INTERNATIONAL DEVICES & DIAGNOSTICS MONITOR

Vol. 5, No. 18
Sept. 16, 2019

IN THIS ISSUE

FDA Seeks Input on Risk-Benefit Reviews for Weight Loss Devices

The FDA laid out its latest thinking on how it will handle risk-benefit reviews for weight-loss devices in a new discussion paper released ahead of planned draft guidance.

Weight-loss devices are an option for patients who have not responded to conservative medical interventions such as drugs, but who want an alternative to bariatric surgery, the agency said.

The FDA "continues to receive a high volume of pre-submissions from industry requesting feedback about the necessary data to support pivotal clinical studies and marketing applications for a wide variety of device designs intended for weight loss," the agency said.

The paper lists factors for consideration as part of the weight-loss device risk-benefit evaluation process. The agency is considering placing devices into one of four benefit categories based on the amount of weight loss demonstrated in a clinical study and the duration of device use.

(See **Weight**, *Page 2)*

FDA's Guidance on Prostate Tissue Ablation Devices Called 'Too Restrictive'

The FDA's draft guidance on clinical testing for prostate tissue ablation devices is too restrictive, industry groups said in written comments to the agency.

The draft guidance provides clinical testing recommendations for devicemakers seeking a general indication for ablation of prostate tissue, whether by high intensity ultrasound or alternative technologies. The FDA said the guidance is intended for a general indication for ablation of prostate tissue and does not address treatment for a specific disease such as prostate cancer.

AdvaMed said it generally supports the FDA's approach in the draft, but it called for some changes to the draft guidance CDRH

(See **Prostate**, *Page 2)*

Weight, *from Page 1*

So far, CDRH has approved nine devices for weight loss. Five are intragastric implants, two are restrictive bands and one is an aspiration therapy system. One device, EnteroMedics' Maestro neuromodulator, was voluntarily removed from the market.

The FDA has held a series of public workshops on the risks and benefits of weight-loss devices. It also consulted with experts about products on the market for insights on adverse events and risk-benefit analyses.

A common understanding of factors that contribute to benefit-risk profiles "would hopefully translate into improving the predictability, consistency and transparency of the review process for all stakeholders in the weight-loss device space while improving patient access to quality therapy," CDRH said.

The comment deadline is Dec. 4. Read the FDA discussion paper here: www.fdanews.com/09-12-19-DiscussionPaper.pdf.

Prostate, *from Page 1*

released in June. The agency had recommended a dataset of a minimum of 100 patients, and AdvaMed said that companies should have the opportunity to present other dataset sizes based on "clinically relevant information," including historical data, clinical studies, literature reviews and other real-world evidence.

The association also said the FDA's study duration of one year of follow up was too restrictive, because "adverse events do not follow a linear progression and should be based on a clinically relevant timepoint." AdvaMed said that depending on the type of prostate ablation being used, the adverse event profile may differ in onset and duration.

It also took issue with language the FDA used in the guidance regarding "endpoints that may be considered for malignancy," particularly when the agency specifically said the guidance was intended for general indications only.

The Medical Imaging and Technology Alliance (MITA) said it didn't agree with requiring one type of effectiveness endpoint such as a biopsy, particularly when "other alternatives are just as effective at measuring the extent of ablation such as post-ablation MRI imaging."

MITA also said that language in the guidance was confusing when it came to "externally controlled trials." The association said that it interpreted this to mean "trials that compare device-specific collected data against data from respected historical data or propensity matched trials." The association said it did not support internally controlled trials, saying they are rarely performed successfully.

Read the draft guidance and comments here: www.fdanews.com/09-13-19-Comment.pdf.

CDRH Finalizes Recommendations On De Novo Requests

The FDA finalized three guidance documents related to de novo classification requests for clearance when there is no predicate device for comparison.

In final guidance on its acceptance review for de novo classification requests, the FDA lays out its minimum threshold of acceptability to evaluate de novo requests for automatic Class III designations. The document provides an acceptance checklist for devicemakers and a recommended content checklist to use when submitting de novo requests.

