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FDA Considers Aligning QSR With ISO 13485

The FDA anticipates publishing a proposed rule early in 2019 on aligning Quality System Regulation, 21 CFR 820, with the international standards of ISO 13485:2016.

"In the spirit of global harmonization of quality management systems, the FDA is considering an evaluation/mapping of the 13485 clauses to the appropriate U.S. regulatory requirements," an agency spokesperson told FDAnews.

However, quality expert Dan O'Leary, president of Ombu Enterprises, notes that any changes to the existing regulation to help create closer alignment between the two standards would not simply replace QSR standards.

Even if it were possible, says O'Leary, it would be a bad idea for the FDA to try to replace 21 CFR 820 with ISO 13485:2016.

(See **ISO 13485***, Page 2)*

India's CDSCO Responds to Questions On Medical Device Rule 2017

India's Central Drugs Standard Control Organization (CDSCO) issued answers to frequently asked questions on its new medical device rules and said licenses granted after Jan. 1, 2018 will remain valid indefinitely.

For applications submitted before Jan. 1 that are still being processed, devicemakers will need to resubmit the application and pay any additional fees, the regulatory authority said.

All new devices must comply with Jan. 1 date, but there is a grace period of 18 months from the date the rules were published to allow manufacturers of devices already on the market time to comply.

The country's new Medical Devices Rules 2017, published on Oct. 27, 2017, marked the first time that India regulated medical devices separately from drug products.

(See **India***, Page 2)*

India, *from Page 1*

New classifications are also in effect. The regulations classify devices into four risk-based categories — Class A to Class D — with Class D devices carrying the highest risk. The classification is in line with the risk-classification system used in most developed countries. For those devices that have a different classification in Global Task Force Harmonization countries, the higher classification will be used in India, CDSCO said.

The regulator clarified that Class C and Class D devices are granted a license after safety and efficacy are established via clinical trials. Licenses for lower-risk Class A and Class B devices may be granted after safety and performance is established via published performance data or clinical data from the country of origin.

For de novo devices that do not have predicate devices, clinical trials conducted in the United Kingdom, Australia, Canada, Japan, or the United States, may satisfy clinical requirements provided the device has been on the market for at least two years.

Applicants will need to obtain an investigational device exemption for each new medical device. For devices that are manufactured at multiple sites, additional fees are required for the additional sites. Postmarketing surveillance is the responsibility of the license holder sor authorized agent.

Manufacturers of devices and in vitro diagnostics will not need to apply for a separate import license for raw materials or components that are intended to be used in manufacturing the finished products, CDSCO said.

The regulations require devices sold in India to have a unique device identifier on the labeling beginning in Jan. 1, 2022.

Read the Q&A document here: www.fdanews.com/02-27-18-IndiaQA.pdf.

ISO 13485, *from Page 1*

"Writing QSR was a major undertaking that took years," he says. "In my opinion, FDA doesn't have the resources, and would not be willing to take on a project of this magnitude."

ISO is useful as an international standard, but there are elements of 21 CFR 820 that are considered better by some regulatory experts, such as the QSR requirements for complaint management and supplier management, which O'Leary thinks the FDA would be reluctant to give up.

Additionally, the QSR is more powerful than the ISO because of its ability to link to important codes within other countries as necessary. ISO "doesn't know what country it is operating in," whereas QSR Part 820 links back to regulations in Canada and the EU, O'Leary says, adding "I've always considered this kind of linkage as a strength of the U.S. system."

Any attempt to revise QSR to more closely align with ISO 13485:2016 will face numerous logistical challenges while doing nothing to improve the safety and effectiveness of medical devices in the United States, he says.
— Donna Scaramastra Gorman

Sensors and Wearables Transform Trials But Challenges Remain, Experts Say

With a multitude of sensors, wearables and mobile devices becoming available for use in clinical trials, sponsors should conduct systematic comparisons before designing protocols, according to experts at the annual SCOPE conference, who presented the work they've done to demonstrate the value of using digital monitoring in their studies, as well as the obstacles they encountered.

