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FDA Guidance on Device Trial Demographics Targets Transparency, Data Consistency

New medical device clinical trial guidance aims to improve participation diversity and increase data consistency and transparency, FDA officials said in an Oct. 31 webinar.

The guidance applies to any devices whose marketing submissions include supporting clinical information. It does not apply to devices intended only for certain ARE groups, such as pediatric patients.

Clinical trials should work to include diverse populations reflecting the intended product population wherever appropriate and possible, according to Katherine Kim of CDRH's division of bioresearch monitoring, the guidance's lead author.

When it comes to age, sponsors should group trial participants into categories appropriate for the disease/condition, Kim said. The guidance defines pediatric populations as those younger than 22, whereas the geriatric or elderly population is not defined.

(See **Guidance**, *Page 2)*

Lawmakers Question FDA On Bayer's Essure Device

Three members of Congress sent a letter to FDA Commissioner Scott Gottlieb to request a meeting to address the agency's inaction on the numerous reports of adverse events associated with Bayer's contraceptive device Essure.

The device is "a prime example of systemic medical device oversight shortfalls and insufficient enforcement to ensure the safety and efficacy of medical devices," wrote Reps. Rosa DeLauro (D-Conn.), Jan Schakowsky (D-Ill.), and Louise Slaughter (D-N.Y.).

They pointed to a 2015 analysis from the Government Accountability Office that showed medical device companies lack incentive to enroll participants in a post-market safety study requested by the FDA, and are slow to report findings.

(See **Device**, *Page 2)*

Guidance, *from Page 1*

Race and ethnicity, meanwhile, are self-reported, and the preferred method is a two-question format that collects race data and ethnicity data separately. In cases where sponsors incorporate international data from countries where asking for racial or ethnic information may be unlawful, Kim said, sponsors should simply make the FDA aware of this limitation and apply the guidance's recommendations to the rest of the data.

Ideally, sponsors should plan to enroll a representative proportion of ARE subgroups consistent with the intended use population of the device, according to Kim. Their considerations should include the incidence or prevalence of the disease in question in subgroups; diagnosis and treatment patterns in those same subgroups; the proportions of subgroups incorporated into past studies; and clinically meaningful subgroup differences in efficacy, safety or risk-benefit.

To enroll more diverse trial subjects, the guidance calls on sponsors to include investigational sites with access to ARE subgroups, allow alternative communication strategies for trial materials, consider expanding enrollment criteria and involve community providers and patient advocacy groups in the recruitment process. If there is low enrollment for ARE subgroups, sponsors should investigate why, and bridge any such gaps with incentives such as compensation for transportation costs or child/elder care.

To improve retention, sponsors should develop follow-up plans that include contact information for proxies and closely track follow-up rates to quickly address any problems. The statistical analysis plan for such trials should pre-specify reporting by subgroup, and data submissions to the FDA should include analysis of primary effectiveness endpoints, primary safety endpoints and key secondary endpoints for any clinically meaningful ARE-specific differences.

Sponsors should both publicly report and submit to the FDA any data on enrollment demographics for ARE subgroups and the results of pre-specified subgroup analyses that suggests subgroup-specific labeling is necessary.

Meanwhile, all outcome differences should be reported to the agency, whereas clinically meaningful and statistically significant outcome differences should be made public, according to Kim. Sponsors and the FDA should discuss the generalizability of results in cases where enrollment is substantially different than prevalence, and sponsors should make public how such differences affect the benefit-risk profile for specific subgroups.

The guidance is based on a 2014 action plan developed under the 2012 FDA Safety and Innovation Act, which directed the agency to examine participation of diverse subgroups based on age, race and ethnicity (ARE), and whether that data was being made available to the public, explained Kathryn O'Callaghan, CDRH's assistant director for strategic programs.
— Zack Budryk

Device, *from Page 1*

"The Bayer post-market study on Essure has held true to those GAO findings," they said, adding that Bayer planned to enroll 78 patients per month but the FDA website indicates there is currently only one patient enrolled in the study.

The FDA's database shows thousands of adverse events reports for Essure, some of which describe device migration and unplanned pregnancies.

The letter lists several questions the congress members hope to ask Gottlieb if their request for a meeting is granted, including: What is the FDA doing to ensure Bayer complies with the timeline for recruiting patients outline in the study plan?

