hospitals.

Ortho Connect allows blood banks and their data to be managed through a central terminal, and enables Ortho Vision immunohematology analyzers to connect with a hospital's laboratory information systems through a single connection.

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

Approvals, *from Page 7*

The middleware allows laboratories to exchange and manage data and complete regulatory process tasks that are difficult to perform alone, and enables them to centralize lab operations across the network.

FDA Clears Haemonetics' NexSys PCS Enhancement

Haemonetics' enhancement of its plasma collection tool, NexSys PCS, earned FDA marketing clearance.

The tool will offer the NexSys PCS device along with the NexLynk DMS donor management software and disposables.

The clearance allows the product to increase the plasma yield per collection.

Haemonetics plans a commercial launch of the tool this summer.

Auris' Monarch Platform Receives 510(k) Clearance

The FDA approved Auris' Monarch system, a flexible endoscope that can be used to diagnose lung cancer.

The device is cleared by the FDA for diagnostic and therapeutic bronchoscopic procedures. It uses computer navigation based on 3D models of the patient's lung anatomy, allowing the user to access hard-to-reach parts of the lung.

SpinTech's SPIN-SWI Software Approved by FDA

The FDA issued a go-ahead for SpinTech's SPIN-SWI software for quantification and detection of neurovascular biomarkers in magnetic resonance images.

The software applies proprietary post-processing techniques to enhance the visualization of small blood vessels in the brain to assess clinical data provided by MR scanners.

The technology can process and evaluate images for conditions such as Parkinson's disease, stroke, traumatic brain injury and vascular dementia.

CurveBeam's Orthopedic Extremity CT Systems Earn CE Mark

CurveBeam received a CE Mark for its LineUP and InReach orthopedic extremity CT systems.

The systems, which can be plugged into standard wall outlets and have minimal shielding requirements, give radiology and orthopedic specialists three-dimensional bone detail of the orthopedic extremities.

The LineUP system allows the patient to stand during the scan so that anatomy can be assessed in the "weight bearing" position. It can perform full-leg bilateral scans, and an adaptive chair scans the hand, wrist and elbow.

Cardiva Medical's Vascular Closure System Finds Further Approval

The FDA approved an expanded indication for Cardiva Medical's Vascade vascular closure system, allowing it to be used for 5-7F femoral venous closures after being previously approved for arterial closures.

The system is intended for patients undergoing interventional cardiac catheterization procedures.

The device consists of a collagen patch and proprietary collapsible disk that achieve hemostasis while minimizing complications.

Sonoma's Post-Laser Skin Therapy Gel Cleared by FDA

Sonoma Pharmaceutical's antimicrobial gel received 510(k) clearance from the FDA to treat the skin of post-nonablative laser therapy and post-microdermabrasion therapy patients, in addition to treating post-superficial chemical peels.

The product is intended for dermatologists and aesthetic clinicians to manage medical procedures and post-procedure itch and pain associated with procedures like laser skin resurfacing.

The gel promotes advanced healing and protection against secondary infections that could occur after treatment.

IMDRF Releases New Draft Documents On Personalized Devices, Standards

The International Medical Device Regulators Forum released new consultation documents on personalized medical devices and on optimizing standards for regulatory use following its March meeting in Shanghai.

The IMDRF committee released a new draft on definitions for personalized medical devices, proposed by Australia at the forum's last meeting in Ottawa. The aim of the consultation is to develop consistent definitions to describe devices that are intended for a particular individual.

"It is now possible to produce medical devices that are individualized, for example, using additive manufacturing (3D printing) methods based on CT scans, on a commercial scale," the document notes.

The draft makes a distinction between personalized medical devices and custom-made medical devices. It clarifies that patient-specific devices are made by an industrial manufacturing process according to the written request of an authorized healthcare provider but are not considered custom-made. However, an orthopedic implant requested by an orthopedist with specific requirements for an individual patient would be considered a custom-made device.

The guidance also suggests clear definitions for patient-specific devices and adaptable devices. Specific design characteristics refer to unique design specifications based on an individual's specific anatomy.

IMDRF's Standards Working Group released a separate 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.

IMDRF also released a final document from its Patient Registries Working Group 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.

Read the consultation documents here: www.fdanews.com/04-13-18-IMDRFdocs.pdf.

UK's MHRA Flags Changes For Device Trials

The UK's Medicines and Healthcare products Regulatory Agency is switching to a new application form for medical device trials beginning April 18 and has announced changes that device-makers should implement immediately.

Manufacturers must inform the MHRA at least 60 days before starting a clinical trial. Those planning to submit an integrated research application system (IRAS) notice should submit it before April 18. If a final form is not completed before that date, a new MHRA form will need to be filed to ensure that the data has been transferred into the new system.

The new form requires significantly more detail about the investigational device and about the study. It also requires electronic sign off rather than printing and signing.

Read the MHRA checklist of required elements here: www.fdanews.com/04-11-18-MHRAchecklist.pdf.

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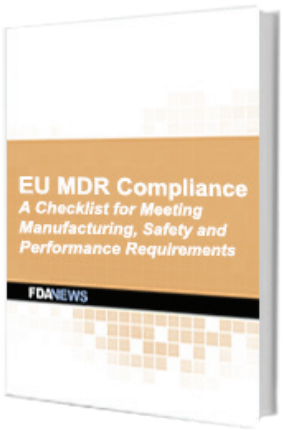

EU MDR Compliance: *A Checklist for Meeting Manufacturing, Safety and Performance Requirements*

The new EU Medical Device Regulation is massive… complex… and confusing… and you must be ready to comply by May 26, 2020.

When the European Union revised its system of rules for medical device manufacturers in 2017, it replaced a longstanding set of directives on specific topics with one large document that covers all aspects of making devices in EU countries.

Not only did they consolidate all the rules, they gave them greater weight. Previously, medical device directives provided guidance but did not have the force of law. The new MDR, however, contains mandates that are legally enforceable by EU member countries.

The FDAnews report **EU MDR Compliance** can help. Our editors have combed through the regulations, picking out the most minute compliance points and building them into a checklist of 200+ requirements you can use to confirm that you are satisfying all the EU mandates for device manufacturing. The report provides:

- Definitions of key terms in the EU MDR
- Knowing where to find specific requirements in the 150+ page regulation
- Checklists that walk you through every aspect of manufacturing, safety and performance requirements
- A training tool for employees new to the regulations

EU MDR Compliance: *A Checklist for Meeting Manufacturing, Safety and Performance Requirements* is the tool that collects all the requirements, explains them and itemized them in an easy-to-use form to ensure compliance.

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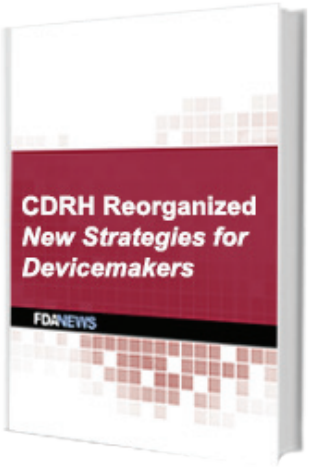

CDRH Reorganized: *New Strategies for Devicemakers*

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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