International Devices & Diagnostics Monitor

Vol. 2, No. 21
May 23, 2016

IN THIS ISSUE

Theranos Voids Two Years' Worth Of Blood-Test Results

In the ongoing Theranos saga, the company has now rescinded test results from the past two years for its Edison blood-testing diagnostics.

The company issued corrected test results to doctors and patients and also voided results for same tests. In addition to filing a plan of correction, the company has suspended further testing.

In March, CMS cited the company's California facility for exposing patients to risk, failing to meet lab testing standards, employing unqualified staff and improperly reviewing patient test results.

In addition to CMS's probes, the company found itself investigated by the SEC and the U.S. Attorney's Office for the Northern District of California.

CMS's concerns initially became public in January after the agency issued a statement of deficiencies, finding five areas where

(See **Theranos**, *Page 2)*

FDA Recommends Best Practices For Electronic Health Record Data

The FDA wants clinical researchers to improve their electronic data capture systems to ensure interoperability with electronic health records used by health care organizations.

In an attempt to bridge the gap between EHRs and EDCs, the FDA is recommending both sides develop system improvements to ensure data integrity as well as easier access to health care information systems, such as radiology and laboratory databases, according to draft guidance issued May 16.

The draft document recommends that certain information be available to facilitate audits, such as the originator of data elements and electronic date and time stamps.

According to the agency, collaboration will be needed between sponsors and health care organizations to make EHR and EDC

(See **EHR**, *Page 4)*

Theranos, *from Page 1*

compliance standards were unmet based on a routine inspection of the California lab.

The firm responded to CMS's concerns and suggested numerous remedial actions, which the agency deemed inadequate (*IDDM*, April 22).

In response, CMS proposed sanctions on Theranos, including banning founder Elizabeth Holmes from the testing business for a minimum of two years and revoking the company's CLIA certificate. The agency also focused on other officials at the firm.

Theranos President and Chief Operating Officer Sunny Balwani subsequently announced his retirement.

As Theranos's main carrier, Walgreen's was included in Theranos's notification chain. In January, the retail chain halted Theranos's laboratory services in California. The company also said it would terminate the partnership unless the company immediately complied with federal regulations.

The pioneering startup recognized for promoting massive personalized diagnostic testing, acknowledged in company records during an inspection of the California lab that the Edison machines often failed to meet the company's accuracy standards, resulting in erroneous lab results.

According to CMS records, the lab conducts roughly 890,000 tests each year. The Edison machines were used for 12 types of tests out of 200 offered to patients. The exact number of voided tests could not be determined.

Voided test results were for calcium, estrogen and testosterone conducted with the Edison test as well as blood-coagulation tests using Siemens equipment that was programmed incorrectly.

Back in October 2015, the FDA slapped the firm with two Form 483s following an August 2015 inspection at its California facility (*IDDM*, Oct. 30, 2015).

Despite the findings, the company said it was preparing to open a third lab facility in Harrisburg, Pennsylvania.

Theranos has yet to release how its tests work and compare to standard blood tests.

A Theranos spokesperson responded to inquiries but refused to answer questions. — Joya Patel

Stryker Units Falter in Infringement Lawsuit Over Hip Implant Patent

Two Stryker units were on the losing end of a recent decision by a federal appeals court in a lawsuit that accused three of its rivals of patent infringement.

In a May 12 ruling, the U.S. Court Appeals for the Federal Circuit affirmed a decision in favor of Zimmer, Wright Medical Technology and Smith & Nephew. It disagreed with a contention by Stryker Ireland and Howmedica Osteonics that the U.S. District Court for the District of New Jersey "erred in its claim construction and abused its discretion by forbidding Stryker from asserting infringement under the doctrine of equivalence," according to the decision.

The case centered on the '243 patent, which covers socket assembly in prosthetic hip implants, specifically, the shell and bearing members and the femoral component. Wright was slapped with the patent suit for sales of its Lineage and Dynasty acetabular cup systems, which Stryker said featured the same dual-locking mechanism claimed in the patent.

Smith & Nephew, meanwhile, was hit for sales of its R3 system, and Zimmer was smacked over marketing its Continuum system.

Stryker brought suit against the three companies and Johnson & Johnson's Depuy Orthopedics unit in 2011. The case against Depuy — which was sued over sales of its Pinnacle and Duraloc systems — was dismissed with prejudice in June 2014.

Read the decision here: www.fdanews.com/05-16-16-opinion.pdf.