The representatives also want a broad discussion about post-market surveillance on Class III devices in general.

The letter can be read here: www.fdanews.com/11-02-17-Essure.pdf.

CDRH Eyes Quality, Program Alignment for 2018 Inspections

Moving into 2018, CDRH is focused on two main objectives to change how inspections of medical device manufacturing facilities are conducted — the case for quality and program alignment.

As the healthcare system shifts its focus toward the quality of services provided, so will the strategy for inspecting and surveilling medical device manufacturers, Captain Sean Boyd, acting director at CDRH's Office of Compliance, said at the 12th Annual FDA Inspection Summit hosted by FDAnews.

Shifting the focus toward quality will help CDRH understand patient needs and expectations to incorporate them into regulatory decision-making, Boyd said.

Compliance will still be important, but there will be an increased focus on quality because a manufacturer that has demonstrated compliance with FDA requirements may not necessarily be providing quality devices, he said.

He pointed to three recently launched programs that the agency hopes will help with its goal of making a case for quality — the Medical Device Single Audit Program, the Case for Quality Voluntary Program, and the PMA Critical to Quality Pilot — which is "providing a venue for breaking down several barriers to quality."

The barriers Boyd identified include: the risk to patients from poor quality products; lack of competition around medical device quality; and lack of investment in new technologies.

The agency aims to improve its routine surveillance and targeted inspections by using the information participants are required to provide through these programs, including performance outcome analytics and dashboards, quality maturity appraisals, and critical-to-quality PMA reviews.

CDRH also is looking to address the information siloes that have made it more challenging to have a full view of everything that is impacting a particular firm or device, by combining all of the offices within the organization that are focused on compliance, PMA reviews, and surveillance and biometrics into several device-specific offices.

The new offices will focus on a particular device area or group of devices or technology to help agency staff "make better decisions more rapidly and have access to all of the information at our fingertips," Boyd said. In addition to obtaining a fuller picture of a firm or device and the industry as a whole when there may be an issue that requires attention, restructuring will allow for organic connections within the organization, streamlined decisions, shared priorities, and professional growth, he said.

FDA Warns German Device Firm Over Adulteration, Misbranding

German-based devicemaker DRG Instruments drew a warning letter from the FDA and the agency said it would refuse entry of the company's medical devices to the U.S. market because they were adulterated and misbranded.

An October 2016 inspection of the firm's manufacturing facility in Marburg revealed GMP nonconformities in process control procedures, CAPA reports and employee training. The agency was not satisfied with responses it received to a Form 483 report issued after the inspection.

The firm reworked ELISA microplates in an attempt to address quality control test failures without establishing written procedures for storing or preparing their antibody vials and solutions, the agency said. A CAPA report reviewed during the inspection showed manufacturing errors that led to many low patient results were caused by a failure to update manufacturing procedures after a design change, the agency said.

In addition, the facility failed to obtain the required FDA approvals or clearances for its Salivary Cortisol ELISA prior to introducing it for commercial distribution with changes that could significantly impact the safety and effective of the device.

Read the DRG Instruments warning letter here: www.fdanews.com/10-31-17-DRGInstrumentsGmbH.pdf. — Ana Mulero

FDA Cites Devicemaker Over MDR, GMP Violations

An inspection in March by the FDA of ELI-Tech Group's facility in Spankeren, The Netherlands prompted a warning letter after the device manufacturer failed to follow through with the promises made in response to a Form 483 report.

The agency said the firm's Selectra Pro S, Selectra Pro M and Viva Junior Analyzer devices were misbranded because the firm lacked adequate medical device reporting procedures and failed to report corrections or removals to the FDA.

GMP violations noted in the 483 resulted in the devices also being deemed adulterated. The violations include placing a CAPA in a postponed stage without any documentation for the practice, and failing to investigate complaints associated with rust residue, a burnt out power connect, and leaking units.

The agency also flagged inadequate processes for validating the facility's water system, and controlling purchased products and accepting incoming products.

In April, the firm provided a draft remediation plan and said it would detailed responses for each observation with supporting documentation. But the agency did not receive any response or documentation, the FDA said.

Read the warning letter here: www.fdanews.com/10-31-17-ELITechGroupBV.pdf. — Ana Mulero

UVLrx Therapeutics Flagged For IDE Violations

The FDA warned investigational medical device sponsor UVLrx Therapeutics for eight violations an FDA investigator observed during an inspection of its Florida facility from March 27 through April 4.

