Coalition for CLIA Waiver Reform
1227 25th St, NW, Suite 700 · Washington, DC 20037

June 1, 2014

The Honorable Fred Upton
Chairman
House Energy and Commerce Committee
2183 Rayburn House Office Building
Washington, D.C. 20515

The Honorable Diana L. DeGette
House Energy and Commerce Committee
2368 Rayburn House Office Building
Washington, D.C. 20515

Re: 21st Century Cures;
CLIA Waiver Reform

Dear Chairman Upton and Congresswoman DeGette:

We are writing to applaud your 21st Century Cures initiative, and to bring your attention to an important public health issue that our organization – the Coalition for CLIA Waiver Reform – was created to address.

Point-of-care testing – that is, using a diagnostic test where the patient and healthcare provider are located, as opposed to sending specimens to off-site laboratories for testing (and waiting days or weeks for results) – saves time and lives, as well as valuable healthcare dollars. Most true point-of-care testing in the U.S. today is done by CLIA "Certificate of Waiver" laboratories, which represent nearly 70% of all laboratories in the United States. These are the labs you normally find at a physician's office, nursing facility, urgent care clinic, or mobile health clinic. By law, these laboratories must only use tests that are assigned a "waived" (low) complexity rating by the U.S. Food and Drug Administration.

Unfortunately, Certificate of Waiver laboratories are unable to test for many diseases and health conditions. The reason for this is not a lack of technology, nor a lack of patient and clinician need: it is the result of problems with the standards FDA applies when reviewing applications to place diagnostics in the "waived" testing category. These problems have their roots in a misinterpretation of law that you and your colleagues tried to correct in 1997 through passage of the Food and Drug Administration Modernization Act ("FDAMA").

Under CLIA, waived tests are defined to include "procedures that have an insignificant risk of an erroneous result including those that...employ methodologies that are so simple and accurate as to render the likelihood of erroneous results by the user negligible." The "by the user" language is very important. Congress added these words through FDAMA to clarify that the CLIA waiver standard is about the effect that the *user* (operator) has on results. The reason for the focus on the user is that Certificate of Waiver labs, unlike labs that use non-waived tests, are not subject to CLIA requirements regarding expertise and training; the easy-to-use design of the test replaces the need for special user skills.

Everyone agrees that if a user needs special training and expertise to run a test, the test should be restricted to moderate and high complexity testing labs. If, on the other hand, "***the test performs the same in the hands of untrained users [as] it does in the hands of laboratory professionals under realistic conditions***," Certificate of Waiver laboratories should have access to the test.

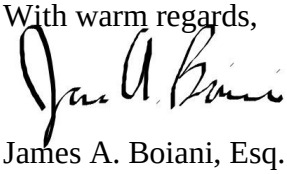
The quoted language above actually comes from a 2001 FDA guidance document; the same guidance also stated that FDA came to this conclusion based on "legislative history and language incorporated into FDAMA." However, FDA changed its interpretation of the law in 2005 through new draft guidance which it then finalized in 2008. Under the new interpretation, for a test to obtain a waiver, it must meet accuracy requirements unrelated to the effect the user has on the test. For example, FDA might effectively demand a test have 90-95% accuracy to receive a CLIA waiver, even though the Agency approved the test for use in non-waived testing labs with 85% accuracy.[1] Further, even if a test can meet FDA's requirements, the required testing generally amounts to a repeat of the clinical study the innovator conducted to receive its original FDA clearance or approval. All of his has three immediate consequences –

1. FDA may not grant a CLIA waiver for a test even if it can be performed equally well by Certificate of Waiver labs and non-waived testing labs.
2. By most program metrics, the performance of the CLIA waiver program is as bad, or worse, than it was in 1997 when Congress first tried to fix situation.
3. The costs of studies to support CLIA waivers have risen exponentially as innovators have tried to accommodate current FDA guidance. Whereas previously a study for a CLIA waiver could be performed for a cost of roughly $50,000, the costs of waiver studies today can well exceed $1,000,000.

