Select Updates for Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices

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Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.
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You should submit comments and suggestions regarding this draft document within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions about this document, please contact the Office of In Vitro Diagnostics and Radiological Health (OIR) at 301-796-5711, Peter Tobin, PhD, 240-402-6169 or by email at peter.tobin@fda.hhs.gov.

When final, this document will update and supersede section V of the Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices guidance, issued on January 30, 2008.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Preface

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction and Scope

FDA has developed this draft guidance to implement section 3057 of the 21st Century Cures Act [P.L. 114-255], which requires FDA to revise "Section V. Demonstrating Insignificant Risk of an Erroneous Result — Accuracy" of the guidance Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices[1] ("2008 CLIA Waiver Guidance") that was issued on January 30, 2008. This draft guidance represents FDA's current thinking regarding "the appropriate use of comparable performance between a waived user and a moderately complex laboratory user to demonstrate accuracy." The 2008 CLIA Waiver Guidance remains in effect, in its current form, until this draft guidance is finalized, at which time the updates in section III of this draft guidance will supersede the recommendations in section V of the 2008 CLIA Waiver Guidance.

FDA will incorporate the final version of this draft guidance into "Section V. Demonstrating Insignificant Risk of an Erroneous Result — Accuracy" of the 2008 CLIA Waiver Guidance.

[1] https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm079632.htm

The remainder of the 2008 CLIA Waiver Guidance, with exception of technical edits for consistency with the newly amended section V, will not be substantively changed and will remain in effect.

For the current edition of the FDA-recognized standard(s) referenced in this document, see the FDA Recognized Consensus Standards Database Web site.[2]

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. Background and Rationale

The Secretary of Health and Human Services has delegated to FDA the authority to determine whether particular tests are "simple" and have "an insignificant risk of an erroneous result" under CLIA and thus are eligible for CLIA waiver (69 FR 22849, April 27, 2004). The Centers for Medicare & Medicaid Services (CMS) is responsible for oversight of clinical laboratories, which includes issuing Certificates of Waiver. CLIA requires that clinical laboratories obtain a certificate before accepting materials derived from the human body for laboratory tests (42 U.S.C. § 263a(b)).

CLIA, 42 U.S.C. § 263a(d)(3) Examinations and Procedures, as modified by the Food and Drug Administration Modernization Act of 1997 (FDAMA), reads as follows regarding tests that may be performed by laboratories with a Certificate of Waiver:

> The examinations and procedures [that may be performed by a laboratory with a Certificate of Waiver]… are laboratory examinations and procedures that have been approved by the Food and Drug Administration for home use or that, as determined by the Secretary, are simple laboratory examinations and 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, or (B) the Secretary has determined pose no unreasonable risk of harm to the patient if performed incorrectly.

The 2008 CLIA Waiver Guidance describes recommendations for device manufacturers about study design and analysis for CLIA Waiver by Application to support an FDA determination as to whether the device meets the statutory criteria for waiver described above.

Manufacturers developing devices designed for the CLIA-waived setting have traditionally taken a sequential route, first obtaining FDA clearance or approval and then submitting data for CLIA waiver determination. The Dual 510(k) and CLIA Waiver application (Dual Submission), in

[2] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

which an applicant can apply for 510(k) clearance and CLIA waiver concurrently within one submission, was established as part of the Medical Device User Fee Amendments of 2012 (MDUFA III). Proposed recommendations for Dual Submissions are provided in the draft guidance Recommendations for Dual 510(k) and CLIA Waiver by Application Studies,[3] which, when finalized, will represent FDA's current thinking on recommendations for Dual Submissions. For more information about CLIA waiver submission options and other administrative details, please see the guidance Administrative Procedures for CLIA Categorization.[4]

This update provides additional approaches for demonstrating that a test meets the criteria in 42 U.S.C. § 263a(d)(3)(A). In developing these recommendations, we have considered interactions with stakeholders since the issuance of the final guidance on January 30, 2008.

III. Revised Section V.

A. Demonstrating Insignificant Risk of an Erroneous Result – "Accuracy"

As stated previously, a CLIA waiver can be granted for, among others, tests that are "simple laboratory examinations and procedures that have an insignificant risk of an erroneous result" (42 U.S.C. § 263a(d)(3)). This includes tests that employ methodologies that are "so simple and accurate" that the "likelihood of an erroneous result by the user" is rendered "negligible" (42 U.S.C. § 263a(d)(3)(A)). One of the key elements for granting a CLIA waiver is that the test is accurate in the hands of the user. With this in mind, there are various ways that a test can be demonstrated to be accurate in the hands of the user, so that it can be granted a CLIA waiver by application.

