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Stakeholders Seek More Clarity On FDA's Combo Products Guidance

Industry stakeholders told FDA that they want to see more clarity on its guidance on combination product premarket reviews.

Issued in February, the draft guidance explained how FDA centers would make approval pathway decisions for drug-device combination products.

The FDA considers that if a product's primary mode of action is a device, then the product would be submitted under a medical device pathway with CDRH; whereas a product with a drug primary mode of action would be submitted under a drug pathway with CDER or CBER.

The Combination Products Coalition (CPC) said in its comments that it believed the guidance has the potential to "drive increased efficiency and consistency in premarket reviews of combination products." But it noted that cross-labeled combination products were "largely excluded from the draft guidance," and it asked the agency

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Canada Details New User Fees For Device Sponsors

Health Canada is increasing fees for device sponsors and will peg ongoing increases to inflation, the agency said in a final report on the planned changes.

Under rules to be phased in over four years from Apr. 1, 2020, device sponsors will have to pay 75 percent of costs for pre-market evaluations, 67 percent of right-to-sell applications and 100 percent for establishment licenses, the agency said in its 50-page report.

"Currently, Health Canada fees are not reflective of the costs to deliver its regulatory programs," the agency said. "New regulatory challenges stemming from increasingly complex submissions; greater risks from counterfeit or contaminated products; and increased volume of products imported into Canada means Health Canada must adapt in

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to provide more guidance on cross-labeling concerns, including issues that would require either one or multiple marketing applications.

The CPC also asked for additional guidance on how to use FDA prior findings of safety or effectiveness or substantial equivalence of an approved constituent part.

For its part, AdvaMed said the draft guidance was too general in parts and that the FDA should clarify that product centers have responsibility and authority for product-specific premarket decisions. AdvaMed flagged several examples of inconsistency in the guidance and asked the agency to "qualify its generalization with the caveat that center staff have authority for premarket review decisions, and they make these decisions on a case-by-case basis."

The association said the guidance should also include a pathway for the use of a device master file for combination products. It said it is not uncommon for drug companies to partner with device companies for containers or delivery devices for drug or biologic products, and a medical device master file "provides a mechanism for the device company to maintain trade secrets or confidential commercial information."

AdvaMed recommended that the FDA adopt mechanisms and infrastructure changes, such as a single portal to store and share information, the ability to cross-reference applications, concurrent reviews and a single point of contact.

The Cook Group encouraged the FDA to regulate low-risk combination products in Class I and Class II under CDRH whenever possible, and to regulate higher-risk Class III devices through the Office of Combination Products.

"Time should not be lost in the approval process determining the primary mode of action when experience has demonstrated the adequacy of regulation under the medical device authorities," Cook said, adding that the FDA's Office of Combination Products "may best service the public by ensuring the agency's drug expertise is properly integrated in the device review process."

Proteus Digital Health applauded the FDA's commitment to enhancing "clarity, predictability, efficiency and consistency of premarket regulatory expectations for combination products." However, Proteus noted the guidance does not specifically address the unique issues related to digital health combination products, which will undoubtedly raise "unique issues and warrant separate applications."

Proteus stressed that digital health tools often change rapidly, and these version changes may represent minor, incremental modifications, and a lengthy review period may result in new versions being stalled before FDA can approve them. The 510(k) and special 510(k) pathways may be the only appropriate premarket pathways for digital health component(s) of a combination product, Proteus said.

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order to continue maintaining the effective and efficient delivery of its regulatory activities."

The agency currently recoups about 43 percent of its operating costs through sponsor fees, whereas regulators in Australia and Europe, for instance, recoup all of their costs from sponsor fees.

Health Canada initially proposed setting fees at 90 percent to 100 percent of operating costs but relented following strong pushback.

The final rules allow carve-outs for small businesses—defined as companies with fewer than 100 employees or between Can$30,000 and Can$5 million ($22,318 and $3.7million) in annual gross revenues. Small businesses will get their first pre-market application free, then get half off subsequent pre-market applications. They will also get 25 percent discounts for right to sell applications and establishment license fees.

