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INSIDE THIS ISSUE

Inside Washington: What's Going on with Regulation of LDTs?

Although things appear to be quiet, progress is actually being made in the quest to create workable regulation of Laboratory Developed Tests (LDTs) developments. Here's a rundown of the latest developments and what to expect going forward.

From DAIA to VALID

Impetus for LDT regulation was initially supplied by the FDA. But after a pair of flaccid draft proposals followed by the agency's decision not to meet the December 2016 deadline for a final proposal, the epicenter shifted to Congress starting with a bi-partisan bill called the Diagnostic Accuracy and Innovation Act (DAIA) proposing to remove diagnostic tests from the definition of a medical device and thus not subject to the FDA's 510(k) process for medical devices requiring test makers to compare their assays to predicate products approved in the 1980s. DAIA would instead establish a new system for regulating in vitro clinical tests (IVCTs).

The FDA countered with a proposal that would keep LDTs within

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FDA Watch: Agency Okays EIA Technology-Based Lyme Assays

Laboratory diagnosis of Lyme disease is based on detecting the presence of antibodies against Borrelia burgdorferi, the bacteria that causes the disease, in a patient's blood. Traditional testing uses a two-tier approach in which a pair of enzyme immunoassays (EIA) are performed followed by a separate protein test called a Western blot to confirm a Lyme disease diagnosis. But on July 29, 2019, the FDA broke new ground by clearing for the first time ever tests that follow a different model relying only on EIA technology-based tests which can be run concurrently or sequentially. The products which were approved via the FDA 510(k) pathway were all developed by Branchburg, NJ-based Zeus Scientific, including:

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the 510(k) framework but modernize predicate device performance criteria and create an alternative 510(k) pre-certification pathway for certain "well-understood" product types.

In response, the original sponsors of DAIA incorporated the FDA's ideas, including the pre-certification program concept, into a new bill called the Verifying Accurate, Leading-edge IVCT Development (VALID) Act. Unlike DAIA, the VALID Act makes FDA's authority to regulate IVCTs, and therefore LDTs, explicit. The aim is to establish a framework for overseeing IVCT's at the FDA.

The lab industry had a mixed reaction to the new approach, signaling interest in the idea of a pre-certification process for IVCTs while expressing concern with the FDA proposal's lack of a clear timeline.

Takeaway: VALID 2, VALID 3, VALID 4, etc.

Meanwhile, it appears that the Congressional sponsors of the VALID Act are planning to propose an updated version of the legislation built around pre-certification process idea. But while consensus is building and progress is being made, there's still a lot of work to be done. Speaking at a recent conference, ACLA President ***Julie Khani*** *suggested that VALID 2 may not be the last iteration of legislation and that working out the details of a pre-certification process for LDTs will be a multiyear process.*

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Enforcement Actions: Doctors Pay $1.1 Million to Settle Genetic Test Kickback Claims

Kickbacks for genetic test referrals has become a focus of recent federal enforcement action. The most recent case involves three doctors and a cardiology practice that allegedly accepted bribes from a now-bankrupt genetic testing company in the Seattle area. The DOJ claims that Natural Molecular Testing Corporation (NMT) paid doctors as much as $10,000 per month in consulting fees in exchange for referrals of high-complexity tests that were billed to Medicare. Rather than risk a trial, three doctors and the practice, all based in Alabama, agreed to settle the claims for a combined $1.1 million.

In 2015, after entering Chapter 11, NMT settled claims related to its part in the scheme for $71.1 million. Claims against the lab included not only payment of kickbacks but also the medical necessity of the tests performed, a lack of documentation around the completion of the testing, multiple billing claims for the same date of service and use of the test for screening purposes (which Medicare doesn't cover).

FDA Watch: FDA Issues Guidance on Submitting NGS Data for Antiviral Drugs

On July 18, the FDA issued final guidance on submission of next-generation sequencing (NGS) data from resistance assessments performed in the development of antiviral drug products. The new Technical Specifications document (Tech Doc) provides nonbinding recommendations on acceptable NGS platforms and the types of information the FDA is looking for sponsors to submit, including NGS protocols and data analysis methods.

