INTERNATIONAL DEVICES & DIAGNOSTICS MONITOR

Vol. 5, No. 8
April 15, 2019

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FDA Proposes Total Product Lifecycle Approach to AI Devices

The FDA is considering a total product lifecycle monitoring approach to emerging artificial intelligence devices, the agency said in a proposed regulatory framework.

The agency may also consider what it calls a predetermined change control plan, with "detailed information … about the types of anticipated modifications based on the algorithm's re-training and update strategy," outgoing Commissioner Scott Gottlieb said in announcing the proposed framework for AI software modifications for devices.

The agency has already approved two AI-driven devices—one that detects diabetic eye damage and the other that monitors patients for strokes. But those devices relied on "locked" algorithms that allow them to perform the same function over and over again. Regulators are hopeful that sponsors can harness machine learning for devices that can adapt to changing conditions.

(See **AI***, Page 2)*

UK Gets Halloween Extension, But Brexit is Still Scary

British Prime Minister Theresa May won yet another delay from European leaders on the UK's exit from the EU, leaving devicemakers no clearer about the ultimate impact of Brexit on the supply chain.

May now has until Oct. 31 to come up with an agreement for a post-EU future. A hard Brexit—a divorce without any kind of agreement—would mean that device companies used to testing their products in the UK will find themselves on the outside looking in, because EU law requires testing in member countries.

The uncertainty is already taking a toll on the industry. UK regulators—who have promised to implement European device guidelines even if the UK crashes out of Europe without a deal—will be excluded from Europe's centralized IT portal for clinical trials and

(See **Brexit***, Page 2)*

Brexit, *from Page 1*

Europe's single assessment model. Trials in the UK are down by at least 25 percent, according to analysts at Fitsch.

On April 10, ahead of the extension, the European Commission did its best to calm nerves saying that most medical products would likely be compliant with EU regulations if the UK crashes out of the union without a formal agreement.

"It is possible, however, that despite best efforts some medicinal products and medical devices may not be compliant in time," the commission added.

"There is, therefore, a risk of shortages if economic operators do not act swiftly to remedy the situation."

The anxiety is especially acute in the Republic of Ireland, whose border with Northern Ireland has proven a major stumbling block to a clean exit.

Between 30 and 40 percent of medical devices in the republic receive their approvals in the UK, currently. — Bill Myers

AI, *from Page 1*

In those cases, the agency may want to conduct a "focused review" on potential AI or training updates after a device has already been approved for market, without necessarily requiring a brand-new submission.

If regulators adopt a total lifecycle approach, it'll likely require manufacturers install "appropriate mechanisms that support transparency and real-world performance monitoring."

"Transparency about the function and modifications of medical devices is a key aspect of their safety," the 20-page framework states. "This is especially important for devices … which change over time."

The goal of the framework is to assure that ongoing algorithm changes follow pre-specified performance objectives and change control plans, use a validation process that ensures improvements to the performance, safety and effectiveness of the artificial intelligence software, and includes real-world monitoring of performance once the device is on the market to ensure safety and effectiveness are maintained," Gottlieb said.

"We're exploring this approach because we believe that it will enable beneficial and innovative artificial intelligence software to come to market while still ensuring the device's benefits continue to outweigh its risks."

Read the notice here: www.fdanews.com/04-02-19-ProposedRegulatoryFramework.pdf.
— Bill Myers

IMDRF Advances Regulatory Convergence in Moscow Meeting

Russia signed an agreement with Brazil, Argentina and Mexico to share best practices and information on quality, efficacy and safety of medical products as well as adverse event information, on the first day of the International Medical Device Regulators Forum held in Moscow, March 19-21.

The Forum Steering Committee discussed current IMDRF working group issues including the terminology of adverse events arising from the use of medical devices, clinical evaluation of medical devices and personalized medical products.

The committee approved final versions of reports on labeling principles for medical devices and IVDs; guidelines on the application of the unique device identification system for devices; adverse event terminology: terms, structure and codes; and electronic registration for medical devices.

