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IN THIS ISSUE



## Theranos Finds Itself In Government's Crosshairs

More federal regulators are knocking on Theranos' door, keen on getting answers to questions about staff qualifications and improper review of patient test results.

Last week, Theranos, which develops finger prick blood tests, was hit with criminal investigations by the SEC, the U.S. Attorney's Office for the Northern District of California and U.S. Department of Justice.

That came after 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.

CMS's concerns became public in January after the agency issued a statement of deficiencies, finding five areas where compliance standards were unmet based on a routine survey of the lab. Theranos responded to CMS's concerns addressing the issues; however, the agency stated they were not adequately met.

*(See* **Theranos**, *Page 6)*

## FDA Provides Roadmap for Technical Evaluation of Digital Pathology Devices

The FDA has instructed providers of digital pathology devices to test components of their technology and conduct system-level assessment prior to the submitting of clinical data.

The recommendation comes in a final guidance document unveiled April 20 that provides insight on what technical performance assessment data sponsors should provide ahead of an evaluation of a whole slide imaging system. It updates a draft version issued in February 2015.

WSI systems consist of an image acquisition subsystem that converts the content of a glass slide into a digital image file or a workstation for viewing the digital images.

*(See* **Pathology**, *Page 2)*

## AVS May Have Distributed Lenses Rejected for Japan, Warning Says

The FDA has slammed Advanced Vision Science for potentially distributing intraocular lenses in the U.S. that were rejected for the Japanese market.

The Goleta, Calif.-based company sold its PMA to Bausch & Lomb in March 2009, according to the April 6 warning letter posted online Tuesday. It also licensed the development, manufacturing and marketing for all regions except Japan.

While the company claimed it was only distributing its lenses in Japan, the letter says there is evidence that AVS has distributed certain IOLs in the U.S. since 2008 and 2012. "That is, lenses for the Japanese market that may be refused based on acceptance criteria are returned to Advanced Vision Science (AVS) and donated/distributed into intrastate commerce for further distribution."

The FDA points out that after selling the PMA in 2009, AVS lacked an approved PMA to market the devices in the U.S., making them adulterated.

AVS did not maintain procedures on its own acceptance criteria, such as tooling marks, or on the acceptance criteria at its customers, according to the letter. After the July 27, 2015, to Aug. 3, 2015, inspection, it told the FDA it had stopped U.S. shipment of IOLs and was considering a humanitarian device exemption. However, the company did not provide the results of its HDE consideration, the letter notes.

It also raps the company for failing to include the location of design documents, and information on changes made to its lenses, in its design history file. Further, its complaint handling procedure did not detail how it will evaluate complaints for Medical Device Reporting.

Advanced Vision Science did not respond to a request for comment by press time. The warning letter is available at www.fdanews.com/04-20-16-AVS.pdf. — April Hollis

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**Pathology,** *from Page 1*

The document provides a laundry list of the descriptions and test methods that should be included in the technical performance assessment.

For example, it recommends that the applicant's premarket submission contain a "block diagram" of the investigational device's sub-components designed for image acquisition and display.

Further, the digital pathology device's light source consists of a lamp and condenser. Sponsors should provide detailed information, such as the bulb type and its expected lifetime. A recommended test for the "measure the spectral distribution of light incident on the slide" is described in the guidance.

The guidance also describes the testing of various other components, including the slide feeder, digital imaging sensor, image processing software and image review manipulation software.

It also provides recommended system-level assessments of color reproducibility, spatial resolution, focus quality, whole slide tissue quality and stitching error, which is a reference to the technique used to combine thousands of sub-images into a single, digital whole slide image.

Sponsors also should report the typical "turnaround time," needed for the software to execute a user command, such as panning or zooming, the FDA says.

Incorporating human factors testing to validate the user interface also is recommended. The items that should be included in the test are described in the guidance.

Finally, sponsors should provide information on quality control procedures, as well as a quality control manual.