The agency said that all elements identified as acceptance items should be included in the application to be deemed acceptable, or the devicemaker should justify why these items are not included in the application. The acceptance review should be conducted within 15 days for original de novo requests, and the agency clarified that acceptance reviews are conducted to assess whether de novo requests contain the needed information to conduct a substantive review.

The final guidance also includes preliminary questions to be answered by the agency's lead reviewer to serve as an initial screening for the acceptability of the de novo request. Most of the questions cover whether the device is a combination product and which center should be conducting the review.

A second guidance covers the review clock and goals established under MDUFA IV. For de novo decisions, the review clock is set at 150 days. If a final decision has not been made within 180 days, the FDA will meet with the applicant to discuss any outstanding issues.

The third guidance covers user fees and refunds for do novo requests. The guidance discusses the types of de novo requests subject to user fees, exceptions to user fees and actions that may result in refunds of fees that have been paid.

Read the three guidances here: www.fdanews.com/09-12-19-Guidances.pdf.

FDA Issues Warning To Indiana Devicemaker

The FDA issued a warning letter to Polymer Technology Systems — doing business as PTS Diagnostics — arising from an inspection earlier this year of its facility in Indianapolis.

The agency investigators found that the company's in vitro diagnostics for diagnosis and management of diabetes, heart disease, kidney function and other chronic diseases were adulterated because the facility was not in compliance with good manufacturing practices.

Problems identified included failure to ensure that a device conformed to specifications, failure to adequately validate a process whose results cannot be fully verified by subsequent inspection and test, failure to validate or verify design changes, and failure to establish and maintain procedures for corrective and preventive actions.

Read the full warning letter here: www.fdanews.com/09-10-19-PolymerTechnSysWL.pdf.

CDRH Posts New Guidances On 510(k) Submissions

As part of its ongoing overhaul of the 510(k) process, CDRH released finalized guidances on its special 510(k) and abbreviated 510(k) programs, on its refuse-to-accept policy for 510(k)s and on formatting recommendations for submissions.

The programs are evolving to reflect advances in materials, digital health, 3D printing and other technologies, as the agency moves ahead with its Medical Device Safety Action Plan unveiled last year.

"The most impactful way that we can promote innovation and improved safety in the 510(k) program is to drive innovators toward reliance on more modern predicate devices or objective performance criteria when they seek to bring new devices to patients," said CDRH Director

(See **510(k)**, *Page 4)*

510(k), *from Page 3*

Jeffrey Shuren, in announcing new steps to modernize the program late last year.

The Special 510(k) program previously only covered reviews of changes that didn't affect the device's intended use or alter its base technology. Now, the agency is focusing on whether the change evaluation methods are well-established. The final guidance clarifies the FDA's policy on changes that are appropriate under the program.

CDRH says the new policies regarding the factors to consider when determining if a change to an existing device can be submitted through the Special 510(k) pathway will be "operationalized immediately."

The final guidance on the Abbreviated 510(k) program, which establishes substantial equivalence based on special controls or voluntary consensus standards, supplements other 510(k) guidances with information on specific submission requirements and recommendations.

The refuse-to-accept policy for 510(k)s guidance explains the agency's procedures and criteria for accepting 510(k)s for substantive review. It describes the content required in traditional, abbreviated and special 510(k) submissions to enable the agency to conduct timely reviews.

The review process "is captured in the acceptance checklists for traditional, abbreviated, and special 510(k) submissions, which FDA staff will use during the acceptance review process," the guidance says.

Although the new policy goes into effect immediately, CDRH anticipates that "both FDA and industry may need up to 60 days to operationalize the associated updates to the refuse-to-accept guidance."

Until Nov. 13, 2019, once the agency has determined a submission is appropriate for review as a Special 510(k), it intends to use the prior final refuse-to-accept guidance to assess whether a submission meets a minimum threshold of acceptability and should be accepted for review.

The final guidance on how to format traditional and abbreviate 510(k)s — which replaces November 2005 guidelines — describes 20 sections each submission should include and lists resources for further information. The document provides "a general framework" and doesn't get into specific device types, special 510(k)s or other submission types.

Read the Special 510(k) guidance here: www.fdanews.com/09-13-19-Special510kProgram.pdf.