EU Commission Publishes Updated Harmonization Standards

The European Commission has published an updated version of harmonized standards that devicemakers and diagnostics makers can reference to ensure their products comply with relevant EU legislation.

The standards are an update to those implemented by the European Council's Directive 93/42/EEC in 1993.

In the directive, changes are listed under categories for implantable, medical and in-vitro devices. When standards have been updated, manufactures need to re-evaluate their products against the updated standards and provide an updated version of their Declaration of Conformity. The date of implementation is June 30 unless otherwise noted.

Here are some of the important updates:

Sterilization:

- An addition of Part 2 to EN 556-2:2015. Sterilization of medical devices — Requirements for medical devices to be designated sterile — Part 2: Requirements for aseptically processed medical devices.
- A new version of EN ISO 11137-1:2015. Sterilization of health care products — Radiation — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices.
- A new version of EN ISO 11137-2:2015. Sterilization of health care products — Radiation — Part 2: Establishing the sterilization dose.

Aseptic:

- A new version of EN ISO 13408-1:2015. Aseptic processing of health care products — Part 1: General requirements.
- A new version of EN ISO 13408-7:2015. Aseptic processing of health care products — Part 7: Alternative processes for medical devices and combination products.

Patient Handling:

- A new version of EN 1865-1:2010+A1:2015. Patient handling equipment used in road ambulances — Part 1: General stretcher systems and patient handling equipment.
- A new version of EN 1865-2:2010+A1:2015. Patient handling equipment used in road ambulances — Part 2: Power assisted stretcher.

In-vitro Diagnostics:

- A new version EN ISO 15197:2015. In vitro diagnostic test systems — Requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus.
- A new version of EN ISO 23640:2015. In vitro diagnostic medical devices — Evaluation of stability of in vitro diagnostic reagents.

Medical Electrical Equipment:

- A new version of EN 60601-1-2:2015. Medical electrical equipment — Part 1-2: General requirements for basic safety and essential performance — Collateral Standard: Electromagnetic disturbances — Requirements and tests IEC 60601-1-2:2014.

Medical Equipment:

- A new version of EN ISO 3826-4:2015. Plastics collapsible containers for human blood and blood components — Part 4: Aphaeresis blood bag systems with integrated features.

Read the updated EU Commission directive here: www.fdanews.com/05-16-16-OfficialJournalofEuropeanUnion.pdf. View the Harmonized Standards by category here: www.fdanews.com/05-16-16-EuropeanCommissionHarmonisedStandard.pdf. The 1993 directive can be found here: www.fdanews.com/05-16-16-1993CouncilDirective93_42_EEC.pdf.
— Joya Patel

EHR, *from Page 1*

interoperable. It recommends automated electronic transmission of EHR data to the EDC system, which would allow EHR data to be automatically entered into electronic case report files.

Such collaborations already are underway, such as the Office of the National Coordinator for Health Information Technology (ONC) Health IT Certification Program, which the agency recommends to address interoperability concerns.

The ONC Health IT Certification Program certifies EHR technology to ensure it meets agency standards for reliable and confidential data derived from interoperable systems.

When EHR data is not ONC certified, the FDA asks sponsors to determine whether the data has adequate controls to ensure confidentiality, integrity and reliability. This can be achieved by:

- Limiting access of electronic systems to authorized users;
- Identifying record authors; and
- Keeping audit trails and maintaining records for FDA inspections.

The FDA expects sponsors who intend to use EHRs as source data in clinical trials to provide a description of electronic data flow between systems. Specifically, sponsors should explain how data are extracted and imported into the sponsor's system. Sponsors should verify data is consistent between sources.

The guidance provides clarity on interoperability, which many clinical research organizations have sought to better understand, according to Doug Peddicord, executive director of ACRO. The draft guidance makes clear the agency's stance on the integration of health care and clinical research data, promoting collaboration.

However, the draft guidance does not tell clinical research organizations how to implement this data in clinical trial design, Peddicord tells *IDDM*. — José Vasquez

A Quality Management Journey: How to Avoid Repeat CAPAs

Having a risk tool to determine what situations require corrective and preventive actions is one strategy devicemakers can use to avoid repeat CAPAs.

In fact, one expert suggested the CAPA process is designed as an opportunity to respond to critical and systemic issues, investigate them, and resolve them to mitigate the risk of recurrence.

However, many companies are doing the process incorrectly, said Alexandre Alain, a life-science product manager at VERSE Solutions during an FDAnews webinar.

