# Guidance for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Criteria for Waiver; Draft Guidance for Industry and FDA

*Draft Guidance – Not for Implementation*

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# Preface

## Public Comment

For 90 days following the date of publication in the Federal Register of the notice announcing the availability of this guidance, comments and suggestions regarding this document should be submitted to the Docket No. assigned to that notice, Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852.

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# Guidance for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Criteria for Waiver; Draft Guidance for Industry and FDA

***This document is intended to provide guidance. It represents the Agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.***

## I. INTRODUCTION

This guidance document is for device manufacturers ("you" throughout this document) submitting CLIA waiver requests to FDA. In this guidance document, FDA is announcing alternative criteria for obtaining CLIA waiver that can be used in place of the proposed criteria that the Health Care Financing Administration (HCFA) and the Centers for Disease Control and Prevention (CDC) published as a Notice of Proposed Rulemaking (NPRM) in the Federal Register (60 FR 47534) on September 13, 1995 ("1995 proposed rule" throughout this document).

***BACKGROUND*** - The CLIA statute, 42 U.S.C. § 263a(d)(3) Examinations and Procedures, as modified by FDAMA, reads:

> "The examinations and procedures [eligible for certificates of waiver] are laboratory examinations and procedures that have been approved by the Food and Drug Administration for home use or that, as determined by the Secretary, are simple laboratory examinations and procedures that have an insignificant risk of an erroneous result, including those that - (A) employ methodologies that are so simple and accurate as to render the likelihood of erroneous results by the user negligible, or (B) the Secretary has determined pose no unreasonable risk of harm to the patient if performed incorrectly."

The legislative history accompanying the Food and Drug Administration Modernization Act (FDAMA) clarifies that (A) and (B) are examples of product types that could satisfy the criteria for waiver (of simple laboratory examinations and procedures that have an insignificant risk of erroneous result). Therefore, a determination that a test may be waived may occasionally be based on something other than subparagraphs (A) and (B).

In addition, any device cleared or approved by FDA for over-the-counter or prescription home use automatically qualifies for CLIA waiver.

This guidance document ***DOES NOT*** eliminate the criteria that HCFA and CDC have proposed. You may still request waiver based on the criteria outlined in the 1995 proposed rule.

This guidance document ***DOES NOT*** change the need for sound scientific evidence in supporting waiver requests.

This guidance document ***DOES*** provide another mechanism that you can use to obtain CLIA waiver using valid scientific evidence. This new mechanism includes new criteria for making waiver decisions. These new criteria are outlined in this guidance document. If you choose to use these new criteria, then FDA will determine whether the criteria for waiver have been met.

FDA recognizes that there will be diverse opinions on the criteria contained in this document, just as there are for the criteria contained in the 1995 proposed rule. Requests for waiver have been complicated by the fact that the complexity categorization program was transferred to FDA prior to promulgation of a final rule clarifying the criteria for waiver. FDA's approach to waiver reviews has also been influenced by the changes to the CLIA statute enacted by Congress on November 21, 1997, as part of the Food and Drug Administration Modernization Act of 1997 (FDAMA). Recognizing this, we are committed to ensuring an open, consistent, reliable process that all parties can understand and comment on as we take steps to finalize a rule. Because FDA believes it will have to repropose a regulation to clarify waiver criteria, we think it will be some time before a final rule is codified. This guidance document represents an interim waiver review process that may continue (depending on comments received on this guidance document) until a reproposal of the regulation to clarify the statutory criteria for waiver is published.

We base the recommendations in this document on our interpretation of the law, our review experience with CLIA complexity reviews, and our interactions with stakeholders throughout the transition of this program from CDC to FDA. One of the interactions with stakeholders was in the form of an open public workshop on August 14 and 15, 2000; we are still evaluating the comments from this workshop. We intend to re-evaluate and revise this guidance document, as circumstances warrant, based on these and future comments.

As you will see as you read this document, FDA is approaching the issue of criteria for CLIA waiver using a systematic, step-wise approach:

***Step 1*** Determine if the test is simple as defined in the 1995 proposed rule, or as defined in section II of this guidance.

*Whenever possible, sample(s) of the test system should be included with your request for waiver to aid FDA in its determination of 'simple'.*

***Step 2*** Determine if the test has an insignificant risk of erroneous result as defined in section III of this guidance.

IF FDA determines that the test is simple (step 1) and has an insignificant risk of erroneous result (step 2)
THEN it is a candidate for waiver

IF FDA determines that the test is not simple or does not have an insignificant risk of erroneous result
THEN the device is not a candidate for waiver

*Failure alert mechanisms, such as having adequate quality control procedures, help to ensure that the test will have an insignificant risk of erroneous result. Refer to sections III and V for more information.*

***Step 3*** Determine if the test is accurate as defined in the 1995 proposed rule, or as defined in section IV of this guidance.

