

## **FDA Webinar: CLIA Waiver Applications Draft Guidances**

**Moderator: Kemba Ford**  
**January 9, 2019**  
**1:00 pm ET**

Coordinator: Welcome and thank you for standing by. At this time, all lines have been placed in listen-only mode until the question-and-answer session. Today's call is being recorded. If anyone has any objections, you may disconnect at this time.

I would now like to turn the call over to Kemba Ford. Thank you. You may begin.

(Kemba Ford): Hello. I am Kemba Ford from FDA's Center for Devices and Radiological Health Office of Communication and Education. I would like to welcome you to today's webinar where we will discuss and answer questions about the two draft guidances published on November 28, 2018 that are intended to help manufacturers of in vitro diagnostic devices apply for and receive Clinical Laboratory Improvement Amendment waivers, also called CLIA waivers.

The first draft is titled Select Updates for Recommendations for Clinical Laboratory Improvement Amendments of 1988 Waiver Applications for Manufacturers of In Vitro Diagnostic Devices. And the second draft guidance

is titled Recommendations for Dual 510(k) and CLIA Waiver by Application Studies.

Today, Peter Tobin, a chemist from FDA's Center for Devices and Radiological Health's Office of In Vitro Diagnostics, will present an overview of these draft guidance documents.

Following his presentation, we will open the line for any questions you may have related to the information provided during this presentation.

Now, I will turn over the webinar to Peter.

Peter Tobin: Good afternoon everyone and thanks for joining us for today's webinar on CLIA waiver application draft guidances.

This webinar covers two complementary draft guidances for CLIA waivers. Throughout this presentation, I'll refer to the Select Updates to the 2008 CLIA Waiver Guidance as the Draft Section V Guidance and the recommendations for Dual 510(k) and CLIA Waiver by Application Studies guidance as the Draft Dual Guidance. I'll also sometimes refer to CLIA waivers by application as CWs. These two draft guidances are not final and not in effect at this time.

Here's the agenda for today's webinar. I'll start off with some background and then cover the highlights for each draft guidance. After my presentation there will also be plenty of time for questions.

The first objective for today's webinar is to understand the two CLIA waiver pathway options covered in the draft guidances -- the stepwise CLIA waiver pathway, which is a CLIA waiver application following clearance or approval,

and the dual submission or dual pathway which is a combined 510(k) and CLIA waiver following a Pre-Submission.

And the second objective is to understand the FDA's current thinking on study designs for both pathways.

As background for discussing the draft guidances, I'm going to cover the following four areas over the next few slides -- the CLIA waiver statutory criteria, 21<sup>st</sup> Century Cures requirements to update the 2008 CLIA Waiver Guidance, CLIA waiver pathways addressed by the two drafts, and why we are reissuing the guidances as drafts.

Here is the CLIA statutory criteria for waiver as modified by FDAMA. Clause B has only been used very rarely so I will concentrate on clause A, shown in bold, that a test “employ methodologies that are so simple and accurate as to render the likelihood of erroneous results by the user negligible,” because this is the clause that is primarily used and is the focus of both draft guidances.

21<sup>st</sup> Century Cures requires an update to Section V of the 2008 CLIA Waiver Guidance. This section covers accuracy studies to support CLIA waiver and we are required to update this section to include the appropriate use of comparable performance between a waived user and a moderately complex laboratory user to demonstrate accuracy.

The 2008 CLIA Waiver Guidance provides recommendations for meeting the CLIA statutory criteria for waiver described earlier, that a test should be “so simple and accurate as to render the likelihood of erroneous results by the user negligible.”

A test that is a candidate for waiver should be simple in that it has both simple test characteristics and labeling that is designed for untrained waived users. For example, a simple test should not require complex sample or reagent manipulation, or complex interpretation of results or error codes.

In order to demonstrate that the likelihood of erroneous results by the user is negligible, the 2008 CLIA Waiver Guidance also recommends that the candidate test manufacturer conducts a comprehensive risk analysis, incorporates fail-safe and failure alert mechanisms to mitigate risks, and conducts flex studies and validation studies to demonstrate system robustness and proper functioning of incorporated risk control mechanisms.

With the exception of Section V on accuracy studies, the rest of the 2008 CLIA Waiver Guidance is not being reopened and will not be substantially changed once Section Five is finalized.

There are currently three pathways to CLIA waived categorization. In the first pathway, shown at the top of the slide, if a test is cleared or approved through one of the nine test types -- this is, excuse me, in 42 CFR 493.15(c) -- such as urinalysis dipstick or non-automated fecal occult blood, or if the test is cleared or approved for home use, then the test will be categorized as waived following clearance or approval.

