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NGS Guidances Lay Foundation For Precision Medicine Initiative

The FDA is creating a new flexible regulatory pathway for genomic tests that sequence the human genome as part of President Obama's Precision Medicine Initiative.

The agency released two complementary draft guidances that set a foundation for the pathway by streamlining submission and review of data supporting clinical validity of next-generation sequencing (NGS)-based in vitro diagnostics.

The agency sought feedback from industry stakeholders during four public meetings before crafting the guidances, which explain how the agency might consider exempting certain NGS-based tests from premarket review, Assistant Commissioner Heidi Marchand said.

The move represents FDA's commitment to harness technology and share genomic findings pouring out of clinical research, she said.

(See **NGS Guidance**, *Page 2)*

CMS Imposes Sanctions on Theranos; Bans CEO from Lab for Two Years

The Centers for Medicare & Medicaid Services imposed sanctions on Theranos following a litany of quality control failures for the blood testing company.

As part of those sanctions, CEO Elizabeth Holmes is banned from owning or operating a laboratory for at least two years.

CMS also yanked the company's CLIA certificate, imposed monetary penalties, suspended the lab's approval to be reimbursed by Medicare and Medicaid and will oversee a directed correction plan for the beleaguered company.

Following a CMS noncompliance determination in March, Theranos rescinded test results from the past two years for its Edison blood-testing diagnostics. The company issued corrected test results to doctors

(See **Theranos**, *Page 4)*

NGS Guidance*, from Page 1*

"This system would be efficient and flexible: as technology advances, standards can be updated to help ensure test accuracy," the FDA said. "Similarly, as clinical evidence improves, new interpretations could be supported."

The first draft guidance, "Use of Standards in FDA Regulatory Oversight of Next Generation Sequencing (NGS)-Based *In Vitro* Diagnostics (IVDs) Used for Diagnosing Germline Diseases," provides recommendations for designing, developing and validating NGS-based tests for hereditary diseases, and addresses the potential for using FDA-recognized standards to demonstrate analytical validity.

Standards for Analytical Validation

Stakeholder feedback indicated that conforming to standards for analytical validation of NGS-based tests would allow for differences in development but could accommodate evolution of newer technology.

"Upon finalization of this guidance, test developers will be able to follow these recommendations when preparing a premarket submission," the guidance said. It stressed that the guidance is limited to targeted and whole exome human DNA sequencing (WES) NGS-based tests to aid in diagnosing suspected germline diseases or other conditions. It does not apply to NGS-based tests intended for stand-alone diagnostic tests. Additional recommendations or controls would also be required for direct-to-consumer NGS-based tests for germline diseases.

The agency said it would be seeking stakeholder comments on expanding the scope but wanted to hear from industry first.

Although the FDA has cleared a few single-gene, disease-specific, targeted NGS-based diagnostics, it has not classified NGS-based tests with a broad intended use for suspected germline diseases. Hence, an NGS-based test would automatically be classified as a Class III device under current regulations. The agency said it would consider *de novo* requests for NGS tests, and that if such a request is granted, then the test could serve as a predicate for future 510(k) submissions.

The FDA could even exempt certain tests from premarket notification requirements. Regardless, NGS tests must demonstrate analytical validity, and using a standards approach could streamline how this validity is demonstrated.

The guidance lays out the typical elements of an NGS-based test for germline diseases, as well as recommendations for design, development and validation of those tests.

The FDA recommends the following test design considerations:

- Indications for use statement that prospectively defines and documents the specific clinical need driving development of the test;
- Specific user needs for the test;
- Specify and document the acceptable specimen types to be used for the test;
- Specify and document the region of the genome that will be interrogated;
- Demonstrate performance needs by defining and documenting a minimum set of metrics and performance thresholds, as well as possible limitations to test performance; and
- Specify and document all test components.

For FDA Recognition

The FDA's second draft guidance, entitled "Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing (NGS)-Based *In Vitro* Diagnostics" describes an approach for test developers to use data from public genomic databases to gain FDA recognition.

The guidance notes that administrators of databases can voluntarily apply to FDA for recognition, and it describes how the agency would review those applications. Administrators

(See **NGS Guidance***, Page 10)*

FDA Issues Guidance on Codevelopment Of Companion Diagnostics, Drugs

In yet another move toward precision medicine this week, the FDA is mapping out co-development pathways for companion diagnostic devices to accompany targeted therapies.