IF FDA determines that the test is simple (step 1), has an insignificant risk of erroneous result (step 2), and is accurate (step 3),
THEN it meets the criteria for waiver

IF FDA determines that the test is simple and has an insignificant risk of erroneous result, but is not accurate
THEN it will not be waived unless the Secretary determines that it poses no unreasonable risk of harm to the patient if performed incorrectly, or if the test is otherwise determined to be simple with an insignificant risk of erroneous result.

***Step 4*** For all tests that are determined to be simple, have an insignificant risk of erroneous result, and are accurate, we will review the labeling to ensure it is consistent with the proposed waiver requirements. Then we will issue a notification of waiver and we will notify HCFA to ensure timely and proper CLIA survey reviews. Test systems approved for waiver will also be published on FDA's website www.fda.gov/cdrh/clia.

To aid with the waiver review process, this guidance document provides the following tools:

Appendix A (Waiver Checklist) is a checklist to help determine whether

- the design and format of your device meet the statutory criteria for waiver

- you have conducted the appropriate studies verifying the criteria have been met
- you can demonstrate that your device has failure alerts (refer to section III)

Appendix B (Waiver Labeling Checklist) is a checklist to help determine whether

- the labeling includes all the waiver elements
- you have prepared the quick reference instructions correctly

We encourage you to refer to and comment on another Center for Devices and Radiological Health (CDRH) guidance document pertaining to CLIA. It is entitled "Guidance for Administrative Procedures for CLIA Categorization," www.fda.gov/cdrh/ode/guidance/1143.html. In it, we provide instructions to device manufacturers on FDA's administrative procedures for CLIA categorization.

***TERMS USED IN THIS DOCUMENT***

| | |
|---|---|
| **Untrained user** | a lay-user with no previous training or hands-on experience in conducting laboratory testing |
| **Laboratory professional** | an individual who meets the qualifications to perform moderate or high complexity testing, such as a medical technologist (MT) or medical laboratory technician (MLT) (Note: ***professional*** and ***laboratory professional*** are used interchangeably in this document) |

# II. DEMONSTRATING "SIMPLE"

FDA considers a test simple when the test has all of the following characteristics:

- Is a fully automated instrument, unitized, or self-contained test
- Uses direct unprocessed specimens
- Requires only basic, non-technique-dependent specimen manipulation
- Requires only basic, non-technique-dependent reagent manipulation
- Has no operator intervention during the analysis
- Requires no technical or specialized training with respect to troubleshooting (interpreting error codes does not constitute troubleshooting)
- Requires no electronic or mechanical maintenance

- Produces a direct readout of result that requires no calibration, interpretation, or calculations

**Examples** of these characteristics of simple tests include, but are not limited to, tests that

- are ready to use (i.e., there is no specimen processing or interaction, etc. prior to testing)
- use capillary blood (fingerstick), nasal swabs, or urine
- require only simple reagent mixing steps, such as 'mix reagent A and reagent B'
- produce results that are read as 'positive or negative'
- produce results that are read as a numerical value
- produce results determined by the clear presence or absence of a line
- produce results determined by obvious color gradations
- contain instructions for use written at no higher than a 7$^{th}$ grade reading level

You may find it helpful to review these FDA guidance documents about labeling and device design. They are available on the Internet as shown:

- "Write it Right," http://www.fda.gov/cdrh/dsma/897.pdf

- "Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management," http://www.fda.gov/cdrh/humfac/1497.html

- "Draft Guidance on Medical Device Patient Labeling," http://www.fda.gov/cdrh/humfac/1128.html

# III. DEMONSTRATING "INSIGNIFICANT RISK OF ERRONEOUS RESULT"

Failure alert mechanisms are necessary to address the part of the CLIA statute that states that waived test systems (examinations and procedures) shall "have an insignificant risk of an erroneous result." A system that contains failure alert mechanisms is not likely to produce erroneous results. Waived test systems should contain failure alert mechanisms that produce no result when a test system malfunctions. In some instances, it is necessary for the operator to run external controls at regular intervals. You, the manufacturer, are ideally positioned to develop test systems that meet failure alert requirements. Your request for waiver should present information that demonstrates that your test system contains failure alert mechanisms. Conclusions from these studies should be based on valid scientific evidence.

Adequate quality control (QC) includes a description of the nature of the QC modality, and instructions for the conditions and frequency of its use. QC for waived tests may be modeled on standard laboratory QC that is devised for laboratory-based methodologies (e.g., external QC, at two levels, once per shift or on each day of testing) or they may consist of alternative QC practices and modalities. Reliable QC procedures consider the unique features of the test system and are linked to the robustness of the assay. In all cases, the benefits and limitations of all QC modalities, whether built-in or external, should be clearly described in the labeling. For information in labeling your system, please refer to the quality control labeling recommendations contained in section V.

