INTERNATIONAL DEVICES & DIAGNOSTICS MONITOR

Vol. 4, No. 49
Dec. 10, 2018

IN THIS ISSUE

FDA to Address 'Narrow' Labeling Of In Vitro Companion Devices for Cancer Drugs

The way in vitro companion diagnostics for cancer drugs are labeled sometimes presents a challenge for oncology care, Commissioner Scott Gottlieb said last week in unveiling new guidance to tackle the problem.

Because in vitro diagnostic test approvals are frequently supported by the studies of one specific drug, the labeling often reflects the diagnostic's use with just that medicine. As a consequence, the drug's labeling can also reflect its use with only that test.

Gottlieb noted an increase in new drugs targeting specific molecular markers that drive the growth and spread of cancer, sometimes with multiple drugs in a class of medicines targeting the same marker nearly the same way. Because of this, a diagnostic test that helps deliver one specific drug could be well-equipped to guide the delivery of all drugs in that class, he said.

(See **IVDs**, *Page 2)*

Device Groups Reject Media Reports Of Inadequate Oversight

International medical device associations rejected a recent report by the International Consortium of Investigative Journalists (ICIJ), which pointed to inadequate oversight of devices globally.

More than 250 journalists from 36 countries combined safety data and adverse events reports to cross-reference approval records, malfunctions, injuries and deaths for the report called "The Implant Files."

The report noted that the biggest repository of information is held by the FDA. FDA data "reveals more than 80,000 deaths and 1.7 million injuries possibly linked to medical devices in the past decade," the report said, but noted that many of the adverse events are not transparent to the public.

"Millions of people's lives have been saved or made better by implanted medical devices, but information about the safety of

(See **Oversight**, *Page 4)*

FDA Recognizes First Human Genetic Variant Database

The FDA has recognized, for the first time, a publicly available genetic variants database that can be used to support clinical claims in diagnostic tests.

The agency acknowledged the Clinical Genome Research (ClinGen) consortium's ClinGen Expert Curated Human Genetic Data as the first public database. Genetic test developers, including those who offer next generation sequencing tests, can access the database through ClinVar, an NIH-funded archive.

"The goal of ClinGen is to bring together clinical and research experts to develop standard processes for reviewing data about gene variants and their connections to health and disease," the agency said.

The recognition means that "genetic test developers can use this data to support the clinical validity of their tests, without the need for additional FDA review to confirm the suitability of the database," the FDA said.

IVDs, *from Page 1*

To address this issue, the agency is issuing new draft guidance that aims to make it easier to obtain class labeling on diagnostic tests for oncology treatments. The draft guidance — which expands on existing policy regarding broader labeling — recommends that the companion diagnostic's intended use name the specific group or class of therapeutic products, if there is evidence to show the companion diagnostic is appropriate for use with that group or class.

The guidance cites a specific example to outline the agency's current thinking: companion diagnostics that identify patients with non-small cell lung cancer (NSCLC) whose tumors have the most common epidermal growth factor receptor (EGFR) mutations, and deletions within exon 19 or exon 21 substitution mutations.

It advises that the oncology community would benefit from a companion diagnostic that detects those exon deletions and substitution mutations to "enable greater flexibility for clinicians in choosing the most appropriate therapeutic product based on a patient's biomarker status" — although it notes that labeling for broader use isn't as simple as matching diagnostic and therapeutic targets, an issue it addresses.

"The policy reflected in this guidance, when finalized, will make it easier for providers to use the same test in helping guide the use of a class of oncology therapeutic products, rather than one specific oncology therapeutic product within that class," Gottlieb said. "We're trying to help sponsors more efficiently meet the requirements to support broader labeling."

The commissioner said the agency is worried that the current labeling isn't ideal for patient care because a clinician might need to order a different companion diagnostic with other therapeutic products on its label, or conduct an additional patient biopsy — or both — in order to have additional treatment options.

"The opportunity has arrived, through science, to make sure that the right patient is getting the right treatment at the right time," he said. "Through more modern policies that enable the efficient transition of these technologies we can help more patients live better lives."

Read the draft guidance here: www.fdanews.com/12-06-18-InVitro.pdf. — James Miessler

FDA Warns MiBo Medical For Design Controls, CAPAs

Seven months after issuing a Form 483 to MiBo Medical Group following an inspection of its Dallas, Texas facility, the FDA warned the devicemaker that it had not fully addressed the problems with design control procedures, CAPA procedures or complaints.