Underscoring the complexity of developing intertwined products, the FDA's draft guidance released July 15 recommends that companies develop them in tandem because the agency supports simultaneous approval and because it could hasten approval. The agency recommends that sponsors of both the IVD and the therapeutic product meet with the appropriate FDA centers prior to launching a trial.

The guidance describes general principles to guide codevelopment of therapies and their companion diagnostics, regulatory requirements that sponsors should be aware of, and considerations for planning clinical trials.

The document — which is applicable to drugs, biologics and devices — notes that clinical trial design will be informed mainly by the device component, as it will point drugmakers to the adequate patient population, the document says.

Herceptin was the first targeted therapy to be approved with a companion diagnostic, the HercepTest, which measures expression of human epidermal growth factor receptor 2 (HER2) in breast cancer. The two products were approved in 1998, and there are now numerous examples of therapies approved with companion diagnostics, the guidance notes.

In vitro companion diagnostics (IVDs) may be used to:

- Identify patients most likely to benefit from a drug;
- Identify patients likely to be at increased risk for serous adverse events as a result of a drug;
- Monitor response to treatment with the goal of adjusting the treatment; and
- Identify patients in the population for whom a therapy has been adequately studied and found to be safe and effective.

When a device is not developed in tandem with the therapy, the agency provides strategies to prove that the clinical outcome is correlated to the device and therapy. Trials should support the claims for both the therapy and companion device.

The agency notes that errors with the devices could introduce bias in recruitment of patient populations. To guard against that bias, the guidance suggests gathering a second set of independent clinical samples and validating those against sample data that includes the device.

Risk Assessment and IDE Requirements

IVDs have generally been classified as high-risk, Class III devices, requiring premarket approval applications; however moderate-risk IVDs could be considered Class II devices, requiring 510(k) premarket notifications or *de novo* requests.

However, risk assessments applied to the use of an investigational IVD in the context of a clinical trial is likely to be different than the risk assessment for marketing purposes. The guidance highlights criteria for examining risk and whether IVDs would be considered exempt, significant risk or non-significant risk. It notes that significant risk would come into play when IVDs are used to make treatment decisions in a trial and an incorrect test result poses potential serious risk to the health, safety, or welfare of a patient.

The document recommends that companies design trials that assess specific markers in patients, because these will establish the clinical validity of the therapy and device. An alternative approach would be to use prospective-retrospective studies, which rely on a plan to collect specimens and then retrospectively analyze them.

When the accompanying device is used outside of its indication during the clinical trials, the agency warns that it should meet the requirements of the investigational device exemption.

Read the draft guidance here: www.fdanews.com/07-14-16-DraftGuidanceDevelopmentofTherapyWithDevice.pdf. — Tamra Sami, José Vasquez

Theranos, *from Page 1*

and patients and also voided results for some tests. In addition to filing a plan of correction, the company suspended further testing (*IDDM*, May 20).

But the firm's response did not go far enough, and CMS said the seriousness of the deficiencies resulted in "immediate jeopardy to patient health and safety."

CMS had threatened sanctions in March if the company could not provide acceptable evidence of correction for the deficiencies.

After receiving unacceptable responses from Theranos, the agency issued a 33-page imposition of sanctions notice on July 7. The letter details a litany of quality control failures.

The laboratory failed to submit documentation of any quality control procedures before May 15, 2014, the letter said. When pressed for information, the laboratory conducted a retrospective analysis for 2014 and 2015, and that data noted multiple and recurrent shifts in QC target means, rule failures and QC CVs "far exceeding limits for a stable testing process."

CMS said the QC failures identified by the retrospective analysis "reflect a global and long-term failure of the quality control program," and the failures "should have alerted the laboratory to correct such an unstable process."

The firm provided patient records via flash drives to the agency, but CMS said the information on the drives was difficult to evaluate because records were spread over numerous drives.

"We are uncertain as to what the laboratory intended to submit as a 'complete record' for each corrected patient test report submitted," the CMS letter said. "Consequently, we could not determine whether the laboratory provided documented evidence showing what corrective actions were taken for all patients found to have been affected by the deficient practice, and what corrective actions were taken for any other patients."

The company has 60 days to appeal the determination to revoke the CLIA certificate. The sanctions also impose a civil monetary penalty of $10,000 per day for each day of noncompliance beginning July 12. The agency directed the firm to provide within 10 days a list of the names and addresses of all physicians and clients who have used some or all of the laboratory's services from January 2014 to now.

Theranos said it was working closely with CMS to resolve the sanctions. "It's important to note that the CMS review pertained to the operations of the company's Newark lab, not its technologies," Theranos said.