We recommend a two tiered approach to demonstrate that your device has appropriate failure alerts. First, conduct a hazard analysis to identify potential test system failures. The hazard analysis should be used as a basis for initiating stress studies to characterize the operational limits of your device. Results of stress testing should be clearly described in your request for waiver, and the ability of recommended QC to address system failures should be validated.

**Developing QC Procedures**

***Hazard analysis***

Potential test system failures are identified by conducting a thorough hazard analysis. This process is fundamental to designing adequate QC consistent with identified risks. A hazard analysis addresses all possible sources of error. Examples of items considered in the hazard analysis include:

**Specimen Handling**

- Specimen collection
- Interfering substances
- Processing and handling
- Specimen storage and/or transport

**Operator error**

- Use of incorrect reagent (not lot or device specific)
- Wrong order of reagent application
- Use of incorrect amount of reagent
- Incorrect application of specimen
- Incorrect timing of analysis
- Incorrect reading or interpreting of test results

**Reagent integrity problem**

- Use of reagent improperly stored
- Use of outdated reagent
- Use of reagent improperly mixed

- Reagent viability
- Use of contaminated reagents and reagents with altered potency or activity

**Hardware and electronics integrity**

- Evaluation of power failure
- Evaluation of failure in hardware
- Evaluation of failure in software
- Evaluation of physical trauma to unit
- Evaluation of electronic failure

**Stability of calibration**

- Studies to demonstrate how long calibration will hold
- Analysis of factors that may interfere with calibration

**Environmental factors**

- Studies to establish the impact of key environmental factors (heat, humidity, sunlight, etc.) on reagents, specimens, and/or test results
- Studies to establish the impact of key environmental factors (including electrical or electromagnetic interference) on instruments, if appropriate

The role of QC in addressing all identified hazards should be clearly described and the ability to mitigate generation of false results explained using appropriate data and/or analysis of systems tested under appropriate conditions of stress.

**Validating QC Procedures**

Validation studies will demonstrate the ability of QC procedures, when implemented according to your instructions, to detect errors in test performance at an acceptable rate. If the robustness of the assay is exceeded in a failure alert system, then QC procedures will alert the user before the patient results are reported. The combination of process controls, electronic checks, and external or internal (built-in) controls will ensure that, in the hands of untrained users, the test system has failure alerts.

Your validation study should target failures associated with the following, as well as any other factors you may identify in the hazard analysis:

- specimen handling
- operator error
- reagent integrity problem
- hardware and electronics integrity
- stability of calibration
- environmental factors

Examples of an approach to demonstrate that the device has failure alerts are illustrated below:

| HAZARD ANALYSIS | TYPE OF STUDY | VALIDATION STUDIES |
|---|---|---|
| What happens when the kit is stored improperly?<br><br>Procedure says to store it at 4°C. | Environmental studies included storing the kit at freezing, 2°, 10°, 25°, and 37°C.<br>Studies showed that when frozen, or stored at 25°C for over 3 days, the device failed. | QC procedures alert the operator to frozen conditions or if it was at 25°C for more than 3 days. |
| What happens when an improper number of drops are added to the test procedure?<br><br>Procedure says 3 drops are to be added. | Flex studies consist of adding 1, 2, 3, 4, 5, and 6 drops and observing when incorrect results are obtained.<br><br>Studies show that <2 drops or >5 drops give erroneous results. | QC procedures alert the operator of an error when <2 drops or > 5 drops are added. |

**General Recommendations for Designing QC**

When designing QC, consider the following:

- battery checks
- built-in controls that check the integrity of the reagent
- internal process controls
- external QC
- internal QC (distinct from process controls)
- internal checks on adverse conditions
- electronic QC
- functions monitored by available QC systems
- sensitivity of QC systems to analytical and test system errors
- flags for improper sample flow
- flags for incorrect use of components
- flags for temperature change

You should consider incorporating lockout functions that do not allow testing if QC has not been performed or if QC does not give expected results. Also, consider incorporating monitors of

environmental conditions (e.g., indicator desiccants) into the device or the kit container to alert the user to environmental conditions that are outside of the recommended storage conditions.

**QC Materials**

You should consider including QC materials in the test kit in order to increase the likelihood of their use. When QC materials are not included in the test kit, we encourage you to recommend the use of specific QC material(s) in the package insert or describe in detail the type or nature of QC material that will ensure optimal verification of the test system. QC 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 QC material. You should describe how QC limits have been established and how these have been shown to provide an adequate assessment of the performance of the test system. If QC materials are not included or recommended, you should explain your rationale and include appropriate limitations in the package insert and Quick Reference Instructions.

For both quantitative and qualitative tests, the levels of the QC materials/modalities should challenge the medical decision level(s). The QC material should be traceable to a reference material whenever possible.

When the matrix of the QC material differs from that of the specimen, define how these differences might affect or limit the information provided by the QC result. You can accomplish this by testing QC materials in parallel with actual patient samples of similar known values and comparing the results of the standard deviations and coefficients of variation observed. This testing will identify matrix differences that may impact on QC results.

