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

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Guidance for Industry and Food and Drug Administration Staff

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See additional PRA statement in Section VIII of the guidance.

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Preface

Public Comment

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Guidance for Industry and Food and Drug Administration Staff

This guidance represents 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 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 the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and are thus eligible for waiver categorization (69 FR 22849, April 29, 2004). The Centers for Medicare & Medicaid Services (CMS) is responsible for oversight of clinical laboratories, which includes issuing waiver certificates. CLIA requires that clinical laboratories obtain a certificate before testing materials derived from the human body.[1] Laboratories that perform only tests that are "simple" and that have an "insignificant risk of an erroneous result" may obtain a Certificate of Waiver.[2]

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

[1] 42 U.S.C. § 263a(b).
[2] 42 U.S.C. § 263a(d)(2).

> 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.

This guidance describes recommendations for device manufacturers seeking to submit information through a CLIA waiver application to FDA to support a determination whether the device meets CLIA 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 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 guidance "Recommendations for Dual 510(k) and CLIA Waiver by Application Studies."[3] For more information about CLIA waiver submission options and other administrative details, please see the guidance "Administrative Procedures for CLIA Categorization."[4]

FDA revised this 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" ("2008 CLIA Waiver Guidance") that was issued on January 30, 2008 to include the "appropriate use of comparable performance between a waived user and a moderately complex laboratory user to demonstrate accuracy." The remainder of this guidance, with exception of technical edits for consistency with the newly amended section V, remains as it was in the 2008 CLIA Waiver Guidance and has not been substantively changed. The guidance provides additional approaches for demonstrating that a test meets the criteria in 42 U.S.C. § 263a(d)(3)(A) and includes FDA's revised thinking regarding "the appropriate use of comparable performance between a waived user and a moderately complex laboratory user to demonstrate accuracy."

This document does not address test systems cleared or approved by FDA for over-the-counter or prescription home use, since these automatically qualify for CLIA waiver.[5]

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[3] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/recommendations-dual-510k-and-clia-waiver-application-studies.

[4] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/administrative-procedures-clia-categorization.

[5] 42 U.S.C. § 263a(d)(3).

For the current edition of the FDA-recognized standard(s) referenced in this document, see the FDA Recognized Consensus Standards Database.[6] For more information regarding use of consensus standards in regulatory submissions, please refer to the FDA guidance titled "Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices."[7]

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 guidance means that something is suggested or recommended, but not required.

II. Components of a CLIA Waiver Application

This guidance discusses the following components, which we recommend that you include in a CLIA waiver application:

- A description of your device that demonstrates it is simple to use. (Section III)
- The results of risk analysis, including the identification of potential sources of error for your device. (Section IV)
- The results of flex studies demonstrating insensitivity of the test system to environmental and usage variations under conditions of stress. (Section IV)
- 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. (Section IV)
- A description of the design and results of studies conducted to demonstrate that the device has an insignificant risk of erroneous result in the hands of the intended user (hereinafter "operator"). (Section V)
- Proposed labeling with instructions for use consistent with a device that is "simple." (Section VI)

III. Demonstrating "Simple"

CLIA requires that tests performed by laboratories with a Certificate of Waiver be "simple."[8] We recommend that, as a first step in the process of deciding whether your device could be a candidate for waiver, you should determine whether your device is simple.

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[6] Available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm.
[7] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/appropriate-use-voluntary-consensus-standards-premarket-submissions-medical-devices.
[8] 42 U.S.C. § 263a(d)(2), (3).

Under the approach recommended in this guidance, FDA believes that a simple test should have characteristics such as the following:

- Is a fully automated instrument or a unitized or self-contained test.
- Uses direct unprocessed specimens, such as capillary blood (fingerstick), venous whole blood, nasal swabs, throat swabs, or urine.
- Needs only basic, non-technique-dependent specimen manipulation, including any for decontamination.
- Needs only basic, non-technique-dependent reagent manipulation, such as "mix reagent A and reagent B."
- Needs no operator intervention during the analysis steps.
- Needs no technical or specialized training with respect to troubleshooting or interpretation of multiple or complex error codes.
- Needs no electronic or mechanical maintenance beyond simple tasks, e.g., changing a battery or power cord.
- Produces results that require no operator calibration, interpretation, or calculation.
- Produces results that are easy to determine, such as 'positive' or 'negative,' a direct readout of numerical values, the clear presence or absence of a line, or obvious color gradations.
- Includes quick reference instructions (Quick Reference Guide, Operator's Instrument Manual (if applicable), etc.) that are written at no higher than a 7th grade reading level (see Section VI).

We believe a test is not simple if it has the following characteristics:

- Sample manipulation is required to perform the assay. (For example, tests that use plasma or serum are not considered simple.) Sample manipulation includes processes such as centrifugation, complex mixing steps, or evaluation of the sample by the operator for conditions such as hemolysis or lipemia.
- Measurement of an analyte could be affected by conditions such as sample turbidity or cell lysis.
- After you consider whether your device is "simple" based on the characteristics listed above, it may be helpful for you to contact FDA for feedback on this issue prior to conducting studies to support waiver.[9] In your waiver application, you should describe features of your device that address the characteristics listed above. Whenever possible (for example, if your test system consists of a unitized device), you should include sample(s) of the device with your waiver application to aid FDA in its determination of whether your device is "simple." You may also schedule a meeting to bring your device to FDA to aid FDA in making this determination.[10]

[9] For information regarding the process for obtaining feedback from the FDA, see the guidance "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program.

