INTERNATIONAL DEVICES & DIAGNOSTICS MONITOR

Vol. 5, No. 13
June 24, 2019

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More Notified Bodies Give Up On EU MDR/IVD Certification

The shortage of notified bodies to certify devices for the new EU medical device and IVD regulations appears to be reaching crisis point as more notified bodies say they won't be offering certification.

Swiss notified body QS Zurich last week announced it will no longer pursue NB designation for the new regulations but will continue to certify for ISO 13485. The announcement came just a week after London-based Lloyd's Register Quality Assurance (LRQA) said it would not offer its NB services under the new regulations.

"Following recent market developments, we have made the strategic business decision to exit from [notified body certification] services," LRQA said. "We are also withdrawing our application to become a Netherlands-based EU Notified Body for these services" and furthermore, will not be applying to become a Notified Body" for MDR or the in-vitro diagnostic devices regulation.

LRQA also said it would continue to provide ISO 13485 and Medical Device Single Audit Program (MDSAP) third-party

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Devicemakers Comment on FDA's Approach to Machine Learning for SaMD

A combination of real-world evidence and periodic reporting to the FDA should be the cornerstone of how the agency regulates AI and machine learning in software as a medical device, Philips said in a comment on the agency's draft framework document.

The FDA is wrestling with how it will keep track of ongoing changes to such software products and is considering focused reviews to ensure that any changes are safe and effective—without requiring an entirely new submission for each iteration of the software.

GE Healthcare urged the agency to consider an expedited pathway for changes and to limit a review to the proposed changes and any new risks. If devicemakers can show that they adhere to

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certification and medical devices-related training to clients in the UK and worldwide.

The company said it's working closely with the UK's Medicines and Healthcare products Regulatory Agency to help its customers that hold certification for the EU directives to transfer to an alternative NB.

So far, only two notified bodies— BSI and TUV SUD—have been designated under the MDR/IVD, and "there is no indication that a significant number of notified bodies will be designated in the next months," according to the European Coordination Committee of the Radiological, Electromedical and Healthcare IT Industry.

Meanwhile, delegations from Germany and Ireland expressed concerns over the shortage of notified bodies in a joint information paper delivered to the European Council ahead of a June 14 meeting.

"While notified body capacity is the most imminent and high-profile challenge, there are many other challenges across the Regulations," the joint paper stated. "These challenges, at national and EU level, are numerous and often highly technical but include system requirements, infrastructure and secondary legislation."

"Fundamentally however there is currently a lack of clarity and available guidance on many requirements of the regulation and what the expectations of the regulatory system will be."

It is imperative that appropriate levels of resources and infrastructure are put in place in each member state and at the EU level to ensure effective implementation and coordination of the regulatory system, the two delegations said.

As suggested next steps, the paper recommends that member states urgently consider their state of preparedness for implementing the new regulations both at a national and European level.

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good machine learning practices and can monitor AI algorithms in the real world, they should be eligible to follow the AI/ML framework regardless of their software precertification status, GE said.

GE welcomed the FDA's proposed total product lifecycle approach saying it would allow for more efficient regulatory oversight because the approach "shares concepts" with the agency's software pre-certification program.

The goal of the agency's framework is to ensure that software changes follow specified change control plans and include validations to ensure updates are safe and effective (*IDDM*, April 12).

Regulators are hopeful that sponsors can use artificial intelligence and machine learning to enable devices to adapt to changing conditions. In such cases, the agency may want to conduct a "focused review" of potential AI or training updates after a device has already been approved, without necessarily requiring a new submission.

The FDA has already approved two AI-driven devices, but they use "locked" algorithms that allow them to perform the same function over and over again.

In a separate comment, the American Medical Association said the proposed framework "selectively highlights the benefits of ML systems" and minimizes the risks of such systems deployed for clinical applications. The agency doesn't mention the potential for bias with machine learning, AMA said.

Also missing from the framework, the association said, are references to patient outcomes. Machine learning systems "may learn to detect features that are closely associated with a diagnosis, but that are divorced from improvements in clinical outcome." A framework that doesn't tie clinical outcomes research to good machine learning practices could lead to AI systems that deviate from outcome-based clinical standards, the association said.

Read the docket here: www.fdanews.com/06-20-19-RegFrameworkModifications.pdf.

EU Committee Sounds Heightened Alarm on Shortage of Notified Bodies

With less than one year before the EU's Medical Device Regulation takes effect, an industry group is raising increasing alarm about the lack of "essential guidance" and the shortage of notified bodies needed to certify products in compliance with the new requirements.

"[V]ery little progress has been made in the implementation of the regulation," says the European Coordination Committee of the Radiological, Electromedical and Healthcare IT Industry (COCIR) said in a new position paper. "Our members have invested considerable resources to be prepared for the MDR, but only as far as possible considering essential guidance information is still missing."