Otherwise, following clearance or approval, tests may be categorized either as moderate or high complexity according to the CLIA categorization criteria listed in 42 CFR 493.17.

The two CLIA waiver pathways that are addressed by the draft guidances are shown in the bottom half of the slide. The stepwise CLIA waiver pathway is covered by the 2008 CLIA Waiver Guidance and the draft Section Five

update. In this pathway, the manufacturer first obtains clearance or approval and a moderate categorization prior to submitting a CLIA waiver application.

In the Dual pathway, a manufacturer first submits a Pre-Submission to inform FDA that it plans to submit a Dual Submission. This Pre-Submission provides a forum for the applicant and the FDA to discuss the proposed study designs for the Dual Submission.

Following the Pre-Submission, the manufacturer submits a complete 510(k) and CLIA waiver application in a single submission package. The draft Dual guidance addresses recommendations for study designs for this CLIA waiver pathway.

Previous drafts of both CLIA waiver guidances were issued in November 2017, and we held a webinar on these drafts in January 2018. Based on comments received and multiple meetings with stakeholders, the new drafts have been thoroughly revised. Because of the significant changes that were made to address stakeholder comments, we are reissuing both guidances in draft to allow stakeholder comments before finalizing.

Before getting into the highlights of the two draft guidances, I want to mention two definitions that are used in both guidances. An “Untrained Operator or Waived User” is a test operator in waived settings who has limited or no training or hands-on experience in conducting laboratory testing. And a “Trained Operator or Moderate Complexity Laboratory User” is a test operator who meets the qualifications to perform moderate complexity testing and with previous training in performing the test.

These definitions connect the “untrained operator” and “trained operator” terminology used in the draft guidances with the “waived user” and

“moderately complex laboratory user” terminology from section 3057 of 21<sup>st</sup> Century Cures.

The revised Section V guidance provides study design recommendations for demonstrating that a test is accurate in the hands of the intended CLIA-waived users as part of a CLIA waiver application following clearance or approval. The FDA believes this guidance will reduce barriers to bringing simple and accurate tests to CLIA-waived settings, such as doctor’s offices.

In response to stakeholder comments, the draft Section V guidance focuses in on study design aspects directly related to meeting the statutory criteria for waiver. Specifically, this draft emphasizes validating that the accuracy of a candidate test is not meaningfully impacted by differences between non-waived and waived use, including: user training and experience, testing environment, or patient populations.

General information on test accuracy issues that are not specific to CLIA-waived tests has been replaced with references to FDA-recognized consensus standards. The availability of publicly posted CLIA waiver decision summaries complements this approach because they provide study design details from successful CLIA waiver applications for a wider variety of test types and circumstances than it would be possible to cover as examples in the guidance.

At the end of fiscal year 2017, FDA began piloting the release of CLIA waiver decision summaries on the CDRH transparency webpage. CLIA waiver decision summaries allow the public to learn how the FDA reviewed an applicant’s data to make a CLIA waiver approval determination and promote consistency and predictability in the CLIA waiver review process.

In response to stakeholder comments, two additional study design options were added to the revised draft Section V guidance for a total of four study design options. The revised draft also provides additional flexibility regarding how manufacturers may leverage existing accuracy data from previous marketing submissions such as 510(k)s, PMAs, or De Novo marketing submissions.

Options 1-3 are appropriate when sufficient valid scientific evidence to demonstrate that a test candidate test meets the CLIA statutory criteria for waiver can be derived from the combination of the performance studies included in previous marketing submissions, and the new CLIA waiver studies described for each option in the revised Section V draft guidance.

Now I'll describe each of the four options.

Option 1, commonly called agreement studies, includes comparison study designs in which the results of the candidate test in the hands of untrained operators are compared to the results of the candidate test in the hands of trained operators. Since pre-market performance studies generally include data establishing the accuracy of the candidate test in the hands of trained operators, the FDA believes that Option 1 will be appropriate for the majority of candidate tests.

Option 2 is one of the new options. Option 2 includes agreement studies modeled after approaches in the FDA guidance on Assay Migration Studies for In Vitro Diagnostic Devices. Under this option, these studies compare performance of the candidate test between untrained and trained users instead of comparing performance between new and old systems as described in the assay migration guidance.

Option 3 is the second new option and it includes flex and human factors engineering studies. As an alternative to comparative study designs for certain test systems, flex and human factors engineering studies may provide sufficient assurance that the change in user populations and environment of use between non-waived and waived settings will not adversely impact the results provided by the candidate test.