Choosing the right device from the outset, in a patient-centric manner, can directly affect adherence and the eventual quality and consistency of the data — as well as on the back end, where certain product choices can cause technical headaches.

Many devices, available at different price points, can return raw data in various formats, with some possibly inappropriate for use in clinical research, said Bhaskar Dutta, principal scientist of AstraZeneca's Advanced Analytics Center.

Some can log missing data as a zero, potentially mirroring an actual measurement — and others don't track heart rates over 100 beats per minute, Dutta said. In addition, certain devices may only report data on a daily basis, or even report some data types every minute and others every four, causing issues in sampling and final analyses.

Selecting the Device

AstraZeneca ran a human factors study of healthy volunteers evaluating the usability of six different body sensors and wearables over the course of a month, with some being worn for eight to 10 hours a day.

"How do you select the right device? That was a mind-boggling question for us… You don't want junk in and junk out" during the course of your clinical study, Dutta said. And when asked if expensive medical devices delivered better quality data compared to consumer-grade activity trackers, Dutta said the short answer was no.

Considering the device's size, weight, water resistance, durability and comfort are all essential — because every time a patient takes it off, there is a chance they do not put it back on, said Amir Lahav, from Pfizer's rare disease research unit.

In addition, the processes for validating digital biomarkers and endpoints derived from remote sensors and wearables in clinical studies should be no less rigorous than any other biologically based measurement, said several experts at the Orlando, Fla. conference.

As the industry begins to pursue the benefits of digital health monitoring in clinical research — such as greater accuracy and richer datasets at a lower cost, as well as the ability to better focus on patient needs, reduce burdens and increase adherence — digital biomarkers and endpoints should not be treated as a company's side project, or even as a technology in its infant stages. "We have to move beyond this concept of exploratory, exploratory, exploratory.

Widely Used

We have to get more robust about it," said Rob DiCicco, VP of clinical innovation and digital platforms at GlaxoSmithKline. "We would not introduce a new tissue biomarker without a lot of methodology work up front."

Mobile devices are being widely used in clinical research, but their utility in assessing benefits in interventional trials continues to be limited, DiCicco said. A lot of work remains to be done in standardizing data capture and use, and eventually having those methods pass regulatory muster.

To define meaningful endpoints, sponsors should take a device-agnostic approach and validate them in a simulated living environment, said Lahav. Patients should also be asked to complete tasks relevant to daily life, not those that measure their ability to bring a finger to their nose, as they would in a clinic, for example.

"They need to be able to type and swipe on a mobile device," Lahav said. "The activities should fit the era we live in."

(See **Wearable***, Page 4)*

Wearable, *from Page 3*

Sponsors need to work together to develop standard algorithms and data collection procedures in order to be validated by the FDA, Lahav said, lest the industry overwhelm the agency with too many different proprietary methods.

Christian Gossens, global head of early development workflows in Roche's Pharma Research and Early Development Informatics group, demonstrated how gathering consistent, real-time sensor data on multiple sclerosis patients in a study became much more valuable than a traditional site visit.

Roche's FLOODLIGHT study evaluated 60 MS patients, scheduling them for three site visits over 24 weeks, while also having them complete daily tests on their smartphones.

Patients evaluated their mood, symptoms and disease impact, and tested their cognition, balance, and their ability to walk, pinch and draw shapes, mirroring other clinically validated endpoints. Passive information was gathered by the devices' gyroscopes and accelerometers as well.

A normal clinical study schedule only offers so many windows on a patient's disease progression, while daily monitoring offers a more granular picture, Gossens said.

In addition, many people cannot remember more than the previous week with any amount of day-to-day detail.

For example, during a site visit one patient did not report a potential onset of a relapse from a few weeks prior — however, they did enter it into their daily smartphone diary, and the following data showed a worsening of certain symptoms.