So far, only two notified bodies — BSI and TUV SUD — have been designated under the MDR, and "there is no indication that a significant number of notified bodies will be designated in the next months," COCIR said, adding that this is far short of the number needed to accommodate devicemakers.

MDSAP

Among other recommendations, the committee suggests that devicemakers that participate in the Medical Device Single Audit Program (MDSAP) should not have to undergo notified body certification.

"By now 38 notified bodies have applied for MDR," Gert Bos, executive director and partner at QServe, told *FDAnews*. "Two received designation as you know, but one in the U.K. might lose it again, so they are not working full power on MDR reviews," said Bos, who was formerly head of regulatory and clinical affairs at BSI Healthcare and head of the notified body at BSI-Germany.

Bos said the European Commission remains optimistic that it will designate up to 20 notified bodies by the end of the year, but most close observers in Brussels expect just ten NBs be designated by the end of the year in a best-case scenario, and 20 by the MDR implementation end of May 2020.

"Then all the work needs to be done during the grace period [for compliance of certain products until 2024]. Most critical will be the products that cannot use the grace period, and that will need an MDR certificate by May 2020, such as the re-usable surgical instruments. That will be extremely hard to manage in time," Bos said.

Manufacturers of Class I devices that need notified body certification should be allowed to take advantage of the grace period, because many of these have been up-classified to Class IIa or higher, and were allowed to self-declare in the past. This means they will not have a valid NB certificate and will not qualify for the grace period that the MDR grants.

Call for Clarity

Because of the missing elements in the MDR framework and the uncertainties in interpreting requirements, "it is even more important that manufacturers can make full use of this grace period to prevent large disruption in the supply of medical devices," COCIR said.

The committee said more clarity is needed on what's considered a significant change and suggested that certificates should remain valid when changes are unrelated to design or the intended purpose of the device.

Bos concurred with the COCIR's recommendations for what's needed, but he said the solutions proposed may not be realistic. The European Parliament "is not expected to agree to an extension" of the implementation dates, he said, noting that many view the problem of notified body designation and the resulting bottleneck of reviews as largely the fault of member state authorities, so they should come up with the solution.

The International Medical Device Regulators Forum is pushing for MDSAP recognition. But there is no provision for this in the MDR legislation, so "this is not easy to implement," Bos said.

(See **Shortage***, Page 4)*

BRIEFS

FDA Issues Draft Guidance On Vitamin B7 Testing in IVDs

The FDA released draft guidance on testing for biotin (vitamin B7) interference in in vitro diagnostics used in donor screening.

The agency said it has become aware of potential biotin interference with IVDs that use biotin/avidin interactions as part of the device technology. Biotin in patient samples can cause falsely high or falsely low results, depending on the test.

The draft spells out how the agency would like the testing to be performed and how the results of the testing should be communicated to end users, including clinical laboratories and clinicians.

Read the draft guidance here: www.fdanews.com/06-21-19-BiotinInterference.pdf.

OriGen Draws FDA Warning For Device Reworking Practices

OriGen Biomedical has been hit with a warning letter following the FDA's inspection of its Austin, Texas facility, which revealed problems with the company's controls for reworked products.

The agency, which inspected the site from June 11 to July 5, 2018, noted that the firm's documentation of device reworking and reevaluation activities lacked an investigation into any adverse effects that resulted from the rework.

The FDA took issue with the firm's rework of its VV14F dual lumen catheters, which were released and distributed despite failing endotoxin testing. The rework included a second ethylene oxide sterilization, but the facility failed to document that this had no adverse effect on the devices.

Read the warning letter here: www.fdanews.com/06-21-19-OriGenBiomedicalWL.pdf.

Devicemaker Admits it Failed To Report Wound Dressing Recall

Maryland-based device manufacturer ACell pleaded guilty to a single misdemeanor count of failing and refusing to report a removal of their MicroMatrix powder wound dressing product — and will pay $15 million to settle the matter.

The Department of Justice said ACell failed comply with the FDA's postmarket compliance requirements when it neglected to alert the agency about the recall, putting patients at risk. The company has agreed to enter into a five-year agreement that requires implementation of a risk assessment and an internal review process.

"By not notifying the FDA nor being forthcoming about their reasons for the product removal, ACell executives placed profit above patient safety," said Acting FDA Commissioner Ned Sharpless.

Shortage, *from Page 3*

Earlier this month, seven device and IVD stakeholders including MedTech Europe, released a joint statement urging the European Commission and member states to accelerate the implementation of the regulatory system to prevent a "cliff-edge" scenario (*IDDM*, June 7).

Read the paper here: www.fdanews.com/06-20-19-MDRAssessment.pdf.

FDA Finds Weak Process Controls At Anesthesia Associates

A March 11-14 inspection of Anesthesia Associates' San Marcos, California facility revealed inadequate process control procedures.