The guidance does not cover subsequent aspects of the review process related to clinical evaluation of safety and effectiveness.

The final guidance is available here: www.fdanews.com/04-21-16-guidance.pdf. — Varun Saxena

## Navigating the Muddy Waters Of Chinese Device Regulations

China has witnessed a bevy of changes to device regulations over the past couple of years. So what should devicemakers keep in mind to avoid running afoul of regulations?

One way to avoid hiccups is to preplan, according to John Balzano, special counsel at Covington and Burling. This planning goes beyond just taking steps to get a license for bringing the product to market; devicemakers must plan on updating their licenses, distributing their products, getting their items priced and moving them to hospitals.

Many companies fail to plan for these additional steps, focusing solely on obtaining a license to market the device. However, Balzano noted during a recent FDAnews webinar that it is important to consider a host of issues, such as whether the device will be manufactured in China.

**Panoply of Documents**

Balzano noted that the China Food and Drug Administration has issued a number of guidances over the last year, and understanding the finer points of those guidances "can influence whether your application gets accepted or rejected at the filing stage, or whether the reviewers at the Center for Medical Device Evaluation are going to have to come back to you and ask you for supplementary materials," Balzano said.

On top of these guidances and recent reforms, devicemakers also should be mindful of the various Chinese medical device standards. Balzano notes that the central government has made it a priority this year to cut down on the number of standards as they have become outdated and could lead to inconsistencies if multiple standards were used.

One area that regulators haven't really touched is combination products. There is no combination product license; rather, sponsors submit their applications, and the CFDA determines whether it should be reviewed as a drug or device.

The use of foreign clinical trial data also is a murky issue, as the agency hasn't articulated a well-formulated opinion on the topic. Typically, the agency decides on a case-by-case basis, and sponsors should inquire ahead of time about whether the data will be acceptable or whether local trials will be required.

Looking to the future, Balzano thinks industry could see legislation related to good clinical practices, as well as the finalization of adverse event regulations. A number of smaller regulations are in the offing, but industry should expect larger structural changes.

Finally, devicemakers should keep advertising laws front and center. Balzano expects more agency action in this area, with more crackdowns. "We've even seen enforcement against social media postings that people think qualify as advertisements," he warned. Penalties can be substantial — in excess of $1 million — for advertisements deemed misleading. — Elizabeth Hollis

## FDA Continues Crackdown On Chinese Devicemakers

Chinese devicemakers continue to land in the FDA's crosshairs, with the agency tacking on two more companies to an import alert list.

Hongkong Canwin Li Health Products and Shenzhen Beierkang Technology have found themselves as the newest members of the "Detention Without Physical Examination" import alert list for devices without approved PMAs or IDEs, or those that are not substantially equivalent without a 510(k).

Shenzhen-based Hongkong Canwin Li Health Products manufactures external penile rigidity devices, and was cited on the alert for its "PowerUp Penis Pump."

Shenzhen Beierkang Technology was hit for its "Multifunction Infrared Thermometer." The FDA says it doesn't have information about the product materials and cannot determine whether it is a device subject to a previously cleared 510(k).
— Michael Cipriano

## Malaysia Seeks Stakeholder Input on Recall Proposal

Malaysia's Medical Device Authority is encouraging companies to include information on how long it will take to complete the recalls in standard operating procedures.

The proposal comes in draft guidance unveiled this month, which notes that the MDA has the authority to suggest or order a recall if the product poses a risk to public health. Further, the authority will monitor the situation until all faulty products are removed from the market, and it will issue communications to stakeholders, when appropriate.

Establishments — which include device manufacturers, authorized representatives, distributors and exporters — should have the SOP identify all personnel involved in the recall action, in addition to their functions and responsibilities. They also should spell out the communication channels used to announce the recall events.