[10] *Ibid*.

IV. Demonstrating "Insignificant Risk of an Erroneous Result" – Failure Alerts and Fail-Safe Mechanisms

Generally, the risk of an erroneous result should be far less for waived tests than non-waived tests. You should demonstrate in your CLIA waiver application that (1) the test system design is robust, i.e., insensitive to environmental and usage variation, and (2) that all known sources of error are effectively controlled. In general, flex studies should be used to demonstrate robust design while risk management should be used to demonstrate identification and effective control of error sources, although the two are not mutually exclusive.

Most risk control measures should be fail-safe measures or failure alert mechanisms. Appropriate fail-safe mechanisms and failure alert mechanisms help assure that a test has "an insignificant risk of an erroneous result."[11] An example of a fail-safe mechanism is a lock-out function to ensure that a test system does not provide a result when test conditions are inappropriate, such as when there is a component malfunction or operator error. Other examples are measures within the system to prevent operator error, such as guides or channels that prevent improper strip placement. We recommend that test system design incorporate fail-safe mechanisms whenever it is technically practicable.

If fail-safe mechanisms are not technically practicable for some risks, failure alert mechanisms should be used. Failure alert mechanisms notify the operator of any test system malfunction or problem. They may include measures such as external controls, internal procedural controls, or electronic controls. Devices with such mechanisms allow the operator to correct the error, or put the operator on notice that the results will be unreliable due to the error. For example, in cases where the result exceeds the reportable range (e.g., extremely high or low glucose result) and the result is a critical value, the device should give a message such as "out of range high" or "out of range low."

We recommend a two-tiered approach, outlined below, to demonstrate that your device is robust and has appropriate and effective risk control measures to ensure insignificant risk of an erroneous result.

Tier 1: Risk Analysis and Flex Studies. You should conduct a systematic and comprehensive risk analysis that identifies all potential sources of error, including test system failures and operator errors, and identifies which of these errors can lead to a risk of a hazardous situation. We recommend that the "Operator error/Human factors" examples on pages 7-8 be used as an analytical aid to complement the risk analysis method(s) used.

You should conduct flex studies: studies that stress the operational limits of your test system. Flex studies should be used to validate the insensitivity of the test system to variation under

[11] 42 U.S.C. § 263a(d)(3).

stress conditions. Where appropriate, flex studies should also be used to verify and/or validate the effectiveness of control measures at operational limits.[12]

The waiver application should include:

- The risk analysis results which serve as a basis for the tabular reporting of risk management results. (See Tier 2.)
- A summary of the design and results of your flex studies.
- Conclusions drawn from the flex studies.

Tier 2: Fail-Safe and Failure Alert Mechanisms. Once you have identified the potential sources of error, you should identify the control measures, including fail-safe and failure alert mechanisms that will reduce risks for these sources of error. When the control measures have been implemented, you should (1) verify that each control measure has been properly implemented, and (2) verify and/or validate the effectiveness of each control measure.

We recommend that this risk management information be presented in tabular form in the waiver application. It should include the following information for each risk, for each potential source of error:

- Identification of each risk and the potential source of error that causes it.
- Identification and physical description of the risk control measure or combination of measures used to reduce risk to an acceptable level. This includes fail-safe mechanisms, failure alert mechanisms, external controls, as well as any other controls used or that you recommend the operator use for your device. It also includes a description of the manner in which the control measure(s) either reduce(s) the probability of occurrence of the error, mitigate(s) the effect of the error, or both.
- Objective evidence verifying that each control measure or combination of measures has been implemented, including a description of the method of verification.
- Objective evidence from testing and confirming the effectiveness of fail-safe and/or failure alert mechanisms in preventing and/or mitigating the effects of false results. The evidence and results should also support the device's recommended control procedures and frequencies. Any limitations of fail-safe and failure alert mechanisms, including all internal and external controls, should be described.

A. Tier 1: Risk Analysis and Flex Studies

As noted above, you should identify all potential sources of error by conducting a systematic and comprehensive risk analysis. This analysis should be part of your risk management process, consisting of risk analysis, evaluation, and control. FDA recognizes the process of the ISO 14971 *Medical devices-Application of risk management to medical devices*. This guidance is consistent with that process and uses the same risk management terminology. In

[12] For further discussion, see "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-content-premarket-submissions-software-contained-medical-devices.

general, the standard and its annexes can be used to obtain more detailed information about risk management concepts and practices.[13]

Based on the results of the risk analysis and identification of potential problems with sensitivity to environmental or usage variation, you should conduct flex studies. Flex studies are designed to challenge the system under conditions of stress to identify potential device deficiencies, including failures, and determine the robustness of the test system. Examples are shown in Table 1.

In your analysis, you should consider multiple skill levels of users, as well as potential instrument and reagent problems.[14]

Examples of potential sources of error to consider for the risk analysis and flex studies are listed below.[15] You should consider each of these potential sources of error, as applicable to your device, and also consider any other potential system failures that may be specific to your device.

