The Coalition for CLIA Waiver Reform

CCWR Newsletter, Issue 1 (Aug. 15, 2017)

Changes on the Horizon in CLIA Waived Testing

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On December 13, 2016, the President signed the 21st Century Cures Act into law. The bipartisan Cures Act requires FDA to update certain policies (guidance) for granting CLIA waivers – these waivers are needed to allow diagnostic and screening tests to be run in doctors' offices, urgent care centers, pharmacy clinics and many other points of care. With the right changes to the policies, these sites may be able to offer many more safe and effective testing options to patients, and ultimately deliver better care. You will have the opportunity to participate in the guidance process by submitting comments to FDA once the draft is released later this year. If you'd like to learn more about getting involved in this process, please check our website www.cliawaiverreform.org or contact our General Counsel, James Boiani, at jboiani@ebglaw.com.

What is a CLIA-Waived Test?

CLIA-waived tests are used to provide real-time test results when a patient is at a doctor's office, pharmacy clinic, urgent care center or other point of care setting. Each year, nearly 10 billion *in vitro* diagnostic tests ("IVDs") are performed in the United States. These tests guide important health decisions that healthcare providers and patients make every day. The United States Food and Drug Administration ("FDA") is charged both with deciding whether a test can be sold in the U.S., and assigning a complexity rating that determines which facilities and individuals can conduct a test.

Tests of "moderate" and "high" complexity may only be run by sophisticated laboratories that meet stringent requirements under the Clinical Laboratory Improvement Amendments of 1988 ("CLIA") for personnel training and expertise; quality systems; proficiency testing; facilities; recordkeeping; and sample retention. Most CLIA requirements are waived, however, if a laboratory only employs tests of low ("waived") complexity. These two kinds of labs are (not surprisingly) referred to as "non-waived" and "waived" labs, respectively.

CLIA-waived tests are the only tests that can be run directly at doctors' offices, health and minute clinics, urgent care centers, small rural hospitals, and many other "points-of-care" where patients arrive when they are feeling sick or need a check-up. Because these facilities can only perform CLIA-waived tests, the only way to expand access to the kinds of tests offered here is to have more CLIA-waived tests available.

How Waived Tests Help Patients

The major benefit of waived tests comes from their expediency – the tests are run in-office, and you can get results while you wait as opposed to days or weeks later, which can get people diagnosed and on the road to wellness faster. Also, for people who do not have ready access to healthcare, their one trip to a medical or testing center may be the sole opportunity to get the diagnosis and treatment plans they need. For example, consider patients who –

Can't get to medical and testing centers easily. For many people, a trip to a medical center may be difficult. People may live far away (e.g., in rural communities), lack easy transportation, or hesitate to burden friends and family for assistance; this is an especially prevalent state of affairs for more vulnerable populations, such as seniors. Also economic concerns and disabilities can significantly impact mobility and access to care.

Are afraid of hearing results. This is a real problem in healthcare. "Loss to follow-up" – a medical term that refers to patients who come in for testing but never come back to get results or further treatment – can be very high, especially for the highest risk diseases, such as HIV testing and cancers. A likely reason is that people are simply scared – it can take a lot of courage to make your way into a doctor's office when you're afraid you might have a serious debilitating, or even life threatening illness. A one-time trip may be all a person can handle so they need to get access to the results, counseling, and treatment options all at the same time.

Are overwhelmed. Most people have difficulty balancing the day-to-day struggles of work, family, and life, and do not seek or follow-up on healthcare visits as they deal with what they consider to be more pressing priorities at the time. It's common to put others first.

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For the types of patients discussed above, making even one trip to see a medical professional can be difficult, which makes it important to get the most out of each visit. Increased CLIA-waived testing has the potential to add value to each visit by offering access to in-office tests results that can aid in diagnosis and development of treatment plans when a patient is in the exam room.

How do Tests Get Waived?

There are a few pathways to a waiver. A handful of old tests were waived directly in regulations about 30 years ago, so they receive a waiver automatically. Tests that are intended for use in the home are also supposed to receive a waiver automatically. A third pathway – which is not automatic, and is reserved for most innovative prescriptions tests – is stated in the CLIA waiver law to be for tests "so *simple* and *accurate* as to render the likelihood of erroneous results by the user negligible."

