



AdvaMedDx

Vital Insights | Transforming Care

March 28, 2018

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2017-D-5570; Draft Guidance on Select Updates for Recommendations for CLIA of 1988 Waiver Applications for Manufacturers of IVD Devices

Dear Sir or Madam:

On behalf of AdvaMedDx, a Division of the Advanced Medical Technology Association (AdvaMed), we provide these comments on the Food and Drug Administration (FDA) “Draft Guidance on Select Updates for Recommendations for Clinical Laboratory Improvements Amendments (or “CLIA”) of 1988 Waiver Applications for Manufacturers of IVD Devices” (hereinafter “guidance”).

AdvaMedDx member companies produce advanced, *in vitro* diagnostic tests that facilitate evidence-based medicine, improve quality of patient care, enable early detection of disease and reduce overall health care costs. Functioning as an association within AdvaMed, AdvaMedDx is the only multi-faceted, policy organization that deals exclusively with issues facing *in vitro* diagnostic companies both domestically in the United States and abroad. Our membership includes manufacturers engaged in the development of innovative technologies that support the public health in the US and promote timely access at the point of care, including doctors’ offices and clinics from traditional tests to advanced molecular technologies (otherwise referred to as “CLIA waived tests”).

GENERAL COMMENTS

AdvaMedDx appreciates the commitment and activities by the FDA (or “Agency”) to support flexible and efficient approaches to ensure US medical product innovation. The future of innovation is rapidly changing, and the Agency has shown great promise in its efforts to explore ways that better fit with particular technologies and help meet public health needs. The diagnostics industry is committed to providing the best tools to diagnose and treat patients. CLIA waived tests are an example of such critical innovation and cornerstone of modern healthcare. By providing new timely tools for healthcare providers to treat their patients where they receive care, we can help meet unmet needs, harness critical window of care, and support patient care through timely, simple to use tests that help address medical needs for the patient at the point of care.

While AdvaMedDx appreciates the efforts of FDA for development of this revised guidance, the guidance is in need of critical updates to meet the commitment in 21st Cures to support today’s modern healthcare system, promote US medical technology innovation, and ensure timely access to diagnostic tests at the point of care, including doctors’ offices and clinics. Despite their valuable role in health care delivery and the increasing need for simple, portable tests in a modern healthcare system to help serve patients and help combat spread of infectious disease, antibiotic resistance, and beyond quickly and efficiently, innovators remain faced with challenges to help

bring new technologies to the US due to a difficult to understand and one-size fits all approach described in the guidance.

Notwithstanding growing scientific knowledge and extraordinary technological advances over nearly two decades in ease and automation and capability of these tests to be performed equally well in non-waived labs by untrained users as with moderate complex laboratory users, CLIA waived tests remain available for only a limited number of testing areas. Further, the lack of clarity regarding appropriate types of comparison studies for purposes of CLIA waiver has served as a barrier to improvements and advances in state of the art CLIA waived testing. We must work collectively to help support improved patient access to testing.

A clear and understandable policy for these valuable yet simple and easy to use tests will go far to support new product development in the space, including both small and large company innovators who are working to serve unmet patient needs and support efficient, effective care. History is telling in an over 17-year period of policy issuance, revision, redraft, and revision. We believe that industry and the Agency would benefit from, and the public health requires, a more clear, consistent, and adaptable approach that can best accommodate the types of technologies now and into the future and can truly help support 21st Cures at the point of care.

We appreciate the FDA's challenges in developing approaches to accommodate the breadth of testing and efforts to provide comprehensive guidance to assist with the most challenging cases, particularly dual submissions where a product has not yet been approved or cleared and concurrent review is sought. However, we note that, for purposes of this guidance, a more streamlined guidance focused on potential options as Congress made clear in the passage of the FDA Modernization Act of 1997 and again in the 21st Century Cures Act (or Cures Act) enacted in 2016 (or 21st Cures) to evaluate the effect that the user of the diagnostic has on test results is required, not a revalidation of previous elements of safety and effectiveness already established in the premarket review process [Section 3057 aims to "focus on the effect that the user has on results, such as a test performs the same in the hands of untrained users as it does in the hands of laboratory professionals" consistent with 42 U.S.C. Sect. 263a(d)(3)(A), see legislative history]. Through clear, consistent guidance and non-duplicative requirements grounded on the statute as set forth by Congress, we will foster robust, high-quality testing while ensuring a transparent and simple to understand guidance for submitters.