For the purposes of this guidance, the following terms are defined as:

- *Untrained Operator or Waived User*: A test operator in waived settings and with limited or no training or hands-on experience in conducting laboratory testing.

- *Trained Operator or Moderate Complexity Laboratory User*: A test operator who meets the qualifications to perform moderate complexity testing (42 CFR 493.1423) and with previous training in performing the test.

- *Quantitative test:* a test that gives numerical results (e.g., concentration of an analyte in a patient sample) which are referenced to a measuring interval and standards.

[3] https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM586502
[4] https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM070889

- *Qualitative test:* a test that provides only two outputs (e.g., positive/negative or yes/no) or multiple nominal categories. Nominal categories are categories with no intrinsic ordering. For example, an IVD test for genotyping HCV that gives results of multiple categories as 1a, 1b, 2, 3, 4, 5 and 6 is a qualitative test.

- *Semi-Quantitative test:* a test with a few ordinal categories (e.g., negative, trace, +, ++, +++) where the order of categories together with the definitions of these categories contain information used during the interpretation of the test results.

This draft guidance outlines recommended approaches for a sequential route to CLIA waiver by application in which the safety and effectiveness or substantial equivalence of a candidate test in the hands of trained operators is established first, followed by a separate application demonstrating that the test is simple to perform and has an insignificant risk of erroneous results in the hands of untrained operators in CLIA-waived settings.

(1) Study Design Options

In vitro diagnostic (IVD) marketing submissions (e.g., PMA, 510(k), De Novo) generally include data sets from studies intended to establish the accuracy and other performance characteristics of a candidate test in the hands of trained operators, in laboratories that perform non-waived testing.

The four study design options below are intended to provide a variety of study design options that an applicant can conduct to demonstrate that a candidate test meets the CLIA statutory criteria for waiver (i.e., 42 U.S.C. § 263a(d)(3)). FDA's analysis of studies conducted in accordance with these recommendations will take into consideration whether differences between non-waived and waived use, such as user training and experience, testing environment, or patient populations, lead to clinically meaningful differences (as described in section III.A.(2)).

Options 1-3, described below, are appropriate when sufficient valid scientific evidence can be derived from the combination of the prior performance studies (i.e., studies included in previous premarket submissions) and the new studies (described for each option below) to demonstrate that a candidate test meets the CLIA statutory criteria for waiver. Since premarket performance studies generally include data sets establishing the accuracy of a candidate test in the hands of trained operators, FDA believes Option 1 will be appropriate for the majority of candidate tests.

Option 1: 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.

Option 2: Comparison study designs modeled after approaches in the FDA guidance on Assay Migration Studies for In Vitro Diagnostic Devices.[5] Under this option, these studies compare

[5] https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM092752

performance of the candidate test between untrained and trained operators instead of comparing performance between "new" and "old" systems (as described in the Assay Migration guidance). This option is appropriate for quantitative test systems and for qualitative and semi-quantitative test systems for which a numeric output is available, as described in the assay migration guidance. This option is not appropriate for qualitative and semi-quantitative assays for which a numeric output is not available (for example, test systems that require an operator to visually detect the presence of some lines).

Option 3: As an alternative to comparison 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; i.e., that the likelihood of erroneous results by the users is negligible. 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.[6] This approach is appropriate for test systems for which:

- collection of a specimen is always performed by a professional (for example, an endocervical swab collected by a doctor) or 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
- intended use patient populations are sufficiently similar.

Another scenario, among others, when 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: 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. This option is also useful for Dual Submissions where a 510(k) and CLIA waiver are being sought concurrently.

For general recommendations for comparison study design and analysis for Options 1 and 4 we recommend you follow appropriate FDA-recognized consensus standards, such as:

- For quantitative tests: CLSI EP09,[7] CLSI EP21,[8] EP27[9]
- For qualitative tests: CLSI EP12.[10]

[6] https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM259760.
[7] CLSI EP09: Measurement Procedure Comparison and Bias Estimation Using Patient Samples.
[8] CLSI EP21: Evaluation of Total Analytical Error for Quantitative Medical Laboratory Measurement Procedures.
[9] CLSI EP27: How to Construct and Interpret an Error Grid for Quantitative Diagnostic Assays; Approved Guideline.
[10] CLSI EP12: User Protocol for Evaluation of Qualitative Test Performance; Approved Guideline.