For quantitative tests, set external quality control tolerance limits according to the precision of the device, as well as the total allowable error for that analyte. Ranges that are too broad may be incapable of reliably detecting unacceptable levels of imprecision or bias. When proposing the use of broad tolerance ranges, incorporate data retention, outlier and trend detection capabilities into the device software that alert the user to the occurrence of random or systematic errors. Account for matrix effects as described above.

**Other QC Concerns**

If not previously submitted in your premarket application, you should provide the following:

- open and closed stability data
- lot-to-lot reproducibility

You should include the acceptable performance limits for open and closed stability data for the QC material. The term "closed" refers to shelf-life stability whereas "open" refers to reconstituted or opened conditions. Support stability claims with accelerated studies, with ongoing real time studies, or with real time data. Lot-to-lot reproducibility studies should be conducted on at least three consecutive lots.

# IV. DEMONSTRATING "ACCURATE"

Based on the legislative history and language incorporated into FDAMA, we interpret ***accurate*** to mean test performance (i.e., the test performs the same in the hands of untrained users is it does in the hands of laboratory professionals when using the device under realistic conditions). To address the ***accurate*** issue, we recommend conducting separate studies of precision and agreement between untrained and professional users in paired samples for quantitative tests. For qualitative tests, you need only conduct a single untrained/professional agreement study. We describe these three study designs in this document.

- Untrained/Professional Precision Study for Quantitative Tests
- Untrained/Professional Agreement Study for Quantitative Tests
- Untrained/Professional Agreement Study for Qualitative Tests

**Universal Precautions**

You should conduct CLIA waiver studies under conditions that comply with Occupational Health and Safety Administration (OSHA) regulations pertaining to biological hazards ("universal precautions"), 29 CFR 1910.1030.

**Financial Disclosure**

If clinical investigators are involved in the study, a Financial Disclosure Statement may be required. For advice on whether the financial disclosure rule applies, please refer to the CDRH guidance, "Guidance for Industry: Financial Disclosure by Clinical Investigators," http://www.fda.gov/oc/guidance/financialdis.html or the final rule on Financial Disclosure published in the Federal Register, February 2, 1998 (63 FR 5233).

**Instructions for Use**

You should provide the untrained users with only the written test procedure. Untrained users should receive no training, coaching, prompting, or written or verbal instructions beyond the written test procedure. They should have no opportunity to discuss the test with or otherwise coach or observe each other.

**Demographic Data**

You should enroll individuals who represent anticipated users. We also recommend recording each participant's occupation, to ensure that participants meet the definition of untrained users. While the participants' occupations should be diverse, they need not be representative of the general population. You should collect and tabulate the demographic data shown below in your request for CLIA waiver.

- age
- gender
- education (including experience and training)
- occupation

**Study Reports**

Provide a report of each study you do. Reports should include the protocol, numbers of subjects studied, procedures for subject selection and exclusion, description of the subject population, description of how specimens were collected and stored, masking (blinding) techniques, discontinuations, complaints, device failures and replacements, pertinent tabulations, and clear descriptions and presentations of the statistical analyses. When applicable, results should be reported by site as well as overall. "Outliers" should not be removed. In the event that a part of the collected data is not included in the analyses, that fact should be clearly identified and justification should be given. You should provide an annotated line listing of the data, and you should be prepared to provide electronic versions of data sets.

**Untrained/Professional Precision Study for Quantitative Tests**

Generally, the testing of three specimen levels (low, medium, and high concentrations) are recommended. These specimens should span the reportable range and reflect the medical decision points of the test. Spiked materials or controls may be used in the study, however, we encourage you to use material specific to the specimen matrix stated in the intended use of the device. You should describe how you prepared the materials and validated the assigned levels.

The objective of the study is to compare untrained user precision to professional precision. An appropriate, simple study design can estimate the desired precision directly. An example of a study (see Table 1) that would usually be adequate for estimating untrained user precision would employ at least 60 untrained users divided equally between three non-laboratory sites (20 users per site). At each site, each user would test all three specimen levels presented in an order that is randomized for each user. At each site, one professional would also test all three specimen levels with 20 replicates at each level. For each specimen level, the standard deviations, pooled across sites, provide the desired estimates of precision.

**Table 1. Untrained/Professional Precision Study for Quantitative Tests**

| | Number of Persons | Number of Observations per Person at Each Specimen Level | | | Total Number of Observations |
|---|---|---|---|---|---|
| | | Low | Medium | High | |
| Untrained Users | 60 (20 per site) | 1 | 1 | 1 | 180 |
| Professionals | 3 (1 per site) | 20 | 20 | 20 | 180 |

Unless features of the test indicate that there are no significant sources of day-to-day variability, and unless those features cannot be influenced by operator technique, it is appropriate to include day-to-day variation in the study design. We recommend having the 20 tests run on 20 separate days (i.e., one untrained user and the professional would test the three levels on each of 20 days, with a different untrained user each day). We encourage you to consult with Division of Clinical Laboratory Devices (DCLD) if you have questions about the need to evaluate day-to-day variability.

