NSF Health Sciences Medical Device Consulting

Why FDA needs to have more enforcement over lab developed tests (LDTs)

Background: What are IVDs and LDTs and how do they relate to one another?

21 CFR 809 defines In vitro diagnostic (IVD) products as: reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body.

A subset of IVDs falls under the classification of Lab Developed Tests (LDTs), which are intended for clinical use as well as designed and manufactured for use within a single Clinical Laboratory Improvement Amendment (CLIA)-certified laboratory. It is important to note that whether IVDs are cleared or approved, commercially manufactured, or designed and manufactured by laboratories as an LDT, all must meet the IVD regulations. The IVD regulations reside under the Medical Device Regulations, which were created in 1976.

At the time the IVD regulations were enacted, FDA chose to use enforcement discretion on LDTs. The logic behind the enforcement discretion was due to the fact that LDTs were designed and validated within small, high complexity labs to detect rare diseases for which a cleared or approved device was not available. The labs were accredited by the Centers for Medicare & Medicaid Services (CMS) against the CLIA requirements. The high complexity labs employed individuals who had the technical expertise and experience to develop and validate the tests, with the results reviewed by pathologists or MDs who understand the diagnosis and consider the various risks to the patient.

So why does the FDA now want to enforce the IVD regulations on LDTs?

Fast forward to the present, where you have a number of labs loosely using the LDT definition to perform testing under the guise of CLIA. As science and technology advances, and clinical labs expand, the definition of “single lab” has become diluted or rationalized. A single lab is just that. If a clinical lab has multiple sites, it cannot conduct the testing under the LDT status. Over the years, “span of control” has been used to justify that testing is being performed within a “single lab” and thus an LDT can be used at multiple sites among multiple states. The FDA’s intention is to ensure that the LDT expertise to analyze as well as interpret the results and potential risks to patients occurs within that single lab environment.

Today, LDTs are often used in laboratories that are independent of the healthcare provider and manufactured with components and complex instrumentation that are not legally marketed for clinical use. The laboratories rely on software algorithms to generate results and to make clinical interpretations versus the expertise of a medical professional. Finally to exacerbate FDA concerns, technological advances have increased to the point that some LDTs are being used for high-risk diseases and conditions, particularly with personalized medicine. The concern is that without proper medical assessment, patients may be undergoing unnecessary medical procedures or may not be receiving the care they need, putting themselves at risk.

FDA IVD regulations and their impact on LDTs

Under the FDA 510(k) or Premarket Approval process, a company needs to establish and submit the test’s analytical and clinical validity. For clinical labs that fall under CLIA and are regulated by the CMS, there is not the same level of control particularly when it comes to design, consistency

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Why FDA needs to have more enforcement over lab developed tests (LDTs), continued...

and even more importantly – safety and effectiveness. A CLIA lab has the ability to begin testing with an LDT, without having the test validated or establishing the test's accuracy. If a patient "assumes" that test X will give results for Y and medical intervention occurs, who is at risk – the lab, doctor or the patient? Another scenario is a false negative where the patient's results do not lead to medical intervention when it is necessary. Again, where does the liability fall – on the lab, doctor or patient?

With any test, you would want to know that 1) it is reliable, 2) the results are accurate and 3) whether medical intervention is necessary. This is particularly true with personalized medicine. With the advancements in technology, we are now able to diagnosis genetics patterns that could potentially result in cancer. However, it may not necessarily result in cancer development, and a patient needs to have the healthcare provider assess ALL the mitigating factors. If the patient is high risk, it is especially important to have a medical professional weigh the risks rather than rely on a software-generated result. As is known, lifestyle and environmental issues as well as other factors can affect the probability of cancer development. Therefore, it is important when conducting a test to have medical oversight and to understand the risks/benefits of the medical procedure. By using the 510(k) or PMA process, companies have to establish the risks associated with the test as well as the clinical validity and accuracy.

It appears that today, a number of start-up companies are NOT focused on the patient but more on the ability to provide a test. Selling a test to the population at a whole is why the FDA is now concerned. The potential safety risks to patients is one of the key drivers for the agency intervention.

At the end of the day, the FDA and the diagnostic industry, as well as the clinical labs, need to come to a resolution and understand how they can efficiently collaborate to provide patients with effective and accurate tests without causing risks through unnecessary medical intervention.

About the Author

Mary C. Getz, Ph.D. is the Vice President of Quality in NSF International's Medical Devices Division.

Dr. Getz has over 30 years of industry experience, which includes wide-ranging expertise in developing quality, compliance and regulatory strategies within the medical device and pharmaceutical industries. Her industry experience includes 20 years at various Johnson and Johnson (JNJ) subsidiaries, starting on the bench in a microbiology lab at Ethicon and working her way up to VP of Quality and Compliance at both Neutrogena and Biosense Webster. From there she went to Quest Diagnostics, where she oversaw both the CLIA lab and the IVD business as the VP, Quality, Regulatory and Clinical Affairs for the FOCUS Diagnostics business unit. Finally her industry journey took her to Abbott Diabetes Care, where she was the DVP of Quality.

Since leaving industry, she ventured into consulting, where she was a subject matter expert for medical devices and quality systems. In 2012, she joined Becker and Associates, which was acquired by NSF International the same year, to help build the Quality and Compliance group. Her system-based approach has led to effective quality system remediation and implementations within the medical device and pharmaceutical industries. Over the past several years, she has engaged with FDA leadership in the Office of Combination Products as well as within CDRH and CDER, and published two articles on combination products.

Dr. Getz received her Ph.D. in microbiology and molecular genetics from Rutgers University and also has a Black Belt Certification in Six Sigma.

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