What's At Stake

Developers of antiviral drugs and related diagnostic tests use NGS to perform sequence-based resistance analysis. But while NGS allows for analysis of individual viruses within a viral population, the data it generates is highly complex and hard to validate, especially since there are currently no standardized bioinformatics analysis approaches for analyzing these large datasets. The significance of the new Tech Doc is in helping sponsors submit next generation nucleotide sequence analysis procedures and data in support of resistance assessments for the development of antiviral drugs and related tests. Specifically, the Tech Doc provides crucial guidance on six key issues.

1. Which NGS Platforms Are Acceptable

The Tech Doc says that the FDA Division of Antiviral Products (Division) will accept nucleotide sequencing data generated from most standard NGS platforms as long as the sponsor submits:

- The appropriate details for the sequencing platform;
- The protocols used for sample preparation;
- The raw NGS data in fastq format; and
- The methods used to analyze the data.

Sponsors should communicate with the Division early in the process and submit a mock NGS dataset before any formal submissions to verify that the appropriate data formats and processes are acceptable.

2. Information about NGS Protocol

Sponsors should also submit a detailed NGS protocol that includes six design elements:

- A description of the subjects, study time points and sample matrices to be analyzed;
- A description of the NGS platform and all associated performance characteristics;
- Target gene region name(s) and size(s) to be analyzed;
- A description of the general analysis strategy;

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The coverage level to be attempted (the Tech Doc recommends a target for coverage of greater than 5,000 reads while recognizing that this may not be possible for samples with lower viral loads); and

A description of the approach used to identify, filter or process sequencing errors.

3. Frequency Tables

Sponsors should provide a frequency table reporting all amino acid substitutions that differ from baseline at frequencies greater than or equal to 1%. The Tech Doc includes a model frequency table:

Model Frequency Table

STUDYID	USUBJID	NGSPL	VISIT	AAPOS	AAREF	AASUB	TCOV	VCOV	AAFREQ
ABC123-999	0123	Illumina	BL	81	R	K	4317	156	0.036
ABC123-999	0123	Illumina	BL	98	K	R	2841	99	0.035
ABC123-999	0123	Illumina	Day 2	98	K	R	9487	366	0.039
ABC123-999	0123	Illumina	Day 3	98	K	R	9474	378	0.040
ABC123-999	0123	Illumina	BL	120	R	Q	4310	200	0.046
ABC123-999	0123	Illumina	Day 2	120	R	Q	12722	470	0.037
ABC123-999	0123	Illumina	Day 3	120	R	Q	12466	489	0.039
ABC123-999	0123	Illumina	BL	147	I	V	3456	742	0.215
ABC123-999	0123	Illumina	Day 2	147	I	V	13456	2709	0.201
ABC123-999	0123	Illumina	Day 3	147	I	V	13297	1934	0.145
ABC123-999	0123	Illumina	BL	150	A	V	3107	43	0.014
ABC123-999	0123	Illumina	Day 2	150	A	T	13116	167	0.013
ABC123-999	0123	Illumina	BL	154	K	R	2987	124	0.042
ABC123-999	0123	Illumina	Day 2	154	K	R	13434	1350	0.101
ABC123-999	0123	Illumina	Day 3	154	K	R	13077	1206	0.092
ABC123-999	0123	Illumina	Day 3	155	R	K	12459	9837	0.781
ABC123-999	0123	Illumina	Day 3	156	P	S	13385	172	0.013
ABC123-999	0123	Illumina	BL	186	V	I	6155	129	0.021
ABC123-999	0123	Illumina	Day 2	186	V	I	17698	269	0.015
ABC123-999	0123	Illumina	Day 3	186	V	I	16474	460	0.028
ABC123-999	0123	Illumina	BL	206	K	H	9698	165	0.017
ABC123-999	0123	Illumina	Day 2	206	K	R	24601	292	0.012
ABC123-999	0123	Illumina	Day 3	210	S	N	23001	255	0.011
ABC123-999	0123	Illumina	Day 3	254	H	R	25145	290	0.012