As an alternative to including professionals in the precision study, it may be possible to compare the untrained users' standard deviation (SD) with the laboratory professionals' SD as presented in your premarket application. This approach may be used if SD estimates are available at the same sample levels and if the previous studies assessed the relevant components of precision. For a device that is exempt from 510(k), you may compare with the precision given in the current labeling. If you use this approach, you should provide a comprehensive description of the professional precision study, including the number of:

- operators
- instruments or units
- days
- runs per day
- levels and nature of the material used

The total estimate of SD should include an equally weighted combination of the components listed in Table 2.

**Table 2. Components of Total Estimate of Precision**

| Component of Total Estimate of Precision |
|---|
| Within-run |
| Between-run |
| Between-day |
| Between-operator |

While the untrained user precision study is different from the professional study, both assess user reproducibility. In your estimate of professional precision, you do not need to include all four of the components listed above. However, you should not include any additional components. If the available data for professional users do not capture all of the components listed above, and if there are concerns that the uncaptured components might have a significant impact on precision, it may be appropriate to conduct a professional user study in parallel with the untrained user study. It may also be appropriate to conduct a professional study if the previous professional precision studies were small, because better estimates of professional precision may help to satisfy the study criteria below.

If you chose to conduct new studies to characterize precision of your device in the hands of professionals beyond what was performed in support of the original premarket application for the device, and you observe a significant difference in the data from the original premarket application, provide an explanation for the shift in performance.

***Precision Target for Quantitative Tests***

You should present SDs and percent CVs for the untrained users and professionals, for each level studied pooled over sites, as well as separately for each site. You should calculate a 95% (two-sided) confidence interval for the ratio of untrained user SD pooled over sites to professional SD pooled over sites. The confidence interval can be based on the F-test for a ratio of variances. For each specimen level, the ratio of standard deviations should not exceed 1.5, and the upper end of the confidence interval should not exceed 2.0.

| **Precision Target for Quantitative Tests** |
|---|
| $SD_{untrained\ user} / SD_{professional} \leq 1.5$, and upper end of 95% Confidence Interval for $(SD_{untrained\ user} / SD_{professional}) \leq 2.0$ at each specimen level. |

**Untrained/Professional Agreement Study for Quantitative Tests**

You should conduct your untrained/professional agreement study on at least 300 matrix-specific specimens equally distributed across the reportable range of the test. We believe that actual patient specimens provide the best assessment of untrained users. However, where impractical, hazardous, or distributed insufficiently to challenge the reportable range, you may substitute or supplement actual patient specimens with spiked or otherwise contrived matrix-specific specimens consistent with the intended use of the device. You should describe how you prepared the contrived specimens and validated the assigned values.

You should enroll at least 300 untrained users. Each untrained user should test one masked specimen. Keeping the specimen value and untrained user's result masked, each specimen should then be randomized to one of three laboratory professionals for analysis. That is,

three laboratory professionals should test these same 300 specimens (split samples), where each laboratory professional analyzes approximately 100 specimens.

**Table 3. Untrained/Professional Agreement Study for Quantitative Tests**

| | Number of Persons | Observations per Person | Total Number of Observations |
|---|---|---|---|
| Untrained Users | 300 | 1 | 300 |
| Professionals | 3 | 100 | 300 |

You should provide the untrained users with only the written test procedure. Untrained users should receive no training, coaching, prompting, or written or verbal instructions beyond the written test procedure. They should have no opportunity to discuss the test with or otherwise coach or observe each other.

*Performance Target for Quantitative Tests*

You should compare results from untrained users with the professionals by Deming regression and an analysis of differences. The following information should be provided:

- Scatter plot of the results (untrained user on the y-axis, professional on the x-axis) with the 45 degree line (y=x) and the Deming regression line superimposed
- Descriptive statistics for both the untrained user and professional results, including the number of results, mean, standard deviation, minimum, median, and maximum
- Deming regression estimates of slope and intercept (based on a ratio of variances equal to one), and the respective 95% confidence intervals

In addition, for each specimen, compute the difference between the untrained user result and the professional result. Calculate both the mean and standard deviation of these differences. Provide a scatter plot of these differences versus the professional results. Also, compute a 95% tolerance interval for 95% of the distribution of differences.

Finally, for each specimen, express the difference as a percentage of the professional result (i.e., the difference between the untrained user result and the professional result, divided by the professional result, multiplied by 100%). Provide a histogram of these percent differences and identify the 97.5th and 2.5th percentiles. Also, provide a scatter plot of these percent differences versus the professional results.