Read the Abbreviated 510(k) guidance here: www.fdanews.com/09-13-19-Abbreviated510k.pdf.

Read the Refuse to Accept policy guidance here: www.fdanews.com/09-13-19-RefuseAccept510k.pdf.

Read the formatting guidance here: www.fdanews.com/09-13-19-format510kguidance.pdf.

— James Miessler

483 Roundup: FDA Hits Three Firms For Quality Management Lapses

Lusys Laboratories: A 16-item Form 483 highlighted a litany of QMS lapses uncovered at Lusys Laboratories' San Diego, California plant during a Jan. 22-Feb. 7 FDA inspection.

The agency investigator found inadequate risk analysis, design controls and acceptance activities, failure to maintain a device master record, and failure to establish procedures for corrective and preventive actions.

The company manufactures IVDs for detecting hepatitis C virus, hepatitis B virus, human immunodeficiency virus, prostate specific antigen and Ebola virus.

Design control procedures didn't provide instructions on how to perform and document design validation activities, and the risk analysis was inadequate, the investigator said. Lusys didn't identify each potential failure mode for its IVD devices, the cause for the failure and the impact that the failure may have on the system and the end user, the agency said.

"Your risk analysis for these devices state that 'no risk factors are expected in the design and

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

How to Maintain Complaint Files

A robust complaint handling process includes four broad stages:

- Receipt and documentation of a complaint;
- Evaluation of the complaint for validity and reportability;
- Investigation into the causes of the problem detailed in the complaint; and
- Action to remediate those causes.

One of the complaint unit's chief responsibilities is to maintain complaint files, which are the records documenting all analysis conducted and actions taken when a company receives a complaint about a device.

Complaint handling procedures should lay out the structure of the complaint files in a way that will help ensure regulatory compliance and aid efficient management of the complaint process. That means devicemakers need file layouts that make it easy for the responsible staff to handle complaints. Each complaint record in the file should:

- Include a clear history of the process steps used to handle the complaint;
- Facilitate complaint analysis; and
- Link to any MDR event file record.

This can be achieved using an electronic system that employs such commonly used software as Excel or Access. However, any software used must be validated in accordance with 21 CFR 820.70(i), which addresses validating software for device manufacturing processes. This applies to custom software developed in-house, as well.

The Complaint Path

Regardless of the system used, an effective and compliant process will follow a certain pathway. When a manufacturer receives a complaint about a device, whether it is written, electronic or oral communication, the trained employees in the designated complaint unit must immediately take action.

Devicemakers need to note that complaints may come in to any part of a company. The complaint-handling process must include systems for funneling all complaints, regardless of where they are initially sent, into the designated unit.

For example, sales representatives and the people who service and maintain manufacturing equipment need to be trained in how to recognize a complaint and how to feed it back to the designated complaint unit.

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

483s, *from Page 5*

development of the products[s]' and that 'the user may experience false positive, false negative or invalid results,'" the 483 noted.

The firm didn't document activities or maintain raw data to demonstrate that its equipment could consistently perform according to predetermined parameters. It also didn't establish procedures for acceptance activities, nor had it adequately maintained a device master record, according to the 483.

In addition, the firm had not initiated any corrective and preventive actions for nonconformities that were identified in 483s issued in 2015 and 2018. In addition, the company received a warning letter in 2015 for many of the same violations.

The firm was found to be lax in establishing QMS procedures such as management reviews, quality audits, document control procedures and personnel training.

New Life Diagnostics: Numerous quality management system lapses, including inadequate process control procedures and failure to initiate corrective and preventive actions were uncovered during a Feb. 25-27 FDA inspection of New Life Diagnostics' Carlsbad, California plant.

The firm, which develops and manufactures a range of in vitro diagnostics for laboratory use, had not established quality control procedures that describe process controls to ensure conformance to specifications, the 483 said. Specifically, the IVD maker had not established quality control testing and product retention procedures for panel characterization and qualification and documentation of samples used in manufacturing and testing its ELISA IVDs.

Also lacking were procedures to ensure that equipment was routinely calibrated, inspected, checked and maintained. There was no documentation of installation qualification of one of the readers used to read microplate absorbance values of positive and negative control samples.