Applicants are strongly recommended to submit a Pre-Submission to obtain feedback from FDA on planned study designs prior to conducting the study. FDA welcomes discussion of additional study design approaches besides the four options presented in this 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.[11]

(2) Considerations in Satisfying CLIA Waiver Requirements

The primary statutory standard for CLIA waiver (i.e., 42 U.S.C. § 263a(d)(3)(A)) centers on the simplicity of the test and whether the user can conduct the test with a negligible likelihood of erroneous results. 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. These factors include intended use, context of use (e.g., patient population, use environment), and the probable benefit(s) and probable risk(s)/harm(s) associated with waived use of the test. FDA intends for its approach to benefit-risk considerations to be consistent with the principles expressed, to the extent applicable, in FDA's other guidances.[12] Accordingly, the appropriate acceptance criteria for the studies performed using the design options described above will vary from test to test. For example, for a qualitative test following Options 1 or 2, the minimum level of agreement between untrained and trained users for demonstrating comparable performance should generally be higher for a test for which erroneous results in waived settings are associated with a higher extent of probable patient risk/harm than for tests with lower probable risk/harm in waived settings.

[11] https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176

[12] Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications (510(k)) with Different Technological Characteristics, https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM404773, and Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications, https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM517504

(3) General Study Design Considerations

For all study design options, FDA recommends that applicants evaluate test performance in settings designed to replicate, as closely as possible, the actual CLIA-waived settings, patients/samples, and test operators. Therefore, study designs should include the following:

- Testing sites that are representative of the intended use of the waived test.
- Subject populations that are representative of the intended patient population(s).
- Intended sample type and matrix.
- Untrained operators representative of those at intended waived settings. We encourage you to enroll operators with the least amount of training that might be encountered at the types of sites for which this device is intended.
- Testing over time, as in the typical intended use setting.

a. Testing sites

You should conduct the study to support CLIA waiver at a minimum of three sites that are representative of both the intended use patient population and the intended operators in CLIA-waived settings. Generally, the sites should include different demographic and geographic locations (e.g., outpatient clinic, physician's office), since patient populations and intended operators typically vary among different demographic locations. In your CLIA waiver application, you should present a brief description of each site, including its name, address, and the date the study was performed. If there were sites that were included at the beginning, but then did not complete the study, you should provide a brief explanation for why those sites did not complete the study.

For Options 1 and 2, trained operators may perform testing at the same sites as the untrained operators, or at a different laboratory site. For Option 4, trained operators should perform testing with the comparative method at an appropriate laboratory site.

b. Study participants

1. Operators

a) Untrained operators

The study should include 1-3 untrained operators at each site and at least nine (9) untrained operators across all sites. You should ensure that the untrained operator study participants enrolled represent anticipated operators of the device you propose for CLIA waiver. We recommend that you record and tabulate the education (including experience and training) and the occupation of each operator to demonstrate that these participants meet the definition of intended operators and include this in your CLIA waiver application. In addition, for each study

site, we ask you to report the same information on other operators that were available at the testing site but that were not chosen to participate.

b) Trained operators

Trained operators should meet the qualifications to perform moderate complexity testing and have previous training in performing the candidate test (for Options 1 and 2) or the comparative method (for Option 4).

c) Instructions for use

You should provide the untrained operators who participate in the study with only the Quick Reference Instructions (see section VI of the 2008 CLIA Waiver Guidance). The untrained operators should receive no additional instructions (e.g., written or verbal training, coaching, or prompting). Likewise, untrained operators should have no opportunity to discuss the test with other participants or otherwise coach or observe each other. Untrained operators may call a toll-free help-line if such a service is to be provided for the device when it is marketed. You should include, in your waiver application, the instructions you provided to untrained operators participating in the study.

d) Universal precautions

You should comply with the Federal Food, Drug, and Cosmetic Act (FD&C Act) and its implementing regulations and should ensure your study complies with all other pertinent laws and regulations, including Occupational Health and Safety Administration (OSHA) regulations pertaining to biological hazards ("universal precautions"), 29 CFR 1910.1030.

e) Operator questionnaire

You should develop an operator questionnaire to be filled out by all untrained operators participating in the study. This questionnaire should be designed to help assess whether the untrained operators understood how to use the device correctly. It is important that the questionnaire be given to test untrained operators *after* the completion of the clinical study, so the questions do not bias the untrained operators during the study. Some questions may ask untrained operators to indicate agreement on a 1-5 scale (1=strongly disagree; 5=strongly agree). The following are examples:

- The instructions were easy to follow.
- It was easy to apply the sample correctly.
- It was easy to see and understand the test results (e.g., appearance of the line, change of color).
- The control line was always distinct and easy to read.
- The instructions clearly explain what to do if a test result does not appear or is invalid.

- I needed help from someone the first time I ran the test.