UVLrx failed to obtain required approvals from its Institutional Review Board, comply with monitoring requirements, maintain records of adverse device effects, or apply proper labeling to its investigational products, the investigator found.

The sponsor enrolled thousands more human subjects in a study protocol than the number approved by the IRB — 3,063 vs. 1,000 subjects — and shipped investigational devices to at least ten unapproved clinical investigators who treated subjects. These are serious violations, the FDA said, because "there is no assurance that the rights and welfare of subjects were adequately protected" without the approvals.

In addition, the FDA investigator saw no documentation that the clinical investigators had completed training or documentation of any potential adverse device effects, which may have impacted the study's subjects and collected data. And the sponsor's failure to include the investigational device caution statement in its labeling before shipping the devices to study sites could lead to incorrect use and adverse event tracking, the warning letter said.

The FDA requested final copies of all of the new and revised SOPs, as well as documentation to show all research staff were adequately trained, and a plan for proper labeling of investigational products, among other corrective actions.

Read the UVLrx Therapeutics warning letter here: www.fdanews.com/11-02-17-UVLrxTherapeutics.pdf. — Ana Mulero

PEOPLE ON THE MOVE

Regenerative devices company **Tissue Regenix Group** appointed **Steve Couldwell** as CEO, effective Nov. 2. Couldwell brings more than 25 years of experience in the device and drug industries, most recently serving as chief operating officer at Global Sanofi Biosurgery.

Kent Imaging announced **Jeff Hydar** will join the company as vice president of sales, USA. Hydar has two decades of experience in the device and pharmaceutical industries. He previously served with Johnson & Johnson, Medline, and LifeCell.

Laser equipment manufacturer **Cutera** named **Elisha Wade Finney** to its board of directors as a non-executive director. Finney spent nearly three decades at Varian Medical Systems in positions including executive vice president and chief financial officer before retiring in 2017 and currently serves as a director of several companies including ICU Medical and Mettler-Toledo International.

Devicemakers Support TGA's Approach To Beefing Up Sanctions And Penalties

Devicemakers were mostly supportive of the Therapeutic Goods Administration's plan to strengthen sanctions and penalties in Australia so it could respond better to repeated non-compliance.

The agency asked for comments on its proposals to strengthen post-market regulations and to deter misleading advertising of devices and diagnostics by imposing graduated penalties. The consultation was part of a broader review of Australia's device regulations that began in 2015.

The Medical Technology Association of Australia (MTAA) said in its comments that it supports the proposed three-tiered system of graduated penalties that would impose strict liability and civil penalties for non-compliant advertising.

The proposed amendments would align regulatory provisions with other Commonwealth regulators, the TGA said, and would give the agency "an expanded suite of possible regulatory actions to address the severity of a compliance breach."

Some proposed amendments introduce substantiation notices and public warnings, and others would enhance sanctions and penalties and introduce the ability to seek an injunction to quickly address serious cases of non-compliant advertising.

The proposed tiered structure for advertising non-compliance would comprise the following alternative offenses:

- A new fault-based offense with an aggravating element (conduct that has or will result in harm or injury, or conduct likely to result in harm or injury) — maximum penalty of 4,000 penalty units and/or five years imprisonment; or
- A new strict liability offense with no aggravating element — maximum penalty of 100 penalty units with no imprisonment; or
- The existing fault-based offense.

The amendment also proposes civil penalties that would allow courts to impose either a maximum 5,000 penalty units for an individual or 50,000 penalty units for a corporation.

MTAA said it supported the proposed changes that include an "additional circumstance of aggravation of 'likelihood of harm or injury to any person.'" The association said the change should better differentiate aggravated criminal offenses from strict liability offenses.

(See **TGA**, *Page 6)*

Health Canada Tweaks its MDSAP to Reduce Audit Times

Health Canada has made significant changes to its Medical Device Single Audit Program with the goal of reducing audit times.

The MDSAP consortium announced Oct. 31 it has tweaked the program, in response to comments received from Canadian medical device license holders, by:

- Reducing the total number of tasks to be accomplished and the overall audit time using a streamlined MDSAP audit approach;
- Introducing a 10 percent reduction in audit time for manufacturers with 45 or fewer employees and a 20 percent reduction for those with 15 or fewer employees;
- Reducing the duration of surveillance and re-certification audits by 20 percent; and
- Clarifying the expectations for annual surveillance audits.