**Untrained/Professional Agreement Study for Qualitative Tests**

While it would be ideal to be able to assess directly whether the test performed by untrained users produces the same clinical sensitivity and specificity as the test performed by professionals, FDA recognizes that it may not be practical to do such a study for most qualitative tests. Generally, the untrained/professional agreement study described below will be adequate to assess the agreement of the untrained user relative to the laboratory professional. We believe that actual patient samples provide the best assessment of untrained users. However, such a study design will sometimes be impractical, hazardous, or provide results distributed insufficiently to challenge the reportable range of the test. Therefore, in some cases, all or part of your untrained/professional agreement study may be performed on contrived specimens using material specific to the specimen matrix stated in the intended use of the device.

You should conduct a small feasibility study of your device to determine the concentrations at which laboratory professionals experience detectable error rates as outlined in Table 4. You should determine the concentrations above and below the medical decision level at which approximately 2% to 5% error rates occur (strong positive and negative samples) and at which approximately 15% to 20% error rates occur (weak positive and negative samples). We define these target concentrations as shown in Table 4. Whenever possible, these concentrations should be correlated with clinically meaningful endpoints. For example, antigen tests for infectious disease should have performance (cutoffs, weak and strong positives) described in terms of colony forming units or other relevant measurements. You should include the data used to determine these target concentrations.

**Table 4. Concentrations for Qualitative Tests**

| Concentration | Professional Error Rate Target |
|---|---|
| Strong Negative | 2 to 5% false positive |
| Weak Negative | 15 to 20% false positive |
| Weak Positive | 15 to 20% false negative |
| Strong Positive | 2 to 5% false negative |

You should conduct your Agreement Study with at least 300 untrained users. They should be divided into three equal cohorts; it is recommended that each cohort be at a different site. A different professional should be assigned to each cohort (for a total of three professionals).

Using the four concentrations from Table 4 above, prepare at least 300 aliquots, one for each untrained user. The concentrations for the aliquots should be distributed across the four concentrations as shown in Table 5 below (or use the same proportional distribution if you have more than 300 untrained users). Each aliquot should be assigned in a masked fashion to a different untrained user (so that there is one aliquot per user). Assignment should be done in such a way that the four different concentrations are distributed as equally as possible across the three cohorts of users.

**Table 5. Distribution of Observations across Target Concentration Levels for Agreement Study for Qualitative Tests**

| Target Concentration | Strong Negative | Weak Negative | Weak Positive | Strong Positive | Total |
|---|---|---|---|---|---|
| Aliquot Distribution | 50 (~16 to 17 per cohort) | 100 (~33 to 34 per cohort) | 100 (~33 to 34 per cohort) | 50 (~16 to 17 per cohort) | 300 (~100 per cohort) |

Each aliquot should be tested by the assigned untrained user. The same aliquot should also be tested by the laboratory professional that is assigned to that user's cohort. Thus, each untrained user performs one test, and each professional performs at least 100 tests (one for each untrained user in the cohort). The professional should also be masked, and the specimens should be presented to the professional in a random order.

**Table 6. Untrained/Professional Agreement Study for Qualitative Tests**

| | Number of Persons | Observations per Person | Total Number of Observations |
|---|---|---|---|
| Untrained Users | 300 | 1 | 300 |
| Professionals | 3 | 100 | 300 |

For a test with more than one medical decision level, you should conduct the study as described with 300 independent untrained users and four target concentrations for each medical decision level.

*Performance Target for Qualitative Tests*

Your study should demonstrate that untrained users and the laboratory professionals obtain results that are within reasonable agreement. You should calculate the percent of positive test results for the untrained users and the professionals at each specimen level. You should also calculate the odds ratios for the untrained users positive rate versus the professional positive rate. The 95% (two-sided) confidence interval for the odds ratios for the Weak Negative and Weak Positive concentrations should fall completely within the range of 0.25 to 4.00. While there are not specific goals for the 95% Negative and 95% Positive concentrations, the untrained user rates for those concentrations should show good agreement with the professionals.

| Performance Targets for Qualitative Tests |
|---|
| 95% Confidence Interval for Odds of Positive$_{\text{untrained user}}$/Odds of Positive$_{\text{professional}}$ should be within the range of 0.25 to 4.00 for Weak Negative and Weak Positive levels |

**Untrained/Professional Agreement Studies for Highly Sensitive or Specific Qualitative Tests**

If the performance characteristics in your labeling indicate that the clinical sensitivity or clinical specificity of the qualitative test is greater than 95%, then the study design and

performance goal(s) should be modified. We recommend that you seek agreement with DCLD that this situation applies to your test. For a highly sensitive test, the distribution of specimen levels should be changed to have 50 specimens at the Weak Positive level and 100 specimens at the 95% Positive level.