Possible study design approaches that may be suitable include flex study designs described in Section IV of the 2008 CLIA Waiver Guidance and human factor study designs described in FDA's guidance Applying Human Factors and Usability Engineering to Medical Devices.

This approach is appropriate for test systems for which collection of a specimen is always performed by a professional -- for example, an endocervical swap collected by a doctor -- or collection of a specimen is always performed by a patient -- for example, a urine specimen collected by the patient, and other pre-analytical steps are very simple -- for example, placement of the entire specimen in the analyzer --, and the intended patient populations are sufficiently similar.

Another possible scenario where this option may be appropriate is a CLIA waiver application for a modification of a previously waived test system where the Quick Reference Instructions were not modified or minimally modified.

Option 4 is the approach included in Section V of the 2008 CLIA waiver guidance and was called "Option 2" in the November 2017 Section V draft. Option 4 includes comparison study designs in which the results of the candidate test in the hands of untrained operators are directly compared to the

results of an appropriate comparative method in the hands of trained operators.

Another aspect of the section V guidance that stakeholders requested additional clarity about was FDA's approach to benefit-risk considerations for CLIA waiver applications. To address this in the revised Section V draft, we've added a new section called "Considerations in Satisfying CLIA Waiver Requirements" that discusses this issue and how we are harmonizing our approach to benefit-risk considerations for CLIA waivers with other FDA benefit-risk guidances.

Thinking about benefit risk considerations for CLIA waivers, we need to go back to the statutory criteria for CLIA waiver, that a test should be "so simple and accurate as to render the likelihood of erroneous results by the user negligible."

All tests have some likelihood of erroneous results, but whether the likelihood of erroneous results in the hands of waived test users is negligible will vary from test to test depending on a number of factors, including: intended use, context of use -- for example, patient population and use environment --, and the probable benefits and probable risks or harms associated with waived use of the test.

Accordingly, the appropriate acceptance criteria for CLIA waiver accuracy studies will vary from test to test. For details about the FDA's current thinking about benefit-risk considerations for medical devices, CDRH benefit-risk guidances are referenced rather than repeating similar material.

One aspect of the revised Section V guidance that has not changed are general CLIA waiver study design considerations. FDA recommends that applicants

evaluate test performance in settings designed to replicate, as closely as possible: intended CLIA-waived settings, patients/samples, test operators, and testing over time, as in the typical intended use setting.

Finally, Pre-Submissions are highly recommended to get feedback from the FDA on study designs for any of the four options before conducting the studies. FDA also welcomes discussion of additional study design approaches besides the four options presented in the guidance.

For additional information on Pre-Submissions, please refer to FDA's guidance Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff.

So now, moving on to the revised draft Dual guidance. In contrast to the stepwise CLIA waiver pathway covered by the draft Section V guidance, the draft Dual guidance is intended for new in vitro diagnostic tests that have not yet been cleared, and so there is not generally accuracy data available yet for these tests.

The draft Dual guidance describes a more efficient single set of comparison and reproducibility study designs with untrained users for a Dual Submission. Similarly to the revised draft section V, in the revised Dual guidance, general information on test accuracy issues not specific to CLIA-waived tests has been replaced with references to FDA-recognized consensus standards.

We've also referenced general study design considerations in the draft Section V guidance rather than repeating similar information in the draft Dual guidance. The FDA believes the Dual pathway is in many instances the least burdensome and fastest approach for manufacturers to obtain a CLIA waiver in addition to 510(k) clearance for new tests.

Over the next few slides, I'm going to compare the types of studies conducted for the Stepwise and Dual CLIA waiver pathways starting with a little more background on the Stepwise pathway.

Historically, under the Stepwise CLIA waiver pathway, manufacturers have conducted separate accurate studies in different clinical settings -- first to support 510(k) clearance and later to support CLIA waiver. Specifically, manufacturers generally conducted comparison and reproducibility studies with trained users at non-waived point of care sites as part of the support for 510(k) clearance, and then later conducted similar studies with untrained users at waived sites to support their CLIA waiver application.

This slide shows a summary of the different types of studies typically performed under the Stepwise and Dual CLIA waiver pathways. For the Stepwise CLIA waiver pathway, the left column shows typical study types for a point-of-care 510(k) -- including the point-of-care comparison and reproducibility studies under the red X --, and the right column shows additional study types typically included in a CLIA waiver application.

The basic idea behind the Dual approach is that it is reasonable to assume that test performance in the hands of trained users will be equal to or better than test performance in the hands of untrained users. Therefore, a single set of comparison and reproducibility studies conducted at sites representative of CLIA waived sites and with intended untrained users can be used as part of the support for both 510(k) clearance and CLIA waiver approval.