Read Health Canada's final report here: www.fdanews.com/05-17-19-HealthCanadaFinalReport.pdf. — Bill Myers

FDA Finds Quality Lapses at Las Vegas Defibrillator Manufacturer

A litany of quality management lapses landed contract manufacturer Rechargeable Power Energy North America a warning letter following a Nov. 5-9, 2018 FDA inspection of its Las Vegas, Nevada facility.

The company is a contract manufacturer that makes Class III automated external defibrillator (AED) batteries that replace original equipment manufacturer batteries.

FDA investigators found that the firm's battery testing and calibration equipment was not validated to demonstrate that results were repeatable for every battery tested. The firm said in its response to the Form 483 that an independent review would be conducted, and a test would be performed to validate the battery's shelf life.

However, the FDA said the company should provide plans to ensure that its production equipment and software are validated, noting that this was a repeat observation from a January 2016 inspection.

The FDA also cited the firm for not establishing complaint handling procedures, and records of complaints received didn't include an evaluation for medical device reporting to the FDA. This was also a repeat observation.

Procedures to ensure that device history records were maintained were not established, and production records didn't document each step of production to prove the device is manufactured according to the established specifications.

The battery maker had no procedures in place to evaluate suppliers, and it hadn't established procedures for acceptance activities to verify incoming products were inspected and tested. Also missing were CAPA procedures and procedures for quality audits. In fact, the company had never conducted a quality audit. Many of these lapses were also repeat observations.

Read the warning letter here: www.fdanews.com/05-23-19-RechargeablePowerEnergyNAWL.pdf.

FDA Warns Orchid Orthopedic For Documentation Failures

Failure to document re-worked nonconforming products and to establish procedures for controlling process parameters were just a few of the many quality system failures documented in a May 13 warning letter to devicemaker Orchid Orthopedic Solutions following a Feb. 4-15 inspection of its Holt, Michigan plant.

Orchid specializes in applying coatings to orthopedic implants that promote bone growth.

The firm failed to establish adequate procedures to monitor the quality of water used in the device cleaning process during manufacturing, the warning letter says. For example, the water system was not always sanitized, and testing for organic carbon was not always performed.

Additional testing procedures were unclear and Orchid's CAPA procedures didn't analyze sources of quality data to identify existing and potential causes of nonconforming products.

Other citations included failure to validate the manual cleaning process for implants, and there was no assurance that the devices were processed under normal or worst-case operating conditions.

Read the warning letter here: www.fdanews.com/05-23-19-OrchidOrthopedicSolutionsWL.pdf.

Zeller Power Products Slammed With Warning for AED Batteries

Failure to validate the design of its AED batteries, lax complaint handling procedures and numerous other quality system repeat observations resulted in a warning letter for AED maker Zeller Power Products following a Nov. 6-9, 2018 inspection of its Wallace, Idaho facility. The FDA said the firm's response to the Form 483 was not acceptable.

Zeller makes Class III AED batteries to replace OEM batteries used in Cardiac Science PowerHeart AEDs.

(See **Zeller***, Page 4)*

FDA Issues Alert for Beckman Coulter Blood Analyzers

The FDA issued an alert over a recall of Beckman Coulter DxH 800, DxH 600 and DxH 900 blood analyzers, updating an urgent medical device correction letter the company issued following complaints of inaccurate blood platelet counts.

"Inaccurate platelet counts may create serious health risks for patients," said Tim Stenzel, director of CDRH's Office of In Vitro Diagnostics and Radiological Health. The agency is urging health care professionals to "be aware of the potential for inaccurate diagnostic results with these analyzers and to take appropriate actions including the use of alternative diagnostic testing or confirming analyzer results with manual scanning or estimate of platelets."

Beckman Coulter first notified its customers in August 2018 that they had identified a trend of erroneously elevated platelet results. Based on additional information provided by the company to the FDA in April 2019, the agency asked Beckman to provide a second urgent medical device correction letter to customers.