All of these consequences are keeping valuable diagnostic tests outside the point of care.

I have attached a brief backgrounder on the issue which provides some additional information on the problems that innovators are facing today and their origins. As we proceed in our work toward regulatory reform, and raising awareness of the value expanded CLIA-waived testing could provide, we will keep the Committee apprised. We would also welcome the opportunity to serve as a resource to the Committee on this issue. If the Coalition can be of service, please contact me at jboiani@ebglaw.com or (202) 861-1891.

With warm regards,



James A. Boiani, Esq.
General Counsel
Coalition for CLIA Waiver Reform

/Attachment

[1] FDA usually imposes these standards by requiring comparison to a "reference method," and through requirements on "total allowable error" of a test; see the attached article for more information.

Legal Backgrounder

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Missing The Point (Of Care): FDA Misreading Of CLIA Waiver Law Undermines Cost-Effective Health Testing

by James A. Boiani and Stuart M. Gerson

The United States Food and Drug Administration's ("FDA") misinterpretation of a single word in the statute establishing standards for granting so-called "CLIA Waivers" has created serious problems for patients and health-care providers alike by restricting access to important diagnostic tests. It is time to fix this problem and bring Americans the health care they deserve and at more reasonable cost.

Laboratory Testing in the U.S. More than 6.8 billion laboratory tests are performed each year in the United States.[1] These tests guide decisions that health care providers and patients make every day in dealing with important health decisions.[2] FDA is charged both with deciding whether a test can be sold in the U.S., and assigning a complexity rating that determines which laboratories 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.[3] 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.

Waived labs account for roughly 60% of the 230,000 clinical laboratories in the United States.[4] The vast majority of waived labs are in physicians' offices and other facilities in close proximity to patients and health-care providers. The closeness of these labs to patients allows for point-of-care testing ("POCT"), where health-care providers get results in real time as opposed to sending patient specimens to off-site laboratories and waiting days or weeks for results. POCT can provide faster diagnosis and treatment decisions, made while a patient is actually in a doctor's office. POCT also may prevent situations where patients fail to return to their provider in order to get the information or treatment they need.[5] In addition some studies have shown that POCT may contribute to improved patient outcomes.[6]

POCT in waived labs also might save health-care dollars. Although large, centralized CLIA labs offer economies of scale, smaller waived labs may have lower administrative costs due to less burdensome regulation, and might reduce ancillary costs (such as specimen transportation and storage). With over 6.8 billion tests being run on specimens annually and a large percentage of testing occurring at off-site, non-waived labs, even pennies saved per test could potentially translate to real economies, especially at a time when health-care dollars are tight.

Logically, waiver decisions must turn on a single question: are CLIA controls 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

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performance in waived and non-waived labs. However, FDA's CLIA Waiver process does not follow this logic, or the law, and is a classic example of history unnecessarily repeating itself.

History of the CLIA Waiver Process. Prior to January 2000, the Centers for Disease Control and Prevention ("CDC"), with support from the Health Care Finance Administration ("HCFA"), was tasked with assigning complexity ratings to FDA-approved/cleared tests.[7] 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.[8] 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,[9] meaning anyone in the U.S. could purchase the test and run it anywhere (home, office, outdoors, non-waived lab) *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.[10] The amendments made it clear that a CLIA Waiver determination *must* focus on test users (non-waived lab experts vs. waived lab users) by adding three words to the law (italicized 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.[11]

The accompanying House Committee report explained that through this change:

> The bill clarifies that this criteria [for a waiver] should focus on the test performance "by the user" and the potential for operator error in performing the test. The purpose of CLIA quality control, proficiency testing, and personnel requirements is to ensure consistent, reliable, and appropriate use of a test system by users of the test. Without the clarifying "by the user," interpretations of "erroneous results" and "accurate" could include the inherent clinical sensitivity/specificity of a test system, parameters that are properly reviewed [in] determining whether to approve of or clear a product for marketing.[12]

In February 1999, CDC, HCFA, and FDA agreed to transfer the CLIA Waiver program to FDA,[13] and in 2001 FDA released new guidance that reflected Congressional intent:

> 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).[14]

Per the guidance, performance by trained technicians in non-waived labs was compared to less sophisticated users' performance in waived labs, and a good correlation meant the test was "accurate" for CLIA Waiver purposes. The fight for a more efficient, and user focused, CLIA Waiver system was apparently won. Then things changed. . .

