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

---

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

Document issued on November 29, 2018.

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draft document within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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, contact 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.

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

Preface

Additional Copies

Additional copies are available from the Internet. You may also send an e-mail request to CDRH-Guidance@fda.hhs.gov to receive a copy of the guidance. Please use the document number 16038 to identify the guidance you are requesting.

Table of Contents

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

---

Draft Guidance for Industry and Food and Drug Administration Staff

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

The purpose of this guidance is to assist manufacturers in using the Dual 510(k) and CLIA Waiver by Application pathway. It describes study designs for generating data that supports *both* 510(k) clearance and CLIA waiver. Use of the Dual 510(k) and CLIA Waiver by Application pathway is optional; however, FDA believes this 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* In Vitro Diagnostic (IVD) devices. FDA believes increased use of this pathway will speed up the process of bringing simple and accurate IVD devices to CLIA-waived settings, which will better serve patients and providers.

For the current edition of the FDA-recognized standard(s) referenced in this document, see the FDA Recognized Consensus Standards Database.[1]

FDA's guidance documents, including this draft 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 guidance means that something is suggested or recommended, but not required.

[1] Available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

II. Background

Typically, in an application for CLIA waiver (CLIA Waiver by Application) a manufacturer submits evidence to FDA that a previously cleared or approved test, initially categorized as moderate complexity, meets the CLIA statutory criteria for waiver, 42 U.S.C. § 263a(d)(3)[2], and requests that FDA categorize the test as waived. This means that historically a CLIA Waiver by Application has followed clearance or approval of an IVD test. For additional information, please see FDA's guidance Administrative Procedures for CLIA Categorization.[3]

While a premarket notification (510(k)) and CLIA Waiver by Application each include discrete elements not required in the other, both submissions generally include comparison and reproducibility studies. For a 510(k), such studies are often performed by trained operators (i.e., test operators who meet the qualifications to perform moderate complexity testing and with previous training in performing the test; sometimes referred to as "moderate complexity users"). For a CLIA Waiver by Application, we believe such studies need to be conducted by the intended user (i.e., test operators in waived settings and with limited or no training or hands-on experience in conducting laboratory testing; sometimes referred to as "untrained operators" or "waived users"[4]) (see 42 U.S.C. § 263a(d)(3)).

An applicant may choose to conduct a single set of comparison and reproducibility studies with untrained operators to satisfy certain requirements to establish both substantial equivalence under section 513(i) of the FD&C Act for 510(k) clearance and simplicity and insignificant risk of erroneous results under 42 U.S.C. § 263a(d)(3) for CLIA waiver. To streamline the review of such data, the Dual 510(k) and CLIA Waiver by Application (Dual Submission) pathway was established as part of the Medical Device User Fee Amendments of 2012 (MDUFA III), allowing the review of both a 510(k) and CLIA Waiver by Application within a single submission with a reduced overall review time compared to sequential submissions.

III. Scope

This draft guidance, when finalized, will aid manufacturers in developing study designs for Dual Submissions. A Dual Submission is especially appropriate for devices that are simple, have fail-safe and failure alert mechanisms, have few pre-analytical steps, and are subject to premarket notification requirements.

---

[2] Tests may obtain a CLIA waiver if the tests "have been approved by the [FDA] for home use or that, as determined by the Secretary, are simple laboratory examinations and procedures that have an insignificant risk of 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." 42 U.S.C. § 263a(d)(3).

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

[4] *Select Updates for Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices*, https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM586506, which, when finalized, will represent FDA's current thinking on this topic.

This guidance focuses on recommendations for designing a single set of comparison and reproducibility studies, such that the data generated will support both 510(k) clearance and CLIA waiver.

While the study design recommendations in this guidance were developed with a Dual Submission in mind, they may also be utilized in a sequential submission approach in which a CLIA Waiver by Application follows marketing authorization. In such cases, the applicant may utilize the studies described herein to support marketing authorization and reference such data in their subsequent CLIA Waiver by Application.