The company has indicated to customers that a software update to the device may serve to alert laboratory personnel to any inaccurate results. But the FDA has not evaluated the software and is working with the company to determine if the software update alone can resolve the matter.

The FDA said it is aware of more than 2,000 laboratories in the U.S. that may be affected, but it hasn't received reports of serious adverse events linked directly to the blood analyzers.

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During the FDA inspection, Zeller was unable to provide documentation validating the shelf life of its batteries as well as the number of shocks as indicated by the device specifications. The firm's management told FDA inspectors that the software installed on the printed circuit board included in each battery were not validated.

The management also told inspectors that the firm had not established design control procedures and was unable to provide documentation of design plans, design inputs, design validation, design reviews or risk analysis.

Procedures for reviewing complaints as well as CAPA procedures had not been established, nor had Zeller established procedures for accepting incoming products. It also had not established procedures to control product that doesn't conform to specifications.

All of these were repeat observations from a previous inspection. The FDA also cited the firm for failing to ensure that labeling met UDI requirements.

Read the warning letter here: www.fdanews.com/05-23-19-ZellerPowerProductsWL.pdf.

Phototherapy Developer Amiss On CAPA, Supplier Audits

Phototherapy developer National Biological Corp. fell short on several quality management systems, the FDA said following a Feb. 4-14 inspection of its Beachwood, Ohio plant.

Validation studies were sloppy in that equipment settings and variables were not used, and not all wire/terminal combinations were tested for the company's phototherapy devices. In addition, the firm's supplier had not validated its process, the Form 483 said.

The facility's corrective and preventive action procedures were also found to be inadequate and more than 1,600 reports of non-conforming material were entered into the database, but many were logged as "scrap" due to damage caused during shipping.

The FDA concluded that the company's risk analysis was inadequate, because there were numerous calculation errors in the failure mode and effect analysis.

National Biological failed to investigate complaint files, and many of them were documented as "results of normal wear," the 483 said. In one case, a sensor was replaced but no investigation was conducted, the FDA said.

In addition, when auditing its suppliers, the firm didn't include significant quality system elements.

Read the National Biological Corp. Form 483 here: www.fdanews.com/05-23-19-nationalbiologicalcorp483.pdf.

Sample Size for Verification and Validation

The ultimate goal of verification and validation testing is to show that there is a minimal risk that a device will not perform as intended. To prove this to the FDA's statistical satisfaction, companies must select sample sizes that will accurately reflect the real risk. To do this, devicemakers need to consider several factors.

These include the product's overall risk profile. "When you get to the verification and validation sample consideration piece, the most important thing is to tie it into your risk management," according to Steven Walfish, president of Statistical Outsourcing Services. "So when you are doing design verification and validation, your design history file and developing a risk plan, the sample size is ultimately going to be tied into that risk plan."

In a nutshell, a company can trade sample size for risk. The less risk a devicemaker is willing to take, the larger the sample size it will need. If more risk is acceptable, a smaller sample size will suffice.

Nonstatistical Techniques

While the bulk of work developing sample sizes for verification and validation testing may center around statistical data and techniques, there are times when a nonstatistical approach—a simple pass/fail, it works or it does not work—is more appropriate. This type of testing can be done on a single unit of a product.

When companies opt to use a nonstatistical method, they must be able to justify that decision. This requires a clear understanding of when nonstatistical techniques are appropriate. Devicemakers must maintain written criteria for when to consider a test to be nonstatistical versus statistical. These criteria can be as simple as a list of the types of tests that a company has deemed to be nonstatistical, Walfish said.

Companies should include the written criteria for statistical versus nonstatistical testing in the validation and verification protocol. The nonstatistical tests may sometimes be referred to as "unit tests," Walfish noted, referring to the ability to get the necessary information by testing just a single unit.

That justification comes down to risk. When the risk to the patient is lower, a nonstatistical unit test is more likely to be appropriate. Sometimes a nonstatistical test can be conducted simply to verify the existence of a feature, for instance. As long as the design includes that feature, and the test indicates that the feature is present, the user requirements have been met.