FDA Strays from the Law. In 2005, FDA abruptly issued a new draft guidance that re-defined "accurate" (and, fairly, removed the statement that its definition was true to "legislative history and language incorporated into FDAMA"):

> [W]e use the term "accurate" tests to refer to those tests that are comparable to a traceable

method, in which the results of measurements can be related to stated references. . .[15]

What this means in laymen's terms is that for FDA to grant a waiver, a test must be shown to be comparable to *another* entirely different test, preferably a gold standard procedure (i.e., the most inherently accurate test).[16] FDA also introduced "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.[17] This gratuitous new interpretation brought back the very problem Congress tried to correct. This new interpretation by FDA was adopted in a final guidance in 2008, despite objections from AdvaMed and others that the guidance was a departure from law.[18]

Why did this happen? One possibility might be issues raised in non-waived lab surveys and CDC studies conducted from 1999 (the year CDC and HCFA agreed to transfer CLIA Waiver responsibilities to FDA) through 2004 (the year before the new guidance was released). Although results of the surveys and studies showed the majority of waived labs "performed tests correctly and provided reliable service," concerns were raised that lack of CLIA controls was resulting in test quality issues, such as users not reading test instructions or performing recommended quality control tests.[19] This information was presented to the Clinical Laboratory Improvement Advisory Committee ("CLIAC"), a multi-agency group that includes CDC and HCFA (now CMS), which advises on CLIA issues and "vetted" the new guidance.[20]

Holding tests to unnecessary accuracy requirements does not address these issues directly (it does not make people read labels or run quality controls), but it does raise CLIA Waiver costs[21] and keeps tests out of waived labs. Perhaps, in light of concerns raised in 2004, FDA – with good intentions – looked for ways to mitigate concerns about waived labs. But the issues raised in the report are best addressed through educational efforts, not limiting test access. Also, with newer instrument-based tests being developed by manufacturers, controls to assure proper use are being built in to prevent these kinds of problems from occurring, so concerns from 2004 do not necessarily translate to concerns of today.

Numbers Don't Lie. The CDC CLIA Waiver redux is now firmly entrenched at FDA, and the results today are sadly similar to what they were prior to the 1997 amendments.

CLIA Applications	CDC (through May 1997)[22]	FDA (FY08-FY12)[23]
Approved	12	15
Denied	8	16
Average Review Time	34 weeks	32 weeks
Longest Review Time	90 weeks	106 weeks

To realize the full benefits of POCT and expand the responsible use of CLIA-waived tests, federal officials need to put the CLIA Waiver process back on track.

Fixing the problem. There are at least three approaches by which the CLIA Waiver process can be brought into compliance with law. Engaging with FDA and the Administration to revisit this issue is one approach. Given that industry objections to the 2005 guidance fell on deaf ears and the "follow the guidance" refrain that waiver applicants hear when they meet with FDA, this approach is unlikely to be effective. But if better health care is the goal of the Administration, reforming the CLIA Waiver process is something it should do right away.

