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IN THIS ISSUE

NESTcc Selects 11 Projects for Medical Device Real-World Evidence Use Cases

In support of the FDA's plan to increase the use of real-world evidence in medical device regulatory decision-making processes, the National Evaluation System for health Technology Coordinating Center launched 11 demonstration projects.

NESTcc — established by the Medical Device Innovation Consortium in 2016 with a $3 million grant from the FDA to explore the use of robust RWE — chose the projects for their "potential to provide proof of concept for innovative and scalable approaches to RWE generation across the medical device total product life cycle (TPLC)."

Under a new five-year cooperative agreement with the FDA, NESTcc received an additional $6 million in funding from device user fees this fiscal year in support of the RWE commitments made in the latest reauthorization of MDUFA. The center is charged with providing the necessary infrastructure for an efficient use of RWE in making pre- and post-market decisions.

(See **Projects**, *Page 4)*

Health Canada Clarifies Factors Used For Medical Device Classifications

Health Canada updated its classification guidance to give industry more clarity on the factors it uses to determine whether a product is a medical device or drug.

Effective Feb. 7, the new guidance updates the agency's January 2013 guidance to reflect revisions to the definition of a medical device under Canada's Food and Drugs Act in November 2014, and the regulatory authority's interpretations, though it does not apply to combination products.

"In most cases, the distinction between devices and drugs is clear and these products can be easily classified according to the definitions," Health Canada said, adding "as new health products and technologies emerge, however, it is sometimes difficult to identify the appropriate regulatory framework that applies."

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

Guidance, *from Page 1*

The agency pointed to the last paragraph in the Act's definition of a medical device as a significant 2014 addition intended to clarify that those products that act "solely by pharmacological, immunological or metabolic means or solely by chemical means in or on the body of a human being or animal" fall outside of its scope. Another key component of the definition relates to the product's purpose or intended use, one of the factors used in making classification decisions.

"A liquid for use as a body cavity filler... could be classified as a drug when considering only paragraph (a) of the drug definition," Health Canada said. "However, since it is intended to play a structural role once it has filed the volume of a cavity, it is best characterized as an article that modifies a body structure" and thus it would "more reasonably be classified as a device."

Other factors the regulatory body considers when making classification determinations include product representation, such as labeling and advertising, as well as product composition, function, and health effect. It may also take into account product classification decisions made by foreign regulatory authorities.

In the event that a classification will be changed as new scientific evidence emerges, Health Canada intends to notify sponsors in advance so they can get the appropriate authorizations.

Read the full guidance here: www.fdanews.com/02-08-18-HealthCanada.pdf. — Ana Mulero

CDER Denies Petition on Generic Combination Products

CDER denied a fourth petition from United Therapeutics calling on the center to impose additional conditions before approving generics for combination products that reference its pulmonary arterial hypertension drug Tyvaso unless they meet specific conditions and measure up to the original in terms of performance and bioequivalence.

The applications should request approval for a specific device and for refill kits with the required device components and document their compatibility with both the generic and Tyvaso delivery systems, the company said.

United had submitted three similar petitions, two in 2016 and one last April, all of which were denied without further comment as the FDA had not made a final decision on how to proceed with such applications. The agency still has not made a decision on whether or not to approve abbreviated new drug applications referencing Tyvaso.

"Therefore, we must determine whether it would be appropriate for us to take final Agency action on the approvability of a specific aspect of an ANDA before taking final action on the approvability of the ANDA as a whole," said CDER Director Janet Woodcock, noting that under CDER's interpretation of the Food, Drug and Cosmetic Act, it is not required to reach a decision on the approvability of specific aspects of an ANDA while its final decision on the approvability of such ANDAs as a whole is still pending.

The FDA denied the petition "on a non-substantive basis," United Therapeutics associate general counsel Shaun Snader told *FDAnews.* "We plan to resubmit our petition and look forward to such time as the FDA can substantively address the issues raised."

Read the full response here: www.fdanews.com/02-05-18-CDER.pdf. — Zack Budryk

Canada's MEDEC Says Proposed Fee Hikes Are Unjustified, Bad for Business

Canada's medtech association MEDEC said Health Canada's proposed fee increases could have a significant negative impact on industry, economic growth, and ultimately patient care.

The association said it was disappointed that the proposal failed to mention further ways the regulator could leverage outcomes and evidence to reduce duplication and improve review time, particularly when the increased fees won't be coupled with better performance standards.