"What we use this for at the moment is internal decisionmaking," Gossens said, adding that the industry still needs to work out how to answer the regulatory questions regarding clinical validation. "It will be an interesting journey… We have strong confidence that the data here are real."

Ieuan Clay, Novartis' group leader for digital endpoints, described how digital sensor data can be used to guide clinical study design. While a typical trial evaluating limping and healing following knee surgery may run six months to a year, any differences in gait between the two legs begin to converge in about one month.

"That helped us design trials going forward, because we knew we had to gather more data points early on," Clay said.

In addition, companies are looking at ways to recapitulate clinical measurements using mobile devices, and exploring the potential of siteless trials.

For example, balance information can be derived from passive sensing of a patient sitting and standing over the course of their daily life, you don't need to ask them to come in to an office to do a balance test, he said. — Conor Hale

PEOPLE ON THE MOVE

Congenica named **David Atkins** as CEO. Atkins has over 25 years' experience as a global leader in a broad range of diagnostics and healthcare businesses. He has held senior positions in R&D, business development, operations and sales and marketing. Prior to joining Congenica, Atkins was CEO of Synevo. He previously served as global head of the advanced staining pathology business unit for Leica Biosystems. He also has over 20 years' experience with Johnson & Johnson's medical device and diagnostic businesses in R&D and business development.

CHF Solutions appointed **Vitaliy Epshteyn** as vice president of operations and engineering. Epshteyn brings 20 years of leadership, management and engineering experience, primarily in the medical device industry. Most recently, he served as chief technology officer and senior director of engineering of the medical business unit at TE Connectivity. Prior to that role, he held several leadership roles at St. Jude Medical where he led for the rapid development and commercialization of multiple product lines.

FDA Cites Digital Heat for Failing to Establish Design Procedures, CAPA

An FDA inspection of Digital Heat's Tempe, Arizona facility conducted in December 2017 resulted in a nine-item Form 483 for failing to establish design procedures for the firm's heated eye pad.

The device manufacturer had not established procedures for design inputs, outputs, verification activities, validation activities, transfer or design changes for the heated eye pad that the firm began distributing in September 2013.

The FDA inspector said the firm failed to establish a design history file to demonstrate that the design was developed to comply with 21 CFR Part 820.

Digital Health also lacked purchasing control procedures to ensure that received products and services conformed to specified requirements. Potential suppliers were not evaluated based on their ability to meet requirements, the agency said.

Procedures for corrective and preventive actions were also not established. Moreover, the firm had not put in place procedures for analyzing potential sources of nonconforming product, or for verifying or validating CAPA actions. Management failed to disseminate information related to quality problems to appropriate personnel, the FDA said.

The firm also lacked procedures for acceptance activities. For example, the company received incoming product that is provided to the contract manufacturer, but no documentation was maintained to verify the product conformed to specified requirements.

The FDA said the firm had not established procedures for management review or for quality audits, and it had not documented a quality audit since it began distributing the heated eye pad.

Read the Digital Heat Form 483 here: www.fdanews.com/02-28-18-digitalheatcorp483.pdf.

Analyzing Complaint Trends

When analyzing potential trends in complaints, devicemakers must establish three parameters to monitor: the time interval for analysis; the number of events in the time interval; and product volume in the market.

For each time interval, manufacturers should record the incident rate, which may be in the form of a fraction or a percentage. To determine this rate, divide the number of events by product volume.