"We accept full responsibility for the issues at our laboratory in Newark and have already worked to undertake comprehensive remedial actions. Those actions include shutting down and subsequently rebuilding the Newark lab from the ground up, rebuilding quality systems, adding highly experienced leadership, personnel and experts, and implementing enhanced quality and training procedures."

"If the revocation of Theranos' Newark lab's CLIA certificate takes effect, it automatically prevents the company from operating any labs for a two-year period; that means the Arizona lab would cease to operate," the firm said.

Congress Wants Answers Too

Members of the House Energy and Commerce Committee also want answers, and they sent a letter to Holmes requesting information about the company's compliance program.

"Given Theranos' disregard for patient safety and its failure to immediately address concerns by federal regulators, we write to request more information about how company policies permitted systematic failures of federal law and how Theranos is working with regulators to address those issues," the letter said.

Specifically, the committee requested the CEO to brief committee staff on the following issues:

- How is Theranos working with regulators to come into compliance with federal law?

(See **Theranos**, *Page 10)*

UK Issues Guidance on Remanufacturing Single-Use Devices

Devicemakers in the UK that remanufacture single-use devices must accept all the obligations and liabilities that an original manufacturer would face, the regulator said.

The UK's Medicines & Healthcare products Regulatory Agency issued its first formal guidance on remanufacturing single-use devices; however, it notes that the medical device directives "do not explicitly permit remanufacturing or reprocessing."

Although single-use devices may be manufactured in the UK, the remanufacturer must ensure that the intended use of the device is the same as the original product.

Class I medical devices are excluded from this policy, however, because there would be no external or independent assessment of CE mark compliance.

The guidance also notes that supply of a remanufactured single-use device (SUD) should be through a closed-loop contract between the remanufacturer and the healthcare provider. "At no time should a remanufacturer or healthcare institution sell or provide a remanufactured SUD to any other third party," it clarifies.

Notified bodies should verify that remanufactured devices meet all the appropriate criteria in terms of performance and safety and should confirm "validity and surety of all manufacturing processes."

The remanufacturer also must determine via clinical and technical testing the maximum number of remanufacturing cycles which the device should be subjected to. It also must track the number of times the device is remanufactured and used.

The guidance also lists requirements for decontamination, cleaning, sterilization, labeling, risk management and postmarket surveillance activities.

Labeling and packaging must include a symbol indicating that the product is a single-use device to be used only once. The remanufacturer also should identify itself on the label with a serial number and unique identifier to ensure traceability.

Read the guidance here: www.fdanews.com/07-14-16-UKsingle-usedevices.pdf. — Tamra Sami

Zimmer Warning Letter Reveals Numerous Quality Deficiencies

Zimmer Biomet had hinted at a warning letter in an SEC filing last month but revealed little details about the exact nature of the deficiencies uncovered at the firm's facility in Montreal, Canada.

Posted to the FDA's website on July 11, the letter revealed numerous serious quality system deficiencies, including CAPA, complaint handling, supplier audits, medical device reporting and maintaining adequate records.

The Canadian facility is the principal location for Zimmer's wholly owned subsidiary ORTHOsoft.

CAPA procedures were found to be lacking because the firms procedures didn't describe how data would be analyzed to detect recurring quality problems. CAPA procedures didn't include requirements to verify or validate that corrective and preventive actions were effective, nor did the firm's procedures ensure that the quality unit was notified about nonconforming products.

FDA inspectors also took issue with the firm's procedures for handling complaints. For example, eight out of 14 complaints reviewed didn't include a medical device report determination, and the firm's procedures didn't require that complaints were handled in a timely manner.

The firm also had not established criteria for auditing suppliers, nor had it established procedures for its own internal quality audits, the warning letter said.

The letter also cited the firm for not reporting removals from the market within required timeframes.

The firm received a Form 483 in January for similar deficiencies, the company stated in a June 6 SEC filing (*IDDM*, June 10).

The firm did not respond to a request for comment. Read the warning letter here: www.fdanews.com/07-15-16-ZimmerWL.pdf. — Tamra Sami

FDA Issues Guidance To Support EMC Claims

The FDA is providing devicemakers with clarity on what to submit to support claims of electromagnetic compatability for premarket submissions, humanitarian device exemptions, premarket notifications and *de novo* requests.

The agency provides a checklist of what manufacturers should include in their submissions for electrically powered medical devices in final guidance issued July 11. The final guidance is little changed from draft guidance released in November 2015.

