INTERNATIONAL DEVICES & DIAGNOSTICS MONITOR

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IN THIS ISSUE

FDA to Require Agency-Wide Training In Use of Patient-Reported Outcomes

The FDA added a new requirement to its Reviewer Certification Program — training in the use of patient-reported health outcomes — the agency said in its first report on PROs in medical device premarket submissions and post-market studies.

The agency developed the training course last spring to reflect the interest seen among devicemakers and study sponsors, and it encourages the use of PROs in pre- and post-market clinical studies and regulatory decisions.

"For regulatory purposes, high quality information from PRO measures con provide valuable evidence for benefit-risk assessments, and can be used in medical device labeling to communicate the effect of a treatment on patient symptoms, functioning and quality of life," the FDA said, adding the number of PRO measures CDRH uses continues to grow.

The center saw an increase of more than 500 percent over a six year period in the number of pre-market submissions that include PRO

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IMDRF Gains 10th Member: Korea's Ministry of Food and Drug Safety

South Korea's Ministry of Food and Drug Safety has joined the International Medical Device Regulatory Forum.

Korea joins the U.S., Europe, Canada, Australia, and Japan — the forum's founding members — as well as Brazil, China, Russia, and Singapore, in the international effort to harmonize medical device regulations via guidance, standards, and auditing practices.

The Medical Device Single Audit Program (MDSAP), a cornerstone of IMDRF's strategy, is designed to recognize a common set of requirements for audits, to avoid duplication and reduce audit times. The Korean ministry has determined that the MDSAP concept could be applied in Korea.

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Harmonized Adverse Event Codes Will Ease Burden, Expert Says

FDA medical device adverse event codes will soon be harmonized with IMDRF terminology — a move that is expected to benefit not just regulatory bodies, but devicemakers and consumers.

The FDA recently provided details of planned changes for certain adverse event codes, among other updates, for the anticipated spring 2018 deployment of CDRH's eMDR system along with the eSubmitter software for preparing submissions. The agency is encouraging firms to begin preparing as soon as possible because the retired codes will be rejected by the updated system.

The remaining codes will eventually be harmonized with the terminology developed through IMDRF — the international consortium involving regulatory bodies in the U.S., Australia, Brazil, Canada, China, Europe, Japan, Russia, Singapore, and latest member country Korea aimed at harmonizing medical device regulations (*IDDM*, Dec. 18, 2017).

The coding harmonization will reduce the burden on device firms of keeping track of all the codes across different regulatory bodies, Bernard Jee, product manager at software company Pilgrim Quality Solutions, which contributed to the creation of eSubmitter, told FDAnews.

It will likely be "especially helpful for smaller firms that do not have the specific resources for regulatory bodies to accurately report on their adverse events….as the management of problem codes across multiple regulatory bodies can be time consuming," he said.

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measures, ranging from general quality of life measures to diseases and/or device-specific measures.

CDRH also saw a spike in PRO measures being used throughout fiscal years 2016 and 2017 within study protocols for clinical trials with investigational device exemptions.

PRO measures, which resulted from engaging with patient groups, healthcare communities, professional societies, and other regulatory bodies, were defined as "patients' perception of their own health status or quality of life." A numeric rating scale of a patient's pain intensity and a patient's diary of seizure episodes are examples of the most commonly used types of PROs.

Under MDUFA IV, CDRH is committed to using patient input in regulatory processes. The report provides examples of how CDRH has been acting on this commitment, such as staff training.

CDRH Director Jeff Shuren said last month that the center has now become 96 percent patient-engaged through a new initiative it calls Partner with Patients (*IDDM*, Dec. 18, 2017).

Read the full report here: www.fdanews.com/12-19-17-PROs.pdf. — Ana Mulero

Korea, *from Page 1*

Despite the addition of new IMDRF members, the MDSAP program has been slow to take off, with only Health Canada so far making it a requirement. The program will be fully operational on Jan. 1, 2019.