After reviewing the firm's initial responses to the May inspection, the FDA found insufficient evidence that the devicemaker had complied with requirements for design controls. The inspectors found the facility lacked a description for design or development activities.

The warning letter also noted that the facility lacked written CAPA procedures. The agency also noted that MiBo provided a list of approved vendors and critical components for its MiBo Thermoflo device, with no effective dates or evidence of review and approval. Two critical components, the AC power cord and rear panel, were listed as supplied by non-approved sources.

The agency also warned the firm for failing to establish procedures for finished device acceptance or protocols or acceptance criteria to ensure they met the criteria or validate test methods for intended use. The letter faulted the firm for its complaint procedures, noting that it had not established procedures or documented any complaints since it began distributing the Thermoflo device in 2014.

The facility also lacked medical device reporting procedures and had no device master record for the Thermoflo device that included the location of all device, quality, production and process, packaging and labeling. No quality policy was available for review during the inspection, and the company could not provide evidence that management had reviewed the quality system.

Read the warning letter here: www.fdanews.com/12-06-18-MiboMedical.pdf. — Zack Budryk

FDA Looks to Devices To Combat Opioid Crisis

CDRH has selected eight medical devices and digital health technologies as potential solutions to help combat the growing opioid crisis in the United States.

CDRH launched an Innovation Challenge in May to spur development of devices, digital health technologies and diagnostics to help detect, treat, and prevent addiction. The agency received more than 250 applications from devicemakers.

"The goal was to provide additional incentives for medical device developers to invest in products that can address the addiction crisis and advance the development of innovative, safe and effective technologies," said CDRH Director Jeff Shuren and CDRH Chief Medical Officer Jonathan Jarow in a joint announcement.

Devices at all stages of development were eligible for the challenge, but firms needed to describe the novelty of their products, the development plan, the team that would be responsible for developing the device, the anticipated benefit to patients and the impact on public health.

The "feasability and the potential impact of the FDA's participation in development to expedite marketing of the device were also factors considered when reviewing the submission," Shuren and Jarow said.

The following devices were chosen under the Innovation Challenge:

- Brainsway Deep Transcranial Magnetic Stimulation device;
- Avanos pain therapy device;
- iPill pill dispenser;
- Masimo's overdose detection device;
- ThermoTek's NanoTherm and VascuTherm systems;
- Milliman's opioid prediction service;
- Algomet RX's rapid drug screen; and
- CogniSense's virtual reality neuropsychological therapy.

(See **Opioid**, *Page 4)*

Oversight, *from Page 1*

devices can be hard to find … even for 250 journalists," the ICIJ report said.

Manufacturers are drawn by Europe's "light-touch regulations," which are less stringent than those of the FDA, the report claimed, pointing to a 2016 ICIJ study showing that devices that were approved first in the EU had a higher rate of safety alerts and recalls than those approved in the United States.

MedTech Europe defended EU regulations, saying the ICIJ's perspective on how the industry works "does not align with ours."

The Implant Files referred to Australia as part of the "free-for-all system," because it relies on Europe to conduct conformity assessments. Only highest risk devices are vetted by the Therapeutic Goods Administration (TGA), and lower-risk devices are audited on a voluntary basis.

Australia's Medical Technology Association of Australia (MTAA) CEO Ian Burgess slammed the report, calling it inaccurate and sensationalist.

He said the inaccuracies would create unwarranted fear that "may cause Australians to avoid seeking treatment that would improve their quality of life." He added that advances in medical technology have "resulted in a 56 percent reduction in hospital stays, 25 percent decline in disability rates, 16 percent decline in annual mortality and increased life expectancy of approximately 3.2 years."

Global Disparities

The ICIJ report pointed to gaping disparities in the way different regions handle recalls and field safety notices. For example, pelvic mesh devices for organ prolapse repair and incontinence were halted by regulators in New Zealand, Ireland, Scotland and England, but continued to be sold in Canada and South Africa and other regions.

Canada's Medical Technology Companies (MEDEC) defended its device regulation saying the medical technology industry has an "extremely strong track record of safety."

MEDEC said that the recent news reports referenced some medical device incidents reported to Health Canada, but that it is not known whether a device was malfunctioning or was the cause of the incident.

"While insights may potentially be found in an incident report, it's important to note that these typically represent a very small percentage of all procedures utilizing a device," MEDEC said, noting that of the hundreds of thousands of hip replacements carried out in Canada every year since 2008, only .03 percent involved potential injury.