Operator error/ Human factors

- Use of incorrect specimen type.
- Incorrect application of the specimen to the device (e.g., incorrect placement, incorrect volume).
- Incorrect handling of reagents including those in self-contained unitized test devices.
- Incorrect placement of device (e.g., non-level surface).
- Incorrect placement of reagents, including strips, or other components that contain reagents.
- Use of incorrect reagents (for example, reagents that are not specific for the particular device or lot or generic reagents).
- Incorrect order of reagent application.
- Use of incorrect amount of reagent.
- Incorrect timing of procedures (e.g., specimen application, running the test, or reading results).
- Incorrect reading of test results.
- Incorrect reading due to color blindness.

[13] However, it may not always be appropriate to justify that risks are acceptable based solely on the "As Low As Reasonably Practicable" principle described in Annex D of ISO 14971:2007.

[14] The following websites contain additional information to consider concerning human factors that may affect test performance: "Human Factors and Medical Devices," available at https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/human-factors-and-medical-devices; and "Premarket Information – Device Design and Documentation Processes," available at https://www.fda.gov/medical-devices/human-factors-and-medical-devices/premarket-information-device-design-and-documentation-processes.

[15] For examples, see also, CLSI EP18 *Risk Management Techniques to Identify and Control Laboratory Error Sources.*

Specimen integrity and handling

- Error in specimen collection.
- Use of inappropriate anticoagulant.
- Clotted specimen.
- Error in specimen handling.
- Incorrect specimen transport and/or storage.
- Presence of interfering substances.
- Presence of bubbles in the specimen.

Reagent integrity (Reagent viability)

- Use of improperly stored reagents.
- Use of outdated reagents.
- Use of improperly mixed reagents.
- Use of contaminated reagents.

Hardware, software, and electronics integrity

- Power failure.
- Power fluctuation.
- Incorrect voltage.
- Repeated plugging and unplugging of the device.
- Hardware failure.
- Software failure.[16]
- Electronic failure.
- Physical trauma to unit.

Stability of calibration and internal controls

- Factors that affect calibrator and calibration stability, including determination of calibration stability over time and after power failures.
- Factors that may interfere with calibration.

Environmental factors

- Impact of key environmental factors (temperature, humidity, barometric pressure changes, altitude (if applicable), sunlight, surface angle, device movement, etc.) on reagents, specimens, and test results.
- Impact of key environmental factors (including electrical or electromagnetic interference) on instruments, if appropriate.

[16] See "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-content-premarket-submissions-software-contained-medical-devices.

B. Tier 2: Fail-Safe and Failure Alert Mechanisms

(1) Points to consider for designing fail-safe and failure alert mechanisms

We recommend that you consider including the items on the following list, as appropriate, and incorporating fail-safe mechanisms, when possible.

- Lock-out functions that do not allow output of results if controls or system checks are not successfully completed.
- Lock-out functions that do not allow output if expired reagents are used.
- Lock-out functions that do not allow output of results if the device was mishandled (e.g., dropped) and the device detects damage during internal electronic system checks.
- Physical features to ensure correct placement of components, such as strips or cartridges.
- Monitors of environmental conditions (e.g., indicator desiccants) incorporated into the test system or the kit container to alert the user to environmental conditions that are outside of the recommended storage conditions.
- Battery checks.
- Internal procedural controls to flag procedural problems such as improper sample flow, incorrect use of components, or improper addition of specimen. (However, procedural controls generally provide limited problem detection and, by themselves, are generally not sufficient to serve as a failure alert mechanism.)
- Internal non-procedural controls (e.g., for checking the integrity of the reagents).
- Controls to check that electronic features of the device are within specifications.
- External control material.

When designing controls, you should consider the unique features of the test system and link control procedures to the robustness of the assay, as determined by your flex studies. The controls you devise to mitigate the identified risks may be based on procedures typical for laboratory-based methodologies (e.g., testing external materials at two levels at a time interval of once per shift or on each day of testing) or may be a combination of features, such as those listed above, that ensure complete system quality monitoring. When designing packaging for your device, you should also consider that the number of tests per kit should depend on the stability of the reagents or the robustness of your device, as demonstrated through testing.

When appropriate, the test system software should incorporate capabilities that allow for data retention, identification of outliers, and trend detection, in order to alert the user to the occurrence of random or systematic errors.

Procedural controls, which are typically internal, are desirable for waived devices. However, these types of controls generally do not replace external controls, especially because they often only control for adequate volume. Flex studies and validation and/or verification studies should evaluate the sensitivity of internal control reagents to all applicable test system errors. The total quality control (QC) system (including all control procedures and internal

checks) should control for all aspects of test performance, including electronic aspects and integrity of reagents.

We do not recommend training as a sole means of mitigating potential sources of harm. Aspects of the device design that are controlled and maintained by the manufacturer can potentially be considered as mitigations.

(2) External control materials

Whenever feasible, you should include external control materials in the test kit. External control materials for waived tests should be ready to use or employ only very simple preparation steps, e.g., breaking a vial in order to mix liquid and dry components of the control material. Reconstitution steps should not require pipetting by the user. For both quantitative and qualitative tests, the levels of the control materials should correspond to the medical decision level(s) relevant to the indications for use for your test. More than one level may be needed in order to ensure accuracy for quantitative tests. For qualitative tests, you should ensure that control materials include those with concentrations sufficiently close to the cutoff to provide adequate assessment of test performance for patient samples near the clinical cutoff.