Alain identified some of the reasons for repeat CAPAs, including poor investigations and root cause analysis. If a devicemaker can't identify the correct cause of an issue, it will fix the wrong problem. Along those lines, companies don't do the legwork to develop the right solution to correct a problem.

Don't Forget Effectiveness Check

Not having an effectiveness check is another leading cause of a repeat CAPA, Alain said, adding that inadequate training of personnel, poor use of data, lack of a risk assessment also lands companies in hot water.

One way to help prevent these recurrences is the creation of a risk table that documents complaints, reports of nonconformance or other events. These tables can include information on severity, frequency or any preassigned risk elements.

Based on that risk table, "the event can either be immediately corrected within the process or put into a critical event and investigated more thoroughly to see, moving forward, if the CAPA is needed," he added.

Training and qualification are also key factors to consider. "Do not think anyone can do a CAPA," he said, adding that it is essential to have the correct personnel in place who understand what is going on. Don't rely on one person doing everything — rather, ensure that there are people with the knowledge and skills to tackle the various steps of the CAPA process.

Deciding When a CAPA Is Needed

The next step is defining whether a CAPA and investigation are warranted. It is crucial at this stage to fully understand and define the problem so others may avoid it in the future. To that end, company personnel should write out the problem description thoroughly.

However, the people documenting the problem are not always the ones who will establish an action plan and conduct the investigation, "so a good problem description is crucial," Alain said.

With that said, a problem description should not contain too much extraneous information — having a clear summary should be the goal.

Full Disclosure

Alain also urged that the description of the problem be truthful, as hiding issues from the management or auditors will prevent companies from effectively tackling the problem.

The next step is the investigation and root cause analysis. The investigation should involve team members from multiple departments to help document information and question personnel to demonstrate the company did its due diligence.

Companies also should become proficient at using root cause analysis techniques to address specific problems. Alain noted there are many techniques, such as the cause-and-effect diagram and Pareto charting, and it's imperative to build internal expertise so personnel can identify root causes easily.

In addition, companies should be aware that there could be multiple root causes that go beyond "operator error" and "lack of training."

Finally, create CAPAs that are deliverable, resisting the urge to rush just to finish them. "Do not focus on due date, but more on correcting the issue," he advised.

China's BMC Medical, U.S. Distributor Earn ITC Scrutiny for CPAPs

The U.S. International Trade Commission again is investigating complaints that a Chinese device company and its American distributor are infringing patents related to ResMed's sleep disorder products.

In the latest in an ongoing feud, ResMed is accusing BMC Medical and distributor 3B Medical of infringing the '453, '551, '691 and '860 patents related to products to combat sleep apnea. ResMed claims that two of BMC's flow generator products — the RESmart and the Luna — infringe claims of these patents. ResMed filed its current complaint with the ITC last month.

As part of its complaint, ResMed is asking the ITC to stop BMC and 3B from importing and selling flow generators in the U.S.

The ITC says it will investigate whether BMC and 3B are in violation of section 337 of the Tariff Act of 1930, which relates to unfair practices in import trade. Despite the investigation, the ITC asserts that it hasn't decided on the merits of the case, which will be assigned to one of the body's administrative law judges. The judge will determine whether a violation has taken place — a decision the commission will then review.

ResMed filed a similar complaint with the ITC in 2013. In addition to the ITC complaint, ResMed has filed a lawsuit in the U.S. District Court for the Southern District of California. ResMed sued BMC in the same court in 2013 for patent infringement.

Both parties have claimed victories in the ongoing dispute. Last June, BMC announced it had won a patent dispute in Germany in a case involving a CPAP respiratory system machine with a detachable water tank. ResMed previously had won an injunction prohibiting BMC from offering, selling or distributing infringing mask products — including Willow and FeaLite nasal pillow masks — in that country.

Groups Fight Back

BMC had urged the ITC to reject ResMed's request. "ResMed's decision to burden the Commission and BMC/3B with serial litigation rather than efficiently asserting all of its allegations in a single investigation should not be rewarded."

For its part, 3B accuses ResMed of monopolistic behavior, adding that it has filed an antitrust action in the U.S. District Court for the Middle District of Florida. In its complaint, 3B cites an instance in which a potential customer said, "'ResMed will shut down anyone who gets near their business.'"

The Chinese company and its Florida distributor do have their backers. In comments to the ITC urging that it reject ResMed's petition, one Florida-based durable medical goods supplier, Lifesavers Home Respiratory, says that 3B has helped it stay in business. Lifesavers has filed for Chapter 11, but is being helped by contracting with 3B.