Opioid, *from Page 3*

CDRH clarified that not all these products will automatically receive marketing authorizations, but said the devicemakers will receive increased interaction with the center as well as guidance for clinical trial development and expedited reviews. The agency said that breakthrough device designation will be granted as long as they meet the statutory criteria.

"We believe the greatest opportunities for medical devices to help prevent opioid use disorder are devices that could help identify people likely to become addicted, devices that manage pain as an alternative to opioids or reduce the need for opioid medication," CDRH said.

For example, a diagnostic device — such as an in vitro diagnostic or a mobile medical app — could identify patients for whom "extra caution should be exercised when prescribing opioids for acute or chronic pain."

CDRH has cleared more than 200 devices in the last few years related to pain management, and the novel devices may reduce the need to administer opioid drugs for patients suffering from acute or chronic pain.

More than 72,000 Americans died from drug overdoses in 2017, including illicit drugs and prescription opioids, according to the FDA. Opioid use disorder affects more than two million Americans.

Texas Neonatal Devicemaker Falls Short on Process Controls

FDA inspectors found shoddy process controls and a lack of validation documentation in a Sept. 17 to Sept. 21 inspection of Footprint Medical's San Antonio, Texas facility.

The company specializes in silicone and plastic catheter manufacturing for the neonatal and pediatric market.

FDA inspectors noted several process validations in the company's manufacturing process for catheters intended to infuse fluids such as medication and parental nutrition in neonatal and small pediatric patients. For example, documentation of validation for a design change to the molding process didn't include a valid statistical rationale for the number of samples run and the number of samples tested, and it failed to document the date and employee who performed the molding qualification operation.

In addition, documentation of a subsequent validation of the molding process to add a new machine didn't include a performance qualification as required for the addition of new process equipment. A corrective and preventive action was opened in October 2015 when process failures were encountered, and the corrective actions included a change in specifications.

The FDA cited the firm for inadequate risk analysis for the polyurethane peripherally inserted central catheter finished devices for infants. High-risk line items included hazards such as biocontamination, patient infection, catheter embolism, loss of fluid, and requiring medical intervention.

The Form 483 notes that risk probability number scores were exceeded but the firm didn't include documentation of risk reduction or mitigation as required.

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

Timelines for Medical Device Reporting

Manufacturers must submit a Medical Device Report either within 30 days of becoming aware of an adverse event or, in the case of possible "unreasonable risk of substantial harm to the public health," within five days of learning about the event.

A manufacturer may report under a 30-day timeframe when it becomes aware of information that suggests one of its devices may have caused or contributed to a death or serious injury, or one of its products has malfunctioned and that device — or a similar device marketed by the company — would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The FDA places a lot of emphasis on the words "may have caused or contributed to." It is the manufacturer's responsibility to completely rule out a causal connection between its device and the event.

The second category of MDR report is a 5-day report. They must be filed when the company becomes aware that a reportable event — obtained through information from any source, including trend analysis — necessitates remedial action to prevent an unreasonable risk of substantial harm to the public health. The FDA can also request a 5-day report from a devicemaker if the agency feels the risk is high.

Pay particular attention to the phrase "becomes aware of" in both the 30-day and 5-day report requirements. In the case of 30-day reports, this applies to any employee of the manufacturer who receives information about or witnesses a reportable event. The clock starts when that employee discovers the event, not when the department responsible for MDRs receives the information.

But in the case of 5-day reportable events, the countdown begins when a person qualified to judge the severity of risk receives information about the event. This could be an employee with management of or supervisory responsibilities over regulatory, scientific or technical staff or someone whose job relates to reporting adverse events.

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

Controls Found Lacking At Contract Manufacturer Thatcher

Contract manufacturer Thatcher Company failed to exercise appropriate controls over computers and related systems to assure that changes in production were only instituted by authorized personnel, FDA inspectors found during a Sept 10 to Sept. 18 inspection of the firm's Salt Lake City, Utah, facility.

The inspector reviewed data for certain PCMX Scrub products and found 52 events listed as a deleted result. The firm's quality director and a lab analyst were "unable to explain what 'deleted result' meant and they were unable to provide records or documentation explaining the events," the 483 said.

The method validation final report for an alternate method for the same product showed that spreadsheets were used to perform calculations but the spreadsheets were not checked or controlled.

The FDA inspector noted several deviations from written production and process control procedures were not recorded or justified. One example showed a change control, but there was no record of additional process validation studies.