We recommend that, as part of the questionnaire, you show various possible test results and control results that are positive, negative, and invalid and ask the untrained operator to read these results. You may wish to present these questions as true/false or multiple choice questions. You should also strongly encourage general comments by the untrained operators. We recommend that you include your survey questions and results with your CLIA waiver application.

c. Subjects (Patients)

You should ensure that subjects from whom you will obtain specimens for the clinical study meet inclusion and exclusion criteria corresponding to the intended use population of the test. Once a subject has been determined to meet appropriate inclusion criteria, he/she should be informed of the study and invited to participate.

You should follow applicable laws and regulations for human subject protection, including patient privacy and informed consent. See section 520(g) of the FD&C Act; 21 CFR parts 50,56, and 812; and the Health Insurance Portability and Accountability Act (HIPAA) [P.L. 104-191]; 45 CFR Part 46.

d. Specimen Collection and Sample Preparation

We recommend using samples from prospectively collected patient specimens to best assess a device in the hands of untrained operators. In order to prevent biases, specimens should be collected from consecutive patients over one month. Depending on the specific clinical site, the prevalence of the disease, or other factors, it may be appropriate to limit consecutive enrollment to two (2) weeks.

Samples should adequately represent all possible values of the test. If possible, applicants should strive to achieve this at each site as well as across all sites. For quantitative and semi-quantitative candidate tests, samples should span the measuring intervals of the device and study data should include a few samples around Medical Decision Levels (MDLs). For qualitative tests, samples in the study should include samples near the cutoffs. In some situations, when samples from some categories are rare, it may be appropriate to supplement prospective patient samples with archived samples. If archived patient samples are not available, it may be appropriate to supplement patient samples with surrogate samples, such as individual spiked or diluted patient samples. Spiked, diluted, or otherwise surrogate samples used in the study should be individual samples (i.e., they should not be aliquots from a single pool). Any archived or surrogate sample matrix should be the same as that of the intended use patient samples. Applicants should describe the origin of such samples and how they were prepared. For qualitative and semi-quantitative tests, archived and surrogate samples should include samples near the cutoffs. Use of archived or surrogate samples should be appropriately justified. In general, archived or surrogate samples should not comprise greater than one third of the total study samples; however, there may be some situations in which more or less would be

appropriate when an adequate justification is provided. The patient and surrogate samples should be as equally distributed among the untrained operators as possible. FDA encourages applicants to discuss planned use of archived or surrogate samples through a Pre-Submission, prior to conducting the study.

Each sample should be split in two parts. One part should be tested by an untrained operator using the candidate test and the other part should be tested by a trained operator using the candidate test (for Options 1 and 2) or the comparative method (for Option 4). If the sample cannot be split into parts, then a second sample from the same patient should be collected within a suitable time interval. We recommend consulting with FDA through a Pre-Submission if the order in which the samples are collected impacts the results of testing. Untrained and trained operators should be blinded to test results from other operators.

e. Financial disclosure

If clinical investigators are involved in the clinical study, you should include a Financial Disclosure Statement with your waiver application. For information on financial disclosure statements, we recommend you consult the FDA guidance Financial Disclosure by Clinical Investigators,[13] and 21 CFR Part 54, Financial Disclosure by Clinical Investigators.

f. Clinical study reports

You should report results of the clinical study intended to support your CLIA waiver application by each intended site and overall, if appropriate. Reports should include the following:

- Protocol description.
- Number of subjects (i.e., patients) studied.
- Procedures for subject inclusion and exclusion.
- Description of the subject population.
- Description of how specimens were collected and stored.
- Masking techniques.
- Discontinuations.
- Complaints, device failures, and replacements.
- Any invalid results and how these were handled.
- Information about QC procedures that were performed.
- Pertinent tabulations.
- Annotated line listings of results (including electronic versions).
- Clear descriptions and presentations of the statistical analyses.
- An explanation for data that are incomplete or missing (Note: You should not remove "outliers").

[13] https://www.fda.gov/RegulatoryInformation/Guidances/UCM341008

You should also report the following for each untrained and trained operator:

- Total number of performed candidate tests.
- Number of initial invalid results.
- Number of retested results.
- Number of final invalid results.

You should calculate and report the percentage of initial and final (if applicable) invalid results with a 95% two-sided confidence interval and then exclude invalid results from calculations of the test performance characteristics. Please provide a rationale as to why the observed percentage of invalid results is clinically acceptable.

As described previously, FDA will incorporate the final version of this draft guidance into "Section V. Demonstrating Insignificant Risk of an Erroneous Result — Accuracy" of the 2008 CLIA Waiver Guidance.