Participants also discussed results of the Open Stakeholder Forum, including regulatory approaches to registering in vitro diagnostics based on next-generation sequencing and the challenges in regulating these devices.

IMDRF has created a new working group to study the principles of classification of medical devices and IVDs that will be chaired by the Russian Federation.

As invited observers of the IMDRF meeting, Saudi Arabia, the Republic of Kazakhstan and the Kyrgyz Republic provided information on the circulation of medical devices in their countries.

The head of Russia's Federal Service for Health Supervision, Mikhail Murashko, stressed the need to develop common approaches for medical devices and said IMDRF is the only such global organization to attempt convergence.

IMDRF Pursues Global Clinical Device Evaluations

The IMDRF's Medical Device Clinical Evaluation Working Group, led by China, released three related consultation documents aimed at integrating regulations across regions to better evaluate clinical data and reduce redundant clinical trials for devices.

One document provides background on what is required for clinical evaluations of medical devices. The second updates definitions of acceptable clinical evidence to demonstrate compliance with essential principles. The third supersedes a GHTF 2010 guidance on when a clinical evaluation should be conducted for a device.

The Chinese working group included representatives of medical device companies, regional coordination organizations and relevant industry associations. Medtronic was one of the first companies to join the group.

The three themes of the clinical evaluation project were: the decision-making principles of clinical trials for medical devices; the basic requirements for the declaration of products and the equivalence of product comparisons during clinical evaluation; and the principles for accepting data from overseas clinical trials.

"In order to better conduct research, we have collected IMDRF and its predecessor, the Global Medical Device Coordination Working Group (GHTF), and more than 340 clinical evaluation documents issued by the official IMDRF member states," said Liu Yinghui, the working group's chair.

Chinese devicemakers want to reduce regulatory costs associated with applying for both CE and FDA certification, according to Jin Xiangdan, manager of the overseas certification and registration department of Lepu Medical.

The draft documents were approved at the IMDRF's March 19-21 meeting in Moscow. China officially joined IMDRF in 2013, and this was the first IMDRF project that China has led.

(See **IMDRF***, Page 6)*

Inova Genomics Lab Warned for Selling Unapproved Genetic Tests

The FDA warned Inova Genomics Lab for marketing pharmacogenomic and whole gene sequencing tests without the agency's approval or clearance.

The Falls Church, Virginia lab marketed MediMap Tests on its website as genetic tests used for predicting a patient's response to medications. The lab also said the tests could be used to determine what medicine and dose patients should take.

The FDA questioned the tests' clinical validity, saying it was "unaware of data establishing the relationships between the genotypes assessed…and assertions regarding drug response for multiple drugs."

The agency said the tests posed "significant public health concerns" because of their potential inaccuracy, which could misinform patients and healthcare providers about increasing, decreasing or stopping medication. For example, the abrupt cessation of antidepressants could cause illness, injury or death in patients due to withdrawal symptoms, the agency said.

The lab argued that the MediMap tests were laboratory developed tests (LDTs) that qualify for agency LDT exemptions, thus sparing them from premarket review or labelling requirements. But the agency saw things differently.

"FDA has not created a legal 'carve-out' for LDTs such that they are not required to comply with the requirements…that otherwise would apply," the agency said. "Although FDA has generally exercised enforcement discretion for LDTs, [it] retains discretion to take action when appropriate, such as when it is appropriate to address significant public health concerns."

The agency threatened regulatory action without further notice if the lab failed to promptly deal with the violations. The lab has since removed the products from its website.

Read the full Inova Genomics Lab warning letter here: www.fdanews.com/04-08-19-InovaGenomicsLab.pdf. — James Miessler

Specification Developer Fails To Submit MDR Reports

Specification developer Circulatory Technology failed to submit medical device reports within 30 days of receiving complaints that its Better Bladder device failed during use, collapsing as a result of leaks, an Aug. 22 to Sept. 26, 2018 FDA inspection revealed.