As the compliance deadline of Jan. 1, 2019 approaches for Canadian manufacturers, the consortium said it is also exploring other ways in which it could improve the program's efficiency and reduce audit times, with plans to announce these sometime in the near future.

Health Canada also encouraged manufacturers to schedule an early transition assessment to determine whether they will be able to accommodate all requests of an auditing organization for transitioning by late 2018. Those that cannot make the transition by the 2019 deadline may face compliance actions, such as the cancellation of medical device licenses.

FDA Adds Contraindication to Labeling Of Ultrasonic Surgical Aspirators

The FDA has recommended the addition of a contraindication for the use of certain ultrasonic surgical aspirator devices for removing uterine fibroids.

In a new labeling guidance document for manufacturers of such devices with indications for use in laparoscopic surgery, open surgery or gynecologic surgery, the agency explained that using the devices during the treatment of symptomatic uterine fibroids on a woman with an occult uterine sarcoma could result in dissemination of the cancer, a risk that outweighs the potential benefits.

The agency said the following contraindication should be added to labeling of the devices, with or without 510(k) clearance, within 120 days of the Oct. 30 release of the guidance:

CONTRAINDICATION: This ultrasonic surgical aspirator device is not indicated for and should not be used for the fragmentation, emulsification, and aspiration of uterine fibroids.

The FDA also called on manufacturers to update other portions of their device labeling, such as the list of procedures for which the aspirator can be used, to make them consistent with the new contraindication.

Read the guidance here: www.fdanews.com/11-03-17-UltrasonicAspirators.pdf.

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Compliance and enforcement actions should only be taken against those that "persistently or deliberately operate outside the regulatory scheme," MTAA said.

The Australian Dental Association also supported the TGA's proposals, but expressed concern that the TGA would have discretion over whether or not to issue an infringement in cases where illegal supply could be demonstrated. It pointed to language in the proposal that says, "in deciding how to deal with a non-compliance matter, we first consider education, guidance material or additional training for those who show a willingness to comply with the regulatory scheme."

ADA said that this language implies that even in instances where illegal supply can be proven, "the TGA may fail to take enforcement action."

The dental equipment association stressed that the TGA should not forgo issuing an infringement notice in favor of a warning, education requirement or other measures when illegal supply can be proven.

Accord Australasia, a raw material and service provider, said it supported most of the reforms, but took issue with proposed provisions that would allow certain authorized persons to enter any premises without a warrant.

The consultation is part of the second wave of device reforms in Australia. The first phase, which focused on assessment pathways, was passed by the Australian parliament in June (*IDDM*, June 26).

FDA to Release a New Version Of Submission Software

FDA software used by medical device manufacturers to submit reports of adverse events, corrections and removals is being updated without any downtime for the first time.

The agency announced last month that it will release version 3.0 of the eSubmitter 2.x.x during November, which will require a new installation. eSubmitter 2.x.x can continue being used until May 7, 2018, when it will be disabled.

Pilgrim Quality Solutions, a software company that contributed to the creation of eSubmitter, says the agency wants to use data analytics as a guide to improve efficiency and make better use of its resources.

It makes sense for the FDA to prepare for future expansions of eSubmitter's capacity to prepare and transmit files to the FDA gateway and this is what version 3.0.0 will allow the agency to do, Bernard Jee, Pilgrim's product manager for the company's eMDR area, told *FDAnews*. The goal is to get a broader view of the available information.

Recent updates to eSubmitter and those in the newest version shows the agency is adapting to new developments in the software world, according to Jee.

Previously, the agency had to notify manufacturers when it planned maintenance on eSubmitter because of the downtime this process required, which left some manufacturers scrambling to submit reports before a deadline in order to avoid compliance actions. But the need for downtime was eliminated about a month ago, Jee said.

Jee believes there are a couple of things the FDA will likely look to accomplish with the changes to its software, such as allow for the use of multiple medical devices and patients within the same report, and centralize submissions to streamline the process of sending information to different FDA centers by updating product codes.

The eSubmitter's information fields have been updated, including those for age and ethnicity data. Some fields have been added, while others were consolidated or made larger, Jee said.
— Ana Mulero

APPROVALS

Quidel Receives FDA Clearance for Solana Assay

Quidel received marketing clearance from the FDA for the Solana respiratory syncytial virus (RSV) and human metapneumovirus (hMPV) assay.