In light of the vital public health imperative for Americans and our shared goal to support the study and approval of beneficial new CLIA waived technologies, we are submitting our specific recommendations in the below proposal along with further specific recommendations. All efforts were made to incorporate necessary flexible study options to reflect the range of testing in today's modern healthcare system and ensure meeting of the Cures commitment in Section 3057 of the Cures Act. We believe these options can be readily implemented, are consistent with shared FDA and industry goals, and will serve the public health through a more clear and understandable policy. We note the proposal is focused on specific requirements for CLIA waiver applications and is not intended to cover assessment of diagnostic tests generally (i.e., FDA premarket review).

To this important end, the attached proposal was developed with stakeholders to help advance patient access to high quality point of care testing improving the public health. It is jointly supported by both AdvaMedDx and the Coalition for CLIA Waiver.

We appreciate your efforts to support U.S. healthcare and look forward to working with you to advance this important public health priority. We are confident that our recommendations will help provide needed clarity in the CLIA waiver process while ensuring confidence in today's modern healthcare system to provide these timely and vital tools for healthcare professionals and their patients at the point of care.

Sincerely,

/s/

Khatereh Calleja
Senior Vice President, Technology and Regulatory Affairs



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The Coalition for CLIA Waiver Reform

AdvaMedDx and Coalition for CLIA Waiver Reform Proposal: Implementation of Section 3057 of the 21st Cures Act— Update of Section V of CLIA Waiver Guidance (2008)

Advancing Innovation in CLIA Waived Testing & Timely Point of Care Diagnostic Information for Physicians and Patients

Background/Purpose

The purpose of this proposal is to outline clear expectations for test developers and FDA in Section V, consistent with Section 3057 of 21st Cures, on how to demonstrate insignificant risk of an erroneous result by CLIA waived users of an *in vitro* diagnostic (“IVD”) for the purposes of CLIA waiver applications. This reflects specific requirements for CLIA waived tests and is not intended to cover requirements for assessment of diagnostic tests generally. CLIA waiver is a separate and distinct process from FDA premarket review for purposes of premarket notification or approval. This is consistent with FDA’s mission to support public health and innovation in the US and promote timely access to technologies at the point of care, including doctors’ offices and clinics.

This document provides proposed revisions to Section V of “Guidance for Industry and FDA Staff: Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices,” (or otherwise referred to as “guidance”) issued in draft updated form on November 29, 2017. This is intended to provide a least burdensome approach for diagnostic developers for demonstrating that there is negligible likelihood of erroneous results in the hands of the user. A developer must meet CLIA waiver requirements in addition to premarket review requirements in order to receive a CLIA waiver.

Overview of Proposed Approach

There are various pathways through which a diagnostic test can be granted a CLIA waiver. One pathway, established by 42 U.S.C. § 263a(d)(3)(A), is a determination by FDA that the test “employ[s] methodologies that are so simple and accurate as to render the likelihood of erroneous results by the user negligible.” An applicant is therefore expected to demonstrate the skill of the user does not have a meaningful

impact on results obtained under intended operating conditions (i.e., as used in Certificate of Waiver testing facilities). The applicant should evaluate the effect that the user of the diagnostic has on test results, not revalidate previous elements of safety and effectiveness.

Study design and analysis must demonstrate that the skill of the user does not meaningfully impact test results for purposes of this section.

For the purposes of this guidance, we define the following user groups:

- Untrained Operator or Waived User: An operator in a waived setting with limited or no recent training or hands on experience conducting laboratory testing beyond testing in a Certificate of Waiver setting, and who has no training on conducting the test to be evaluated.¹
- Trained Operator or Moderate Complexity Laboratory User: A laboratory professional who meets the qualifications to perform moderate complexity testing and/or has previous training in performing the test to be evaluated.

The assessment of “simplicity” in the CLIA Waiver context – which includes evaluation of usability, fail safes, and safe guards to ensure proper use of the device in individuals at any experience level – provides considerable assurance that the transition from trained to untrained users will not adversely affect performance. Apart from CLIA waiver, manufacturer commitment to quality is reflected in CLIA waived product development and design. For example, products can utilize either integrated calibration/control schemes or simple stand-alone materials while maintaining timely and easy-to-use technologies to advance patient care at the point of care in today’s modern healthcare system. The studies to assess whether a test may be shown to render “the likelihood of erroneous results by the user negligible” offer additional confirmation of what is already known from the simplicity assessment addressed elsewhere in this guidance.