***Performance Target for Highly Sensitive Qualitative Tests***

The performance target for the Weak Positive level is replaced by the goal that the positive rate of untrained users for the Strong Positive level should be at least 90.0%, and the lower end of the 95% (two-sided) confidence interval should not fall below 88.0%.

| **Performance Target for Highly Sensitive Qualitative Tests** |
|---|
| Positive $Rate_{untrained\ user} \geq 90.0\%$, and lower end of 95% Confidence Interval for Positive $Rate_{untrained\ user} \geq 88.0\%$ for the Strong Positive level |

Analogously, if the test is highly specific, the distribution of samples should be shifted to provide 100 samples at the Strong Negative level. The performance goal for the Strong Negative level is replaced by a goal analogous to that above, but with the untrained user negative rate replacing the untrained user positive rate.

# V. WAIVER LABELING

Labeling (package insert) for in vitro diagnostic devices must meet all applicable labeling requirements as stated in 21 CFR 809.10(b).

**Quick Reference Instructions**

You should include Quick Reference Instructions as a part of the labeling, but separate from the package insert. It should be written at no higher than a $7^{th}$ grade reading level and include all the items below that are applicable to your test system:

- Warning to read the test procedure first
- Contraindications and other pertinent warnings and limitations
- Safety considerations on safe test operation that particularly apply to untrained users
- Step-by-step operating instructions that include instructions for reading/reporting results
- Non-technical maintenance, such as cleaning
- Preparation of reagents and control materials
- Storage of reagents and control materials
- QC procedures, frequencies and acceptable ranges

- Electronic and other calibration procedures
- Action to be taken if QC results are out of range
- Action to be taken when electronic or other calibration fails
- Action to be taken when the system becomes inoperable
- Interpretation of results, including
    - Action to be taken when the test result is not obtained or is out of the reportable range, and who to call (for a quantitative test)
    - Action to be taken when the test result is in an equivocal range (for a qualitative test)
    - When appropriate, warnings about clinical errors that can occur even when the test result is analytically correct
    - When appropriate, additional testing that should be done (e.g., negative results should be confirmed by cell culture)
    - When applicable, a statement similar to: "This device provides a presumptive result and should be used in conjunction with culture and/or other methods of diagnosis."

FDA also recommends that you include the following in the package insert.

- Identification of the test as CLIA waived
- Brief description and summary of the results from the waiver studies under the heading "Expected Waiver Performance"
- A statement that if the laboratory modifies the test system instructions, then the test is considered high complexity and subject to all applicable CLIA requirements
- Appropriate QC recommendations (see below)

**Quality Control Labeling Recommendations**

Quality control instructions should clearly and plainly explain why quality control is needed and should emphasize the value of repeat external quality control testing at regular intervals for ensuring operator competency and reagent and instrument (when appropriate) integrity. The limitations of the internal process controls should be clearly described.

Quality control instructions should include the following:

- step by step information on how to run quality control
- how to interpret results
- actions to take when results are out of control
- limitations identified during the hazard analysis described earlier

Explanations of quality control systems should include a description of what is being measured by all elements of both internal and external quality controls in place and recommended for a particular test system. To aid in dealing with quality control problems, manufacturers should provide a toll-free telephone number for technical assistance. FDA recommends that quality control instructions be based on data generated through actual field studies of each device. In the absence of specific data, for unitized devices, suggested possible minimum frequency recommendations are as follows:

- each new lot or shipment of materials
- each new opened kit
- each new operator (defined as an individual who has not run the test in the past 2 weeks)
- weekly, as a check on continued storage conditions
- whenever problems (storage, operator, instrument, or other) are identified
- if otherwise required by your laboratory's standard QC procedures

Manufacturers may choose to include good laboratory practice information in the package insert, in accessory educational material, in accessory technical material, or through the development of formal educational training programs. Issues that may be of value to users of waived tests include the general purpose of quality control, the value of using quality control within a broader system of quality assurance, the need for proper operator training, the need for reading instructions and following all details related to storage, preparation, and expiration dating, and the need for proper record keeping.

Instructions on performing quality control should be as explicit as possible. For example, for a unitized test the following may be considered:

> "Test (*xyz*) contains built-in control features that monitor device functions (e.g., the presence of the control line shows that sufficient capillary flow has occurred). Obtaining the correct reading on the built-in control does not mean that your patient result is correct because the built-in control does not monitor the entire

assay. Good laboratory practice recommends the use of external positive and negative controls to assure the test reagents are working properly and that the user has performed the test correctly. If the controls do not perform as expected, review the instructions for use to see if the test was performed correctly; repeat the test or contact technical assistance before performing patient specimens."

# VI. VOLUNTARY SAFEGUARDS FOR WAIVED TESTS

1. FDA believes that manufacturers should consider innovative mechanisms and technical assistance for laboratories to ensure they read and understand the labeling information. FDA also believes that manufacturers should take responsibility for ensuring that the performance of their products is understood and that those products are used correctly.

   Manufacturers can fulfill these responsibilities by assisting laboratories performing waiver testing to become better educated on proper laboratory techniques.