Devicemakers also must establish a baseline for the expected incident rate to compare to their actual rate so they can detect an unfavorable trend. Baselines are typically based one of three common methods:

- Historical Data—To develop a baseline based on historical data, analyze data collected over a representative number of periods, using the average of the numbers as the baseline.
- Risk Analysis—Risk is defined as the intersection of probability and harm. For example, if a devicemaker produces and ships 4,500 single-use devices in a month and Complaint Management for Devicemakers: From Receiving and Investigating to Analyzing Trends 25 the risk analysis estimates a certain harm occurs once per 750 uses, the company would determine the per-month risk analysis baseline by dividing the devices produced by 750, for a risk level of six events per month, or 0.13 percent.
- Expert Judgment—This analysis method can be applied to determining both the baseline and the reporting threshold. It can take several specific forms, including: Individual expert; Group consensus; Nominal group technique, in which each member of a group offers a solution and the group ranks all solutions in order of preference; and The Delphi Method, in which a panel of experts answers questionnaires in multiple rounds to arrive at an opinion.

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

India Releases Final Audit Fees for Notified Bodies

India's Drugs Controller General released its final audit fees for notified bodies under its new medical device regulations.

Annual surveillance assessments are expected to take one to three days, and organizations that are already certified to ISO 13485 from a notified body or CE mark for the same product will have a reduced fee schedule and audit.

The calculation of fees will be based on the number of products, risk class, number of employees and prior experience, according to CE marking/ISO 13485.

Overall, the fee is Rs 20,000 ($308) per day per auditor for conducting a manufacturing site audit, including a product assessment. If two days are required, a fee of Rs 25,000 ($385) would be charged for the two-day audit.

These fees do not include travel costs, which are not expected to cost more than Rs 12,000 ($184) per auditor per visit.

The DCGI estimated that an audit for one to five products would take two days, an audit of six to 10 products would likely take three days, 11 to 15 products would be four days, and more than 15 products would take five days.

The regulator clarified that the calculation was based on one round of technical file review, and additional fees would apply to additional rounds as required.

If on-site audits are not required, assessments will be based on quality management system and product certificates issued from notified bodies. Manufacturers will need to submit a full technical file to the notified body.

Devicemakers of Class A and Class B devices can choose their own notified bodies to verify quality management system conformance provided they meet competency requirements and are accredited. Notified body requirements are listed in Part I of Schedule Three of the new regulation.

Read the document here: www.fdanews.com/02-27-18-Indianoticedbodies.pdf.

Nashville's Mid South Precision Lands 483 for Validation, QS Failures

Validation procedures for production processes such as milling and lathe processes were found lacking during an October 2017 inspection of Mid South Precision's Nashville, Tennessee facility.

According to the Form 483, contract manufacturer Mid South Precision lacked procedures for receiving, reviewing and evaluating complaints. The FDA inspector found that returned products were not logged on the customer returns log, no complaint record was opened, and it was not investigated for MDR reportability.

The company also failed to establish a device master record for any of the devices it manufactured, including the femoral array.

The FDA said the firm's procedures for controlling nonconforming product was inadequate because products returned by customers were not adequately identified and controlled. Nonconformance reports were not opened for certain nonconforming products, and the final disposition of the products was not documented.

For example, one product was returned due to pits in the weld, and a nonconformance report was not opened and the final disposition was not documented.

Rework and reevaluation activities were also found to be missing in the device history record. For example, for the same product returned, the pieces were reworked, but there was no documentation of rework activities in the device history record.

CAPA procedures were also inadequate. A quality audit was performed in June 2017, which identified deficiencies, but corrective actions were not initiated until October 2017, after the FDA inspection was announced, the agency said.

In addition, the FDA found fault with the firm's supplier selection, evaluation and approval procedures. Procedures in place didn't ensure that suppliers, contractors and consultants were being evaluated by their ability to meet specified requirements. Mid South Precision also did not establish and maintain acceptable records of its suppliers, and it lacked records of supply agreements.

Read the Mid South Precision Form 483 here: www.fdanews.com/03-01-18-midsouthprecisioninc483.pdf.

APPROVALS

Three Rivers Medical Earns CE Mark For Rio Embolization Coil System

Three Rivers Medical received a CE Mark for its Rio Embolization Coil System. The product includes an embolization coil line and visual detachment system for treatment of cerebral aneurysms and other vascular malformations.

