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IN THIS ISSUE

FDA To Propose Quality Metrics For Devicemakers By Oct. 1

The FDA plans to unveil by Oct. 1 its own quality metrics for devicemakers based on three metrics from a pilot program conducted by Xavier Health and the Medical Device Innovation Consortium.

The three metrics developed under the MDIC/Xavier Health pilot are:

- The total number of product changes related to product or process failures during pre-production activities compared to the total number of projects;
- The number of units manufactured without nonconformances (i.e., right first-time rate) during production; and
- Post-market indicators such as complaints, service records, installation failures, medical device reports and recalls.

(See **Metrics**, *Page 2)*

FDA, UK Change Combination Product Determination Process

FDA officials said the agency will allow earlier interaction with sponsors to determine the regulatory pathway for combination products. In a similar move, the UK issued updated guidance to help sponsors make those determinations.

Previously, devicemakers would submit a Request for Determination (RFD) to the FDA's Office of Combination Products to help them make decisions about whether the agency would regulate the combination product as a drug or device.

Manufacturers can now engage FDA officials earlier in the process under a Pre-Request for Designation (Pre-RFD) process, which will allow them to make decisions earlier in the product development cycle.

Once OCP receives a request for classification or center assignment, the office will respond within 60 days.

(See **Combo Products**, *Page 4)*

Metrics, *from Page 1*

Pre-production metrics were identified as the most difficult to track because very few companies track the number of changes due to inadequate product and process development.

That is partly due to the nature of continuous trial and error in the pre-production phase that loops back to research and development (*IDDM*, July 1).

Ideally, the pre-production metric is designed to track the number of changes that occur during the transfer stage that was triggered by the product or process inadequacies, says a best practices document released after the pilot program.

Additionally, it was difficult to segregate which of the planned changes were due to inadequacies versus improvements. Tracking the number of changes can also be an indication of the effectiveness of design controls, the best practices document says.

This metric provides an indication of the reliability of the R&D process and increases overall awareness of those shortcomings within a company. The metric also provides estimates for the overall time and cost of getting a product to market.

Definitions were found lacking for the second metric — the number of units manufactured without non-conformances compared to the number of units started — because the term "units" could refer to finished, in-process material or sub-components.

For this reason, participants revised the metric to compare the number of units manufactured right the first time (RFT) within or across lots compared to the number of units started.

The revised metric would be more useful in feeding information back to R&D to improve development. The ability to track and trend

(See **Metrics**, *Page 6)*

Finalized Metrics for Pilot Study

Phase/Metric Name/Goal	Metric Calculation
Pre- Production: Design Robustness Indicator Assess the number of product changes that are related to product or process inadequacies or failures	total # of product changes ——————— total # of products with initial sales in the period
Production: Right First Time Rate Assess the number of production failures related to product and process inadequacies or failures	# of units mfg. without non-conformances ——————— # of units started
Post- Production: Post-Market Index Assess an aggregate of post-market indicators with root causes of product or process inadequacies or failures	Index: Complaints * (0.20) + Service Records * (0.10) + Installation Failures * (0.20) + MDRs * (0.20) + Recalls (units) * (0.20) + Recalls (total) * (0.10)

Source: Xavier Health

Expert: How to Build a Strong Supplier Auditing Program

Over the past few years, poor supplier controls remain one of the top five FDA citations for device manufacturers.

Although the agency allows quite a bit of flexibility on how companies manage their suppliers, devicemakers should conduct an internal risk assessment to define what their supplier controls should look like within their companies.

First, companies need to define their company profile and set goals accordingly, said David Parkin, group lead for Philips Healthcare, during a recent FDAnews webinar.

The first step in setting goals is to create a supplier-focused team and perform site-level audits. Audits include quality management system-type audits, as well as process and technical-focused audits.

Companies should first look at their high-profile suppliers, and then assess the risk of all their suppliers and components, identifying sole-source over single-source suppliers.

Suppliers fall into critical, major and minor categories when it comes to risk. Critical suppliers — those that could have an immediate effect on patients — get annual site audits. Major suppliers would get audited every two years, and minor suppliers should get surveyed every three years or so.

To Certify or Not to Certify?