The number of participating MDSAP manufacturer sites went from just seven in the Q3 2014 to 417 as of Q2 2017, with at least 266 added in 2017, according to Nancy Shadeed, special advisor for international programs at Health Canada (*IDDM*, Sept. 22, 2017). — Ana Mulero

FDA Expands Least Burdensome Principles Across the Product Lifecycle

The FDA said a "least burdensome" approach should be applied throughout the medical device product lifecycle, rather than just in premarket regulatory decisions.

The FDA intends to provide significant updates to its 2002 least burdensome guidance as provisions in the Food and Drug Administration Safety and Innovation Act and the 21st Century Cures Act "further recognized the role of post-market activities as they relate to premarket decisions."

The FDA and industry share a responsibility to rely more on post-market activities, such as post-approval studies and post-market surveillance, when using the least burdensome approach in order to ensure timely patient access to safe and effective medical devices, the agency said.

"Through the application of the least burdensome approach, we've moved much closer to achieving our vision of patients in the U.S. having access to high-quality, safe and effective medical devices of public health importance first in the world," said FDA Commissioner Scott Gottlieb and CDRH Director Jeffrey Shuren in a blog post.

One major change to the 2002 guidance is how "least burdensome" is defined. It was previously defined as: "A successful means of addressing a premarket issue that involves the most appropriate investment of time, effort, and resources on the part of industry and FDA." The agency wants to change it to: "The minimum amount of information necessary to adequately address a regulatory question or issue through the most efficient manner at the right time."

The policy updates would expand the approach to include de novo requests; investigational device exemption applications; major deficiency letters; device reclassifications; and guidance documents, among several others.

The new least burdensome guiding principles include:

- FDA intends to request the minimum information needed to address the regulatory question or issue at hand;
- Industry should submit material, including premarket submissions, to FDA that are least burdensome for FDA to review;
- The right information should be provided at the right time to address the right questions.

"Striking the right balance between premarket and post-market information needs is a key principle of the least burdensome concept," the agency said. "This balance is intended to address obtaining the minimum necessary information at the right time in the total product lifecycle."

The draft also provides more examples for applying the principles. These include how to leverage existing data, such as peer-reviewed literature, to inform regulatory decisions. The agency also offers new details on the use of real-world evidence from sources like electronic health records. The FDA issued final guidance on using RWE to inform regulatory decision-making in August (*IDDM*, Sept. 1, 2017).

For industry, clarifications were added on reducing redundancies in marketing submissions to limit the amount of regulatory information in need of review, and using medical device development tools (MDDTs) to reduce costs and review times.

The agency cleared the Kansas City Cardiomyopathy Questionnaire — a clinical outcome assessment questionnaire for measuring patient-reported outcomes — earlier this year, as the first MDDT in the voluntary program for stakeholders (*IDDM*, Oct. 27, 2017).

It also recently drafted guidance to encourage using the 510(k)-Clinical Laboratory Improvement Amendments waiver dual application pathway for new in vitro diagnostic devices, arguing it enhances the submission process for both the agency and industry (*IDDM*, Dec. 1, 2017).

Read the full draft guidance here: www.fdanews.com/12-22-17-LeastBurdensome.pdf.

— Ana Mulero

IVD Devices: FDA Drafts Guidances On Clinical Trials, Replacing Reagents

The FDA issued draft guidance on the use of investigational in vitro diagnostic devices in therapeutic product clinical trials, and a separate guidance for updates on IVD replacement reagents.

According to the agency, the growing interest in personalized medicine, otherwise known as precision medicine, called for new policy clarifications. Personalized medicine relies on the use of IVDs to detect and measure biomarkers and other individual characteristics of diseases or other conditions with the goal of better directing patient treatment, the agency said.

More investigational device exemption applications have received timely FDA approval, agency officials wrote in December FDA Voice blog post.

Under CDRH's Early Feasibility Study Program, the number of IDEs submitted totaled 57 in FY 2017, compared to 26 in 2013, when the agency issued guidance on the program (*IDDM*, Dec. 15, 2017).