"Specifically, pricing with 3B for an auto CPAP is $219 — the ResMed price is over $500," the company notes in a filing with the ITC. Lifesavers contends that ResMed goes after doctors who refer Lifesavers. Further, it encourages doctors not to use homecare companies that refuse to sign a contract giving ResMed most of their businesses.

Nationwide Recall Issued on Laser Probe Used in NeuroBiate System

Monteris Medical initiated a nationwide recall of its SideFire Select 2.2 mm Directional Laser Probe, following reports of fracture that resulted in CO2 introduction in the brain.

FDA determined the device design was the reason for recalling 121 probes that are a part of the NeuroBiate system used during neurosurgery.

In late 2015, Monteris received a report that the sapphire lens on a 2.2SF probe fractured during a procedure, with resulted in the introduction of CO2 in the patient's brain.

In response, Monteris Medical physically removed devices from each site and the company is removing all unexpired models from the market.

Read the recall notice here: www.fdanews.com/05-17-16-RecallNeuroBiateSystem.pdf.
— Joya Patel

Eclipse Cited for Misclassification In FDA Warning Letter

The FDA issued a warning letter to Eclipse Aesthetics because it had concerns that the firm's MicroPen Elite dermabrasion device has the potential to damage vessels and nerves.

Eclipse Aesthetics failed to submit a premarket approval application or an investigational device exemption for the device before marketing it, the May 28 warning letter said.

The agency noted that dermabrasion devices that don't require premarket approval have abrasion substrates, which are brushes and burrs that abrade and remove layers of skin. However, the Eclipse MicroPen is intended to achieve its clinical effect by penetrating the skin.

The Eclipse MicroPen Elite, which is classified as a Class I device for microdermabrasion and treatment of scars, consists of microneedles and uses a "different fundamental scientific technology than a device classified under 21 CFR 878.4820," the letter says.

Noting that the device was not exempt from premarket notification due to the penetration depths of the needles and speeds of the device, the agency said that safe ranges for needle lengths, penetration depths, and speeds of the device are not known.

"Therefore, FDA has safety concerns regarding the potential for the needles to damage vessels and nerves," the letter concludes.

The FDA deemed the device misbranded and adulterated and requested that the firm stop selling the device immediately.

Read the warning letter here: www.fdanews.com/05-18-16-EclipseWarningLetter.pdf.
— Joya Patel

House Passes Bill to Develop Zika Virus Diagnostics, Vaccines

The House passed a bill May 18 that includes $103 million for developing rapid diagnostic tests and vaccines to fight the Zika virus.

The Zika Response Appropriations Act (H.R. 56242) includes $622.1 million in total funding, which includes $230 million for the NIH to support preclinical and clinical development of vaccines. The Centers for Disease and Control would get $170 million to detect the virus globally to protect public health. The remainder would be funded by discretionary funding.

Read the legislation here: www.fdanews.com/05-18-16-ZikaSupplementalAppropriationsBill.pdf.

In related news, the FDA granted Altona Diagnostics an emergency use authorization for its RealStar Kit to detect the Zika virus.

The in-vitro diagnostic test detects Zika Virus RNA in serum or urine samples, and it rules out Dengue and Chikungunya viruses.

The FDA has not cleared or approved tests to confirm Zika virus infection but it has authorized EUA's for detection. Altona's test is 1 of 4 to be given an EUA by the FDA for use by laboratories certified under the Clinical Laboratory Improvement Amendments. Read the EUA here: www.fdanews.com/05-16-16-AltonaZikaEUA.pdf. — Joya Patel

B. Braun Resolves Criminal Liability For Contaminated Syringes

B. Braun Medical has agreed to resolve criminal liability allegations by paying $4.8 million in penalties and forfeiting an additional $4 million in restitution for selling contaminated pre-filled saline flush syringes in 2007, the Department of Justice announced.

The company also agreed to increase oversight of third party suppliers to prevent future sales of contaminated products.

The syringes carried B. Braun labels but were manufactured by AM2PAT, a third-party manufacturing company in North Carolina.

The use of the contaminated syringes led to an estimated five deaths and multiple infections.

A Series of Missteps

According to documents, B. Braun started working with AM2PAT in 2006, and it was aware of manufacturing problems at the time. The FDA also uncovered GMP deficiencies during a 2007 inspection. Around that time, AM2PAT told B. Braun it would be moving its manufacturing plant, and that it would be changing its sterilization process.