Options for Developers

As a follow-up to discussions with FDA, there are several options that may be used to evaluate tests in the CLIA-waived setting, four of which are described below. We believe they reflect least burdensome approaches to support innovation in timely, high quality CLIA waived technologies. While option 1 may be used for most tests to demonstrate comparable results in the hands of untrained and trained operators, we

¹ In general, for evaluating the performance of tests in the real-world setting, untrained users should include a representative sampling of potential users who may be found in a certificate of waiver environment, e.g., physicians, nurses, medical technicians, among others.

offer other options to provide efficient and flexible options to support innovation in CLIA waiver testing for purposes of discussion with FDA. All these options are appropriate and acceptable for purposes of meeting the statutory standard and Section V of the guidance. The sponsor will select the study design, taking into account test considerations, and no preference is indicated for any one approach for applicants (not a one size fits all).

Option 1: Sponsors may demonstrate agreement of test performance in the hands of trained and untrained users. For example, the study may employ trained and untrained users who obtain results with the same test on the same patients and/or samples in a real or simulated environment (i.e., use of surrogate samples). Agreement would be assessed according to pre-specified criteria. These criteria would be developed by the sponsor based on various considerations, including the known inherent variability of the test method and risk profile of the test. Given that the studies are intended to detect significant deviations from what would be expected from design evaluations in terms of obtaining samples, narrow criteria would generally not be required.

Option 2: Comparison study designs modeled after concepts in the FDA guidance on Assay Migration Studies for IVD Devices at Sections VI. A.2.b and VI. B.2.b comparing the performance of the candidate test between trained and untrained operators are also appropriate for those who opt for such approach.

Option 3: Human factors engineering studies may also provide sufficient assurance that the change in user populations and environment of use will not adversely impact the results provided by the diagnostic test. Such approach could be used as an alternative to comparison studies to assess negligible risk of erroneous results reflective of the intended user population. This option, which is often employed in the medical device process, may aid bringing new advances in waived technologies.

Option 4: Sponsors may demonstrate accuracy in the hands of untrained operators where accuracy is calculated using an appropriate comparator. This was the basis for prior recommendations in FDA's 2008 Guidance. This may be useful in the case of dual submissions where a 510(k) and CLIA waiver is being sought concurrently under that pathway.

Some additional considerations below focus on study designs that are potentially applicable to Options 1 and 4 for both quantitative and qualitative tests.

Some Additional Considerations

Option 1

Generally, a test may be shown to render “the likelihood of erroneous results by the user negligible” if Trained Users and Untrained Users achieve a sufficient level of agreement.

For this approach to be used, it is necessary to determine the degree to which results must agree (and, for quantitative tests, the amount of variation between Trained User and Untrained User groups that would be considered to agree). In some instances, during the 510(k) or PMA process, FDA has, in effect, agreed to criteria developed by the sponsor that reflects acceptable operator performance with Trained Users. In those cases, a sponsor may rely upon the same criteria for Untrained Users for the purposes of a CLIA waiver application.

Option 4

A test may also be shown to render the likelihood of erroneous results by the user negligible if a set of appropriate and representative samples with assigned values are analyzed by both a group of Trained Users and a group of Untrained Users, and the two groups achieve equivalent performance.

There also might be instances where Trained User performance data in prior 510(k) or PMA submissions can be used as a historical control. If sufficiently similar sample sets are used,² the performance of a group of Untrained Users is compared to the performance obtained by Trained Users that was observed in studies from a 510(k) or PMA submission. The data sets in 510(k) and PMA submissions addressing inter-operator performance of Trained Users may be particularly useful if this option is appropriate and used. In this case, only Untrained Users would participate in the CLIA waiver study, but sufficient information must be provided to establish that variation in the time, samples used and conditions under which the study was performed (beyond the difference in users being studied) will not affect the interpretation of results. We note that the use of archived or surrogate specimens may be used in most other study options.

² Sufficient similarity is a matter of scientific judgment, and we recommend discussing this approach with FDA prior to initiating studies. In some instances, sufficient similarity to allow for a cross-study comparison of results would require the use of banked samples from the original study. In other instances, separate samples sets would be acceptable provided the demographics of subjects and essential properties of samples collected were comparable.