You should alert operators about control procedures and the availability of control materials and integrate instructions for external control testing within the test procedure instructions (Quick Reference Guide and package insert), in order to increase the likelihood that operators will perform QC correctly. The test instructions should specify minimum frequency for running controls and include recommended levels of control materials that correspond to medical decision levels. The labeling should indicate in bold why external controls are important and the consequences of not performing all QC procedures.

In addition, when control materials are not included in the test kit, you should also recommend, in the Quick Reference Guide and package insert the use of specific control material(s) that will ensure optimal verification of the test system performance. Providing or recommending external control materials may not be critical in those limited cases where sufficient fail-safe mechanisms are in place for the entire system. Although we are currently unaware of any such systems, should you develop one, we recommend that you explain, in your waiver application, your rationale for omitting these control materials.

You should describe, in your application, how you established the QC limits and how you demonstrated that the chosen limits provide adequate assessment of test performance with patient samples. For quantitative tests, you should consider the precision of the test system, as well as the total allowable error for the particular analyte. Ranges that are too broad may be incapable of reliably detecting unacceptable levels of imprecision or bias.

Control materials should mimic performance of patient samples as closely as possible. When the matrix of the material differs from that of the specimen, you should determine and describe in your application how these differences may affect or limit the information provided by the control result. You can accomplish this by testing control materials in parallel with actual patient samples of similar known values and comparing the results of the

control material and patient samples with respect to precision or bias observed. You should account for matrix effects when setting the limits for control material to be used with your test.

(3) Additional points concerning control materials

If you did not previously submit information addressing the items below in a premarket submission, you should provide them in your waiver application:

- Opened and unopened control material stability data. This should include acceptance criteria and results. The term "unopened" refers to shelf-life stability whereas "opened" refers to reconstituted conditions, or other conditions after the vial is initially opened by the user.
- Lot-to-lot reproducibility, conducted on at least three consecutive lots of control material.

C. Validating Fail-Safe and Failure Alert Mechanisms, Including External Control Procedures

You should conduct studies that validate all fail-safe and failure alert mechanisms (including any procedures you recommend that use external control materials) that address all the causes of test errors identified in the risk analysis. These studies should be conducted under conditions that stress the device in order to demonstrate how fail-safe and failure alert mechanisms respond to such conditions. You should describe your validation and/or verification studies, and the results of these studies, in your waiver application, and indicate how the results support the ability of fail-safe and failure alert mechanisms to detect and mitigate test errors. You should include a description of how your recommendations for external control materials and procedures (including frequency) are supported by your validation and/or verification studies and confirmed by the studies described in Section V, below.

Table 1 - Examples of approaches to flex studies and control validation studies under conditions of stress

POTENTIAL SOURCE OF ERROR	EXAMPLES OF FLEX STUDIES	EXAMPLES OF VALIDATION STUDIES
Operational storage is 2-4° C. What happens when the kit is stored improperly?	Environmental studies included storing the kit at 0°, 2°, 10°, 25°, and 37° C. Studies showed that when frozen, or stored at 25° C for over 3 days, the device failed.	Studies to validate that fail-safe mechanisms, or failure alerts, including external control procedures, alert the operator to frozen conditions or storage at 25° C for more than 3 days.

POTENTIAL SOURCE OF ERROR	EXAMPLES OF FLEX STUDIES	EXAMPLES OF VALIDATION STUDIES
Procedure is to add 3 drops. What happens when an improper number of drops are added to the test procedure?	Flex studies consist of adding 1, 2, 3, 4, 5, and 6 drops and observing when incorrect results are obtained. Studies show that <2 drops or >5 drops give erroneous results.	Studies to validate that fail-safe mechanisms, or failure alerts, including control procedures, alert the operator of an error when <2 drops or >5 drops are added.

V. 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."[17] 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."[18] One of the key elements for granting a CLIA waiver is whether the test is accurate in the hands of the user. With this in mind, FDA identifies 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:[19]

- **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.[20]

A. Study Design Options

This 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.

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

[17] 42 U.S.C. § 263a(d)(3).
[18] 42 U.S.C. § 263a(d)(3)(A).
[19] Please see Appendix B for additional definitions.
[20] 42 CFR 493.1423.

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 use to demonstrate that a candidate test meets the CLIA statutory criteria for waiver.[21] FDA's analysis of studies conducted in accordance with these recommendations will consider 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 V.B, below).

FDA believes Options 1-3, described below, are appropriate when sufficient valid scientific evidence can be derived from the combination of the prior performance studies (e.g., 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."[22] Under this option, these studies compare 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). FDA believes this option is generally 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. FDA believes this option is generally 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 above and human factor study designs described in FDA's guidance "Applying Human Factors and Usability Engineering

[21] 42 U.S.C. § 263a(d)(3).
[22] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assay-migration-studies-vitro-diagnostic-devices.

to Medical Devices."[23] FDA believes this approach is generally appropriate for test systems for which:

- collection of a specimen is either always performed by a professional (for example, an endocervical swab collected by a doctor) or always 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.