MEDEC said the steep increases for devices are not justified, particularly when most increases amount to more than 100 percent. For example, a license application for a Class III medical device would increase from $5,691 (US$4,528) to $13,861 (US$11,029). A Class III device application for a near-patient in vitro diagnostic device would increase from $9,687 (US$7,708) to $32,267 (US$25,675).

Fee Hikes

Under the proposal, fees to review changes in manufacturing processes, facility, equipment or quality control procedures would increase from $1,433 (US$1,140) to $9,956 (US$7,922). A Class III significant change would jump from $5,330 (US$4,241) to $11,127 (US$8,854), under the proposal.

Health Canada proposed fee hikes for reviewing medical devices, as well as licensing and postmarket surveillance and enforcement activities last October. Fees, last revised in 2011, fall short of the agency's new goal of covering 90 percent to 100 percent of costs, Health Canada said in its proposal (*IDDM*, Oct. 20, 2017).

"We understand the need for annual increases to keep pace with the cost of living. The current cost recovery fee schedule has a built-in annual increase for fees of 2 percent as well as a 50/50 ratio for public/private cost sharing," MEDEC said. "According to data from the Medical Devices Bureau the application volume has remained relatively stable in recent years," and therefore the significant increase in fees is not warranted.

MEDEC stressed that Canada's 2017 federal budget announced its intent to modernize business fees so businesses pay their "fair share" for the services the government provides.

Fees Don't Represent 'Fair Share'

Paying 90 percent to 100 percent of the fees does not constitute a "fair share," the association said, noting that Canadians see numerous benefits from new medical technologies that can even "lower the incredible burden of health care costs on all levels of government."

The association stressed that Canada only represents 2 percent of the global market for medical technologies, and the Canadian market is already less attractive to the medtech industry compared to some other countries.

"With fees for new license applications increasing by 127 percent to 233 percent and amendments by 429 percent to 595 percent, manufacturers will reconsider bringing new and emerging health technologies and/or iterative innovations to Canada," the group said.

Fee increases for amendments "will significantly impact software-driven advances," and manufacturers could choose to delay upgrades, the association warned, adding that some device-makers may review the devices they currently sell in Canada and re-assess whether or not they will renew those licenses.

The association called on the government to provide clarity and justification for new fee unit costs and the rationale for a "fair share" of 90 percent to 100 percent fee setting ratio. It also called for an independent external review of Health Canada costs to see if the increases are justified.

It suggested that the regulator consider a staggered implementation period to reduce the burden on industry.

Read MEDEC's comments here: www.fdanews.com/02-06-18-Canadafees.pdf.

Projects, *from Page 1*

The selected 11 projects, expected to be completed by year's end, will shed light on challenges and lessons learned in the design and execution of RWE studies, and will also identify gaps where NESTcc can help accelerate the use of medical device RWE to "support regulatory, coverage, patient, and clinical decision-making," said NESTcc Executive Director Rachael Fleurance.

From artificial intelligence algorithms capturing performance metrics in a national registry for measures of safety and effectiveness to mHealth apps' collection of patient-reported health outcomes to expand RWE use in post-market settings, the projects explore a wide range of health technologies. Sources of real-word data include administrative claims, electronic health records, as well as patient- and device-generated data.

"The use of real-world data seeks to capture a larger, more representative assessment of device performance while increasing efficiency and lowering costs," NESTcc said in its description of a demonstration project involving Abbott, Boston Scientific, the American College of Cardiology, LivaNova, Medtronic, the FDA, Duke, and Yale, among others.

The project — Electrophysiology Predictable and Sustainable Implementation of National Registries — seeks to shift away from patient follow-up assessments in post-approval studies towards a real world evidence approach by leveraging existing sources of data, including EHR data, remote patient monitoring with periodic contact, administrative claims, and patient registries.

The two largest demonstration projects, based on participation, are focused on developing an RWE-based infrastructure to improve the interoperability of IVD-related information by harmonizing and mapping relevant codes, and objective performance criteria with the goal of expediting label expansions for peripheral vascular intervention devices.

Another study is aimed at "producing a scalable model to inform an industry-wide roadmap toward the use of EHR-based data networks for the responsible access and use of practice data, in both the pre-market and post-market space." This project involves a devicemaker-healthcare provider collaboration (Medtronic and Maryland-based Mercy Medical Center) to validate the use of existing EHR data on heart failure patients for generating medical device RWE.