The Oyster Bay, New York, facility received five complaints that its Better Bladder device failed during use, but the firm did not investigate the failures or report the malfunction to the FDA. This was a repeat observation from a July 8, 2016 inspection, the agency said.

The FDA inspector requested documents pertaining to the leak tests and pressure tests conducted, but the firm did not provide any documentation to show that such tests were conducted. The 483 notes that the firm received 13 complaints about the bladder devices from September 2016 to April 2018.

The investigator listed several other repeat observations. The firm did not have evidence to show that any investigations were conducted. In addition, the firm made a design change to its Better Bladder, but it didn't revalidate the manufacturing processes or update its risk analysis plan. The firm had not opened any CAPAs to address the collapsed bladder—another repeat observation.

The FDA said the firm failed to evaluate its suppliers and contractors, and it couldn't provide

(See **483***, Page 6)*

CAPA Verification

Failure to correctly verify CAPAs is another citation that could appear in a warning letter. Verification should prove that the actions taken will fix the root causes and mitigate the failure found. For instance, if the root cause analysis confirmed that a procedural problem led to the issue noted in the product, the verification would include a review and management approval of any procedural changes. In such a case, a manufacturer might want to conduct a pilot test of the updated procedure and any associated training materials for staff. Such actions would validate and test that the planned actions will take care of the failure and prevent it from happening again.

Document the verification process, including the specific results from verification and validation, and sign-off from a person in authority. Make this documentation available as part of a CAPA report presented to the FDA.

"If you've confirmed the root cause, verified your actions and implemented them, effectiveness testing should be fairly easy," said Deborah Lydick, president of Catalyst Advantage Group.

Writing a verification plan before implementation is a best practice, she added. This helps keep the need to verify on the radar screen and ensure that the actions will truly address the failure.

The verification plan will include acceptance criteria, which can also help guide the implementation plan and ensure its success, essentially incorporating the effectiveness check into the actual implementation, thus saving time as well as better targeting the overall CAPA plan.

Manufacturers will need to document the effectiveness check, including specific acceptance criteria, responsible parties and timing. Lydick cautioned against expecting zero defects in the future; that will depend on the severity of that defect. If a CAPA effectiveness check sets zero as the benchmark and uncovers even one defect, it will be deemed ineffective. So, companies need to be reasonable when setting acceptance criteria.

Companies should have CAPA investigation procedures that include regular management reporting, Lydick advised. A weekly or biweekly "CAPA board" meeting that includes management is one way of doing this, she suggested. The format of the management reporting is less important than the fact that it is done, documented and included as an appendix to a CAPA report. Also important, Lydick said, is a mechanism to escalate issues to management any time there is a safety-related or otherwise high product risk.

Excerpted from the FDAnews management report: *Creating QSR-Compliant CAPA Systems: A Practical Guide for Devicemakers*.

FDA Issues List Of Class 1 Accessories

The FDA has finalized a list of accessories that can be classified as Class 1 devices. The listing was required under the FDA Reauthorization Act of 2017.

The agency said it was willing to classify accessories as low-risk as long as they don't support or sustain life, don't present an unreasonable risk of injuries or illnesses and if Class 1 general controls assure reasonably low-risk.

The list includes specific accessories for biopsy instruments, stents and catheters, as well as other accessories used in surgery. The agency did not consider an accessory eligible for the list if it is not automated with computer software but would require design controls to provide reasonable assurance of safety and effectiveness.

The new classifications go into effect on May 13. The FDA said it will engage with industry stakeholders to resolve additional questions regarding the existing policy or future proposals for distinct classification of accessories.

Read the final action here: www.fdanews.com/04-11-19-FinalAction.pdf.

Documentation Failures Plague Hyperbaric Technologies

Failure to document numerous activities including validation, corrective and preventive actions, process changes and others landed Hyperbaric Technologies a Form 483 following a Sept. 19-26, 2018, inspection of its Amsterdam, New York, manufacturing facility.