Additionally, another 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 Guide was not modified (or minimally modified). FDA encourages manufacturers considering modification of a test system previously waived by application to contact FDA through a Pre-Submission to discuss planned modifications, as well as study designs and analyses to validate that the modified test system meets the statutory criteria for CLIA waiver.[24]

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 on 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 EP21,[25] CLSI EP27.[26]
- For qualitative tests: CLSI EP12.[27]

For Options 1, 2, and 4, if sufficient valid scientific evidence on the imprecision of the test and the performance of the test at low levels (limit of detection and limit of quantitation) when performed by untrained operators is not available from the studies described above, additional studies should be performed to allow comparison of the imprecision and limit of detection/limit of quantitation of the test when performed by untrained and trained operators. We recommend following appropriate FDA-recognized consensus standards (e.g., CLSI EP05,[28] CLSI EP12, CLSI EP17[29]) for these studies.

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[23] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/applying-human-factors-and-usability-engineering-medical-devices.

[24] A Pre-Submission is a type of Q-Submission. For information regarding the process for obtaining feedback from the FDA, see the guidance "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program.

[25] CLSI EP21 *Evaluation of Total Analytical Error for Quantitative Medical Laboratory Measurement Procedures.*

[26] CLSI EP27 *How to Construct and Interpret an Error Grid for Quantitative Diagnostic Assays.*

[27] CLSI EP12: *User Protocol for Evaluation of Qualitative Test Performance.*

[28] CLSI EP05 *Evaluation of Precision of Quantitative Measurement Procedures.*

[29] CLSI EP17 *Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures.*

Applicants are strongly encouraged 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.[30]

B. Considerations in Satisfying CLIA Waiver Requirements

One statutory criteria that a test can meet to obtain a CLIA waiver centers on the simplicity of the test and whether the user can conduct the test with a negligible likelihood of erroneous results.[31] 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.[32] 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 performed following study Options 1 or 2, the minimum level of agreement between results of the test in the hands of 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.

C. 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, 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.

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[30] For information regarding the process for obtaining feedback from the FDA, see the guidance "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program.

[31] 42 U.S.C. § 263a(d)(3)(A).

[32] See, for example, "Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications (510(k)) with Different Technological Characteristics,," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/benefit-risk-factors-consider-when-determining-substantial-equivalence-premarket-notifications-510k, and "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/factors-consider-when-making-benefit-risk-determinations-medical-device-premarket-approval-and-de.

- 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 should be integrated into the daily workflow of the facility where the operators are often multitasking between patient care, testing, and other duties.

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

(2) 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. Untrained operators should have limited or no training or hands-on experience in conducting laboratory testing and should not have previous training or experience with the candidate test, but may have limited experience with other waived or home use tests. Untrained operators should be personnel currently employed in the selected intended use sites and testing should be integrated into the daily workflow of the facility where the operators are often multitasking between patient care, testing, and other duties. We recommend that you record and tabulate the education (including experience and training) and the occupation of each untrained 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 recommend you report the same information on other personnel 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. Additionally, for study Options 1 and 2, trained operators should have previous training and/or experience with the candidate test , and for study Option 4 trained operators should meet the appropriate CLIA non-waived qualifications to perform the comparative method and have previous training and/or experience with the comparative method.

c. Instructions for use

You should provide the untrained operators who participate in the study with only the instructions and training materials that are intended for untrained operators and are "simple" (see Section III), and that will be provided with the test kit in the actual intended use settings when the test is marketed. This may include the proposed Quick Reference Guide, Operator's Instrument Manual, etc. (see Section VI). 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").[33]

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.

[33] 29 CFR 1910.1030.

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.

(3) 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 is determined to meet appropriate inclusion criteria, he/she should be informed of the study and invited to participate in the study. You must follow applicable laws and regulations for human subject protection, including patient privacy and informed consent.[34]

(4) 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. For more information regarding the use of archived samples, please refer to the FDA guidance "Design Considerations for Pivotal Clinical Investigations for Medical Devices."[35] 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

[34] See §520(g) of the FD&C Act (21 U.S.C. § 360j(g)); 21 CFR Parts 50,56, and 812; the Health Insurance Portability and Accountability Act (HIPAA) [P.L. 104-191]; and 45 CFR Part 46.
[35] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/design-considerations-pivotal-clinical-investigations-medical-devices.

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.[36]

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 study Options 1 and 2) or the comparative method (for study 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.[37] Untrained and trained operators should be blinded to test results from other operators.

(5) 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."[38]

(6) Clinical study reports

You should report results of the clinical study intended to support your CLIA waiver application by each intended site and if appropriate, overall. To aid FDA's review, we recommend that the report include the following:

- Protocol description.
- Number of subjects (i.e., patients/samples) studied.
- Procedures for subject inclusion and exclusion.
- Description of the subject population.
- Description of how specimens were collected and stored (if applicable).
- 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.

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[36] For information regarding the process for obtaining feedback from the FDA, see the guidance "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program.

[37] *Ibid.*

[38] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/financial-disclosure-clinical-investigators. See also 21 CFR Part 54, Financial Disclosure by Clinical Investigators.

- 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").

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. You should also provide a rationale as to why the observed percentage of invalid results is clinically acceptable.