Continued growth of precision medicine has led to more therapeutic product clinical trials using investigational IVDs to help guide the management of participating subjects. But CDRH remains concerned that study sponsors and Institutional Review Boards are unaware that many of the IVDs are investigational, so their safety and effectiveness are still being assessed.

All clinical trials or studies that include IVDs are subject to the agency's IDE regulation, the draft guidance states. It includes details on the roles and responsibilities of sponsors and IRBs in complying with IDE requirements, IVD risk assessment information and recommendations for including this information in IDE applications.

The draft guidance on replacement reagents, when finalized, will replace the policy set forth in 2003, which described how devicemakers can apply an assay that previously received FDA clearance — or an assay in an instrument family with at least one FDA-cleared device — to an existing device.

The draft includes initial considerations for determining whether the agency's replacement reagent policy or instrument family policy is applicable.

The recommendations and concepts are similar to those in the FDA's final guidance on deciding when a new 510(k) is required for non-software or software changes to an existing device (*IDDM*, Oct. 27, 2017). For example, labeling changes to assays that are "clinically significant in terms of clinical decision-making are likely to require a 510(k)," the agency said in the draft guidance.

Read the Investigational IVDs for Therapeutic Product Clinical Studies draft guidance here: www.fdanews.com/12-22-17-IVD.pdf.

Read the Replacement Reagent and Instrument Family for IVDs draft guidance here: www.fdanews.com/12-22-17-IVD2.pdf. — Ana Mulero

Warning Letter Roundup: Firms in India, Lithuania and Texas Draw Warnings

Facilities in India, Lithuania and Texas drew warnings from the FDA for a variety of noncompliances, including inadequate device history records.

GPC Medical: The FDA warned an Indian devicemaker for noncompliances relating to process validation, device acceptance and labeling.

The agency inspected a GPC Medical facility in New Delhi in June of 2017 and found that the firm failed to ensure process corrections would be performed because it did not provide a plan for such corrections or any documentation supporting the corrections. The company also did not properly document finished device sampling procedures.

While the completed product testing plan indicated 100 percent inspection for dimensional acceptance, the product testing report deviated from this plan without any documented justification. The firm's response to the agency's Form 483 report, the firm said it would make corrections but failed to include a plan or documentation.

The company also did not include label accountability in its device history records or a copy of each size of label within a batch. The records only included a copy of the label in a single size. Again, the company's response to the FDA observation only included assurances the corrections would be made rather than a detailed plan or documentation.

Telemed: Lithuanian device manufacturer Telemed landed an FDA warning letter when it failed to satisfy the agency with responses to problems identified during a July-August inspection.

In its inspection of the Vilnius facility, the agency found that the firm lacked an adequate design plan for its 2013-2015 MicrUS ultrasound imaging system.

In its response, the firm acknowledged the design plan template should comply with revised design control procedures, but it did not say how it would correct the issues or provide a design plan procedure for the FDA to review.

The company also did not implement adequate design verification features. It promised the agency to provide design verification procedures and a description of how each action would be implemented, but failed to do so. The firm did not establish proper design transfer procedures to describe how the design was translated into product specifications.

The warning letter also faulted the facility for its complaint procedures, which did not include elements required for an investigation record, including a definition of what is considered a complaint or a medical device reporting determination. A review of 12 complaint records between April 2016 and May 2017 found no MDR determinations for any complaints or any reply to the complainant.

Nurse Assist: Nurse Assist, a Texas-based manufacturer of sterile IV saline flush syringes, failed to maintain adequate device history records, perform CAPA actions or control labeling activities, according to an FDA warning letter.

An FDA site inspection, conducted less than two weeks after the firm began recalling some lots in October 2016 over reports of *B. cepacia* infections, revealed that several cases of its IV saline syringes had not been sterilized. Also, the device history records for the recalled lots did not include the final quantity of products reviewed, approved and released for distribution.