Congress added the words "by the user" in 1997 as part of the FDA Modernization Act ("FDAMA") because regulators were asking the wrong questions when they reviewed CLIA waivers and it was blocking safe and effective CLIA-waived tests from coming to market. The main problem was that regulators were setting a higher standard for tests in the physician's office than the laboratory. Also, it created the need for redundant, time consuming and unnecessary studies to support waivers. Through FDAMA, Congress wanted FDA to "focus on the potential for operator [user] error in performing the test." And for a while, it did, and patients saw the advantages in new CLIA-waived tests, such as the first CLIA-waived HIV test in 2003. Unfortunately, over time, the old thinking has crept back in...

What's the Problem?

Because the old thinking has crept back in, it has become harder to get CLIA waivers for innovative tests which could be helping people at the point-of-care. Some innovators have withdrawn from pursuit of waivers altogether. Others who do try to get through the FDA process can be rejected *not* because the test cannot be performed in the physician's office, urgent care center, or clinic, but because of policies that add unnecessary requirements and years to product development. To understand the problem, it helps to know more about the development of waived tests.

Generally, there are three steps in the development of a CLIA-waived test.

1. An IVD innovator submits studies performed by laboratory professionals.
2. FDA determines the test is sufficiently accurate (sensitive and specific) to be safe and effective for its use (through review of a marketing application like a 510(k) or PMA), and allows the IVD to be used by laboratory professionals in moderate & high complexity laboratories.
3. The IVD innovator later goes back to FDA for a CLIA waiver to expand the use of the IVD to "Certificate of Waiver" sites (e.g., doctors' offices, urgent care centers, etc.) where non-laboratorians, such as physicians,

> nurses, and medical technicians, are permitted to conduct tests, provided that those tests are CLIA-waived.[1]

Logically, these waiver decisions must turn on a single question: are CLIA controls (primarily lab training) used in non-waived labs needed to safely and effectively run a test? If the answer is "no," there is no need to restrict test access to non-waived labs. It also follows that the way to decide if CLIA controls are needed is to compare test performance in waived and non-waived labs. Simple ease-of-use analyses and comparative agreement studies to show results obtained with an IVD by trained laboratorians generally agree with those obtained with the IVD by physicians, nurses, techs, and pharmacists ("untrained" laboratorians) should be all that is needed. However, FDA's CLIA Waiver process does not follow this logic. To further appreciate the problem, it helps to understand the history of CLIA waivers.

Prior to January 2000, the Centers for Disease Control and Prevention ("CDC"), with support from the Health Care Finance Administration ("HCFA"), were tasked with assigning complexity ratings to FDA-approved/cleared tests.[2] The standards that CDC applied for a waiver went far beyond determining whether waived and non-waived labs had comparable test performance. Only tests with high inherent accuracy (i.e., accuracy that depends on both the user and the technological limitations of the test) could receive a waiver.[3] Sometimes CDC required tests to perform better in waived labs than non-waived labs. In at least one instance, CDC denied a CLIA Waiver to a test that FDA had approved for over-the-counter use,[4] meaning anyone in the U.S. could purchase the test and run it anywhere (e.g., home, office, outdoors, non-waived lab, etc.) except in a waived lab. This focus on inherent accuracy was the root cause of lengthy review cycles and high rejection rates during the CDC CLIA Waiver regime.

In response to these problems, diagnostics manufacturers and trade associations advocated for changes that were ultimately adopted in clarifying amendments to statutory standards for CLIA Waivers.[5] The amendments made it clear that a CLIA Waiver determination must focus on test users (non-waived lab expert users vs. waived lab users) by adding three words to the law (underlined below):

> *[CLIA waived tests are] procedures that have an insignificant risk of an erroneous result, including those that— (A) employ methodologies that are so simple and accurate as to render the likelihood of erroneous results* ***by the user*** *negligible.*[6]

Congress made it clear that it wanted this change to mean that the assessment of accuracy "should focus on the test performance 'by the user' and the potential for operator error in performing the test."[7] Later, CDC, HCFA, and FDA agreed to transfer the CLIA Waiver program from CDC to FDA,[8] and in 2001, FDA released new guidance that reflected Congressional intent, saying