During the inspection, the firm's president said that assembly instructions for the firm's non-rebreathing valve were not documented.

The device is a Class II life-sustaining medical device. The company manufactures and distributes durable reusable products for anesthesia and respiratory care, including the Jet Ventilator, a Class II life-sustaining device.

The inspection revealed that medical device reporting procedures were not maintained.

The company's medical device flow charts, which the president identified as the firm's MDR procedures, didn't include requirements for submitting MDR reports or recordkeeping requirements, the FDA said.

He also told investigators that the employee had been trained to assemble the device, "but could not produce training records for this process," the Form 483 said.

Also missing was documentation on the evaluation of suppliers, inspectors said, noting that the president said the evaluation of its vendor was not documented.

Read the Anesthesia Associates Form 483 here: www.fdanews.com/06-20-19-anesthesiaassocinc483.pdf.

Sample Collection for Validation and Verification

Once a company has calculated a sample size for validation and verification testing, it must turn its attention to the process of collecting the samples, which the FDA also will scrutinize. Actual sample collection is "the hard part of the process," according to Steven Walfish, president of Statistical Outsourcing Services. "How do I know that I can take seven devices and do four replicates each, or if I can do four devices and do seven replicates each?"

There are four general methods to collecting samples. The first and most common is known as simple random sampling, which involves randomly selecting the correct number of samples from the parts made. Each unit is selected independently, so that any and all samples are equally likely to be selected into making up sample size n.

"That makes a lot of sense if I'm going to make 30,000 injection-molded parts and I need to get a sample size of 300," Walfish said. "I'll randomly pick 300."

A company making a more complex device, such as an X-ray machine, may want to be able to break up the testing into discrete points around a functional feature or features of the device.

"So, I might take an X-ray tube sub-assembly and do some samples at a very low dose, some at a very high dose and some at a medium dose," Walfish said. "And say I have determined I have to do 28 tests; I'll make it 30 and do 10 tests each at the low, medium and high dose levels. If all 30 pass, then I'm going to say that the design passes."

A second and also common approach, particularly for high-volume devices, is systematic sampling. For instance, Walfish said, a company might decide to pull for testing every 100th device manufactured. For a manufacturing run of 3,000 devices, that would provide a sample size of 30.

A third approach is known as composite sampling, in which a company takes parts and combines them into a single test. This approach can save costs, but does not provide complete information about the individual sampling units.

"Composite sampling doesn't really work very well in medical devices," Walfish cautioned. "But if you have a chemical process or an in vitro device, for instance, composite sampling can work in many cases."

The fourth approach is stratified random sampling. It ensures that a sample represents each of various predefined strata.

Excerpted from the FDAnews management report: *Choosing the Best Device Sample Size for Verification and Validation.*

International Hospital Products Cited for Numerous QMS Failures

Process validation failures, documentation lapses and failure to establish corrective and preventive actions were just a few of the quality lapses found during a March 15-19 inspection of International Hospital Products' Littleton, Colorado facility.

The 11-item Form 483 notes that the firm received and distributed sterilized Jejunostomy tubes, but without documenting sterilization validation following a change in the manufacturing supplier.

The agency found inadequate documentation of pouch sealing validation in that the firm's contract manufacturer didn't demonstrate that pouch sealing was performed according to established procedures—including a validation protocol, validation activities, raw data, equipment used and a final report.

The devicemaker also failed to establish procedures for finished device acceptance as well as procedures to ensure that all received products conformed to specifications.

International Hospital Products is the specification developer, manufacturer and distributor of the Baker Jejunostomy tube, but it hadn't established finished device acceptance steps to ensure that each production run or lot of finished devices met acceptance criteria.

The firm had not established quality system requirements to ensure devices complied with regulatory requirements. The facility lacked a device history record, a device master record, and procedures for design change.

Also missing were specific requirements for sterilization validation process evaluation and monitoring and acceptance testing, the investigator said.

Read the International Hospital Products Form 483 here: www.fdanews.com/06-20-19-intlhospitalprodinc483.pdf.

Cosmetic Devicemaker Fails To Submit MDRs on Time

The FDA cited Carol Cole Company for failure to submit timely medical device reports of its devices that use microcurrents to tone, firm and reduce wrinkles, according to a Form 483 that was issued following a March 20-22 inspection of the firm's Vista, Calif. facility.

The firm received at least five complaints that involved reported burns to the face, and it failed to follow up with end users or to report the adverse events, the 483 says.

The investigators noted that 10 of 11 complaint records were not closed within the required timeframe, and all 11 of the complaint investigations lacked a review of quality records. The 483 notes that the firm lacked procedures for receiving, reviewing and evaluating complaints by a formally designated unit.

Read the Carol Cole Company Form 483 here: www.fdanews.com/06-20-19-carolcoleco483.pdf.