IV. Process and Content of a Dual Submission

In the MDUFA IV commitment letter, industry committed to an applicant informing FDA that it plans to submit a Dual Submission during a Pre-Submission. FDA recommends using this interaction to discuss planned study designs for comparison and reproducibility studies that support both 510(k) clearance and CLIA waiver. 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.[5]

A Dual Submission should be submitted following a Pre-Submission. For administrative details regarding the submission process for a Dual Submission, please see FDA's guidance Administrative Procedures for CLIA Categorization.

A Dual Submission should contain the same information as a complete 510(k) and CLIA Waiver by Application.[6] Content related to the comparison and reproducibility studies may overlap and so a single set of comparison and reproducibility studies may be used to support both 510(k) clearance and CLIA Waiver by Application. All other content that would otherwise be included in separate, sequential 510(k) and CLIA Waiver by Application submissions should be included in a Dual Submission.

In addition to the elements required for a 510(k) submission,[7] the following FDA guidances are applicable:

- Format for Traditional and Abbreviated 510(k)s,[8]

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

[6] For information on the content of each submission 21 CFR 807 subpart E, *Administrative Procedures for CLIA Categorization*, https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM070889

[7] 21 CFR 807.87

[8] https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm084365.htm

- Refuse to Accept Policy for 510(k)s,[9] and available device-specific guidances.

Additionally, FDA recommends you include the following in a Dual Submission:

- *Device Description and Determination That Device is "Simple"*
  A description of your device that demonstrates it is simple to use. See Section III of FDA's guidance Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices.[10]

- *Risk Analysis*
  The results of a risk analysis for your device, including the identification of potential sources of error for your device. See Section IV of FDA's guidance Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices and ISO 14971: *Medical Devices-Application of Risk Management to Medical Devices*.

- *Failure-Alert and Fail-Safe Mechanisms*
  The results of risk evaluation and control including a description of (1) measures you have implemented to mitigate the risk of errors, and (2) validation and/or verification studies demonstrating the ability of failure alert, fail-safe mechanisms, and other control measures that you have incorporated into your device to mitigate the risk of errors, even under conditions of stress. See Section IV of FDA's guidance Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices.

- *Flex Studies*
  The results of flex studies demonstrating insensitivity of the test system to environmental and usage variations under conditions of stress. See Section IV of FDA's guidance Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices.

- *Analytical Studies*
  A description of the design and results of analytical studies of the device conducted at an internal site including, but not limited to, the following:
  - Analytical sensitivity (Limit of Detection (LoD) or C5-C95 for qualitative test),
  - Measuring interval (Limit of Quantitation (LoQ) and Limit of Blank (LoB)/LoD (if applicable)) for quantitative test,
  - Analytical specificity (interferences, cross-reactivity, etc.),
  - Linearity (for quantitative test),

[9] https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM315014

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

- Precision (if needed for lot-to-lot variability and/or other issues),
- Carry-over (if applicable),
- Reagent stability, and
- Sample stability.

- *Comparison Study*
  A description of the study design and results of comparison studies you conducted to demonstrate that the device has an insignificant risk of erroneous result performed by the intended user (hereinafter referred to as an untrained operator). See Section V "General Study Design Considerations" below.

- *Reproducibility Study*
  A description of the study design and results of reproducibility studies of the device performed by untrained operators. See Section V "General Study Design Considerations" below.

- *Clinical Performance Study*
  Most 510(k)s and Dual Submissions do not include a clinical performance study. However, for some devices, a clinical performance study may be needed for either a 510(k) or Dual Submission (please contact FDA through a Pre-Submission for further discussion).

- *Labeling*
  Proposed device labeling, including instructions for use consistent with a device that is "simple." See Section VI of FDA's guidance Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices.

V. General Study Design Considerations

When designing comparison and reproducibility studies to support a Dual Submission, 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.
- For a comparison study, testing over time, as in the typical intended use setting.