The standard operating procedure in question lacked "specific directions and limits for accuracy and precision, nor did it include provisions for remedial action to re-establish the limits to evaluate whether there was any adverse effect on the device's quality," the FDA said.

The IVD maker had no documentation for qualification of its suppliers, and acceptance activities were not documented. In addition, it failed to initiate CAPAs for nine complaints.

Stetrix: Design verification and validation procedures were found to be lax during a Feb. 5-6 FDA inspection at Stetrix's Bartlett, Tennessee facility.

The design inputs for the Class II Hem-Avert peri-anal stabilizer were not adequately defined and documented, and they didn't address requirements for physical and performance characteristics, sterility shelf life, labeling or packaging, and design inputs were not reviewed and approved by a designated person, the FDA said.

The specification developer failed to adequately document the design history file to confirm that design output met design input requirements. This was a repeat observation from a Nov. 7, 2008 inspection, and the firm was still unable to demonstrate that acceptance criteria was established for a verification study.

In addition, the facility couldn't demonstrate acceptance criteria were established prior to the validation study, and results were not documented in the design history file.

The firm failed to evaluate potential risks associated with the sterility of the device and with a new indication for use in reducing the occurrence of caesarean delivery, the FDA said.

Read the Lusys Laboratories Form 483 here: www.fdanews.com/09-12-19-lusyslabsinc483.pdf.

Read the New Life Diagnostics Form 483 here: www.fdanews.com/09-12-19-newlifediagnosticsllc483.pdf.

Read the Stetrix Form 483 here: www.fdanews.com/09-12-19-stetrixinc483.pdf.

Russia Implements New Quality Control Requirements

Russia's Ministry of Health has rolled out new requirements for internal quality control and monitoring of the safety of devices in medical facilities.

The authority also plans to conduct scheduled and unscheduled inspections of medical facilities for quality and safety. It will also collect statistical data on the quality and safety of medical activities, including adverse events.

Medical organizations will have to provide the agency with information on their monitoring of device safety and on the availability of devices.

The requirements were approved following a pilot project that began in 2016, which showed positive results in improving the quality and safety of medical devices. Currently, more than 140 medical organizations in the Russian Federation have signed on for the new controls.

All medical devices in the Russian Federation must be registered with Roszdravnadzor, Russia's Federal Service for Surveillance in Healthcare.

The head of Roszdravnadzor, Mikhail Murashko, called internal controls for quality and safety "the basic level" of control underpinning the system.

APPROVALS

HemoSonics' New Diagnostic For Hemostasis System Gains CE Mark

HemoSonics has gained the CE Mark for its QStat Cartridge, allowing its Quantra Hemostasis System to be used in trauma surgery and liver transplants settings in hospitals.

The disposable cartridge offers a panel of blood tests for gauging clot time, clot stiffness, fibrinogen and platelet contribution to clot stiffness and clot stability to lysis.

All tests except the clot stability to lysis diagnostic take 25 minutes or less to produce results, which are read on a user-friendly dials interface that requires little training, the device-maker said.

FDA Grants Breakthrough Status For Electrostimulation System

Checkpoint Surgical has earned the FDA's breakthrough designation for its brief electrostimulation therapy system (BEST), a device designed to treat nerve injuries.

The device is intended to be used in combination with surgical intervention following nerve injury to speed up patient recovery.

BEST uses low-level electrical currents to stimulate a patient's peripheral nerves and encourage nerve regeneration.

EBR Systems Nabs Breakthrough Status For Wireless Cardiac Pacing System

EBR Systems' WiSE (wireless stimulation endocardially) cardiac resynchronization therapy (CRT) device has earned breakthrough designation from the FDA for treating heart failure.

The wireless device synchronizes the heart's left and right ventricles to more efficiently distribute blood, improving its pumping ability. The system controls pacing through the use of a wireless electrode.

The system is implanted in the left ventricle wall in a minimally invasive procedure, giving better options for pacing locations.

Exact Imaging's Transperineal Needle Guide Grabs CE Mark

Exact Imaging has received the CE Mark for its sterile transperineal needle guide for use with its EV29L transducer on the ExactVu micro-ultrasound system.