The company plans to begin commercialization through distributors in territories that recognize the CE Mark and is pursuing additional regulatory approvals in key global markets.

FDA Grants EAP Designation To Guardant's NGS-Based Liquid Biopsy

The FDA granted Guardant Health Expedited Access Pathway designation for its Guardant360 assay, a next-generation sequencing-based liquid biopsy test for advanced cancer.

The assay has been marketed as a laboratory-developed test since 2014 and is available in more than 30 countries. The company plans to submit a PMA to the FDA for the assay by year end.

Pure-Vu System Earns CE Mark

Motus GI secured a CE mark in the European Union for its Pure-Vu system.

The device fits over most standard colonoscopes and allows physicians to clean poorly-prepped colons to improve clinical outcomes. It has already secured 510(k) approval from the FDA and is being piloted in the United States.

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

Approvals, *from Page 7*

The company received CE mark approval based on positive clinical study results it reported last November and it plans to continue post-approval trials over the next year.

Getinge Wins 510(k) Clearance For PulsioFlex Monitoring System

Getinge received FDA 510(k) clearance for its PulsioFlex Monitoring System and PiCCO Module.

The diagnostic aid is used to measure and monitor blood pressure and cardiopulmonary, circulatory and organ function variables in patients in intensive care units.

The PiCCO Module is used for hemodynamic management of critically ill patients, providing cardiac output measurements both continuously and intermittently.

Endomag's Magseed Marker Cleared for Long-Term and Soft Tissue Implantation

Endomag received 510(k) marketing clearance to extend the indication of its Magseed magnetic marker to include both the marking of soft tissue and long-term implantation. The marker is used to locate lesion for breast cancer.

The device is a wire-free localization device that can be implanted into any soft tissue with no restrictions on the length of time the marker can remain in the body. It is compatible for imaging under ultrasound, X-ray and MRI.

The system is designed to guide the accurate removal of cancer, and to maximize the amount of healthy tissue retained.

Medtronic Wins FDA Nod For Guardian Sensor

The FDA cleared Medtronic's Guardian sensor, part of the Medtech's MiniMed 670G automated insulin delivery system.

The device is a continuous glucose monitor and is used with a hybrid-closed loop system to control insulin delivery.

The system uses Medtronic's SmartGuard algorithm to automatically adjust insulin delivery every five minutes based on data provided by the Guardian Sensor 3.

Reva Earns CE Mark for Fantom Encore Bioresorbable Scaffold

Reva received a CE mark and reported the first implant of the Fantom Encore bioresorbable scaffold.

Bioresorbable scaffolds were developed as an alternative to metal drug-eluting stents for the treatment of coronary artery disease. The Fantom Encore offers a thin profile without compromising strength or X-ray visibility, using improved polymer processing and manufacturing techniques.

REVA expects to launch the entire Fantom Encore product line later this year.

Siemens Healthineers Receives FDA Clearance for MRI Application

Siemens Healthineers received FDA clearance for GOKnee3D, a magnetic resonance imaging application used for diagnostic exams of the knee.

The device enables a push-button diagnostic 3D knee exam in 10 minutes and high-resolution isotropic 3D images enables flexible evaluation of the images in all planes.

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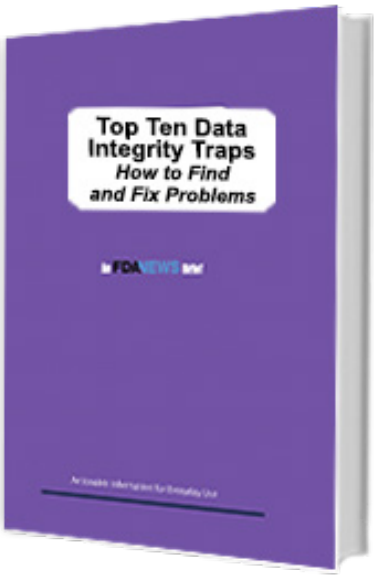

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