The assay uses Quidel's novel reverse-transcriptase amplification technology, generating results for 12 samples in approximately 45 minutes.

Solana received a CE Mark in August.

FDA Approves New Nebulizer For Tyvaso Inhalation System

United Therapeutics received FDA approval for its TD-300/A inhalation device for use with its Tyvaso (treprostinil) inhalation solution.

Tyvaso is a vasodilator indicated for the treatment of pulmonary arterial hypertension to improve exercise ability.

Tyvaso was originally approved by the FDA for the treatment of PAH in 2009, under a new drug application covering a drug-device combination consisting of the drug, an ultrasonic nebulizer and accessories.

Renishaw Wins FDA Approval For Neurosurgery Planning Software

The FDA granted 510(k) clearance for Renishaw's neuroinspire software that blends MRI and CT datasets into a 3D format, enabling neurosurgeons to identify regions deep within the brain tissue.

The device is designed to minimize the chance of hitting key anatomy during the procedure.

Neurosurgeons can use the software to create plans based on procedure type with tools tailored to the procedure.

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

Approvals, *from Page 7*

Medineering Wins CE Mark For Its Positioning Arm

Munich, Germany-based Medineering received a CE Mark from the European Commission for its Positioning Arm to position passive adapters and robots in ear, nose and throat surgery, neurosurgery and spinal surgery.

The company describes the product as the basis of "a completely new concept of robotic assistance."

The technology is designed to assist surgeons in complex anatomical areas.

Ortek Wins Marketing Clearance For Cavity Detection Device

Ortek Therapeutics received 510(k) clearance for its electronic dental cavity detection device. The tabletop unit allows dental professionals to diagnose and monitor cavities in the biting surfaces of molars and premolars.

The device detects tiny lesions in the tooth enamel before a cavity is formed, and measures the amount of dentinal fluid in the pits and fissures of molars and premolars.

Tooth enamel is electrically non-conductive unless breached by a fracture or demineralization. The more fluid the device detects, the greater the severity of the lesion.

Acutus Gets FDA Clearance for Advanced Cardiac Mapping Technology

Acutus Medical received FDA clearance for its AcQMap high resolution imaging and mapping system and the AcQMap 3D imaging and mapping catheter.

The system combines ultrasound anatomy construction with the ability to map the electrical-conduction of each heartbeat to identify complex arrhythmias.

Medacta Receives FDA Clearance for Anatomic and Reverse Shoulder Systems

Medacta received marketing clearance from the FDA for the Anatomic Shoulder and Reverse Shoulder components of its modular Medacta Shoulder System.

The device's instrumentation and implants allow for anatomic restoration, resulting in an efficient surgery. The modular system features wide-ranging sizes, adjustable offset, and innovative configurations.

Nitiloop Wins FDA 510(k) Clearance for Microcatheters

Nitiloop received FDA marketing clearance for its new Nova Cross Extreme and Nova Cross BTK.

The microcatheters combine low profile technology with enhanced guidewire and catheter support for safer and more effective lesion crossing.

Alcyone Wins CE Mark for Alivio Ventricular Catheter and Flusher System

Alcyone Lifesciences received a CE Mark for its Alivio ventricular catheter and flusher system for the treatment of Hydrocephalus.

The shunts are implantable devices inserted by neurosurgeons to treat hydrocephalus, a condition in which an excess of cerebrospinal fluid accumulates in the ventricles and can increase intracranial pressure in the brain, creating a potentially life-threatening condition.

The system, used in conjunction with any CSF shunt, is designed to unblock ventricular catheters.

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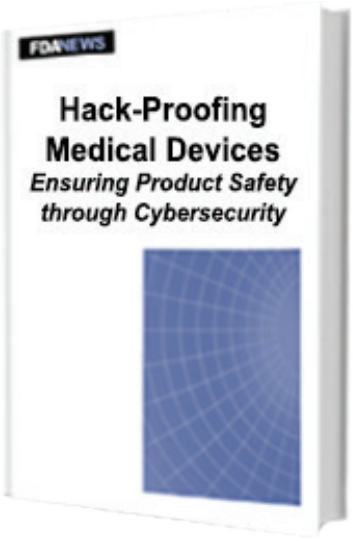

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