STUDYID = study protocol number; **USUBJID** = unique subject ID; **NGSPL** = next generation sequencing platform used for sequencing; **VISIT** = study visit that the sample was collected from; **AAPOS** = amino acid position in the target gene; **AAREF** = amino acid present at this position in the reference sequence; **AASUB** = amino acid substitution detected by sequencing; **TCOV** = total coverage at the nucleotide site; **VCOV** = total coverage at the nucleotide position of the variant; **AAFREQ** = frequency of the substitution detected; **BL** = baseline.

4. Information about Sample Preparation

Noting that the key to reliable sequencing results is sample preparation and ensuring that the sample sequenced is representative of the population analyzed, the Tech Doc recommends that sponsors list their methods for:

- Extracting nucleic acids from samples;

- Purifying viral sequences from contaminating background nucleic acids;
- Concentrating viral nucleic acids, including the estimated target copy number input for reverse transcription polymerase chain reaction (RT-PCR) (viral RNA) or PCR (viral DNA) reactions for each sample;
- Denaturing secondary structure;
- Generating double stranded DNA (dsDNA), including a description of the primers;
- Purifying dsDNA for sequencing;
- NGS library preparation; and
- Adding barcodes for multiplexing (if applicable).

Additional Standards for PCR Amplification

The Tech Doc says that any protocol that uses a PCR amplification step before NGS should provide evidence that amplifications are representative of the target population and that minor variants would still be present in the NGS data. The FDA recommends using approaches that correct for PCR resampling bias and (RT-)PCR and sequencing error, such as complementary DNA barcoding.

5. Information about Data Analysis & Reporting Results

Submissions of sequence data must include a thorough description of the analysis pipeline used to analyze the sequencing dataset and the raw sequence information so that the Division can conduct an independent analysis of the data. That would include the following information:

- Summary statistics for each sequence run, including total number of reads sequenced per sequence run, quality scores and average length of reads;
- A description of how sequence barcodes were processed;
- Contig and mapping reports—the Tech Doc recommends two data analysis approaches and establishes standards for each: i. mapping of short reads to a reference sequence; or ii. de novo assembly of short reads to assemble contigs.

6. Which Data File Types Are Acceptable

The Tech Doc calls on sponsor to provide all of the raw NGS data from each sequence run in the fastq format, which may also include an assembled read mapping in .fas, .ace, .sam, or .bam formats along with the appropriate reference sequences and accession numbers used for any reference mappings. For reference mapping to a baseline sample or gene of interest, the sponsor should provide the baseline or reference consensus sequence

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and state how this sequence was derived. For de novo assemblies, the sponsor should provide all contigs greater than 200 nucleotides in the fastq format.

The raw NGS data and frequency tables should and frequency tables should be sent to the Division on a secured, portable hard drive following the FDA Transmitting Electronic Submissions Using eCTD Specifications (April 2019) guidelines. Don't include any additional files on the hard drive, e.g., .exe extensions, or the submission may be rejected.

Takeaway: The new Tech Doc should make it easier to use NGS data to secure approval for antiviral drugs and companion tests. Although it's final guidance, the FDA is still accepting public comments on the document.

LDTs: FDA Gets Tough with Non-Approved PGx Testing Claims

The FDA has apparently set its enforcement sights on Laboratory Developed Tests (LDTs) that claim to predict patients' responses to medications. It began in 2018, when the FDA warned consumers and doctors that pharmacogenetics services (PGx tests) making such claims without premarket clearance or approval have not been validated. Since then, the FDA has been active in regulating labs offering PGx testing and services.

The FDA's PGx Concerns

PGx tests look for and report genetic variants that are associated with drugs, explains **Steven Tjoe**, an attorney with Goodwin Procter LLP in Washington, D.C. and former regulatory counsel in FDA's Center for Devices and Radiological Health. Genetic variants occur throughout the population. Some are benign, some may be known to cause specific diseases, and others may be associated with variable response to specific medications. These variants occur in genes that, for example, code for drug-metabolizing enzymes or drug targets.