Recalls would be placed in one of three classes, with 1 being the most serious and 3 the lowest risk. MDA must be notified of a Class 1 recall within 48 hours, a Class 2 recall within three working days and a Class 3 recall within five working days, according to the document. A final report must be submitted within 30 days of a recall's completion that notes the results of the steps taken and actions initiated to prevent a recurrence.

MDA expects that establishments shall retain recall records for five years after the device's projected useful life.

The document also includes a process flowchart for recalls and a template to notify users.

Interested parties may provide feedback to fezriaziz@mdb.gov.my before April 29.

Read the draft proposal here: www.fdanews.com/04-21-16-malaysia.pdf. — Elizabeth Hollis

## New Report Outlines Inspection Strategies For Devicemakers

This year should be a busy one for devicemakers as CDRH looks to enforce the UDI regulations.

"There are a number of UDI-specific quality system regulation elements that changed back in 2013," according to John Avellanet, managing director and principal of Cerulean Associates. Avellanet said this will be the year the agency will look to ensure devicemakers are in compliance.

Even Class 1 devicemakers — which don't need to comply with UDI requirements this year — should update forms and complaint database fields, according to an FDAnews management report.

It's difficult to predict what other areas CDRH will look to enforce. However, Avellanet advises companies to review what areas the agency has emphasized over the last year, as well as trends over time.

**Looking Back**

Looking back over 2015, Avellanet says the most frequently cited item in 483s was CAPA, which should remain a top enforcement area. "But other areas have waxed and waned since 2012, often in response to past enforcement action," he notes.

Avellanet expects the FDA to concentrate on four key areas during inspections this year: procedural controls and their effectiveness, supplier controls and oversight, record and data integrity and postmarket surveillance. Data integrity has been the focus of many 483s lately, he says, and devicemakers should take note.

"Last year, the FDA finished training all its CDRH investigators on the basics of data integrity," he explains, "So I think we're going to start seeing more and more data integrity inspections, much as we have in the pharma and biotech world for the past several years."

He anticipates that the FDA will pay special attention to the following areas: data from automated processes associated with production or product testing; lot release data; sterility and safety data; and postmarket surveillance data.

A big trend for the agency over the coming years will be an emphasis on specialized inspections. Inspection teams will include a quality systems generalist and an expert on the device being manufactured.

Further, companies should anticipate big changes in the inspection model, as there is a "strong possibility" that the Medical Device Single Audit Program could replace the existing one.

Avellant provides his list of strategies devicemakers should keep in mind to avoid running afoul of the FDA:

- Make sure you retain clear records to demonstrate safety and efficacy throughout the product's lifecycle;
- Expect two investigators in each inspection — one with more technical expertise than devicemakers may be used to;
- Expect Class 2 device costs to increase as a result of phased-in UDI requirements;
- Expect increased QMS costs for the year, as companies will have to update various SOPs, forms and databases to reflect the new rules;
- Demonstrate progress on data integrity compliance;
- Plan for increased liability risks from public enforcement of poor design control records and postmarket surveillance actions;
- Improve supply chain controls to avoid public enforcement;
- Expect FDA internal processes to change due to revisions of older guidance documents;
- Consider restructuring your QMS to follow the seven-area MDSAP framework; and
- Include relevant international guidelines as references in standard operating procedures.

For more information on the report CDRH in Transition, visit: www.fdanews.com/CDRHinTransition. — Elizabeth Hollis

**Theranos**, *from Page 1*

In a March 18 letter, CMS states Theranos failed to adequately address critical deficiencies at the company's Newark, Calif. lab.

If Theranos had failed to respond within 10 days, possible sanctions included revoking the company's CLIA certificate, suspending and canceling the lab's approval to receive Medicare payments, imposing a two-year ban on CEO Elizabeth Holmes and certain other employees from owning or operating a clinical laboratory, assessing $10,000 per day in civil fines and requiring disclosure to CMS of all potentially affected customers.