VI. Labeling for Waived Devices

In order to ensure that the device is "simple" and has "an insignificant risk of an erroneous result," your labeling should include quick reference instructions (Quick Reference Guide, Operator's Instrument Manual (if applicable)) for accurately running the test and reporting results that are written at a level appropriate for untrained operators, which for a "simple" device should be at a 7th grade reading level, or lower.[39]

You should include your proposed labeling, including Quick Reference Guide, Operator's Instrument Manual (if applicable), package insert, and outer labels in your waiver application. (Note that labeling for in vitro diagnostic devices must meet all applicable labeling requirements as stated in 21 CFR 809.10.)

A. Quick Reference Guide (QRG) and Operator's Instrument Manual (if applicable)

You should include a QRG in your application. Preferably, the QRG should be laminated and attached to the test system. These instructions should be clear, easy to understand, in a readable font of size 12 or greater, and, when possible, include pictures. You should write instructions at no higher than a 7th grade level. For recommendations on what to include in the QRG, see Appendix A. You should include all the items listed in Appendix A that are applicable to your test system, as well as any other appropriate information specific to your

[39] It may be helpful for you to refer to the following guidance documents: "Applying Human Factors and Usability Engineering to Medical Devices," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/applying-human-factors-and-usability-engineering-medical-devices; and "Guidance on Medical Device Patient Labeling," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-medical-device-patient-labeling.

test system. If applicable, you should also include an Operator's Instrument Manual that is written at no higher than a 7th grade level and includes instructions for start-up of the instrument, long term maintenance including calibration (if applicable), error codes, etc.

B. Package Insert

The package insert for waived test systems should include additional information appropriate for use in CLIA-waived settings, including:[40]

- Facilities performing testing must have a CLIA Certificate of Waiver.[41] Also, the labeling should identify your test system as waived and note that all applicable state and local laws must be met.
- A statement that laboratories eligible for a Certificate of Waiver must follow the test system instructions, including use with only the waived specimen type(s), instructions for limitations/intended use, and performance of QC testing as a failure-alert mechanism.[42] You should state that any modification to the test or the manufacturer's instructions will result in the test being classified as high complexity.[43]
- Results of studies that supported CLIA waiver of the test. The performance information in your labeling can be finalized in consultation with FDA after study results are reviewed and the test is determined to be waived by FDA.

For waived test systems, the package insert should be intended for the medical professional prescribing the test and does not need to be written at a 7th grade reading level.

C. Quality Control (QC) Labeling Recommendations

Instructions should clearly explain why QC is needed and emphasize the value of external control testing at regular intervals for ensuring operator competency, as well as reagent and, when appropriate, instrument integrity. Instructions on how to perform control procedures using external controls are always recommended and are critical if you are using them as a failure alert to help ensure "insignificant risk of an erroneous result." Instructions relating to procedures used for QC should be integrated within the instructions for performing the test and should include the following:

- Step by step information on how to test control material, including testing frequency and concentration of materials.
- How to read results of control procedures.
- How to determine if results are invalid. For example, for tests with an internal procedural control line, the test is not valid if the line is not present.
- Actions to take when control results are out of range or invalid. For example, the directions should direct the user to call technical assistance when control results are out of range or invalid and state that the results should not be reported.

[40] See also Appendix A for more detailed recommendations.
[41] 42 USC 263a(c)(2).
[42] 42 CFR 493.15(e).
[43] 42 CFR 493.17(c)(4)

- The limitations on all control mechanisms, including procedural controls, which you identified during the risk assessment. For example, if your procedural controls only test that a liquid was applied, this limitation needs to be communicated to the user.

Your explanations of QC systems should include a description of what is being measured by all elements of both internal and external quality controls for a particular test system. To aid in addressing QC problems, you should provide a toll-free telephone number for technical assistance. We recommend that QC instructions take into account information obtained during the studies described in Section V, as well as results of flex studies and validation and/or verification studies under conditions of stress (Section IV).

You should include discussions of benefits and limitations of the various device controls. For example, for a unitized test, the following may be appropriate and could be indicated in bold in the labeling for emphasis:

> When you run test (xyz), you should always see an extra line (the control line) in addition to the test line. This extra line lets you know that you added the correct sample volume. Good laboratory practice recommends that you also use additional positive and negative control materials that are not built in to the test. (They are external controls.) You can order external controls from [insert information here]. External controls can monitor test features such as whether test reagents are working properly or whether the test was performed correctly. If any of the controls do not perform as expected, do not report patient results. Review the instructions to see if the test was performed correctly, and then repeat the test. If the controls still do not give the expected results, contact technical assistance before testing patient samples.

Examples of possible minimum frequency recommendations for running external controls are listed below. You should base your *specific* recommendations on data from your studies.

- Each new lot.
- Each new shipment of materials, even if it is the same lot previously received.
- Each new operator (i.e., operator who has not performed the test recently).
- Monthly, as a check on continued storage conditions.
- When problems (storage, operator, instrument, or other) are suspected or identified.
- If otherwise required by your laboratory's standard QC procedures.