The supplier inspection should include data monitoring activities. The supplier has data that is valuable to the device manufacturer, and the supplier should be willing to share that data.

Parkin suggests using a portal where a supplier enters lot data when product is ready to go. The portal would then tell the supplier whether or not the lot can ship or not, depending on the upper or lower control limits and tolerance built into the system.

"A lot of people have heartburn about just letting the supplier have control," Parkin said. "But if you've done your homework upfront, you know what the supplier is capable of doing, and you know how they can manage that and provide you data that will benefit you, as well."

Overall, the "charter is to drive goals and expectations of our parts that come in, and we expect a certain quality and a certain type of reliability in that they've used the materials properly and they've made them right," he stressed.

To push suppliers toward certification, he suggests reassessing the critical-to-quality requirements and how that relates to risk, and then dovetail those suppliers right into the Failure Modes and Effects Analysis (FMEA) work.

Audits are a good indicator to ensure that suppliers have a process to monitor their own data and that they're reporting that data properly.

The audit should also include business reviews, including quality agreements and supply agreements. Make the business review count, so that it's a two-way discussion, he said, stressing that working with suppliers is about managing long-term business relationships. Devicemakers should focus on their key suppliers and stay in contact with them frequently.

"As quality individuals we're looking at the quality aspects and patient harm to drive some of the decisions we make," Parkin said.

For quality agreements, companies should focus on answering questions about what happens when things go wrong. The biggest obstacle with quality agreements is that companies usually try to put in too much detail, and by the time they sign off on them, they're already out of date.

Similarly, supply agreements start to get too big once legal and other entities get involved. Supply agreements should focus on the inventory logistics and pricing, as well as forecasting.
— Tamra Sami

Combo Products, *from Page 1*

The agency notes that the assessment "depends on sponsors providing a complete, clear and detailed product description, which includes the product's indication for use, its composition/ingredients, and an explanation of how it works."

Device manufacturers can initiate the Pre-RFD process at any time during product development – even when a company is contemplating whether to develop a specific product or want advice on what configuration to pursue. During this time that sponsors don't need to recommend a classification for the product or discuss classification of other marketed products, the agency said.

The FDA is in the process of developing draft guidance about the Pre-RFD process, which will provide details on what information sponsors should provide in a Pre-RFD. The agency also will publish a list of product classifications for various types of products.

UK Guidance

The UK's Medicines and Healthcare products Regulatory Agency issued updated guidance on how manufacturers can make decisions on whether their products would fall under a device or a drug pathway.

The updated guidance discusses what the agency terms "borderline products," including medical devices, biocides, herbal products, machinery and laboratory equipment.

The guidance notes that the claims being made and the mode of action will distinguish which regulatory pathway would apply.

Medical devices fall into one of three different categories, as each type is governed by a different EU directive:

- Medical devices (covered by the Medical Devices Directive 93/42/EEC);
- In vitro diagnostic medical devices (covered by Directive 98/79/EC); and
- Active implantable medical devices (covered by Directive 90/385/EEC0.

Companies should not assume that if a product is considered a medical device outside the EU that it will be a medical device in the EU as well.

The guidance offers descriptions on products that have recently been reclassified as devices, including ophthalmological products, devices that deliver drug products, drug-coated devices, and sutures and ligatures.

The guidance adds information on standalone software and offers an advice form for borderline products.

Read the guidance here: www.fdanews.com/08-12-16-UKguidance.pdf. — Tamra Sami

More Postmarket Data Collection Could Allow Shift From Class III to Class II

The FDA is announcing a new set of product codes that it is considering reclassifying as lower risk and is seeking industry comment.

The reclassification effort is connected with the Center for Devices and Radiological Health's strategic priorities to reduce premarket data and rely more on postmarket data when appropriate to increase patient access to needed devices.

The agency acknowledges that it is a balancing act to determine how much premarket data is necessary to assure safety and efficacy of devices in the premarket setting.

To better understand when it would be appropriate to shift premarket data collection to the postmarket setting, the agency released guidance in April 2015 that outlined how it would consider postmarket data to support premarket approvals via en expedited access pathway.