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

Singapore Diagnostics Maker Fails To Establish SOPs for Investigations

Failure to establish standard operating procedures for investigations landed Singapore-based diagnostics maker MP Biomedicals Asia Pacific in hot water with the FDA following a Dec. 10-12, 2018 inspection of its Singapore facility.

Recurring events such as dirty marks on nitrocellulose strips were identified, but a protocol defining when investigations should be conducted had not been developed, the 483 said.

Complaint records at the Singapore-based firm were found to be deficient in that they didn't include findings and trend analyses, and CAPA procedures were not initiated.

The FDA said there were "no scientific justifications for the production process non-conformance report … for recurring investigations regarding patches and dirty marks on the HTLV Blot 2.4 Western Blot Assay Nitrocellulose antigen strips."

Read the MP Biomedicals Form 483 here: www.fdanews.com/05-23-19-biomedlcalsasiapacificpteltd483.pdf.

Sloppy Validation, Complaint Handling Found at Duke Empirical

Process validation issues and failure to document complaints and corrective and preventive actions landed devicemaker Duke Empirical an FDA Form 483 following a Dec. 3-21, 2018, inspection of its Santa Cruz, California plant.

From eight customer complaint reports, three stated that a CAPA would not be documented, but corrective measures were implemented with no effectiveness checks conducted. The company specializes in medical device tubing and catheter components.

"A CAPA will not be issued since this is an isolated incident and not a systemic issue. Patient risk is low due to multiple inspection points where this non-conformance would be detected prior to patient contact," one report said.

The report added that the complaint was reviewed with all inspectors to raise awareness of the issues observed. However, no documentation was available to show whether this action was effective in identifying the non-conformities. Two similar entries were noted on the Form 483 justifying why CAPAs were not opened for non-conforming products.

During a review of Duke's production and process control subsystem for its extrusion process for extrusion tubing, no documentation or evaluation was available to confirm if the process of disassembling and reassembling certain extruders would have an effect on the validated process, the 483 said.

Finally, inspectors noted that no complaint reports were generated for 14 supplier corrective action requests, and no explanations were given as to why investigations were not conducted.

Read the Duke Empirical Form 483 here: www.fdanews.com/05-23-19-dukeempiricalinc483.pdf.

BRIEFS

FDA Flags Unauthorized Devices For Diabetes Management

The FDA warned that some manufacturers have been marketing illegal diabetes management devices, including automated insulin dosing systems and insulin pumps. Components used with other devices, such as continuous glucose monitors, have also been unlawfully marketed, the agency said.

The products haven't been evaluated by the FDA for safety and effectiveness and can potentially pose serious risks to diabetic patients, such as inaccurate glucose level readings or unsafe insulin dosing.

Using unapproved or unauthorized devices for managing diabetes could lead to serious injury or death as their safety and effectiveness hasn't been confirmed by the FDA, the agency said in a safety notice.

"The FDA will continue to closely monitor reports of adverse events associated with the use of unauthorized devices for diabetes management and will keep the public informed if new information becomes available," the agency said.

TÜV SÜD Gains Second EU MDR Designation

TÜV SÜD Product Service has become the second notified body to be accredited under the EU's new medical device regulation (MDR), meaning the product certifier is now authorized to provide certification services under the new MDR.

European device groups such as the European Association for Medical Devices of Notified Bodies (Team-NB) are alarmed at the shortage of notified bodies to conduct audits and certify devicemakers in time to comply with the new regulations. In January, Team-NB said the May 2017 to May 2020 implementation period was too short, given that many details for both manufacturers and notified bodies are still under discussion (*IDDM*, Jan. 4).

In April, MedTech Europe warned that the EU's new regulatory system for devices won't be ready on time (*IDDM*, April 26).

APPROVALS

FDA Clears ControlRad's C-Arm Radiation Reducer Solution

The FDA granted ControlRad 510(k) clearance for its ControlRad Trace technology that is integrated into mobile C-arms to reduce radiation during fluoroscopic imaging procedures.