Theranos spokeswoman Brooke Buchanan told *IDDM* that the company responded within the 10-day timeframe and addressed all of CMS' concerns, referring *IDDM* to a March 31 statement discussing a plan of correction sent to the agency.

Further, earlier this month, Theranos announced it added eight new medical experts to its Scientific and Medical Advisory board. Theranos added the experts to the board to review their systems, devices, data and medical technology.

In addition to government probes, the company has had to fight back against at least one study that questioned the accuracy of its test results.

A study in the *Journal of Clinical Investigation* determined that Theranos flagged abnormal test results roughly 1.5 times more often than Quest Diagnostics and LabCorp, something that could cause patient harm (*IDDM*, April 1).

The company's reputation with partners also has taken a hit. Walgreens has been distancing itself, telling the company in January that it must stop sending any clinical laboratory tests provided through Theranos Wellness Centers at Walgreens to the California lab for analysis. In addition, Walgreens halted Theranos laboratory services at its Palo Alto, Calif., store (*IDDM*, Jan. 29). — Joya Patel

## Stakeholders to FDA: Get Tougher on Cybersecurity

Stakeholders are encouraging the FDA to beef up its stance on cybersecurity, making suggestions provided in draft guidance mandatory rather than voluntary.

The comments came in response to draft guidance issued in January that received 51 responses. The draft recommendations were intended to provide for cybersecurity protocols in preplanning to guard the growing number of networked medical devices against malicious attacks (*IDDM*, Jan. 22).

Among the recommendations is that manufacturers should implement a structured and systematic comprehensive cybersecurity risk management program and respond in a timely fashion to identified vulnerabilities.

However, as the Mayo Clinic points out, grave concerns remain. "The current practice of not requiring manufacturers to take steps to address cyber security vulnerabilities in medical devices has not had the significant effect that was desired," it writes. Mayo cites previous voluntary efforts that have proven unsuccessful in the cybersecurity, including one covering networked medical devices containing off-the-shelf software.

Mayo also said there should be additional references to NIST standards, which can inform specific actions manufacturers can take during the design and manufacturing processes.

Dexcom, which makes continuous glucose monitoring devices, recommended that the FDA narrow the scope of the document, saying that too many alerts on low-risk vulnerabilities could lead to user fatigue.

The company also would like the FDA to address platform vulnerabilities for operating systems and the associated software. "It is unreasonable to make manufacturers responsible for reporting vulnerabilities of another organization," the company says, adding that relationships could be damaged if there is disagreement between partnering organizations over whether a vulnerability should be reported.

At least one commenter praised the FDA's efforts. Rep. Jim Langevin (D-R.I.), co-founder and co-chair of the Congressional Cybersecurity Caucus, said he approved of the voluntary approach. "By stating willingness to forebear enforcing these requirements, FDA provides an incentive for manufacturers to adopt measures, including a thirty-day remediation timeline and membership in an Information Sharing and Analysis Organization," he writes.

Mayo's comments are here: www.fdanews.com/04-22-16-mayo.pdf and Dexcom's are here: www.fdanews.com/04-22-16-dexcom.pdf.

Read Langevin's comments here: www.fdanews.com/04-22-16-cyber-guidance.pdf. — Joya Patel

## FDA Hits Wexford Labs Over Quality Control Procedures

Wexford Labs was cited in a three-observation Form 483 over supposedly lax quality control procedures.

The document accuses the company of failing to establish sanitary procedures, neglecting to conduct internal audits of its quality control processes and disregarding training procedures. These accusations stem from a Jan. 6 to 7 inspection of the company's plant in Kirkwood, Mo.

The agency's first complaint is that the company lacks the necessary procedures to ensure sterility in equipment and products. According to the FDA, Wexford had no established procedure for cleaning stainless steel mixing tanks. Personnel said that product-specific tanks "are almost never cleaned." Additionally, the 483 noted that the tanks also lack closing lids to prevent foreign materials from entering them.