Read the Thatcher Company Form 483 here: www.fdanews.com/12-06-18-thatcherco483.pdf.

483, *from Page 5*

Footprint Medical's medical device reporting procedure didn't include a standardized review for determining when events were reportable. The inspectors said that 11 of 11 complaints for failures of PIIC catheter finished devices such as leaking at the hub and catheter breaks did not include documentation of a review and evaluation for MDR reportability.

The FDA found that the firm's process control procedures for manufacturing the polyurethane catheters were not sufficient to ensure that the device conformed to its specifications.

Read the Footprint Medical Form 483 here: www.fdanews.com/12-06-18-footprintmedicalinc483.pdf.

Medtronic Agrees to $51 Million Payout to Settle Three Claims

Medtronic agreed to make payments totaling $51 million to settle claims by the Department of Justice against Covidien and ev3, two firms it acquired in 2015.

The company will hand over $20 million to the DOJ to settle an investigation of market-development and physician engagement activities by Covidien and ev3 Peripheral Vascular and endoVenous businesses. Covidien acquired ev3 in 2010.

Ev3 has agreed to plead guilty to misdemeanor charges that it encouraged unproven and potentially dangerous uses of its Onyx Liquid Embolic System. The firm will pay criminal and other fines of $17.9 million and will adopt new compliance and reporting terms for three years.

The embolic agent was only approved by the FDA for use as a liquid embolization device surgically injected into the brain to block blood flow to arteriovenous formations, but ev3 sales representatives encouraged surgeons to use large amounts of the product for surgical procedures outside the brain from 2005 to 2009, endangering patients, DOJ said. This occurred despite the FDA's specific safety concerns regarding the product's use outside the brain.

The DOJ said that company sales reps attended surgical procedures and instructed surgeons on using the product for unapproved procedures, using greater quantities of Onyx than they would use in the brain. Additionally, they set up a program that incentivized, through bonuses and quotas, the sale of the product for unapproved uses.

"Incentivizing employees to promote surgical devices outside approved protocols violates FDA regulations, places patients at risk, and are unacceptable business practices," said Harold Shaw, Special Agent in Charge of the FBI's Boston Division. "In this case, ev3 ignored serious patient safety concerns when it gave sales representatives the green light to promote its device for unapproved uses."

FDA Commissioner Scott Gottlieb called ev3 a "bad actor" that put patients in potential danger.

Medtronic also agreed to pay $13 million to resolve a DOJ investigation of its Systematic Evaluation of Patients Treated With Stroke Devices for Acute Ischemic Stroke (STRATIS) registry, but it didn't admit to any unlawful action.

Medtronic said the plea agreement and settlements "all concern matters that took place either largely or entirely prior to Medtronic acquiring the businesses in which the activities took place." — James Miessler

FDA Releases Proposed Rule on De Novo Pathway for Novel Devices

The FDA published a proposed rule that would further streamline the agency's De Novo classification process.

If finalized in its current form, the rule would establish new procedures for submitting and withdrawing De Novo requests, along with procedures and criteria for the agency to accept, review, grant and decline them.

"Our goal is to make the De Novo pathway significantly more efficient and transparent by clarifying the requirements for submission and our processes for review," FDA Commissioner Scott Gottlieb said. "As a result, we expect to see more developers take advantage of the De Novo pathway for novel devices."

Since the agency started granting marketing authorizations for De Novo devices, it's given the green light for 235 devices, Gottlieb said. The agency approved 170 of those after 2012, when it introduced changes to streamline the pathway.

Read the proposed rule here: www.fdanews.com/12-06-18-DeNovo.pdf. — James Miessler

APPROVALS

ElectroCore's Nerve Stimulator Receives Expanded Clearance

The FDA granted 510(k) clearance for an expanded label for ElectroCore's GammaCore non-invasive vagus nerve stimulator therapy for the preventive treatment of cluster headache in adults.

Also known as "suicide headaches," cluster headaches last a relatively short time but cause extreme pain, affecting approximately 350,000 patients in the US.

The device is the only product cleared by the FDA for prevention of cluster headache and is only available through prescription.

Quidel Gains CE Mark For High-Sensitivity Troponin I Test

Quidel earned the CE Mark for its TriageTrue near-patient diagnostic troponin assay, used for diagnosing heart attacks.

The single-use fluorescence immunoassay detects a subunit of the troponin complex that heart muscle cells release after a myocardial infarction.

The test uses whole blood or plasma specimens that have been anticoagulated with EDTA on Quidel's Triage Meter Pro device.