The FDA is participating in six of the 11 demonstration projects, while Medtronic is taking part in four. Abbott and startup company Me2Health, a developer of cloud-based health platform called Hugo, are tied in third place with two projects.

FDA guidance on RWE use for regulatory decision-making for medical devices was finalized last September. It encourages RWE use by clarifying the factors that should be used when determining whether real-word-data collected can be used for RWE purposes, such as the timeliness of data entry (*IDDM*, Sept. 4, 2017).
— Ana Mulero

FDA Flags Spate of Repeat Nonconformities at Zimmer Biomet

In a rare exception to the FDA's normal practice, the agency posted a Form 483 flagging several GMP and MDR nonconformities — most of which are repeat observations — at a Zimmer Biomet medical device manufacturing facility in Indiana.

Out of the eight nonconformities the FDA investigators noted, five were first observed during site inspections dating back to 2011 or 2015, with the last one concluding in October 2017. The firm's CAPA procedures and lack of written MDR procedures are among those flagged on more than one occasion.

A CAPA investigation regarding the use of existing nonconforming products was closed last August after the firm initiated a recall of its Class II hip and Class II/III knee implants to address a customer complaint "alleging that a surgeon opened a femoral implant and found parts of the plastic bag sticking to the implant," the FDA said.

In an attempt to correct the problem, the firm acted to replace the implants' old Low Density Polyethylene bag with a new one for future packaging, and concluded the complaint investigation by stating that "the plastic bag sticking on the implant was the 'old style poly bag,'" the FDA investigators said. But the "scope of the containment action was not sufficient to correct and prevent the recurrence of the nonconformity." The issue was first noted in 2011.

In addition, Zimmer Biomet had yet to implement written MDR instructions for at least four of its procedures, including those for complaint handling and device reporting, that the FDA reviewed during inspections in 2015 and 2017. The procedures "do not ensure that MDRs for serious injuries are reported as required," the

(See **Zimmer***, Page 6)*

Medical Device Reporting Requirements

MDR requirements are an outgrowth of complaint management regulations. The FDA's regulations in 21 CFR Part 803 – Medical Device Reporting require that companies evaluate all device complaints to determine if they involve an adverse event that must be reported to the agency.

Malfunctions must be reported when the chance of death or serious injury resulting from recurrent malfunctions is not remote. Malfunctions also need to be reported when the consequences of the malfunction affect the device in a catastrophic manner that might lead to a death or serious injury.

Manufacturers often have the most trouble determining when the likelihood of a future malfunction resulting in death or serious injury is not remote. One of the factors the FDA looks at is whether or not that particular type of malfunction has caused a death or serious injury in the past two years. If it has, the agency concludes that the risk is not remote and the event must be reported.

In addition, manufacturers must report malfunctions when:

- They cause the device to fail to perform its essential function, compromising the device's therapeutic, monitoring or diagnostic effectiveness, and could cause or contribute to a death or serious injury, or other significant adverse device experience;
- They would prevent a long-term device implant from performing its function;
- The device is considered life-supporting or life-sustaining, and thus essential to maintaining human life; or
- The manufacturer takes or would be required to take action under Section 518 or 519(f) of the Food, Drug and Cosmetic Act, which deals with recalls and tracking products.

The timeline for reporting an event to the FDA depends on the immediacy and severity of the problem. Manufacturers must submit an MDR either within 30 days of becoming aware of an event or, in the case of possible "unreasonable risk of substantial harm to the public health," within five days of learning about the event.

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

Regulatory Hurdles for Design Changes Stall BSI's Market Comeback

Boston Scientific is facing regulatory hurdles with its proposed manufacturing process and design changes to bring its transcatheter aortic valve back to the U.S. and EU markets.

The devicemaker giant launched a global voluntary recall of all its Lotus valve devices nearly a year ago due to issues with locking mechanisms.

The company had received "reports of premature release of a pin connecting the Lotus Valve to the delivery system," according to a Feb. 23, 2017 notice to investors. "As with the prior announced suspension of our Lotus Edge Valve System device, we believe that the issue is caused by excess tension in the pin mechanism introduced during the manufacturing process," it said.

At the time, BSI expected to return its valve devices to commercial markets and clinical sites by the fourth quarter of 2017. By last November, it had adjusted the timeline to re-introduce the valves with newly implemented manufacturing process and design specification changes during Q1. In its latest earnings call, however, the company confirmed the valves will remain off commercial markets until at least 2019.