However, before B. Braun's quality department approved the new plant and sterilization process, AM2PAT began selling syringes manufactured at the new plant, the DOJ said.

B. Braun approved the changes to the manufacturing process even after the company received complaints about the syringes changing color, the DOJ said. Moreover, B. Braun approved AM2PAT's facility "without overseeing AM2PAT's operations at its new facility or confirming AM2PAT's representations that it had properly validated its clean room and equipment after the move."

Less than two months after moving to the new facility, B. Braun had to recall all of the syringes manufactured at AM2PAT's facility because the radiation sterilization process caused white particles to develop in the saline.

In connection with the dirty syringes, AM2PAT's quality control director and plant manager pleaded guilty and were sentenced to 54 months in prison in 2009. The former president fled the country and is on the FDA's Office of Criminal Investigations' "Most Wanted" list, DOJ said.

Read the DOJ release here: www.fdanews.com/05-19-16-DOJBBraunRelease.pdf — Joya Patel

Indian Devicemakers' Association Wants Mandatory Device Certification

The Indian devicemakers' association is pushing for mandatory certification for all devices marketed in the country.

The Indian Certification of Medical Devices Scheme was unveiled in March as the first domestic quality assurance system in the country.

There are two certification options under the scheme — ICMED 9000 (an ISO 9001 plus additional requirements) for low-risk devices and ICMED 13485 (an ISO 13485 plus additional requirements) for medium- and high-risk devices (*IDDM*, March 25).

A third level, which would introduce device specifications developed by the Health Ministry's National Health System Resource Centre, will be launched later this year.

The industry is still mapping out a plan for manufacturers and importers to register medical devices via an online government portal, said Ragiv Nath, forum coordinator for the Association of Indian Medical Device Industry (AiMeD), which represents domestic devicemakers.

He told *IDDM* that the association was pleased to see India gaining traction to have separate rules governing medical devices. He also stressed the need to register low-risk and moderate-risk devices for third-party manufacturers.

AiMED advocates mandatory ICMED certification to fill in regulatory gaps in quality for medical devices, Nath said. — Joya Patel

BRIEFS

Roche's PD-L1 Companion Dx Approved

The FDA marked a first with its approval of Roche's companion diagnostic Ventana PD-L1.

The assay is a companion diagnostic to Roche's FDA approved immunotherapy treatment Tecentriq, used for metastatic urothelial cancer, a common type of bladder cancer.

Tecentriq is the first FDA-approved PD-L1 inhibitor and the latest of three in the broader class of PD-1/PD-L1 targeted biologics approved by the FDA.

The companion in-vitro diagnostic is not required for use of Tecentriq but is a method of evaluation for clinicians to evaluate PD-L1 status, respectively guiding immunotherapy options.

Biofrontera's Drug-Device Combo Cleared

The FDA has approved Biofrontera's drug-device topical Ameluz and BF-RhodoLED for treatment of mild to moderate actinic keratosis on the face and scalp, the German startup announced Wednesday.

The combination uses photodynamic therapy to target lesions caused by prolonged exposure to UV rays.

Ameluz was granted marketing authorization by the EMA in December 2011 for the same indication, and the device was approved in the EU in November 2012.

FDA Lifts Custom Ultrasonics' Recall

The FDA has lifted a recall affecting Custom Ultrasonics' automated endoscope reprocessors while the company carries out corrective actions, the company announced Monday.

The FDA ordered Custom Ultrasonics to recall its AERs last November, following a slew of infection outbreaks related to duodenoscopes, according to a company statement.

Moving forward, the company is working with the agency to correct its procedures and protocols. The lift does not apply to duodenoscopes.

J&J Gets in the 3D Printing Game

Johnson and Johnson is taking a step toward 3D printing technologies by inking a deal with HP to create customized medical devices.

Both companies have begun merging their scientific, clinical, material science and technological knowledge to develop on-demand customizable products in orthopedics, eye health and consumer products.

Using advances in data mining and software, 3D printing could enable patient-specific products, therapies and solutions that deliver better outcomes, better economics and improved global accessibility, J&J said.

Medtronic to Pick Up Smith & Nephew's Business

Medtronic has entered into an agreement to acquire Smith & Nephew's gynecology business for an estimated $350 million, the device giant announced Wednesday.

The acquisition will expand Medtronic's collection of minimally invasive surgical offerings and enhance its existing GYN business.

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