Proposed general study design considerations for CLIA waiver studies are provided in the draft guidance Select Updates for Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices[11] which, when finalized, will represent FDA's current thinking on this topic. General recommendations in sections III.A.(2), III.A.(3), and specific recommendations in section III for Option 4 studies (i.e., comparison studies 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) are also applicable to Dual Submissions. Additional general study design considerations for Dual Submissions are described below.

The appropriate design of the studies and data analysis is strongly influenced by the type of the candidate test. For the purposes of this guidance:

- A **quantitative test** is 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.

- A **binary qualitative** test is a test that provides only two outputs (e.g., positive/negative or yes/no).

This section includes recommendations for quantitative and binary qualitative tests. If your test is a different type of test from the two types described above (e.g., qualitative with multiple nominal categories, semi-quantitative, a multi-analyte assay with algorithmic analyses), please contact FDA through a Pre-Submission regarding study design recommendations.

If the candidate test is intended to be used at Point-of-Care (POC) non-waived sites in addition to waived sites and the intended use patient population at the CLIA-waived sites in the comparison study does not sufficiently represent an intended use patient population at POC non-waived sites, FDA recommends that you address this issue by including additionally one or a few POC non-waived sites. At any included POC non-waived sites, trained operators representative of those at intended POC non-waived sites should perform testing with the candidate test.

The recommendations for comparison and reproducibility studies described in this guidance are for studies that include the type of samples that are typical of CLIA-waived devices (for example, capillary whole blood samples). If you plan to pursue a 510(k) clearance for POC (non-waived) use for additional sample types beyond those for which you are requesting CLIA waiver in your Dual Submission, please contact FDA through a Pre-Submission for discussion of study designs.

[11] https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM586506

A. Comparison Study Designs

For comparison study design and analysis to establish performance characteristics related to the accuracy of the candidate test we recommend you follow appropriate FDA-recognized consensus standards, such as:

- For quantitative tests: CLSI EP09,[12] CLSI EP21,[13] EP27[14]
- For qualitative tests: CLSI EP12.[15]

These standards include discussion of the importance of selecting an appropriate comparative method (CM) and describe quality hierarchies of preferred CM types for quantitative and binary qualitative tests. Comparison to higher quality CMs (e.g., reference methods or methods traceable to higher order references), when available, provide more absolute information about the accuracy of the candidate test while comparison to lower quality CMs may provide only relative performance information. Where there is no generally accepted CM for an IVD device area, the use of a legally marketed predicate device or other well-documented method as the CM would generally be appropriate. We recommend discussing the selection of an appropriate CM as part of a Pre-Submission prior to conducting the comparison study.

(1) Quantitative Tests

- An appropriate type of regression analysis should be performed and biases at the medical decision levels and at the lower and upper limits of the measuring interval should be calculated along with the confidence interval of each bias estimate.

- Total error (central 95% region of observed differences between the candidate test and CM) should be estimated for the entire measuring interval of the candidate test, and for 3 subintervals (low, medium and high) as described in CLSI EP21.

- The measuring interval of the CM should be at least as wide as the measuring interval of the candidate test. If there are samples with either candidate test or CM values outside of the corresponding measuring intervals, these samples should be analyzed separately.

- If one of the medically important points of the candidate test includes the Limit of Blank(LoB)/Limit of Detection(LoD)/Limit of Quantitation(LoQ), then some additional calculations for samples with very low levels of analyte may be needed for appropriate evaluation and comparison of the LoB/LoD/LoQ of the candidate test in the hands of untrained operators.