The agency also conducted a retrospective analysis of all PMA product codes with active PMAs prior to 2010 to better understand if premarket data collection could be shifted to the postmarket setting.

The study analyzed postmarket performance data, technology and performance considerations for each procode to determine the current benefit-risk profile.

Postmarket performance data analyzed included PMA annual reports, literature reviews, total product lifecycle reports, medical device reporting, market penetration and recalls.

The study recommends certain devices be reclassified from Class III to Class II to allow for reduced premarket data collection. Comments are due Oct. 7.

See the list of recommended products and procodes here: www.fdanews.com/08-10-16-FDA PMAanalysis.pdf, and read the FDA notice here: www.fdanews.com/08-09-16-PMAreview.pdf.
— Tamra Sami

FDA Seeks Feedback On Classification Of Antimicrobial Wound Care Products

The FDA will hold a public meeting on Sept. 20-21 to discuss the classification of certain wound care products containing antimicrobials.

These products are regulated under product code FRO, "Dressing, Wound, Drug," and are considered "pre-amendments" because they were in commercial distribution before the Medical Devices Amendments were enacted, and have not yet been classified.

The FDA is seeking input on the indications for use, risks to health, and safety and effectiveness of these wound care products, and how they should be classified. Some of these products may meet the definition of Class II, and some may meet the definition of Class III.

The agency is also requesting pubic comment on the risk of antimicrobial resistance in light of the increasingly significant national public health concern posed by AMR.

Interested parties may submit comments at Docket No. FDA-2016-N-2147. For information about attending, email: Evella.Washington@fda.hhs.gov.

TGA Lays out Transition to ISO Quality Management Standard

Australia's Therapeutic Goods Administration will transition to the ISO 13485:2016 standard governing medical device quality management systems over the next three years.

The agency clarified that the 2003 standard and the 2016 standard will co-exist during the three-year transition period.

Users of ISO 13485:2003 should work with the TGA or their EU Notified Body or the Medical Devices Single Audit Program organization to schedule an upgrade audit during the transition period.

The deadline for compliance to the new standard is January 2019.

Metrics, *from Page 2*

within and across lots on a rolling basis would allow devicemakers to identify highest risk areas and to assess production efficiencies.

The post-production metric was found to be problematic because it was unclear if measuring in the aggregate was more informative than tracking separately. Also unclear was the impact to tracing complaints and MDRs for products that don't have service and installation.

Participants suggested several multi-step options instead, such as:

- Calculating each post-production indicator separately with defined equations provided;
- Aggregating post-production indicators using weighting factors based on product and process risk profiles; and
- Using a comparative analysis through dashboards, score cards or heat maps.

The FDA anticipates announcing a voluntary pilot program in December. It hopes to officially roll out the metrics a year later. The agency will also focus on how third-party servicers fit into the scheme.

The current focus is leading indicators of quality, and an aggregate scoring system still needs to be developed. Such a scoring system could also make public the list of firms that fall into the highest category. Top-level firms would also not have to go through inspections, suggested William MacFarland, director of the Division of Manufacturing and Quality within CDRH. Those firms that met a "quality floor" would warrant less extensive inspections than companies that don't meet the quality floor.

Read the best practices document here: www.fdanews.com/08-10-16-Qualitymetricsbestpractices.pdf, and FDA presentation here: www.fdanews.com/08-10-16-FDAmetricsplan.pdf.
— Tamra Sami

Comments: 3-D Printing Guidance Needs More Work

The FDA's draft guidance on 3-D printing, or additive manufacturing of medical devices, needs a fair amount of work, according to 23 comments received by the agency.

The draft guidance — which builds on discussions from an October 2014 workshop on AM —is what the agency calls a "leap-frog guidance," aimed to provide the agency's initial perspective on emerging technologies (*IDDM*, May 13).

The Medical Imaging and Technology Alliance, said that although the FDA acknowledged that additive manufacturing is bringing rapid change to the medical device industry, the agency needs to consider how it would coordinate printing with medical imaging.

How to Ensure Calibration

For example, the agency acknowledged in the draft guidance that AM has the potential to create anatomically matched medical devices and surgical implementation based on an individual patient's medical imaging, but the agency has not considered how it would ensure that devices used for AM are properly calibrated and that the images from which they are copied provide sufficient detail for accurate reproduction, MITA said.