The most notable change is the addition of the requirement that manufacturers define the environment for which the medical device is intended to be used.

Devicemakers should also include the following to support EMC claims:

- A summary of the testing that was performed to support EMC and the specifications of the standard that were met;
- A summary of the device-specific pass/fail criteria used;
- The specific functions of the device tested and how these functions were monitored;
- Specific information about the performance of the device during each test;
- An identification of and a justification for any of the standard's allowances that were used;
- A description of and justification for any deviations from the specification of the referenced standard;
- The device labeling and evidence of compliance with the reference standard's labeling; and
- A detailed description of all changes or modifications that were made to the tested version of the device in order to pass any of the EMC tests. — Tamra Sami

OOS Products, Internal Audits Cited in Morris Form 483

Morris Innovative received a six-observation Form 483 for its handling of out-of-specification products, internal audits and CAPA issues.

The head of quality for the Bloomington, Ind., company conducts all internal audits, including for functions he oversees, according to the Jan. 26 form. Those functions include complaint handling, CAPA and management reviews. The form also notes that management with executive responsibility had not reviewed the quality system's effectiveness at set intervals.

The company released product lots with OOS data points, but it had no evidence that it identified, investigated or handled nonconformance the way its process requires. Six out of 11 device history records reviewed during the inspection included OOS data points.

During the inspection, management told the FDA that a testing apparatus had not been validated or qualified, despite the fact that it had been in use since 2007.

The form also called out CAPA issues. For example:

- Verification of effectiveness is not required in the company's CAPA or nonconforming product procedures. One CAPA on tip protectors dislodging was closed in February 2013 without evidence of verification. Another CAPA was opened in November 2013 for the same issue but the company took a different corrective action;
- One CAPA was opened more than two months after a complaint on failure of the CB hub during a surgery. This was about seven weeks after a second complaint for the same issue; and
- CAPA and nonconforming product procedures do not discuss analysis of sources of quality data.

According to the form, Morris' management "confirmed that it has not recently conducted such analysis of data."

Out of 17 complaints received since February 2013, none had evidence of evaluation to determine if an investigation was needed. "Your management explained that it did examine product in inventory but could only produce documented evidence that this occurred for one of the 17 complaints," the form says.

Morris Innovative could not be reached by press time. The Form 483 is available at www.fdanews.com/06-28-16-Morris.pdf. — April Hollis

Gel Maker Pleads Guilty to Criminal Charges for Contamination

Pharmaceutical Innovations pled guilty to criminal and civil charges arising from its distribution of ultrasound gel contaminated with bacteria, according to the Department of Justice.

The Newark, N.J.-based company was charged with two misdemeanor counts of introducing adulterated medical devices into interstate commerce. The company was placed on probation for two years and ordered to pay a criminal fine of $50,000 and to forfeit an additional $50,000.

A related civil settlement was also resolved on July 6, under which the company agreed to destroy gel products that tested exceptionally high for infectious bacteria. The firm agreed to a consent decree of permanent injunction that requires independent auditors to conduct regular inspections at the company's expense.

The charges link back to 2012 when a Michigan hospital reported 16 patients with bacterial infections believed to be associated with Pharmaceutical Innovations' gel.

DOJ filed suit in October 2014 against the company and its founder and owner. The civil complaint alleged that the company was selling unapproved devices, and that it was violating GMP regulations.

The consent decree of permanent injunction requires the company to submit a detailed compliance plan to the FDA within 20 days.
— Tamra Sami

Poor Supplier Controls Net 483 for Fluke Biomedical

Fluke Biomedical was handed a five-observation Form 483 because it failed to properly select any of the suppliers for its CLEAR-Pb X-Ray shielding products.

The Cincinnati-based company's supplier assessment request form — used to qualify suppliers — does not require quality system information to evaluate their ability, according to the Feb. 9 Form 483. Four out of the five suppliers had no certification, such as ISO, and no documented evidence of an adequate quality system. Additionally, Fluke did not determine whether they validate and monitor processes for manufacturing Fluke's components.

According to the purchasing procedure, if a supplier has a quality rating of less than 80 percent for three months in a row, Fluke must review the nonconformities, conduct evaluations, share the results with the supplier and open a supplier corrective action. The company gave an unacceptable rating to one of its suppliers since at least March 2015, but there was no evidence of supplier communications or a supplier corrective action request.

According to Fluke's supplier handbook, supplier status should be noted on an approved supplier list. However, this was not the case for any of the CLEAR-Pb suppliers.