Risk Benefit and Test Considerations in Satisfying CLIA Waiver Requirements

What constitutes comparable performance of Trained Operator and Untrained Operator performance, or the minimum level of agreement that must be achieved between Trained User and Untrained User groups, can vary from test to test. In general, acceptance criteria and minimum levels of agreement should be determined based on risk/benefit and test performance factors, including but not limited to: (1) the clinical use of the test; (2) the clinical importance of the parameter being evaluated; (3) the role of the test in diagnosis (e.g., is the test intended to be determinative, or as an aid in diagnosis in which other clinical presentation and information is available); (4) whether confirmation is required; and (5) the performance of the test when performed by Trained Users.

ADVAMEDDX SPECIFIC COMMENTS ON
 FDA Draft Guidance re.
Select Updates for Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA)
Waiver Applications for Manufacturers of In Vitro Diagnostic Devices

Edit No. – Comment number
 Section – Section of the guidance
 Line No. – Guidance line number

Proposed Change – Proposed change to the guidance
 Comment/Rationale – Reason for proposed change

Edit No.	Section	Line No.	Proposed Change	Comment/Rationale
1	III.A	146-152	<p>Delete lines 146-150 and the word “result,” on line 151. Add “in the hands of the user” after “accurate” on line 152. This will focus on what is required for CLIA waiver to support accuracy, i.e., specifically reflect that the CLIA waiver test is accurate as to render “the likelihood of erroneous results by the user negligible, and ensure focus on agreement of test performance in the hands of trained and untrained users using the device.</p> <p>Assessment of test accuracy is established in the 510(k) process. Accuracy in the context of CLIA waiver may be demonstrated in comparison of results obtained from trained and untrained users. It does not require the manufacturer to re-prove accuracy of the device itself.</p>	<p>This paragraph, while not inaccurate from a scientific perspective, confuses the guidance with its blanket reference to a reference standard, and what is required/accurate for CLIA waiver—which is distinct from premarket review—for purposes of the statute and implementation of CLIA waiver Section 3057 of the 21st Century Cures Act (which requires that FDA revise Section V. of its 2008 Guidance to “include the appropriate use of comparable performance between a waived user and a moderately complex laboratory user to demonstrate accuracy”). The legislative history of the Act further makes clear that Congress intended that FDA align its guidance with the intent that “if the results by trained and untrained users are comparable, a test is considered to be accurate for CLIA Waiver purposes.”</p> <p>Such proposed clarification will help support a clear guidance, consistency with Congressional intent, and avoid duplicate accuracy requirements in the 510(k) and CLIA process.</p>

2	III.A	144	Add at the end of line 144 after “accurate” “in the hands of the user.”	See comment 1. Document should be focused on accuracy in the hands of the user.
3	III and IV	160 and 623-627	Clarify that a "Trained Operator" need not be a laboratory professional. They can also be a trained Health Care Professional.	Laboratory professionals do not always perform finger-stick tests. Also, a CLIA Waived site may be unlikely to have a lab professional on site. The key requirement should be comparability between an untrained user and a user who has previous training on the candidate test.
4	III	176	Revise to “accuracy in the hands of the user in a CLIA-waived setting.”	Similar to previous comments.
5	III	178-194	Replace with options as outlined in the AdvaMedDx proposal.	The options should be revised to reflect a range of appropriate study design options. See previous comments and AdvaMedDx proposal contained on “Implementation of 3057 of the 21 st Cures Act— Update of Section V of CLIA Waiver Guidance (2008); <i>Advancing Innovation in CLIA Waived Testing & Timely Point of Care Diagnostic Information for Physicians and Patients</i> ” (or the “proposal”). This would better reflect emphasis on option 1 per AdvaMedDx proposal (In the waiver by application submission, which takes place after the clearance of the device, the sponsor can demonstrate accuracy in the hands of the user by demonstrating agreement between the results of the test when performed by untrained operators and trained operators.) as well as subsequent options including that a sponsor could alternatively demonstrate accuracy in the hands of the untrained user through direct comparison with an acceptable comparator method; this last referenced option may be useful when performed as part of the study supporting the original clearance of the device. For considerations concerning this last referenced option, please see “Recommendations for Dual