> *Based on the legislative history and language incorporated into FDAMA [(the law amending the CLIA Waiver standard)], we interpret "accurate" to mean test performance (i.e., the test performs the same in the hands of untrained users [as] it does in the hands of laboratory professionals under realistic conditions).*[9]

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[1] Sometimes developers will submit "dual applications" for a 510(k) and waiver, but because this process can add years to development during which an innovator cannot sell the test to anyone, it is often not practical.
[2] 64 Fed. Reg. 73561 (Dec. 30, 1999).
[3] *See* Public Health Service, CLIA Program; Categorization of Waived Tests, Proposed Rule (Sept. 13, 1995).
[4] H.R. Rep. No. 105-310, Sec. 21 (1997).
[5] B. Thompson, CLIA Reform: Present and Future, IVD Technology (May 1, 1998).
[6] Codified at 42 U.S.C. § 263a(d)(3).
[7] H.R. Rep. No. 105-310, Sec. 21 (1997).
[8] Memorandum of Understanding Between FDA, CDC, and HCFA regarding transfer of CLIA test complexity and waiver program to FDA.
[9] FDA Draft CLIA (Mar. 2001)

Unfortunately, FDA the decided to re-define "accurate" to follow the old CDC waiver program, and eliminate the focus on user error, redefining "accurate" to mean "those tests that are comparable to a traceable method, in which the results of measurements can be related to stated references"[10] FDA also introduced concepts like "allowable *total* error" into its evaluation of accuracy, which as its name suggests, is the test error from all sources, not just user/lab sources.[11] This new interpretation brought back the very problem Congress tried to correct, and clearly contradicts FDAMA.

So, as it was 20 years ago under CDC, CLIA waivers may not be granted even where tests can be performed equally well in non-waived labs by untrained users and in moderate/high complexity labs by professional users. Using the wrong definition has also led to prescriptive study design recommendations that set many tests up to fail even though they would be safe and effective in the hands of untrained users.

Although some innovative infectious disease tests have received CLIA waivers within the last few years (such as fourth-generation HIV tests, and a rapid test for syphilis)***, these successes took years to achieve and required a significant level of effort and focus to overcome regulatory barriers that do not protect patients and should not have existed.***

For example, FDA waived the Syphilis Health Check on December 15, 2014, over three years after it was originally cleared by FDA as a moderate complexity test. Compare this to the CLIA waiver for Oraquick, the first rapid HIV test, which received a waiver less than three months after its FDA approval in 2003, when FDA was following FDAMA requirements.

Every day needed to receive a waiver matters to patients who will go undiagnosed or untreated but for a CLIA-waived test option. Every additional day also matters to the public health in terms of reducing the impact of disease, preventing infection, and the many other benefits that flow from rapid diagnosis and treatment.

What's the Solution?

On December 13, 2016, the President signed the 21st Century Cures Act into law. The bipartisan Cures Act requires FDA to update certain policies (guidance) for granting CLIA waivers – the waivers needed that allow diagnostic and screening tests to be run in doctors' offices, urgent care centers, pharmacy clinics and other points of care. With the right changes to the policies, these sites will be able to offer more innovative tests and better care.

We believe the solution is to have guidance which adopts the correct definition of accuracy, which Congress has made clear – if "trained" and "untrained" users can perform the test equally well, a test should be waived. Also, there needs to be greater flexibility in how to evaluate accuracy. Several good proposals are available.

How Do I Get Involved?

On or before December 13, 2017, FDA must publish a draft guidance for comment by the public. That means *everyone* will have the opportunity to provide comments within 60 days of seeing the draft. It is important when the guidance comes out to make your opinions known about –

- The value of CLIA Waived testing;
- The importance of following FDAMA;
- The importance of having a system that encourages innovation while protecting the public health.

If you'd like to learn more about getting involved in the process, please check our website www.cliawaiverreform.org or contact our General Counsel, James Boiani, at jboiani@ebglaw.com to join our mailing list.

[10] FDA CLIA Waiver Guidance (Jan. 2008).
[11] *Id.* ("Total Error" is defined as the limit between the differences in the proposed waived method and the reference or comparative method).