The different types of studies typically performed for a Dual Submission incorporates both the left and right columns but does not include the point-of-

care comparison and reproducibility studies with trained users under the large red X.

The Dual pathway can provide considerable study efficiencies compared to the Stepwise approach to CLIA waiver. Additionally, overall FDA review time is also generally shorter for Dual Submissions with a maximum of 180 FDA days versus potentially up to 250 FDA days for the Stepwise route of a traditional 510(k) followed by a CLIA Record and then a CLIA waiver application.

We've seen increasing interest in the Dual Submission pathway over the last few years, and in fiscal year 2018 Duals became the preferred CLIA waiver pathway, accounting for almost three-quarters of the CLIA waivers received.

Due to the study efficiencies possible with Dual Submissions, we expect that Duals will continue to be popular. We hope that the Dual guidance, when finalized, will help more manufacturers use this pathway to bring new simple and accurate in vitro diagnostic tests to CLIA-waived settings.

Greater access to these tests is expected to benefit patients and public health by allowing faster diagnosis and treatment decisions and reduced loss to follow-up.

I've now finished the highlights of the two revised draft guidances. Here are some resources for you, including links to the draft guidances covered today and the docket numbers and links to the pages in Regulations.gov where you can comment on these draft guidances through February 27, 2019.

Links to the two final CLIA waiver guidances which are currently in effect are also provided, specifically the 2008 CLIA Waiver Guidance and the Administrative Procedures Guidance which was updated in 2017.

I've also included a link to the CDRH transparency page where CLIA waiver decision summaries are posted.

Thank you again for your interest in these draft guidances. We are interested in your feedback and I would be happy to answer any questions you have about the CLIA waiver draft guidances.

Coordinator: Thank you. At this time if you'd like to ask a question, please press star 1 and please record your name when prompted. If you'd like to withdraw the request, you may press star 2. Again, to ask a question please press star 1 and please record your name when prompted. One moment please for the first question.

Peter Tobin: While the Q&A portion is getting set up, I'd just like to encourage you again to comment on the draft CLIA waiver guidances. Also, if you think of questions later on after the webinar, please send them to [CLIA@fda.hhs.gov](mailto:CLIA@fda.hhs.gov). It's on the screen.

If you have other CLIA waiver or CLIA categorization questions that are not related to the draft CLIA waiver guidances, please also feel free to email us at [CLIA@fda.hhs.gov](mailto:CLIA@fda.hhs.gov) and we'd be happy to help you.

Coordinator: Thank you. We do have a question from I believe it's (Martha). Please go ahead with your question.

(Martha): Hi. My question is regarding the Section V draft guidance and pursuing option one or an agreement study demonstrating accuracy. Will ATE and LER zones still need to be defined under that option?

Peter Tobin: So one of the things that we're doing with this revised draft is we're trying to broaden available possibilities of study types and approaches that are available. And across different types of devices, certain approaches may be more common than others. And we're also trying to sort of harmonize approaches to how we evaluate tests across different submission types.

So as you'll see, we still are recommending various CLSI guidelines that include discussion of ATE and LER. But we are also open to the possibility of other approaches perhaps where you're looking separately at, you know, different elements of accuracy such as looking, you know, at bias and precision elements separately.

There can be a number of different possible approaches and we want to leave open various possibilities although the, you know, the ATE and LER approach is a good approach and continues to be one of the approaches we recommend. But we do recognize that for certain types of tests, other approaches are common and we welcome discussion of those other approaches through the Pre-Submission process.

(Martha): Thank you.

Coordinator: Thank you. And once again if you'd like to ask a question, please press star 1 and please record your name when prompted. One moment, please. And at this time I'm showing no further questions.

Kemba Ford: Thank you. This is Kemba Ford. We appreciate your participation and thoughtful questions during today's webinar. Today's presentation and transcript will be available on the CDRH Learn Web page at [www.fda.gov/training/cdhrhlearn](http://www.fda.gov/training/cdhrhlearn) on Thursday, January 17.

If you have additional questions about today's presentation, please contact us using the information on the screen.

As always, we appreciate your feedback. Following the conclusion of the webinar, please complete a short 13 question survey about your FDA CDRH webinar experience. The survey can be found at [www.fda.gov/cdrhwebinar](http://www.fda.gov/cdrhwebinar) immediately following the conclusion of this live webinar.

Again, thank you for your participation in today's webinar and this concludes our webinar.

Coordinator: Thank you. This concludes today's conference. You may disconnect at this time.

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