Aziyo's Bioscaffold Cleared By FDA for Expanded Use

The FDA has granted 510(k) clearance for Aziyo's CanGaroo envelope, a naturally occurring bioscaffold used to hold cardiac implantable electronic devices (CIEDs).

The bioscaffold conforms to the implantable device to provide a stabilized environment for CIEDs like pacemakers and defibrillators after implantation.

The device can help to improve patient comfort, reduce device migration and make device removal easier for exchanges or revisions.

Asuragen's DM1 Assay Gets CE Mark

Asuragen's myotonic dystrophy type I (DM1) assay, the AmpliedeX DM1 Dx Kit, has earned the CE Mark.

The device helps in the diagnosis of DM1, also known as Steinert's disease, an inherited form of muscular dystrophy.

The kit includes reagents to accurately measure every expansion of the disease using as little as 20 nanograms of DNA.

FDA Approves Test For Herpes Virus in Newborns

The FDA approved Meridian Bioscience's diagnostic test for detecting cytomegalovirus (CMV), a type of herpes virus that occurs in newborns.

Most babies with CMV will show no signs or symptoms of infection, but some can develop hearing problems or other long-term health issues from the virus.

The test diagnoses CMV in newborns less than three weeks old by detecting virus DNA from a saliva swab.

Diabetes Management System Earns CE Mark

Diabeloop's DBLG1, a hybrid closed-loop diabetes management system that serves as an artificial pancreas, earned a CE Mark.

The artificial pancreas-like device provides glucose measurements every five minutes.

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: Jeff Grizzel
+1 (703) 538-7669
jgrizzel@fdanews.com

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

Reporters: Zack Budryk, James Miessler, Bill Myers

President: Cynthia Carter

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
- Pre- and postmarket risk management considerations

In addition to outlining effective risk management factors, the report includes the following downloadable tools:

- 510(k) Change Analysis Decision Flowcharts
- Level of Concern Calculator
- Software Safety Classification Guide

Device Software Development: ***A Guide to Risk Management Requirements*** shows you know what risk management methods and requirements you need to follow to get approval to market your device.

FOUR EASY WAYS TO ORDER

1. **PHONE:** Toll free (888) 838-5578
   or +1 (703) 538-7600
2. **WEB:** www.fdanews.com/56544
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 ***Device Software Development: A Guide to Risk Management Requirements*** 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. _____

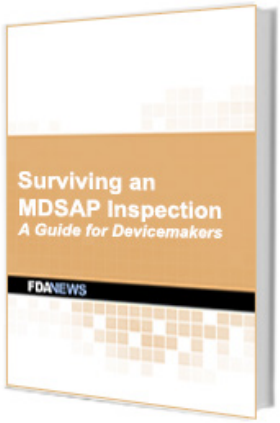
Expiration date _____

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

Virginia customers add 6% sales tax.

18FLYR-N

FDANEWS



Surviving an MDSAP Inspection: *A Guide for Devicemakers*

Currently, Australia, Brazil, Canada, Japan and the United States are participating in the MDSAP program. If you pass one MDSAP inspection you'll be ready to pursue marketing authorization in five separate countries.

But, if you're going through MDSAP for the first time your experience will be very different from regulatory inspections you've gone through in the past.

- You'll know exactly when and how often to expect an audit
- You'll know exactly how long the audit will be
- You'll know exactly what questions the auditor will ask

The prescriptive nature of the MDSAP model makes it relatively easy to prepare for an audit — if you know what to expect. **Surviving an MDSAP Inspection** provides all the information you'll need to understand the MDSAP model. You'll learn:

- The standard schedule for and duration of audits
- Specific areas auditors will examine and questions they will ask
- Different types of audits involved, such as initial certification, surveillance, desk and site audits
- How to create a checklist to make sure all your bases are covered
- The MDSAP grading system and how nonconformance issues can be escalated — and consequences of getting a bad grade

The management report also includes a copy of the MDSAP Companion document — the official guide — auditors will follow.

Order your copy of **Surviving an MDSAP Inspection: *A Guide for Devicemakers*** and know what to expect from an MDSAP audit and how to prepare for it.

FOUR EASY WAYS TO ORDER

1. **PHONE:** Toll free (888) 838-5578 or +1 (703) 538-7600
2. **WEB:** www.fdanews.com/56226
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 ***Surviving an MDSAP Inspection: A Guide for Devicemakers*** 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.

18FLYR-N