"Pending our ability to clear certain technical and regulatory hurdles" the new goal is to launch the Lotus valve devices in the U.S. and EU markets in 2019, the company said.

These are not the only devices with which BSI has faced manufacturing problems. It issued an alert last August over a fatal incident involving one of its pacemakers for which it prepared a software patch to prevent environmental radiation from corrupting the devices' memory (*IDDM*, Aug. 7, 2017). And the Department of Homeland Security issued a warning last October about two cyber security vulnerabilities in BSI's portable cardiac rhythm management systems that may allow hackers to remotely obtain patients' health information (*IDDM*, Oct. 30, 2017).

Zimmer, *from Page 5*

investigators added. A total of 55 instances were identified as serious injuries that should have been reported to the FDA via MDR submissions.

Another repeat observation relates to the firm's device packaging procedure, which did not provide "adequate assurance that all packaging systems will provide physical protection and maintain the integrity of the sterile barrier system through normally anticipated hazards associated with shipping." And its climate conditioning for new or design-changed products differed from those "required for legacy packaging configurations," according to the FDA.

The firm's inadequate procedures for ensuring all pieces of equipment are routinely calibrated as required and a complaint handling procedure that did not describe a mechanism for determining complaint status are the remaining two repeat observations.

Newly identified issues relate to an inefficient control of nonconforming products, including those found to have been contaminated, a lack of Issue Evaluations for at least four instances of exceeded control limits, as well as a validation process performed on software being used for making quality hold determinations that did not conform to specified requirements.

Read the Zimmer Biomet Form 483 here: www.fdanews.com/02-08-18-Zimmer.pdf.
— Ana Mulero

PEOPLE ON THE MOVE

Surefire Medical appointed **Mary T. Szela** as CEO and president. Szela brings nearly 30 years of experience in the biotechnology, medical products, and pharmaceutical industries. She previously served as CEO of Novelion Therapeutics, a rare disease company. Prior to Novelion, Szela was CEO of Melinta Therapeutic, and previously served at Abbott Laboratories as president of the company's U.S. pharmaceutical business, and as vice president for global strategic marketing and services.

Q&A on Brazil's Regulatory Changes for Devices

Marcelo do Ó, managing director and partner at L.E.K. Consulting, in São Paulo, Brazil, talked with FDAnews about recent changes by Brazil's National Surveillance Agency.

FDAnews: *ANVISA has extended the registration period for high-risk Class III and Class IV devices and in vitro diagnostics from five years to 10 years. What are the implications of this change?*

Answer: According to ANVISA, 94 percent of device renewals are approved, and this control does not release the need for the initial approval, modification approval and technology vigilance processes. The extension from five years to 10 years for renewal should not be confused with lack of control procedures, since they continue in place. Note that a few countries, including Australia and the USA do not require renewals.

For classes III and IV, it is important to note that there is a reasonable level of rigor to approve the product in the first place. So as long as there is no material modification or negative techno vigilance data, the product safety should be secured from the moment the analysis was conducted for the initial registration.

Q: *ANVISA has made a lot of changes geared toward streamlining operations. One of those was to ease restrictions on imports. Why is the agency making these changes?*

A: There is an effort at ANVISA to reduce bureaucracy and streamline internal processes. They have been criticized for taking two years to approve a generic product or more than that for renewing products. Just as an example, an approved product, in perfect registration condition, could take two years or more to be transferred from one company to another (in the case of licensing for example) even without changing the manufacturing site. This resulted in a backlog that was becoming difficult to manage.

We should continue to see progress as ANVISA addresses the inefficiencies. ANVISA was considering at one point granting registration, or temporary registration, if a product was approved by a major recognized regulatory authority, such as the FDA or EMA.

Q: *What will these recent changes mean for device manufacturers wanting to expand their market in Brazil?*

A: Multinational companies typically welcome improvements that do not put patient safety at risk. We've seen some companies push for tougher regulation (biosimilars for example) to make the approval bar higher. But in general, this move will require less regulatory resources and encourage innovation.

ANVISA has been recognized as a high quality technical authority, but inefficient in terms of timelines, discouraging competition, innovation adoption and delaying patient access to new products. A move that generates higher efficiency without sacrificing good quality and safety for the public is welcomed by all.

APPROVALS

Molecular Matrix Snags FDA Clearance for Bone Graft Technology

Molecular Matric received FDA 510(k) clearance for its Osteo-P musculoskeletal technology for bone regeneration.