The firm's CAPA actions were inadequate in that out-of-specification endotoxin test results for its water and saline distributed product lots were not investigated. The company also failed to investigate bioburden samples from some lots that exceeded the action limits in testing instructions, the agency said.

A December 2016 response to the Form 483 observations and a January incident report submitted by the firm did not fully address the issues. The company did not inform the FDA

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FDA Clarifies Pathways For Medical Device Accessories

For the third time in under a year, the FDA issued a final guidance on medical device accessories, clarifying that a New Accessory Request can be included as part of a PMA, PMA supplement or a 510(k) submission.

The December 2017 guidance clarifies that the de novo classification process is not the only mechanism available for classifying a new accessory type. The FDA had previously encouraged device manufacturers to use the de novo classification process for new types of accessories that had not been previously classified (*IDDM*, Dec. 30, 2016).

In the updated guidance, the agency said the request should be submitted together with the parent device submission and should include a cover letter that clearly identifies that the submission includes a New Accessory Request.

If an accessory request included in a cleared or approved premarket submission is denied, the new accessory type "may be legally marketed but will be considered to be in the same classification as the parent device," the agency said.

Manufacturers also have the option of requesting a reclassification of an accessory that was previously cleared or approved as part of a premarket submission for use on another device.

Read the full guidance here: www.fdanews.com/12-22-17-DeviceAccessory.pdf. — Ana Mulero

Warning, *from Page 5*

whether it had taken or planned to take corrective action to "ensure accountability of the labels used, rejected, or returned to storage for all medical device products."

The agency requested a certification from a third party expert consultant for an audit of the firm's manufacturing and quality assurance systems.

Read the GPC Medical warning letter here: www.fdanews.com/12-28-17-GPC.pdf.

Read the Telemed warning letter can be read here: www.fdanews.com/12-28-17-Telemed.pdf.

Read the Nurse Assist warning letter here: www.fdanews.com/12-22-17-NurseAssist.pdf. — Zack Budryk, Ana Mulero

What the FDA Wants to See in a Device History Record

The point of the device history record is to document that you carried out—accurately and completely—the activities and specifications recorded in the device master record.

"So the device master record is the recipe," and the DHR "is the objective evidence that you followed the recipe," says consultant Dan O'Leary, president of Ombu Enterprises.

The five items listed in 21 CFR Part 820.184 are the minimum requirements for the DHR:

- Dates of Manufacture of the Finished Device – This is not just the date a device is complete and ready for market. When the regulation says "finished device" it means a device that is capable of working but may not yet be distributable.
- Quantity Manufactured – This is the total number of that particular device that you produced, which is not necessarily the same as the next item.
- Quantity Released for Distribution – The quantity manufactured minus the quantity released should equal the quantity of product left in inventory.
- Acceptance Records – The data needed to complete this part of the DHR will be found in the records you kept in order to comply with section 820.80.
- Labels and Labeling – The regulation requires only the primary identification label and labeling to be included in the DHR.
- Identification and Control Numbers.

Excerpted from the FDAnews management report: *Device Documentation — A Guide to Managing Four Critical Production Files*.

PTAB Sides with Minerva Surgical, Nixes Hologic Patent

The PTO's Patent Trial and Appeal Board invalidated a Hologic patent on the use of its NovaSure endometrial ablation system in an inter partes review requested by Minerva Surgical.

Numerous predated patents — issued years before Hologic's patent, No. 6,872,183, was granted in March 2005 — were entered as evidence, rendering all its claims "unpatentable," the board said. These include two medical device patents from 1975 and 1999 that describe ablation methods and systems, the patent judges noted in a Dec. 15 final decision.

Despite Hologic's argument that a decision to combine ideas from the two patents would not have been obvious, the judges agreed with Minerva that a trained professional "would have been motivated to…improve the safety of the ablation device" by doing so.

The substitute claims proposed by Hologic were also found to be unpatentable based on a preponderance of the evidence and prior art.