Thus, test results might suggest that a doctor or a patient should adjust the dosage of a medication or choose a different drug altogether. But, Tjoe explains, the FDA's position is that there may be insufficient evidence to support claims for how a patient will respond to specific medications for PGx tests the FDA hasn't reviewed.

The November Warning Shot

On Nov. 1, 2018, the FDA issued a Safety Communication to alert patients and physicians that genetic lab tests which purport to predict a patient's

response to specific medications have not been reviewed by the FDA and may not be supported by sufficient scientific or clinical evidence. The FDA cites genetic tests that claim to be capable of predicting whether certain medications used to treat depression may be less effective or have an increased chance of side effects. The relationship between variations and the effectiveness of antidepressant medication has never been established, the Safety Communication states. So, changing drug treatment based on the results from such tests could result in inappropriate and potentially harmful treatment decisions.

The Follow-Up Enforcement

In the Safety Communication, the FDA also says it's looking into certain developers that may be inappropriately selling genetic tests for the unapproved uses and will take compliance actions when appropriate. Since the Safety Communication was published, the agency has, in fact, directed its attention to several firms over the marketing of predictive medication response PGx tests where the relationship between genetic (DNA) variations and the medication's effects hasn't been established.

In April, the FDA issued a warning letter to Inova Genomics Laboratory for marketing genetic tests that claim to predict patients' responses to specific medications without FDA clearance or approval See *Lab Industry Report (LIR), April 29, 2019*. In response to that letter, Inova has reportedly stopped offering its PGx tests. Inova is far from alone, says Tjoe, with other labs similarly being contacted by FDA regarding their PGx test offerings.

Impact on Labs

Tjoe notes that labs offering PGx tests, including those that haven't gotten an FDA warning letter, are currently trying to figure out what to do. Many labs have reportedly stopped reporting drug information and no longer mention any drugs on their websites and marketing materials. Tjoe advises clinical labs that are reviewing their LDT marketing materials, test menus, test reports and other labeling to closely monitor the FDA's actions while being cognizant of the agency's past compliance activities and concerns in initiating this latest round of enforcement action.

Perspective: Recognize that the FDA's current enforcement activities against clinical labs offering PGx tests as LDTs are part of the larger discussion among the agency, Congress, regulators and labs about whether and how to regulate LDTs (See the related story on page 1.) Labs need to pay close attention to these conversations, not only for clues as to FDA's enforcement priorities but also to see what the FDA, Congress and other regulators will actually do about LDTs regulation.

Newly Proposed: CMS Hospital Transparency Rules & their Impact on Labs

It's an all too common occurrence. You or a loved one require an in-hospital procedure, but you have no idea of what the out-of-pocket costs will be. Afterwards, you get hit with an enormous bill that you have to struggle to pay. But now CMS is trying to fix that problem. Proposed new "consumer-friendly" price transparency rules require hospitals to publish more detailed price information so that patients can determine what they'll have to pay before accessing care. "All Americans have the right to know the price of their healthcare up front," said CMS Administrator **Seema Verma** in a press release. But while it may sound good, the new rules may also have some unforeseen and unfavorable ramifications not only for hospitals but also labs.

Medicare Price Transparency

Price transparency for Medicare hospitals isn't a novel idea. On Jan. 1, 2019, CMS began requiring hospitals to publish retail charges for healthcare services, a move which has been criticized as unhelpful to consumers since patients rarely pay those rates. (See *National Intelligence Report (NIR), Sept. 24, 2018*.) The new proposed rule issued in late July would go a step further by requiring hospitals to publish not only their gross charges, or list prices, but also the negotiated price by specific payer and plan for a set of "shoppable" services. Such services could include anything that can be scheduled by a patient in advance.