[12] CLSI EP09: *Measurement Procedure Comparison and Bias Estimation Using Patient Samples.*
[13] CLSI EP21: *Evaluation of Total Analytical Error for Quantitative Medical Laboratory Measurement Procedures.*
[14] CLSI EP27: *How to Construct and Interpret an Error Grid for Quantitative Diagnostic Assays; Approved Guideline.*
[15] CLSI EP12: *User Protocol for Evaluation of Qualitative Test Performance; Approved Guideline.*

(2) Binary Qualitative Tests

- Binary qualitative tests with an analytical cutoff: For some qualitative tests (e.g., when non-diseased subject samples have a true zero concentration of the analyte of interest), clinical performance and analytical accuracy of the qualitative tests are the same concepts, and therefore, in most situations, a study for evaluation of analytical accuracy can be considered as a study for clinical performance evaluation with measures such as clinical sensitivity, clinical specificity, positive and negative likelihood ratios, and positive and negative predictive values for a binary qualitative test. When certain types of CMs are used in the study, measures such as positive percent agreement (PPA) and negative percent agreement (NPA) should be estimated instead, see CLSI EP12 for additional details.

- Binary qualitative tests with a clinical cutoff: For some qualitative tests, clinical performance related to the target condition (for example, cancer present or absent) and analytical accuracy related to the amount of the analyte detected are different concepts and the cutoff for the qualitative test is chosen to optimize clinical sensitivity and clinical specificity of the test based on a clinical data set. Note that the scientific evidence recommended to support a CLIA waiver for a qualitative test in this section is related to the analytical accuracy of the qualitative test. Issues related to the clinical performance of a qualitative test are out of the scope of the guidance (please contact FDA through a Pre-Submission for further discussion).

- Each untrained operator should run the candidate test with a minimum of 5 samples that are positive by the CM and 5 samples that are negative by the CM.

B. Reproducibility Study Designs

You should conduct a reproducibility study at 3 sites that were included in the comparison study and are representative of the intended use of the waived test. To facilitate statistical analysis, the same number of untrained operators (2 or 3) should be included at each site of the reproducibility study. For reproducibility study design and analysis, we recommend you follow FDA-recognized consensus standards (e.g., CLSI EP05, CLSI EP12). We recommend that you include the following sources of variability: different sites, different untrained operators, different days, different runs, different lots (if applicable) and a few replicates. If the candidate device is a unitized device, contact FDA through a Pre-Submission to discuss how you should evaluate repeatability.

Two possible study designs for evaluation of lot-to-lot variability are described below:

- Design 1: Include three different lots at each of three sites in the reproducibility study in such a way that the between-lot component can be evaluated.

- Design 2: Evaluate lot-to-lot variability in a separate small study at one internal site where patient (or surrogate) samples and controls are tested over a few days. An

example of this study with 3 days and reagent lots A, B, and C is presented in Table 1 below:

Table 1. Example of Design 2: Single Site Lot-to-Lot Variability Study Design

Day	Reagent lots		
1	A	B	C
2	B	C	A
3	C	A	B

Note that the same lot is then included at each site in the main reproducibility study.

A reproducibility study design where each site uses a different lot is generally undesirable, especially for new technologies, because it would be impossible to determine whether observed differences are lot-related or site-related.

If specimens used with the candidate test are not stable (for example, capillary whole blood), attempts to use small-scale repeatability/reproducibility studies that use the intended use clinical samples should be explored (please contact FDA through a Pre-Submission to discuss study designs for precision/reproducibility studies).

We recommend that you include in the reproducibility study the following samples:

- For quantitative tests the following levels of analyte should be included: close to the lower limit of the measuring interval, below the medical decision level (MDL), around the MDL, above the MDL, and close to the upper limit of the measuring interval. If the candidate device has more than one MDL, then samples with concentrations around these MDLs should be evaluated. It is understood that some tests will not have specific MDLs, but rather a range of values; in such cases, the reproducibility panel should contain samples scattered throughout the measuring interval of the candidate test.

- For binary qualitative tests with an analytical cutoff: true negative, close to the LoD, and moderate positive samples should be included. For binary qualitative tests with a clinical cutoff: true negative, high negative (close to C5), low positive (close to C95) and moderate positive samples should be included. C5 is a sample concentration which yields a positive result 5% of the time (and a negative result 95% of the time), and C95 is a is a sample concentration which yields a positive result 95% of the time (and a negative result 5% of the time), see CLSI EP12 for additional details.

- In addition, you should run the appropriate quality control samples associated with the candidate test.