Meanwhile, the company does not have a dedicated area to segregate nonconforming products. "During this inspection, nonconforming product was found in the same area as released and un-inspected product," the form says.

It also notes that according to the company's deviation procedure, "a deviation is a temporary or short-term approval of a change that is applied to a limited number of units or components." The inspection found Fluke had been creating temporary deviations for nonconforming product from one supplier since at least June 2011.

A review of eight returned material authorizations over the past three years showed three instances that appeared to meet the definition of a complaint for the CLEAR-Pb radiation shield products. However, the company had not opened any complaint files.

A review of nine device history records over the past year of shipments for the mobile radiation shield also showed Fluke is not following its procedures for device history records. For example:

- There is no documented release or QA review of product before shipment;
- Nonconforming components are not linked to specific device history records, which means the company cannot identify which devices were shipped with nonconforming components;
- Fluke did not document the results of inspection activities; and
- The company's testing specifications for components do not always match the drawing/specification for the component.

Fluke did not respond to a request for comment by press time. The Form 483 is available at www.fdanews.com/06-28-16-Fluke.pdf. — April Hollis

FDA Approves MRI-guided Ultrasound for Tremors

The FDA approved InSightec's focused ultrasound device to treat essential tremors in patients who have not responded to medication.

ExAblate Neuro uses magnetic resonance images to deliver focused ultrasound to destroy brain tissue in a tiny area thought to be responsible for causing tremors.

The condition is also treated with beta blockers or anticonvulsants, and when medications fail to control symptoms, essential tremor can be treated with surgery or a deep brain stimulation device.

Those undergoing treatment, lie in an MRI scanner that takes images to help a doctor identify the targeted area in the brain's thalamus. Treatment with transcranial focused ultrasound energy is administered with incremental increases in energy until patients achieve a reduction of tremor. Patients are awake and responsive during the treatment.

NGS Guidance, *from Page 2*

seeking recognition of their genetic variant database should contact the FDA through the pre-submission program.

The guidance stresses the importance of public databases because much of the data that could be used to support clinical validity of NGS-based tests are not publicly accessible. Aggregation of clinical genotype-phenotype associations and evaluating that evidence would promote rapid translation of genetic information into useful clinical evidence.

The agency defines a "genetic variant database" as a publicly accessible database that aggregates and curates reports of phenotype-genotype relationships to a disease with publicly available documentation of evidence supporting those linkages.

In interpreting data, the guidance stresses the importance of using qualified experts to make informed conclusions about genetic variants and their meaning for clinical decisions.

The guidance draws parallels between the use of evidence standards with the types of evidence to support FDA premarket submissions. As such, clinical validity is based on the "totality of available evidence" and not on isolated case reports or summary literature.

Comments are due Oct. 6. Read the guidances here: www.fdanews.com/07-13-16-NGSpublicdatabase.pdf and here www.fdanews.com/07-13-16-NGSclinicalguidance.pdf. — Tamra Sami

Theranos, *from Page 4*

- How has Theranos changed its internal policies to prevent future compliance issues associated with its laboratories?
- Is Theranos conducting an internal investigation into company policies and the actions of relevant personnel to determine the root cause of these widespread compliance failures?
- What steps is Theranos taking to assist medical professionals and patients who may have been harmed by inaccurate test results?

Read the E&C letter here: www.fdanews.com/07-12-16-CongressTheranos.pdf, and the CMS letter here: www.fdanews.com/07-12-16-TheranosCMS.pdf. — Tamra Sami

FDA Approves Absorbable Stent

The FDA approved Abbott's fully absorbable stent to treat coronary artery disease. The Absorb GT1 Bioresorbable Vascular Scaffold System releases everolimus to limit the growth of scar tissue and is gradually absorbed by the body in roughly three years.

The drug-eluting stent is manufactured from a biodegradable polymer called poly(L-lactide), which is similar to materials used in other types of absorbable medical devices, such as sutures. The device's absorption by the body gradually eliminates the presence of foreign material in the artery once the stent is no longer needed.

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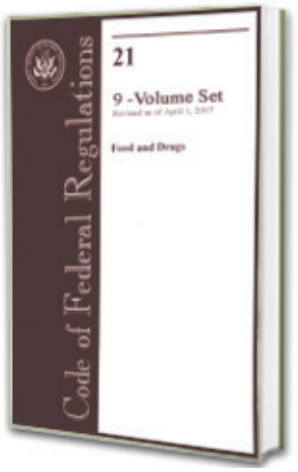

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