What the New Transparency Rules Require

If the proposed rule becomes law, starting on Jan. 1, 2020, hospitals would have to make real negotiated prices known to patients. Specifically, hospitals would be required to make public their "standard charges" for both gross charges and payer-specific negotiated charges for all items and services.

Pricing information would also have to be available on the Internet in a machine-readable file and include information such as common billing or accounting codes used by the hospital, along with a description of the particular item or service. The pricing information would also have to be "consumer friendly" and include payer-specific negotiated charges for common "shoppable" services.

"Shoppable services" are those that can be scheduled by a healthcare consumer in advance, theoretically in the interest of shopping out the best price or deal. That would, of course, include most lab tests, as well as x-rays, outpatient visits, imaging tests and bundled services like pre- and post-delivery care and cesarean deliveries.

Hospitals would have to display negotiated charges for at least 300 services, including 70 selected by the CMS and 230 selected by the hospitals. The

services could include both inpatient and outpatient procedures and affect all patients, not just Medicare beneficiaries. (CMS cites the Public Health Service Act as the source of its authority to impose these pricing requirements on hospitals not in Medicare.).

"Consumer-friendly" means the hospital charge information must be made public in a prominent location online (or in written form upon request) that's easily accessible, without barriers, and searchable. Product and service descriptions would also have to be in "plain language" with the shoppable service charges displayed and grouped with charges for any ancillary services the hospital customarily provides with the primary shoppable service. Hospitals would also have to update their posted pricing information at least annually.

The agency also said it wants to enforce the price transparency requirements by monitoring, auditing and imposing civil monetary penalties of up to $300 a day and more than $100,000 per year for hospitals that don't comply.

What the Transparency Rules Don't Require

However, the CMS transparency proposal stops short of requiring hospitals to post patient-specific price information, e.g., information showing particular patients where they are in meeting their deductibles.

Pushback & Impact on Labs

Hospital and healthcare industry groups are giving the proposal the thumbs down. Rick Pollack, CEO of the American Hospital Association (AHA), in a press release stated that requiring hospitals to post negotiated rates "could seriously limit the choices available to patients in the private market and fuel anticompetitive behavior among commercial health insurers in an already highly concentrated insurance industry." The AHA also questions the legality of the proposal.

There's also real concern about the potential costs and risks associated with the proposed transparency rules, particularly in terms of patient relations and expectations. Standard charges, for example, are based on customary care and don't take into account emergency or acute situations. In other words, standard pricing assumes a best-case scenario which doesn't always prove to be realistic. This puts labs in a ticklish position when actual patient charges end up being higher than the previously quoted prices. The potential result is damage to not only customer relations but the trust on which the patient relationship is based.

Takeaway: While price transparency and consumer empowerment are laudable objectives, the CMS proposal imposes new administrative burdens and puts potential new strains on patient relations. It remains to be seen whether the rule will actually take effect and, if so, with what changes. The deadline for submitting comments is Sept. 27.

Environmental Briefing: New EPA Laws Ban Flushing of Opioids & Other Hazardous Pharmaceuticals

On Aug. 21, a new federal rule took effect banning labs and other healthcare facilities from flushing hazardous waste pharmaceuticals into the sewer system. If you haven't already done so, you'll need to establish protocols and procedures to ensure compliance and avoid stiff penalties.

The New Anti-Flushing Law

The new rule is part of an existing piece of federal environmental legislation called the Resource Conservation and Recovery Act (RCRA), which regulates the treatment, storage and disposal of hazardous wastes. In February, the U.S. Environmental Protection Agency (EPA) published a new Final Rule (Final Rule) extending RCRA to hazardous drugs that harm the environment by, among other things, prohibiting the disposal of hazardous waste pharmaceuticals down the drain.

Who Must Comply?

The new hazardous pharmaceuticals restrictions apply to "healthcare facilities," including:

- Pharmacies;
- Veterinary clinics;
- Physicians' offices;
- Optical and dental providers;
- Outpatient care centers;
- Chiropractors;
- Hospitals;
- Surgical centers;
- Nursing care facilities; and
- Medical examiners, and coroners' offices.