The manufacturer of hyperbaric chambers and mountain bags failed to document process validation activities and results such as the sealing process for its Gamow nylon hyperbaric bags.

Also missing was documentation for corrective and preventive activities. The FDA said the devicemaker implemented design changes but a CAPA report wasn't maintained to show a description of records revised such as engineering drawings and a bill of materials to show changes were effective.

The FDA noted that batches released with the modifications displayed small tears near the seal.

The firm's device history record lacked evidence that relief valves were tested as outlined in the firm's standard operating procedures, and the DHRs for all products lacked evidence of leak test results.

The FDA inspector found a device master record was not maintained and testing protocols were incomplete with numerous specifications missing.

Read the Hyperbaric Technologies Form 483 here: www.fdanews.com/04-11-19-hyperbarictechinc483.pdf.

IMDRF, *from Page 3*

China hosted the 13th IMDRF Management Committee meeting in Shanghai in March 2018. At that meeting, it proposed the new work project for clinical evaluation of medical devices. The working group will present a final document at the next IMDRF meeting in September.

Currently there are 10 official members of the IMDRF: the U.S., the European Union, Japan, Australia, Canada, Brazil, China, Russia, Singapore and South Korea.

Read the consultation documents here: bit.ly/2Kvhkxn.

483, *from Page 5*

documentation that it visited its suppliers or evaluated their manufacturing processes. This was also a repeat observation.

Read the Circulatory Technology Form 483 here: www.fdanews.com/04-11-19-circulatorytechinc483.pdf.

LC Medical Warned Over Validations for Wound Therapy Kits

LC Medical Concepts' sterilization operations were not adequately validated to demonstrate sterility of its wound therapy kits, an Oct. 16-23, 2018, FDA inspection of the devicemaker's Rochester, New York, facility revealed.

The firm's manufacturing plant was moved, and manufacturing conditions had changed but no assessment was conducted on the effects of these changes on the sterilization process, the FDA said.

The FDA was not satisfied with the firm's Nov. 12, 2018 response to the Form 483 and it issued a Jan. 31 warning letter.

The warning letter said the firm's response did not include a retrospective review of the facility changes to assess the need for revalidation.

The agency required the manufacturer to provide a summary of its documented assessment of the product and the process changes for the appropriateness of the sterilization process as well as plans to revalidate the sterilization process, including a protocol and acceptance criteria.

Not only did the firm not comply with its own sampling plan, but it failed to ensure that manufacturing equipment was routinely calibrated. It also failed to verify that corrective and preventive actions were effective and that they didn't adversely affect the finished product.

The warning letter noted that two out of three CAPAs did not include verification or validation of CAPA effectiveness, and both CAPAs were closed on the same day they were initiated.

Read the LC Medical Concepts Form 483 here: www.fdanews.com/04-11-19-lcmedicalconceptsinc483.pdf.

Read the warning letter here: www.fdanews.com/04-11-19-LCMedicalConceptsWL.pdf.

APPROVALS

FDA Grants Clearance for Ortho Clinical's Chemistry Product Slides

The FDA granted 510(k) clearance for Ortho Clinical Diagnostics' Vitros XT microslides, a product that couples various tests that physicians usually order together.

The test pairs, which can run simultaneously using the Vitros XT 7600 integrated system, include urea and creatinine, glucose and calcium, and triglycerides and cholesterol.

The microslides enable a higher test throughput without the need for additional or larger analyzers and require smaller blood samples, which is helpful for vulnerable patients and patients with venous access issues.

Avinger's Image-Guided Atherectomy Device Cleared by FDA

Avinger received 510(k) clearance for its Pantheris SV product, a small vessel image-guided atherectomy system.

The Pantheris SV is an extension of the devicemaker's Lumivascular image-guided atherectomy platform that is indicated for diagnosing and treating peripheral artery disease in vessels two to four millimeters in diameter.

The device offers improvements like an improved cutter design, a shaft with improved pushability and a superior optical coherence tomography imager.