In addition, the agency needs to consider how it would treat the software that will translate a medical image into a file that can be applied by a 3D printer.

MITA also noted that the guidance does not apply to devices that involve bioprinting or point-of-care manufacturing, which "further complicate the regulation of AM."

Community Based Personalized Healthcare, based in Victoria, Australia, said that the FDA "needs to realize that a complete paradigm shift is required to truly regulate the quality and cost effectiveness of medical devices and products in the future."

The association noted that additive manufacturing would actually reduce risk to patients because the greater risk is the current "off-the-shelf medical device industry," which affects thousands of patients over a period of many years.

"Now patient-specific designs can be continually improved by way of iteration in a quality process that is impossible with mass manufacture," the association said, adding that "a regulated process can create reimbursable devices using distributed community-based manufacturing."

Read the comments here: www.fdanews.com/08-10-16-3Dcomments.pdf. — Tamra Sami

Philips, Mayo Climb Mt. Kilimanjaro To Test Cardiac Technology

Philips and the Mayo Clinic are embarking on a research expedition to climb Africa's Mount Kilimanjaro to test monitoring equipment that will measure how the body reacts to high altitudes.

Using app-based digital technologies to record vital signs, researchers hope to better understand how oxygen deprivation affects the body. Hypoxia mimics what happens to the body during a cardiac event and can provide clues in better diagnosing and treating cadiac events, the company said.

The technology being tested for the 10-day journey includes contactless monitoring for checking heart rate, arterial blood oxygenation, respiration rate and activity. Philips' portable CX50 xMatrix will be used to study heart measurements, and its Lumify ultrasound system will check pulmonary measurements.

The company's sleep diagnostics system, the Alice NightOne wireless sleeping system, will also collect data on sleep quality associated with increased heart rates and reduced oxygen.

FDA Revises Tips for Electrosurgical Device, Vessel Sealer Submissions

Sponsors of 510(k)s for electrosurgical devices and bipolar electrosurgical vessel sealers meant for general surgery can skip studies on FDA-approved components, the FDA says.

In a pair of final guidance documents released Friday, the FDA is now advising sponsors to rely on an original 510(k) as a reference, allowing sponsors to avoid additional trials for the component or accessory. This, however, does not exempt sponsors from having to demonstrate compatibility between components or accessories and the proposed device.

The final guidance documents contain minimal revisions from their draft versions, both of which were released in March 2014.

An exemption for additional trials applies to system testing for vessel sealers, the FDA says. When the 510(k) falls within a family of closely related devices — with identical jaw geometry, surface characteristics, materials, clamping force, output power and generator control algorithm — it's unnecessary to repeat system tests, according to the final guidance.

Otherwise, the FDA still recommends system tests to demonstrate bipolar electrosurgical vessel sealer performance for new sealing systems or those modified to an extent that there might be a substantial effect. For instance, if the jaw surface characteristic or clamping force is modified, the agency expects system tests.

The final guidance documents bring to the fore labeling expectations that had previously been placed in the margins. The documents remind sponsors that although labeling is not a requirement for clearance, any product labels must comply with the requirements laid out in 21 C.F.R. §801.

Recommendations Virtually Unchanged

The labeling recommendations for the vessel sealers and electrosurgical devices remain virtually unchanged. The FDA suggested a new warning statement for electrosurgical devices, recommending sponsors with reusable instruments include a statement "that visual inspection alone may not be sufficient to ensure that the insulation is intact."

Descriptions of device designs should include exploded view or assembly view, or else connection diagrams, the final document states. The draft version of the guidance documents had recommended sponsors submit either block diagrams or connection diagrams.

In the final document, the agency defines term certain terms as well, such as force to jaw failure, as it discusses performance data for the devices. The guidance documents define force to jaw failure "as the force required to cause the actuating component to no longer be able to grasp or close on the target tissue."

Test recommendations provide further detail for sponsors in the final versions, however, the crux of the agency's advice is consistent with those made in the draft version. For example, as it relates to vessel sealers, the FDA expands on its prior recommendations for system tests on thermal spread on vessels.