D. Educational Information

As part of an overall plan to ensure that the likelihood of erroneous results by the user is negligible, we encourage manufacturers to consider innovative mechanisms to provide educational information and technical assistance to CLIA-waived laboratories (e.g., a downloadable version of the test procedure with computer animation showing the correct steps for performing the test). We also recommend that manufacturers assist laboratories performing waived tests in becoming better educated on proper laboratory techniques. For example, we recommend that you participate in the development and promotion of good laboratory practice guidelines by developing training and education programs for the end operator. We also encourage you to incorporate proficiency testing, when feasible, and to

promote laboratory participation in proficiency programs. In addition, we recommend that you include good laboratory practice information in the package insert, in accessory educational or technical material, and through the development of formal educational training programs. We recommend that you provide information on the following topics to operators:

- Importance of retaining a current version of the package insert with the latest revision date.
- Importance of following the test instructions in the sequence given in the instructions.
- Need for proper operator training and retraining in order to maintain competency.
- Need for users to follow all instructions related to storage, preparation, and expiration dating in order to maintain adequate test performance.
- Importance of documenting results and maintaining records as needed for proper performance of the test and patient management.
- General purpose of quality control and value of using quality control within a broader system of quality assurance.
- Common errors – errors that are likely to occur. For example, incorrect timing that may be mitigated by use of a mechanical timer with an alarm.

We recommend that you consult CDC's resources regarding good laboratory practices for waived testing sites including: "Survey findings from testing sites holding a Certificate of Waiver under the Clinical Laboratory Improvement Amendments of 1988, and Recommendations for Promoting Quality Testing,"[44] and the booklets "To Test or Not to Test?" and "Ready? Set? Test!" available at https://www.cdc.gov/clia/waived-tests.html.

VII. Safeguards for Waived Tests

1. FDA also recommends that manufacturers of waived tests put a brief description of the MedWatch medical products reporting program, along with the MedWatch phone number (1-800-FDA-1088), fax number (1-800-FDA-0178), and website (www.fda.gov/medwatch) in the package insert. You may also describe how the MedWatch program works, which failures should be reported to both the company and FDA, and when failures should be reported to ensure proper tracking and reporting of waived testing issues.
2. Manufacturers of devices must maintain and implement medical device reporting procedures, as required by 21 CFR 803.17, and must establish and maintain medical device report (MDR) event files, as required by 21 CFR 803.18.[45]
3. Manufacturers of devices must submit MDRs of individual adverse events, as required by 21 CFR 803.10(c).

[44] Centers for Disease Control and Prevention. Good laboratory practices for waived testing sites; survey findings from testing sites holding a Certificate of Waiver under the Clinical Laboratory Improvement Amendments of 1988 and Recommendations for Promoting Quality Testing. MMWR 2005; 54 (No.RR-13):1-25, available at https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5413a1.htm.

[45] See also 21 CFR 803.20 and 21 CFR Part 803, Subpart E.

VIII. Paperwork Reduction Act of 1995

This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520).
The time required to complete this information collection is estimated to average 780 hours per response, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. Send comments regarding this burden estimate or suggestions for reducing this burden to:

FDA PRA Staff,
Office of Operations,
Food and Drug Administration,
PRAStaff@fda.hhs.gov

This guidance also refers to previously approved collections of information found in FDA regulations. The collections of information in 21 CFR part 803 have been approved under OMB control number 0910-0437; and the collections of information in 21 CFR part 809 have been approved under OMB control number 0910-0485.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control number for this information collection is 0910-0598 (expires 9/30/2022).

Appendix A: Labeling

SPECIFIC LABELING RECOMMENDATIONS FOR WAIVED DEVICES

QUICK REFERENCE GUIDE (QRG) WITH PICTURES AND DIAGRAMS should generally contain the following, as well as any other sections appropriate for your specific device. The QRG should be written at no higher than a 7th grade reading level:
The name of the test and a statement that labs with a Certificate of Waiver may use it.
A statement clearly listing the specimen type, e.g., this test is only waived for urine specimens.
A statement that users should read the complete test procedure, including recommended QC procedures, before performing the test. If appropriate, a statement that users should perform control procedures before performing the test.
A statement that laboratories with a Certificate of Waiver must follow the manufacturer's instructions for performing the test.[46]
Step-by-step test instructions. Include, as appropriate: physical environmental specifications/conditions for test performance; specifications for specimen collection, handling, storage, and preservation; preparation of reagents and control materials; storage of reagents and control materials; and calibration procedures. Utilize diagrams and flowcharts to illustrate how to run the test when helpful.
Step-by-step instructions for all control procedures, including frequencies and action to be taken if control results are out of range or invalid, or if other failure alert or fail-safe mechanisms are activated.
Interpretation of results, including diagrams on how to read and assess validity of test results and control results.
A warning addressing color blindness when waived tests use color-coded reagents and/or endpoints.
Safety considerations for test operation that particularly apply to untrained users.
Critical maintenance, such as cleaning (including safety considerations).
Telephone number to contact manufacturer for technical assistance or troubleshooting the test system. Direct the user to call for assistance when the device or the control materials do not work as specified by the manufacturer.

[46] 42 CFR 493.15(e)(1).