				510(k) and CLIA Waiver by Application Studies” guidance document (or “dual submission guidance” once finalized) and AdvaMedDx comments submitted to docket on this separate draft guidance.
6	III	195-262	Delete lines 197-262	Removes unnecessary information about unnecessary dual analysis. See comment 6 regarding content for consideration in dual submission guidance.
7	III	271	Replace “how accuracy is determined” with “the appropriate study design”.	Minor edit for clarification, consistent with previous comments on designs to demonstrate accuracy in the hands of the user.
8	III	273-369	<p>Move this content regarding reference method to dual submission guidance.</p> <p>Further technical or redline edits are needed, e.g. among others:</p> <p>Change lines 276-282 to “results obtained by untrained operators in CLIA-waived settings are comparable to either the results obtained by trained operators on the same device (Option 1); or directly to an appropriate comparator method. (Option 2). Either case would allow conclusion can be made that the candidate test has a negligible likelihood of erroneous results by untrained operators.</p> <p>Delete lines 284-363.</p> <p>Add the appropriate study design by adding the text from lines 252-256 here except change Line 253 to replace “CM results with trained operators” with “test results with untrained operators” and line 254 to replace “CM” with “Test_{untrained}”.</p> <p>Add “For Option 2 please see Dual Waiver study guidance.”</p>	<p>As noted in our general comments, we support a flexible approach describing least burdensome study options of comparable performance between trained and untrained operators. The following comments are specific, however, to how the draft guidance is currently written:</p> <p>Revise to focus on the comparison between trained and untrained users.</p> <p>The other descriptions of the order of references (appropriately modified) can be moved to the Dual Waiver guidance.</p> <p>The discussion of appropriate reference method and ATE, etc are not necessary for the comparative study design.</p> <p>We imported the few lines of text that describe the appropriate study design.</p>

			End line 368 after “proposed study design” and delete line 369.	
9	III	370-491	<p>Move this content regarding reference method to dual submission guidance.</p> <p>Further technical or redline edits are needed, e.g., among others:</p> <p>Change lines 364-381 to “results obtained by untrained operators in CLIA-waived settings are comparable to either the results obtained by trained operators on the same device (Option 1); or directly to an appropriate comparator method. (Option 2). Either case would allow conclusion can be made that the candidate test has a negligible likelihood of erroneous results by untrained operators.</p> <p>Delete lines 383-454.</p> <p>Retain lines 455-472. They represent trained vs untrained study design.</p> <p>In lines 473-476, revise “between test and CM” to “between test in hands of trained and untrained users”</p> <p>Replace 483-488 with “For Option 2 please see CLIA waiver guidance”</p> <p>Address typo in Line 490 to replace “study sample” with “study design”</p>	<p>Per the previous comment, we support a flexible approach describing least burdensome study options of comparable performance between trained and untrained operators. The following comments are specific, however, to how the draft guidance is currently written:</p> <p>Rewrite to focus specifically on the comparison between trained and untrained users.</p> <p>The other descriptions of the order of references (appropriately modified) can be moved to the Dual Waiver guidance.</p> <p>The discussion of appropriate reference method etc. are not necessary for the comparative study design.</p> <p>Retain text that describe the appropriate study design.</p>
10	III	493-585	<p>Move this content regarding reference method to dual submission guidance.</p> <p>Further technical or redline edits are needed, e.g., among others:</p> <p>In lines 497-500, replace with obtained by</p>	<p>Per the previous comment, we support a flexible approach describing least burdensome study options of comparable performance between trained and untrained operators. The following comments are specific, however, to how the draft guidance is currently written:</p>

			<p>untrained operators in CLIA-waived settings are comparable to either the results obtained by trained operators on the same device (Option 1); or directly to an appropriate comparator method. (Option 2). Either case would allow conclusion can be made that the candidate test has a negligible likelihood of erroneous results by untrained operators.</p> <p>Delete 508-540.</p> <p>Keep 541-560.</p> <p>Replace lines 561-566 with “For Option 2, See Dual Study Waiver”</p> <p>Delete lines 572-573 sentence about Option 2</p> <p>Delete 575-582.</p>	<p>Rewrite to focus on the comparison between trained and untrained users.</p> <p>The discussion of appropriate reference method etc. are not necessary for the comparative study design.</p> <p>Retained text that describe the appropriate study design.</p>
11	IV	714	<p>Confirm and clarify that “up to one third of contrived samples may be allowed.”</p>	<p>While use of archived/contrived/surrogate samples can be a necessity, we recommend FDA ensure the suggestion is in line with MDIC guidelines, upon which FDA reviewers have been trained.</p>