After the Federal Circuit's October ruling in *Aqua Products v. Matal*, the PTAB issued a first-of-its-kind extension to reach a final decision on this patent review to have more time for analyzing the new guidance. The ruling, which made it easier for challenged patent owners to propose substitute claims to resolve infringement issues, was expected to improve their chances (*IDDM*, Oct. 27, 2017).

The PTAB denied Hologic's motion to exclude evidence from devicemaker startup Minerva, including doctors' testimonies and Ethicons' ThermaChoice manual, though Hologic's evidence relating to NovaSure's commercial success was also considered.

Meanwhile, a patent infringement lawsuit brought by Minerva in 2015 in the U.S. District Court of Delaware to challenge the now-invalidated patent is ongoing.

Minerva has yet to launch its rival device, the Aurora endometrial ablation system, though it received FDA premarket approval in June 2015. Hologic's NovaSure was launched in the U.S. in February 2017 (*IDDM*, April 14, 2017). — Ana Mulero

CDRH Proposes New Medical Device Malfunction Reporting Program

CDRH is proposing a new industry program for reporting certain medical device malfunctions.

The new voluntary program is intended to "streamline this process through a summary reporting system that would enable us to more efficiently detect potential safety issues and free up agency resources to better focus on addressing them," said CDRH Director Jeff Shuren.

While manufacturers must report certain device malfunctions to the FDA, individual reports often "describe the same problem, creating a process where the FDA conducts duplicate reviews of common malfunctions," Shuren said.

The standard industry MDR reporting requirements for deaths and serious injuries associated with devices will remain unchanged, the agency said.

The Voluntary Malfunction Summary Reporting Program would use six overarching principles, based on findings from a 2015 pilot:

- The collection of information in summary format should allow FDA to collect sufficient detail to understand reportable malfunction events;
- To increase efficiency, summary malfunction reporting should occur in a common format for the electronic reporting system used;
- Information about reportable malfunctions should be transparent to FDA and to the public, regardless of whether the information is reported as an individual

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MDR or a summary report. Information contained in a summary malfunction report that is protected from public disclosure under applicable disclosure laws would be redacted prior to release of the report;

- Manufacturers should communicate information regarding an imminent hazard at the earliest time possible;
- Summary reporting is meant to streamline the process of reporting malfunctions. It does not change regulatory requirements for MDR-related investigations or record-keeping by manufacturers; and
- Summary reporting information should not be duplicative of information received through other MDR reporting processes.

Participants in the pilot program, conducted to study summary MDR malfunction formats, saw an 87 percent reduction in the volume of reports "while preserving the essential information regarding the context around malfunction events," the agency said.

As outlined in MDUFA IV, participating manufacturers of devices under certain product codes would be required to submit summary malfunction reports on a quarterly basis.

CDRH is inviting comments on the proposed program and on the product codes that should be eligible. The program does not apply to device importers or user facilities. — Ana Mulero

APPROVALS

THINK Surgical Gets CE Mark For Total Knee Arthroplasty System

THINK Surgical snagged a CE mark for its TSolution One surgical system.

The system provides active robotic precision for total knee arthroplasty procedures.

The robot removes diseased bone and prepares the bone cavity and the joint surface so surgeons can accurately fit and align the joint implant.

CompactCath Receives CE Mark For Its Intermittent Urinary Catheter

CompactCath received a CE Mark for its intermittent urinary catheter as a Class III medical device.

The device features a drainage control mechanism and non-touch insertion.

Omnia Medical VBR Receives FDA 510(k) Clearance

Omnia Medical VBR received FDA 510(k) clearance for a vertebral body replacement system.

The device was manufactured from an osteoconductive polymer for use in the thoracolumbar spine to replace a collapsed, damaged, or unstable vertebral body.

The enhanced biomaterial offers clinical advantages such as stiffness similar to cortical bone, reduced stress shielding and artifact-free imaging that allows for clear assessments of fusion.

FDA Clears XableCath Blunt Tip Catheter

The FDA cleared XableCath's blunt tip support catheter indicated for treating peripheral arterial disease.