Part 806 Reports — When to Submit Them and How to Avoid Pitfalls

Covington & Burling attorney Pamela Forrest offered insights into when devicemakers must file recall reports with the FDA to comply with 21 CFR Part 806 in a recent *FDAnews* webinar, flagging areas of confusion and how to avoid common errors.

Part 806 addresses the circumstances under which voluntary device recalls must be reported to the FDA. Failure to comply with Part 806 requirements can have liability consequences and can lead the FDA to distrust a manufacturer.

"If, in fact, the manufacturer of a device should have reported the recall to FDA and didn't, that could potentially weaken the defense in the product liability context," she said.

The umbrella term "recall" includes both corrections and removals, she explained. Part 806 notification requirements depend on the health risk.

Any recall that could be classified by the FDA as Class I or II must be reported within 10 days. The firm must make a reasonable estimation of the health risk, although only the FDA officially determines a recall classification.

Avoiding Errors

The 10-day reporting requirement turns on when the firm made the decision to initiate the action, not when the action began.

"The reason I emphasize that is because we often see 483 observations and warning letters that cite late reporting," she said.

One frequent misstep regarding Part 806 revolves around the definition of a stock recovery, which is exempt from notification. A stock recovery is the removal or correction of a device that has not left the control of the manufacturer.

The FDA defines "control" very conservatively, Forrest explained. For example, a product that has been sent to a distributor, but has not yet been released to the market, could be viewed by the FDA as no longer under the direct control of the manufacturer. And if any portion of an affected lot of a product has left the direct control of the firm, the agency must be notified.

So-called backdoor or silent recalls can also be a violation under Part 806. An example of this could be a software update that provides new functionality but also fixes a problem that could have a health effect. This would be considered a correction and would need to be reported.

Technical bulletins and advisories can also fall into this category if there is a health effect. This includes workarounds or other additional instructions. The FDA defines health effects very conservatively, Forrest said.

Warning Letters

She offered examples of warning letters from the FDA, highlighting the range of ways a manufacturer can fail to report under Part 806.

She reiterated that any action taken to reduce a health risk triggers the notification requirement. This includes "fix on failure," where technicians repair a device only after a known safety issue presents.

Another frequent mistake firms make is not keeping records of recalls that don't fall under Part 806 notification requirements.

Any recall must have documentation explaining the firm's justification for not notifying the agency. For example, if a device is recalled for a reason not related to a health effect, there must be documentation to support that decision.

FDA inspectors often ask for records of a firm's unreported recalls, Forrest said.

Access the webinar *Part 806 Reports: When to Submit?* here: www.fdanews.com/products/57620. — Dave Stroup

APPROVALS

Materialise Cardio Planning Software Cleared

The FDA granted Materialise 510(k) clearance for its Mimics Enlight product, a suite of cardiovascular planning software that create 3D models for use in transcatheter mitral valve replacement (TMVR) procedures.

The device provides clinicians with accurate 3D models for consistent patient screening. It also helps clinicians to determine the appropriate size and placement of TMVR devices.

Biocorp Earns CE Mark for Insulin Tracker

Biocorp has gained approval in Europe for the Mallya smart sensor, a device that records key treatment information for diabetic patients.

The sensor connects conventional insulin pens to a mobile app, tracking the selected dose, date and time of injection. The automated recording eliminates the need for logbooks and manual recordkeeping.

The device also creates a summary report of a patient's injected doses over the previous three months.

Heart Murmur Sensor Gains CE Mark

Austria-based eMurmur has earned the CE Mark for its heart murmur sensor, a mobile device that uses cloud technology in conjunction with a third-party electronic stethoscope.

The device makes use of advanced machine learning to identify pathologic and innocent heart murmurs, as well as the absence of a heart murmur.

The system uses machine learning, a mobile app and a web portal to help healthcare providers with cardiac auscultations.

This usually requires providers to have good hearing and the ability to distinguish different pitches and timing.

CorMatrix Epicardial Patch Cleared

The FDA granted CorMatrix Cardiovascular 510(k) clearance for its Cor PATCH epicardial patch, used to support and repair heart tissue in adults and patients.

The device is able to provide epicardial support and repair of atrial and ventricular walls of the heart that have been reduced or damaged by a heart attack.

Jubilant DraxImage Rubidium Elution System Receives CE Mark

Jubilant DraxImage's RUBY Rubidium Elution System (RbES) and its accompanying accessories have earned the CE Mark for use in myocardial imaging.

The elution system delivers customized patient doses of rubidium chloride injection, a radioactive diagnostic agent used in PET imaging. The doses are generated using the company's RUBY-FILL device and require an elution system due to their short half-life.

The radioactive diagnostic agent is indicated for PET imaging of the myocardium under rest or stress conditions to assess regional myocardial perfusion in adult patients that have or may have coronary artery disease.

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