The device allows urologists to conduct targeted prostate biopsies using Exact Imaging's micro-ultrasound device for transperineal-based biopsies.

The needle biopsies take prostate tissue samples for microscopic examination to look for cancer cells.

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

Approvals, *from Page 7*

Netech Grabs FDA Clearance For Defibrillator/Pacemaker Analyzer

Netech has received 510(k) clearance for its Delta 3300 device, a defibrillator and pacemaker analyzer that tests and validates the functions of semi-automated and automated defibrillators.

The portable product also measures external pacemakers.

The device tests for various metrics, including energy, peak discharge voltage and the simulation of ECG and arrhythmia waveforms, among others.

Bardy's 14-Day Ambulatory Cardiac Patch Monitor Cleared

The FDA granted Bardy Diagnostics 510(k) clearance for the 14-day version of its Carnation Ambulatory Monitor (CAM) patch, a wearable device used to diagnose arrhythmia and assist in patient management.

The extended wear version detects and records the P-wave, a small amplitude signal of the ECG originating in the heart's upper chamber. The wave is important in accurately diagnosing arrhythmia, Bardy said.

The new version uses the same P-wave focused technology as the company's two- and seven-day CAM patches. Its extended duration may help detect less frequent arrhythmias, the company said.

FDA Clears Masimo's Updated Cerebral Oxygenation Monitor

The FDA has cleared additional measurements by Masimo's O3 cerebral oxygenation monitor, enabling the device to show more information on changes in the blood used to calculate cerebral oxygen saturation.

The agency has cleared the indices for changes in deoxyhemoglobin, oxyhemoglobin, and the sum of deoxyhemoglobin and oxyhemoglobin.

The O3 uses spectroscopy to monitor cerebral oxygenation in situations where peripheral pulse oximetry may not fully indicate oxygen levels in the brain, the company said.

FDA Hands SoniVie Breakthrough Designation for PAH Treatment

The FDA granted SoniVie breakthrough device designation for its Therapeutic Intravascular Ultrasound (TIVUS) system in patients with pulmonary arterial hypertension.

The system, a dedicated ultrasound catheter, is placed in the pulmonary artery during a heart catheterization procedure to ablate nerves associated with the disease's effects.

The debilitating, life-threatening rare disease occurs when patients have high blood pressure in the vessels that move blood from the heart to the lungs.

Occlutech Grabs CE Mark For Atrial Flow Regulator

Occlutech's atrial flow regulator device has been cleared on the European market for treating heart failure symptoms through decompression.

The intra-atrial shunt is placed in the patient's septum between the left and right atriums via a minimally invasive procedure to decompress abnormal pressure.

The device comes in a variety of sizes to allow individualized treatment.

FDANEWS
wcg market intelligence & insights

Customer Service
(888) 838-5578 • +1 (703) 538-7600
customerservice@fdanews.com

Editorial: Declan Conroy
+1 (703) 538-7644
dconroy@fdanews.com

Ad Sales: Jim Desborough
+1 (703) 538-7647
jdesborough@fdanews.com

Multi-User Sales: Bailey Sterrett
+1 (703) 538-7637
bsterrett@fdanews.com

300 N. Washington St., Suite 200 • Falls Church, VA 22046-3431 • www.fdanews.com

Reporters: James Miessler, Jordan Williams, Colin Stoecker

President: Cynthia Carter

FDANEWS

Complaint Management for Devicemakers: *From Receiving and Investigating to Analyzing Trends*

Complaint management is essential to a functioning quality management system.

Understanding the FDA's Quality System Regulation isn't enough — you must also master ISO 13485:2016 and the new EU MDR. They all require devicemakers to conduct trending in some form or another. But none of them tell you HOW.

This new edition of the best-selling **Medical Device Complaint Management** fills in that gap for you.

In addition to teaching the principles of successful complaint management …

- Receiving, documenting and investigating complaints
- Determining when complaints are reportable
- Using complaints to update risk management data …

… the new report teaches you how to analyze trends in your complaint files to spot opportunities for product and program improvement.