The catheter is designed to facilitate over-the-wire the passage of true lumen through lesions above and below the knee in the peripheral vasculature.

The company said it expects the device to be used in the first U.S. surgical procedures during the first half of 2018.

German Devicemaker Gets CE-IVD Mark for Lung Cancer Assay

Epigenomics, a Germany-based molecular diagnostics company, received the CE-IVD mark for its blood-based lung cancer test Epi proLung.

The device includes the company's proprietary DNA methylation biomarkers.

The European Commission provided funding for the assay's development.

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K2M Group Receives CE Mark For 3D-Printed Expandable Cage System

K2M Group earned a CE Mark for its 3D-printed expandable cage system, the first 3D-printed expandable device on the market to facilitate continuous in-situ height expansion and endplate angulation in the cervical spine.

The system, which features the company's Lamellar 3D titanium technology, is designed to stabilize the cervical spine in patients needing treatment for trauma or tumors.

French Device Firm Snags CE Mark for Smart Sensor

France-based BIOCORP received a CE mark for its Epi proLung for use with insulin delivery injectors.

The device includes a smart cap sensor designed to turn all traditional pen injectors into connected devices. It captures treatment information, including dosages, date and time, which is then transferred to a patient monitoring mobile app.

FDA Grants Early Marketing Approval to Biom'Up Flagship Device

French device manufacturer Biom'Up announced it secured FDA marketing approval for its Hemoblast Bellows device seven months ahead of schedule.

The device is used to control bleeding during surgery. The FDA based the approval on a 412-patient clinical trial that met all clinical endpoints with high statistical significance.

The company plans to market the device in the United States by next summer.

TGA Signs Off on Glucose Monitor for iPhones

Australia's Therapeutic Goods Administration issued a TGA Mark for DarioHealth's blood glucose monitoring system for iPhone use.

The system was previously unapproved for the Lightning connector found in later-model Apple smartphones. The approval ensures users in the United Kingdom will have access to the Lightning-enabled Dario device at the end of December. Sales of the device in Australia will begin in January, the company said.

FDA Clears Laser Endomicroscopy Platform

Mauna Kea received 510(k) clearance from the FDA for its Cellvizio multidisciplinary confocal laser endomicroscopy platform.

The agency based the clearance on data from peer-reviewed medical journals that validated the device's capacity to image tissue microstructures.

Clearing this hurdle will allow the company to shift its focus from imaging to identification, according to the firm's founder and CEO Sacha Loiseau.

Senzime's OnZurf Probe Scores CE Mark

Senzime's OnZurf Probe device received CE Mark approval within Europe, with an initial direct sales period in Scandinavia planned.

The device is intended for use after gastrointestinal tract procedures. It continuously collects organ surface samples. It can monitor postsurgical healing and flag warning signs of post-operative complications. The company anticipates CE approval for its corresponding analyzer by the second half of 2018.

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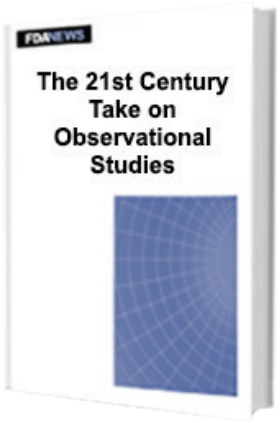

The 21st Century Take on Observational Studies: *Using Real-World Evidence in the New Millennium*

Passage of the 21st Century Cures Act reaffirmed Congress's and the FDA's commitment to using real-world evidence to supplement or even replace traditional clinical trials.

More flexible, faster and cheaper research methods, including observational studies, are now acceptable in the FDA's approval process.

Observational research requires an entirely different set of procedures and careful planning to ensure the real-world evidence collected is valid and reliable.

The 21st Century Take on Observational Studies walks you through everything you need to know about the opportunities and pitfalls observational studies can offer. The report looks at the growing trend toward observational research and how provisions in the 21st Century Cures Act create even more incentives to rely on real-world evidence in the development of medical products. The report covers:

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