Returning to Capitol Hill might be a more promising option, if a vehicle could be found that Congress would act upon. Advocates successfully lobbied for reform previously and realized some initial gains. The legislation required would be quite simple as well: Congress could simply direct FDA to apply the interpretation of "accurate" from its 2001 draft guidance. There is recent precedent for this approach, found in the 2012

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Food and Drug Administration Safety and Innovation Act, in which Congress required FDA to use a previously developed guidance after a new guidance had been written.[24]

A third option would be to seek relief from the courts. The courts will afford FDA considerable deference in its interpretations of law, but will also consider the text of the CLIA Waiver statute, the legislative history, and FDA's own prior reading of the law. FDA may have misconstrued the CLIA Waiver law so fundamentally that a court could find its interpretation of "accurate" to be arbitrary, capricious, and contrary to law under the Administrative Procedure Act. In addition, given the number of denials that have been issued in recent years, finding plaintiffs with standing should not be a significant hurdle.

Ultimately, whatever avenue is pursued, there is good reason to believe that success will lead to increased access to POCT and better results for the public health.

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[1] The Lewin Group, *Laboratory Medicine: A National Status Report, Prepared for the U.S. Center for Disease Control and Prevention* (May 2008).
[2] *Id.*
[3] 42 C.F.R. part 493, subparts H-M.
[4] COLA, *Patient Centered Laboratory Excellence Program* (Aug. 2012).
[5] A. Taege, *Seek and treat: HIV update 2011*, Cleveland Clinic J. of Med. Feb. 2011 vol. 78 2 95-100 (about 1/3 of patients do not return for test results); K. Workowski et al., *Sexually Transmitted Diseases Treatment Guidelines*, 2010;59(RR12); 1-110 *("*Use of rapid HIV tests [which are CLIA waived] should be considered, especially in clinics where a high proportion of patients do not return for HIV test results.")
[6] *E.g.,* V. Sblendorio and B. Palmieri, *Accuracy of analyses for lipid profile parameters as measured with the CR3000 system*, Eur. Rev. Med. Pharmacol. Sci. 2008 May-Jun; 12(3):191-6; A.F. Rossi and D. Khan, *Point of care testing: improving pediatric outcomes*, Clin. Biochem. 2004 Jun; 37(6):456-61.
[7] 64 Fed. Reg. 73561 (Dec. 30, 1999) (summarizing history of CLIA program).
[8] *See* Public Health Service; CLIA Program; Categorization of Waived Tests; Proposed Rule (Sept. 13, 1995).
[9] H.R. Rep. No. 105-310, Sec. 21 (1997).
[10] B. Thompson, *CLIA Reform: Present and Future, IVD Technology* (May 1, 1998).
[11] *Codified at* 42 U.S.C. § 263a(d)(3).
[12] H.R. Rep. No. 105-310, Sec. 21.
[13] *Memorandum of Understanding Between FDA, CDC, and HCFA regarding transfer of CLIA test complexity and waiver program to FDA*.
[14] Guidance on Clinical Laboratory Improvement Amendments of 1988 (CLIA) Criteria for Waiver: Draft Guidance for Industry and FDA, 10 (Mar. 2001)
[15] FDA Draft Guidance, *Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices* (Sept. 2005).
[16] *Id.; see also* FDA Final Guidance, *Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices* (Jan. 2008).
[17] FDA Final Guidance ("Total Error" is defined as the limit between the differences in the proposed waived method and the reference or comparative method).
[18] AdvaMed Comment to Docket No. 2001D-0044 (Dec. 6, 2005).
[19] MMWR, *Good Laboratory Practices for Waived Testing Sites*, 2005; Vol. 54; No. RR-13.
[20] S. Gutman, FDA, *A CLIA Carol – FDA Perspectives*.
[21] AdvaMed has estimated that a CLIA waiver application would cost $350,000 (primarily due to the accuracy studies being required by FDA) on top of costs required to receive marketing clearance. AdvaMedDx Letter to Docket No. FDA-2012-N-0937. For small companies this is a very large investment that, as shown below, is more likely to result in failure than success.
[22] B. Thompson, *CLIA Reform: Present and Future*, *supra* n. 10.
[23] FDA Quarterly Update on Medical Device Performance Goals, CLIA Waiver Review Times (July 30, 2013).
[24] Food, Drug, and Cosmetic Act § 510(n)(2)(B)-(C).

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