You'll learn:

- The difference between a record and a report
- Acceptable trend analysis methods (NEW)
- How not to write yourself into a corner on complaint SOPs
- And more…

It's certain that your complaint management system will come under intense scrutiny in your next GMP inspection. Make sure you can show investigators not only how you have reacted to problems but also how you learn from them and use that information to drive continual improvement.

FOUR EASY WAYS TO ORDER

1. **PHONE:** Toll free (888) 838-5578
   or +1 (703) 538-7600
2. **WEB:** www.fdanews.com/54565
3. **FAX:** +1 (703) 538-7676
4. **MAIL:** FDAnews
   300 N. Washington St., Suite 200
   Falls Church, VA 22046-3431

☑**Yes!** Please send me ____ copy(ies) of ***Complaint Management for Devicemakers: From Receiving and Investigating to Analyzing Trends*** at the price of $397 for each PDF.

Name _____

Title _____

Company _____

Address _____

City_____ State _____ Zip code _____

Country _____

Telephone _____

Fax _____

Email _____

METHOD OF PAYMENT

❑ Check enclosed (payable to FDAnews)

❑ Bill me/my company. Our P.O.# _____

❑ Charge my credit card:
❑ Visa ❑ MasterCard ❑ American Express

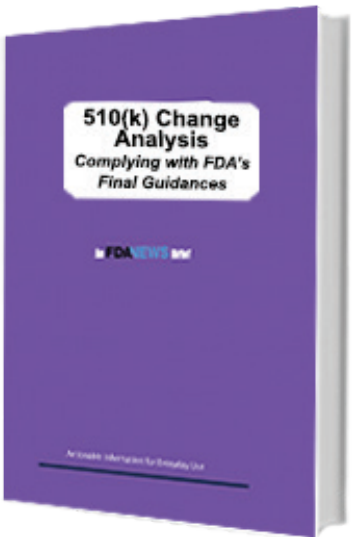
Credit card no. _____

Expiration date _____

Signature _____
(Signature required on credit card and bill-me orders)

Virginia customers add 6% sales tax.

19FLYR-N



510(k) Change Analysis: *Complying with FDA's Final Guidances*

510(k) Change Analysis: *Complying with FDA's Final Guidances* breaks down the guidances finalized in October, 2017 — *Deciding When to Submit a 510(k) for a Change to an Existing Device* and *Deciding When to Submit a 510(k) for a Software Change to an Existing Device* — and provides a step-by-step method for making the right call for submitting a new 510(k) application. Expert-developed spreadsheets walk you through the questions you must ask and lead you to the proper conclusion.

After reading this book, you'll understand:

- What kinds of changes trigger the need for a new 510(k) application and which don't
- How to evaluate the effect of the change on the device's safety and effectiveness
- How to assess the risk the change may introduce
- The components of risk as described in ISO 14971
- How to follow the complex flowcharts the guidances present
- How to develop a risk matrix
- How to document the decision-making process, including justifying a decision not to file a new 510(k)

In addition to the decision-making spreadsheets that all but do the work for you, the report includes copies of both guidances and an example of a change analysis effort.

Order your copy of the **510(k) Change Analysis** brief for step-by-step instruction on deciding whether you need to submit a new 510(k) if you change an existing device.

FOUR EASY WAYS TO ORDER

1. **PHONE:** Toll free (888) 838-5578 or +1 (703) 538-7600
2. **WEB:** www.fdanews.com/55213
3. **FAX:** +1 (703) 538-7676
4. **MAIL:** FDAnews 300 N. Washington St., Suite 200 Falls Church, VA 22046-3431

☑**Yes!** Please send me ____ copy(ies) of ***510(k) Change Analysis: Complying with FDA's Final Guidances*** at the price of $197 for each PDF.

Name _____

Title _____

Company _____

Address _____

City_____ State _____ Zip code _____

Country _____

Telephone _____

Fax _____

Email _____

METHOD OF PAYMENT

❑ Check enclosed (payable to FDAnews)

❑ Bill me/my company. Our P.O.# _____

❑ Charge my credit card:
❑ Visa ❑ MasterCard ❑ American Express

Credit card no. _____

Expiration date _____

Signature _____
(Signature required on credit card and bill-me orders)

Virginia customers add 6% sales tax.

19FLYR-N