Although clinical labs aren't on the list, they could still be subject to the flushing rules if they're part of a hospital, physician's office or other named facility or if they generate 100 kilograms or less per month of hazardous waste or one kilogram or less per month of acutely hazardous waste.

Facilities that are not subject to the Final Rule include:

- Pharmaceutical manufacturers;
- Production facilities; and
- Other types of generators of hazardous waste pharmaceuticals, including households, farmers, ranchers and fisheries.

The Final Rule also applies to what are called "reverse distributors," i.e., entities such as forward distributors and third-party logistics providers that help healthcare facilities calculate and receive credit from pharmaceutical manufacturers when healthcare facilities have unused pharmaceuticals that are no longer needed.

Takeaway: The maximum fine for violating the new rules is $70,000 dollars per violation, per day. That makes it imperative to establish protocol providing for compliance with requirements for, among other things:

- *Personnel training;*
- *Containers, labeling and handling shipments of hazardous pharmaceuticals;*
- *Reporting incidents involving spills or disposals of hazardous pharmaceuticals; and*
- *Recordkeeping.*

FDA Watch: Agency Okays EIA Technology-Based Lyme Assays, *from page 1*

- The ZEUS ELISA Borrelia VlsE1/pepC10 IgG/IgM Test System;
- The ZEUS ELISA Borrelia burgdorferi IgG/IgM Test System;
- The ZEUS ELISA Borrelia burgdorferi IgM Test System; and
- The ZEUS ELISA Borrelia burgdorferi IgG Test System

In granting 510(k) clearance, the FDA relied on data from clinical studies demonstrating that the alternative modified two-tier test approach is just as accurate as current methods for detecting antibodies for assessing exposure to Borrelia burgdorferi. The FDA also reiterated in announcing the clearance that CDC recommendations should be followed for the diagnosis of Lyme disease and for determining when laboratory tests are appropriate.

New FDA Approvals

Here's a look at other new product approvals announced recently:

NEW FDA APPROVALS

Manufacturer(s)	Product(s)
Zeus Scientific	Clearance for four EIA-based Lyme disease tests (see above for list)
Siemens Healthineers	Clearance for Atellica CH Amylase 2 assay running on firm's Atellica CH Analyzer to measure amylase activity in serum, plasma and urine and diagnose acute pancreatitis
Siemens Healthineers	Clearance for Advia Centaur Zika test to detect immunoglobulin M antibodies to Zika virus in serum and plasma specimens using the Siemens Advia Centaur XP + Advia Centaur XPT systems
Agilent Technologies	Expanded clearance for use of its Dako PD-L1 IHC 22C3 pharmDx assay as companion diagnostic test for Merck's anti-PDL-1 immunotherapy pembrolizumab (Keytruda) for esophageal squamous cell carcinoma (ESCC)
Becton Dickinson	Clearance for BD Phoenix Automated Microbiology System – GN Ceftaroline (0.0156-4 µg/mL)

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FDA Watch: Agency Okays EIA Technology-Based Lyme Assays, *from page 11*

Manufacturer(s)	Product(s)
Drawbridge Health	510(k) clearance for OneDraw A1C Test System, which includes a blood collection device and HbA1c test
Hycor Biomedical	Clearance for Noveos Specific IgE Assay, Capture Reagent House Dust Mite D002, Dermatophagoides Farina
Abbott	510(k) clearance for software modification to the ID Now Influenza A & B 2 test (previously called the Alere i), rapid multiplex nucleic acid assay for detection and differentiation of influenza A and influenza B in patients with respiratory infection symptoms
Roche Diagnostics	510(k) clearance for software modification to its Cobas Influenza A/B test running on Cobas Liat point-of-care system
Healthy.io	Clearance for its ACR LAB Urine Analysis Test System consisting of a smartphone app, color board + ACR reagent strips
iCubate	Breakthrough Device designation for its iC-Myco Assay for detection and identification of potentially pathogenic non-tuberculosis Mycobacterium (NTM)