Trace is designed to reduce the ionizing radiation patients and radiologists are exposed to during procedures, which can increase their lifetime risk of cancer. Radiation produced during C-arm procedures can also increase a patient's risk of cataracts, atherosclerosis and strokes.

The company says ControlRad Trace reduces radiation up to 89 percent without compromising image quality or workflow.

Kurin's Blood Culture Contaminant Diverter Gets CE Mark

Kurin has earned the CE Mark for its Kurin Lock, allowing the devicemaker's FDA-cleared blood culture collection sets to be marketed in the European Economic Area with the novel contaminant diverter.

The Kurin Lock specimen diversion device works with Kurin's blood culture set to automatically divert the initial portion of blood in each draw, which can contain potential contaminants.

Patients may be exposed to unnecessary antibiotics as a result of contaminated blood cultures, the company said, which can also lead to extended hospital stays.

Stryker Grabs PMA For Aneurysm Adjunctive Stent

The FDA has granted Stryker premarket approval for its Neuroform Atlas aneurysm adjunctive stent for treating wide-neck, intracranial aneurysms.

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The self-expanding nitinol stent is approved for use alongside metal coils to pack weakened blood vessels in the brain. It received prior approval under a humanitarian device exemption, confining its use to approved hospitals.

The stent features improved conformability and a "low-profile" delivery system that assists in the treatment of difficult aneurysms.

FDA Clears MagStim's Horizon Performance Platform

MagStim has earned the FDA's go-ahead for its Horizon Performance platform, a device used to treat patients with depression through magnetic pulse therapy.

By using transcranial magnetic stimulation, the device allows patients to avoid the side effects of drugs and invasive treatments.

The platform has been used in situations where antidepressant treatments are ineffective and before therapies such as electroconvulsive therapy are considered.

Qiagen's Syndromic Testing System Cleared by FDA

The FDA granted Qiagen 510(k) clearance for its QIAstat-Dx syndromic testing system and respiratory assay panel for detection of multiple respiratory viral and bacterial pathogens. The panel provides simultaneous testing for more than 20 pathogens.

Syndromic testing with molecular diagnostics can identify illnesses that manifest as a set of symptoms with uncertain causes, such as influenza or pneumonia.

Qiagen said it expects to release numerous diagnostics for infectious diseases, oncology and other areas. The company plans to launch a gastrointestinal panel later this year.

The QIAstat-Dx system earned a CE-IVD Mark in January 2018.

DiaSorin Molecular's Herpes Assay Grabs CE Mark

DiaSorin Molecular earned the CE Mark for its Simplexa HSV 1/2 and VZV Universal Direct MDx assay, a diagnostic for the herpes simplex and varicella-zoster viruses.

The assay is designed for use on the device-maker's Liaison MDx instrument. It can detect and differentiate between DNA associated with herpes 1 and 2 and the varicella-zoster virus, which causes shingles and chickenpox.

The real-time PCR assay does not require upfront extraction, produces results in about an hour and involves minimal hands-on interaction.

Flat Medical's Epidural Protector Cleared by FDA

The FDA granted Flat Medical with 510(k) clearance for its EpiFaith syringe, a device used for delivering safe epidural injections.

The indicating syringe is a physician-oriented safeguard for epidural analgesia during labor, chronic pain management and surgical anesthesia.

The device alerts anesthesiologists to the moment it has arrived at the epidural space, avoiding the risk of paralysis, prolonged admission times and associated costs.

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Device Software Development: *A Guide to Risk Management Requirements*

Medical device risk management — specifically device *software* risk management — calls for a solid understanding of a myriad of requirements.

The FDA Quality Systems Regulation, ISO 14971, the new EU Medical Device Regulation all stress the importance of building risk management into the development process of software that will be used in or as a medical device.

Device Software Development — based on a presentation by quality systems expert Dan O'Leary — is a comprehensive, point-by-point guide to developing software that meets all FDA and international standards for successful market clearance. You'll learn:

- Which ISO standards touch on software development and risk management and what guidance is available
- What requirements the new EU MDR places on software development
- How to assess the level of a hazard's severity
- How to identify software's safety classification
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