The musculoskeletal solution is intended for filling bone defects caused by surgical procedures or traumatic injuries. The bone graft substitute is made with a hyper-crosslinked carbohydrate polymer.

Topcon Medical Systems Wins FDA Nod for Imaging Device

Ophthalmic instrumentation developer Topcon Medical Systems received 510(k) marketing clearance for its DRI OCT Triton Series.

The imaging device features a built-in retinal camera for tracking eye movement while capturing selected scans.

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

Approvals, *from Page 7*

LivaNova Line of Arterial Cannulae Suite Scores CE Mark

London-based devicemaker giant LivaNova received CE Marking for its line of PureFlex adult arterial cannulae.

The portfolio offers a variety of curved and straight tip cannulae options to meet clinical needs.

The products feature a wire-reinforcement spring to deliver flexibility without kinking.

Siemens Healthineers Wins FDA Clearance for Blood Analysis Assays

The FDA cleared two point-of-care blood analysis tests manufactured by Siemens Healthineers.

The company's Blood Urea Nitrogen test and its Total Carbon Dioxide test are intended to aid clinicians in diagnosing renal diseases and metabolic imbalances.

The tests can be performed on Siemens' handheld epoc Blood Analysis System at the patient's side to enable faster clinical decisionmaking.

Asuragen Expands CE Mark On Cancer Monitoring Assays

Molecular diagnostic product developer Asuragen expanded its CE Mark on two chronic myeloid leukemia monitoring assays for use on the Roche Diagnostics cobas z-480 analyzer.

The QuantideX qPCR BCR-ABL IS Kit and the QuantideX qPCR BCR-ABL minor Kit can detect and quantify major or minor fusion transcripts, with automated reporting of results.

They are intended to provide improved sensitivity for clinical assessments of patients' response to tyrosine kinase inhibitor therapies.

FDA Clears Ultrasound Diagnostic Systems From French Device Firm

SuperSonic Imagine, a France-based medical device company, received FDA 510(k) clearance for its Aixplorer and Aixplorer Ultimate ultrasound diagnostic systems.

The clearance is for noninvasive clinical assessments of hepatic fibrosis and steatosis.

The Aixplorer systems provide imaging and measures of liver and spleen stiffness in real-time.

FDA Clears Teleflex Peripheral Snare Devices

The FDA cleared Teleflex's new versions of its Expire Elite and Sympro Elite snares.

The snares are used to retrieve or reposition intravascular foreign objects, such as balloons, coils or catheters.

Both products come preassembled in a one-piece design that allows rapid deployment through any 0.035" compatible lumen, the company said.

Amiko Medication Sensors Snag CE Mark For Use With Three Inhalers

Amiko Digital Health, a London-based developer of digital health tools powered by artificial intelligence, received a CE Mark for its Respiro medication sensors for use with inhalers from three different pharmaceutical companies.

The new certificate allows for the devices to be integrated in the EU into Teva's Spiromax inhaler, Chiesi's Nexthaler inhaler, and GlaxoSmithKline's Ellipta inhaler.

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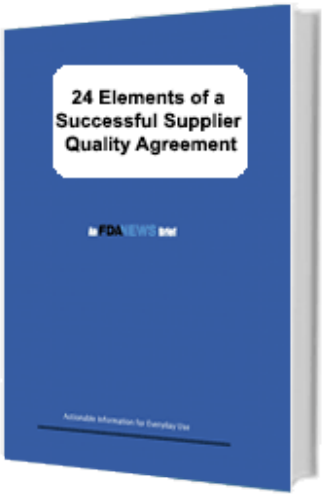

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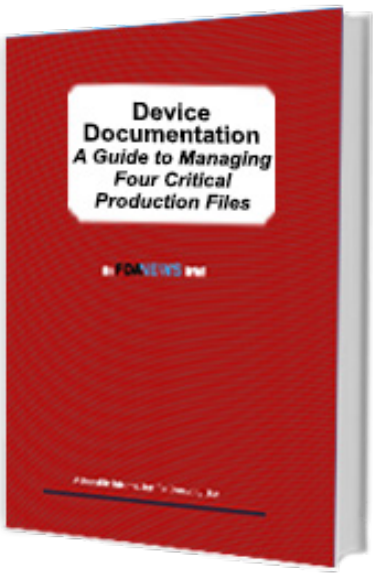

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