The 483 also noted that Wexford has yet to conduct internal audits as specified in the company's operating procedures and internal audit schedule.

Lastly, the inspector contended that the company lacks a procedure to govern training and a matrix for identifying employee training needs.

Read the 483 here: www.fdanews.com/04-25-16-Wexford.pdf.— Cameron Ayers

# BRIEFS

## Bionik Completes Interactive Motion Buy

Bionik Laboratories has finalized its acquisition of Interactive Motion Technologies, a developer of robotic tools for neurorehabilitation. The Toronto-based devicemaker will gain all of IMT's outstanding shares, assets and liabilities. Bionik's pipeline now will include three upper extremity clinical rehabilitation products, a lower-body product and other candidates in the pipeline.

## FDA Clears Vevo MD Ultrasound System

A Fujifilm SonoSite subsidiary has garnered clearance for its ultra-high frequency ultrasound Vevo MD, which delivers image resolution down to 30 mm. The system is compatible with the company's transducer technology that can generate frequencies up to 70 MHz, an increase in resolution versus traditional ultrasounds, according to the company.

## Ortho Kinematics Nabs CE Mark

Ortho Kinematics has earned CE marking for its Vertebral Motion Analysis diagnostic test, intended to assess spinal motion and radiographic instability. The test increases sensitivity in the detection of radiographic instability with no reduction in specificity versus the standard test. The company plans to begin marketing in the UK later in the year.

## EMBLEM S-ICD Systems Gets CE Mark

Device giant Boston Scientific has been granted CE marking for its Emblem MRI subcutaneous implantable defibrillator system, along with magnetic resonance conditional labeling for all implanted Emblem S-ICD systems. The system is designed to minimize the risk of complications linked to transvenous implantable cardioverter-defibrillators in patients at risk of sudden cardiac arrest that leaves the heart and vasculature unharmed. A full European launch is expected early this summer, the company says. The product is not available in the U.S.

## Bill Aims to Amend CMS Process

A lawmaker has proposed legislation that would streamline Medicare coverage for technologies approved through the FDA's medical device expedited review process. Rep. Charles Boustany (R-La.) introduced the bill, which would allow any new FDA-approved device or diagnostic labeled as a breakthrough to receive transitional coverage for a three-year period by CMS. During this time, the therapy would receive reimbursement, and CMS could specify, if necessary, additional data that would be needed for continued coverage after the three-year period.

## FDA Greenlights Nevro Leads

The FDA has approved Nevro's new surgical leads, which are intended for use with Senza Spinal Cord Stimulation, a neuromodulation platform delivering HF10 therapy. The SCS therapy system delivers electrical pulses via a compact battery-powered generator implanted under the skin located near the spinal cord to treat chronic leg and back pain.

## Toshiba's Aquilion Lightning CT Cleared

Toshiba America Medical Systems has gained FDA clearance for its Aquilion Lightning CT system for routine volumetric scanning. The 16-detector row system features ViSION CT detector technology and AIDR 3D Enhanced to minimize dosage and enhance patient safety, according to the company.

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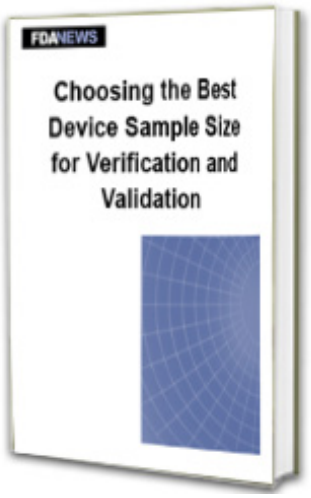


# Choosing the Best Device Sample Size for Verification and Validation

If you're like many manufacturers, you understand the essence of the *21 CFR 820.30* requirement: you must run enough test samples of a product so its test results can be successfully applied to full-scale production runs. And, like many manufacturers, you've probably had trouble for years determining exactly how many units of a product you should test to satisfy the FDA.

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