PACKAGE INSERT – Should contain considerations for waived tests (in addition to requirements specified in 21 CFR 809.10 and any other considerations specific for your device type)
Identification of the test as CLIA waived, a statement that a Certificate of Waiver is required to perform the test in a waived setting, and information on how users can obtain a certificate.
A statement that laboratories with a Certificate of Waiver must follow the manufacturer's instructions for performing the test.[47]
Test operation safety considerations that particularly apply to untrained users.
The physical environmental specifications/conditions for performing the test.
A warning addressing color blindness when waived tests use color-coded reagents and/or endpoints.
Step-by-step operating instructions for performing the test, which are integrated with instructions for all control procedures.
Action to be taken when no test result is obtained or when the result is out of the reportable range.
Study results demonstrating how the test compares to a known method that is traceable to a reference method, if applicable.
A brief description and summary of the results from the waiver studies.
When appropriate, warnings about clinical errors that can occur even when the test result is analytically correct.
Instructions indicating when and how additional testing should be done (e.g., in cases where results should be confirmed by a reference procedure performed by an appropriately certified laboratory).
Any other limitations, restrictions, and special considerations for your test system.
Appropriate QC recommendations or requirements (see below, "Quality Control Labeling Recommendations").
Information on reporting test system problems to the manufacturer and/or FDA, such as www.fda.gov/medwatch. You should include statements encouraging users to contact you and/or FDA so that you can track and account for device problems.
Manufacturer contact information (phone number and the party to contact with a valid email address, if available).
Quality Control Labeling Recommendations
Step by step information on how to test control materials.
Frequency for testing control materials.
How to read control results and procedural controls.
Actions to take when control results are out of range or invalid.
Limitations of the device's controls that were identified during the risk assessment.

[47] 42 CFR 493.15(e)(1).

Appendix B: Definition of Terms as Used in this Document[48]

TERM	DEFINITION
Control material	Material used to verify performance characteristics of a medical device.
Control measure	Protective measure implemented for reducing risks. (Fail-safe mechanisms and failure alerts are control measures.)
Control procedures	Operational techniques and activities at the point of use to monitor the performance of the device and fulfill the laboratory's requirements for quality. Any single control procedure might monitor all or part of the measurement procedure, ranging from the collection of samples to reporting the result of the measurement.
External control material	Control material that is not built into the device. Typically, this is in a similar matrix as the intended use specimen and is processed using the same procedures as patient specimens. External control materials for waived tests should be ready to use or employ only very simple preparation steps, e.g., breaking a vial in order to mix liquid and dry components of the control material.
Fail-safe mechanisms	Mechanisms to ensure that a test system does not provide a result when test conditions are inappropriate or when the result is based on faulty test functioning. This includes measures that prevent improper operation of the device (for example, guides or channels that prevent improper strip placement).
Failure alert mechanisms	Mechanisms that notify the operator of any test system malfunction or problem. Failure alert mechanisms ideally include built-in controls or checks. Procedures that use external control material can also be considered failure alert mechanisms.
Flex studies	Studies performed using the device under conditions of operational stress. These studies are performed to identify potential sources of error as part of the risk assessment.

[48] Also see the CLSI Harmonized Terminology Database, available at http://htd.clsi.org/, for further details and more general use of the terms. This website is maintained by CLSI and is not controlled by FDA (last accessed on May 31, 2019).

TERM	DEFINITION
Hazards (for IVDs)	Potential source of harm (to a patient or test operator). For IVDs, hazards for patients are generally incorrect patient results or operator injuries.
Internal control	A control, or system check, built into the device system, meaning the user does not need to use additional reagents to perform that particular control process.
Matrix	The totality of components within a patient specimen, control(s), or calibrator(s), other than the analyte.
Matrix effects	The influence of a property of the sample, other than the analyte, on the device's performance characteristics. Examples: (a) The test values for a particular analyte in whole blood collected via a venous sample may differ from those for a fingerstick. (b) Control material in a matrix different from that of the specimen should be tested to ensure that test performance is the same as that for the specimen.
Operator's Instrument Manual	A short version of the instrument manual that is intended for untrained operators and includes instructions for start-up of the instrument, long term maintenance including calibration (if applicable), error codes, etc.
Procedural control	Controls or indicators to monitor whether specific aspects of the procedure were performed correctly. Often, procedural controls are in the form of control lines on a single use cassette or dip devices, and indicate whether sufficient sample was applied. Procedural controls generally do not serve as a control for the entire test system.
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.
Quality control (QC)	The entire set of procedures and system checks designed to monitor the test method and the results to assure acceptable test system performance.
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.

TERM	DEFINITION
Quick Reference Guide (QRG)	A short (usually one or two page) version of the test instructions, preferably laminated and attached to the test system. It is intended for untrained operators and contains the step by step instructions needed to perform the test with a negligible likelihood of erroneous results
Risk analysis	Systematic use of available information to identify hazards and estimate risk.
Risk control	Process through which decisions are reached and protective measures are implemented for reducing risks to or ensuring specified levels.
Risk evaluation	Judgment of whether acceptable risk has been achieved based on risk analysis.
Risk management	Systematic application of management policies, procedures, and practices to analyze, evaluate, and control risk.
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.
Source of error	A component of the device, measurement method, or operator practice that can lead to device failure and, thus, create a risk for patients, operators, or other individuals.
Trained operator (or moderate complexity laboratory user)	A test operator who meets the qualifications to perform moderate complexity testing.[49]
Unitized test device	A self-contained test device to which a specimen is added directly and in which all steps of the testing process occur. A unitized device is used for a single test and must be discarded after testing.
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.

[49] 42 CFR 493.1423.