Two-dimensional histological assessments are "minimally acceptable measurements," the agency says in one of the final documents. Three-dimensional histological assessments, on the other hand, are recommended as they are needed to quantify thermal spread in seals. In particular, the agency says the three-dimensional histological assessments should apply to seals that generate special growth characteristics, such as asymmetrical growth.

As in the draft version, the final document recommends that sponsors conduct basic electrical, thermal and electromagnetic performance testing to check for electrical safety and electromagnetic compatibility.

Read the final guidance document on premarket notification submissions for electrosurgical devices here: www.fdanews.com/08-12-16-GuidanceElectrosurgicalDevices.pdf.

Read the final guidance document on premarket notification submissions for bipolar electrosurgical vessel sealers for here: www.fdanews.com/08-12-16-GuidanceBipolarElectrosurgicalVesselSealer.pdf. — José Vasquez

BRIEFS

TGA Yanks Alere InRatio Monitors, Strips

Australia's TGA is withdrawing from the market the Alere INRatio and Alere INRatio 2 PT/INR monitors, as well as the INRatio Test Strips due to innacurate test results.

However, Alere will continue to manufacture and distribute the test strips for a period of time to allow patients to safely transition to another monitoring method. Alere recommends that patients have periodic verification of their INR using a laboratory INR method as soon as possible.

UK Warns on Nipro Glucose Strips

The UK's Medicines and Healthcare products Regulatory Agency warned people with diabetes to stop using Nipro Diagnostics' TRUEresult glucose test strips due to a manufacturing fault that could lead to false low blood sugar results.

The manufacturer discovered an issue with the packaging of certain lots, and the test strips were not sealed properly. Read the warning here: www.fdanews.com/08-11-16-UKsafetyalert.pdf.

Boston Scientific's Emblem MRI Approved

Boston Scientific received FDA approval for its Emblem MRI subcutaneous implantable defibrillator (S-ICD) system, as well as magnetic resonance conditional labeling for previously implanted Emblem S-ICD systems.

The Emblem MRI S-ICD System is a treatment option for patients at risk of sudden cardiac arrest, leaving the heart and vasculature untouched. Boston Scientific also received CE Mark approval for the system earlier this year.

FDA Clears Hammertoe Correction System

Centric Medical has been granted a 510(k) marketing clearance for a foot-phalange device for hammertoe patients.

The Hammertoe Correction System is a dual-threaded device and is placed between the proximal and middle phalanges, so that both threads grip the phalangeal canal of the toe and compress the joint. This is an alternative treatment to wire pins, which can break and dislodge.

InSeal Gets CE Mark for InClosure

InSeal Medical has received CE Mark approval for the InClosure vascular closure device.

The device's technology is based on a biodegradable internal membrane that seals the puncture by using blood pressure to improve sealing.

InClosure is implanted percutaneously and requires no pre-procedure. The internal membrane fully biodegrades within several months of the procedure.

Medtronic Gets CE Mark for DBS Software

Ireland-based Medtronic received CE Mark approval for its SureTune2 software for use in deep brain therapy devices.

The software allows for patient-specific visualization during DBS therapy. The therapy device emits mild electrical stimulation to targets in the brain in order to modulate specific symptom control. SureTune2 is currently not approved in the United States.

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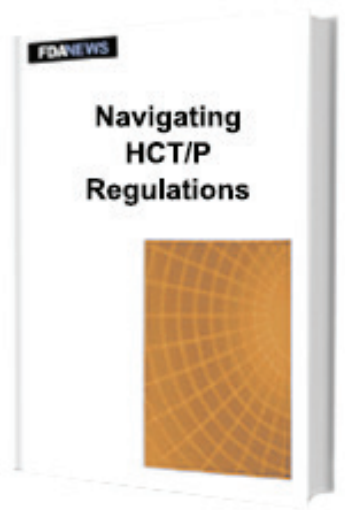

Navigating HCT/P Regulations: *Risks and Opportunities for Drug and Device Manufacturers*

The regenerative medicine industry is rapidly growing and, with major court decisions, new and significant FDA guidance, and government enforcement actions, the regulatory landscape is more complex than ever.

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