Nanobiotix's Nanoparticle Radioenhancer Receives CE Mark

Nanobiotix has earned the CE Mark for its Hensify radioenhancer, an injected nanoparticle device that amplifies the effectiveness of standard radiotherapy.

The device introduces a new mechanism of action that, in combination with radiotherapy, helps to physically eliminate tumors and kick a

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

CDRH Flags Ongoing Concerns Over Contaminated Duodenoscopes

CDRH Director Jeff Shuren said the center is considering regulatory actions because of ongoing concerns over contaminated duodenoscopes.

In 2015, the FDA required three manufacturers, Olympus, Fujifilm and Pentax, to conduct two postmarket surveillance studies of reprocessed duodenoscopes. The preliminary findings showed a three percent contamination rate for "high concern" organisms. But updated data showed that up to 5.4 percent of samples tested positive for "high concern" organisms, such as pathogenic E. coli or Staphylococcus.

When the sampling studies were designed, the FDA "expected to see a total contamination rate for any type of organism of less than one percent or as close to zero as possible for duodenoscopes," Shuren said. 'Let me be clear, the percent of contaminated samples based on these interim results shows that improvements are necessary, and we are committed to taking additional steps to reduce infections and contamination even further."

The FDA required the manufacturers to conduct root cause analyses following the preliminary results announced in December. Final results are expected later this year.

The agency is considering whether supplemental measures, such as sterilization, in addition to meticulous cleaning, might be more effective. But this will take careful consideration "because we know some sterilization methods could damage the duodenoscope over time and lead to a shorter lifespan for the expensive device," Shuren said.

The agency issued warning letters to the three manufacturers last March for failure to comply with the surveillance study commitments. The firms are still not in compliance with the agreed timetable. "If the companies continue to fail to adequately respond to our concerns, the FDA will take additional action, Shuren warned.

The agency also is working with manufacturers on new designs that could reduce the risk of contamination as well as disposable duodenoscopes that would avoid the need for reprocessing.

Approvals, *from Page 7*

patient's immune system into gear for local control and systemic disease treatment.

Hensify is an aqueous suspension of crystalline hafnium oxide nanoparticles that is injected into a tumor after initial radiotherapy treatment.

Insera Gains European Clearance For Stroke Thrombectomy Device

Insera has earned the CE Mark for its CLEAR system, a suction device used for removal of blood clots.

The system is indicated for use in patients with acute ischemic stroke and secondarily for intracranial large vessel occlusive disease. It is also secondarily indicated for removing blood clots from the sinuses.

The CLEAR system can be also be used to remove clots via a guide catheter or balloon guide in the neck arteries.

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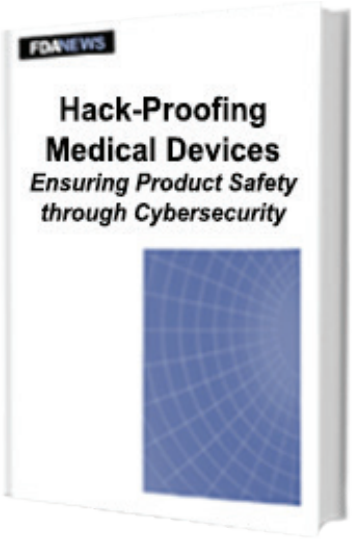

Hack-Proofing Medical Devices: *Ensuring Product Safety through Cybersecurity*

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- And much more!

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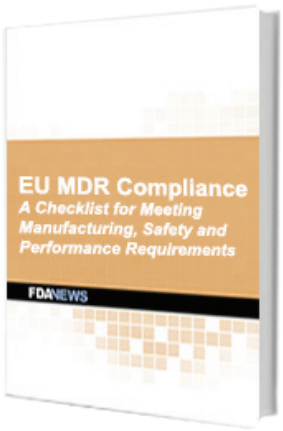

EU MDR Compliance: *A Checklist for Meeting Manufacturing, Safety and Performance Requirements*

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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