2. FDA is requesting 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.

3. Manufacturers of waived devices should also submit a detailed surveillance plan for how they will monitor performance of their waived device, under conditions of actual use (in waived laboratories). This plan should include, at a minimum, information on

   - How you will define, detect, and correct unacceptable analytical bias and precision among users in field use
   - How you will define, detect, and correct changes in device performance (drifts or trends) over time
   - How you will ensure proper and consistent use of your device in waived settings
   - What types of corrective action programs will be used to address problems in the above three bullets
   - How you will confirm that waived devices are functioning with failure alerts and are providing results with the same accuracy as contained in your request for waiver

4. In addition, FDA is requesting that manufacturers annually submit as an add-to-file (510(k)) or in the annual report (PMA) (for the first 3 years of test use) an analysis of results of the surveillance plan outlined above, along with the following information:

   - MDR records
   - Recalls and the frequency that devices have exceeded defined performance criteria
   - Results of customer satisfaction surveys and a list of common errors made by users
   - Real-world (field) QC results of the device in use
   - Proficiency testing (using manufacturer or third party materials) from a randomly selected group of users
   - An executive summary of design control validation information from the previous year of use
   - All published reports associated with the device
   - External quality assurance programs, if applicable

# VII. REFERENCES

HCFA/PHS: Regulations Implementing the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 57 FR 7002, February 28, 1992.

HCFA and PHS: Proposed Rule, CLIA Program; Categorization of Waived Tests, 60 FR 47534, September 13, 1995.

Fleiss, J.L., Statistical Methods for Rates and Proportions, 2nd ed. New York: John Wiley & Sons, 1981.

# APPENDIX A - Waiver Checklist

Simple

| Characteristics | Check here |
|---|---|
| Is a fully automated instrument, unitized, or self-contained test | |
| Contains failure alert mechanisms | |
| Uses direct unprocessed specimens | |
| Requires only basic, non-technique-dependent specimen manipulation | |
| Requires only basic, non-technique-dependent reagent manipulation | |
| Has no operator intervention during the analysis | |
| Requires no technical or specialized training with respect to troubleshooting | |
| Requires no electronic or mechanical maintenance | |
| Produces a direct readout of result that requires no calibration, interpretation, or calculations | |

Insignificant Risk of Erroneous Result

| Characteristics | Check here |
|---|---|
| **Specimen Handling** | |
| Specimen collection | |
| Interfering substances | |
| Processing and handling | |
| Specimen storage and/or transport | |
| **Operator error** | |
| Use of incorrect reagent (not lot or device specific) | |
| Wrong order of reagent application | |
| Use of incorrect amount of reagent | |
| Incorrect application of specimen | |
| Incorrect timing of analysis | |
| Incorrect reading or interpreting of test results | |
| **Reagent integrity problem** | |
| Use of reagent improperly stored | |
| Use of outdated reagent | |
| Use of reagent improperly mixed | |
| Reagent viability | |
| Use of contaminated reagents and reagents with altered potency or activity | |
| **Hardware and electronics integrity** | |
| Evaluation of power failure | |
| Evaluation of failure in hardware | |
| Evaluation of failure in software | |
| Evaluation of physical trauma to unit | |
| Evaluation of electronic failure | |

Insignificant Risk of Erroneous Result (con't)

| **Stability of calibration** | |
|---|---|
| Studies to demonstrate how long calibration will hold | |
| Analysis of factors that may interfere with calibration | |
| **Environmental factors** | |
| Studies to establish the impact of key environmental factors (heat, humidity, sunlight, etc.) on reagents, specimens, and/or test results | |
| Studies to establish the impact of key environmental factors (including electrical or electromagnetic interference) on instruments, if appropriate | |
| **QC Validation Studies that target failures associated with:** | **Check here** |
| Specimen Handling | |
| Operator error | |
| Reagent integrity | |
| Hardware and electronics integrity | |
| Stability of calibration | |
| Environmental factors | |

Accurate

| **Quantitative test** | **Check here** |
|---|---|
| Untrained/Professional Precision: 60 untrained users/3 professionals/3 sites/ 3 levels | |
| Untrained/Professional Agreement: 300 untrained users/3 professionals/300 specimens (split samples) | |
| **Qualitative test** | **Check here** |
| Untrained/Professional Agreement: 300 untrained users/3 professionals/300 specimens (split samples)/4 levels | |

# APPENDIX B - Waiver Labeling Checklist

## Package Insert

| | Check here |
|---|---|
| Meets 21 CFR 809.10(b) | |
| Written at no higher than a 7th grade reading level | |
| **Contains:** | **Check here** |
| Identification of the test as CLIA waived | |
| Brief description and summary of the results from the waiver studies under the heading "Expected Waiver Performance" | |
| A statement that if the laboratory modifies the test system instructions, then the test is considered high complexity and subject to all applicable CLIA requirements | |
| Appropriate QC recommendations | |

## Quick Reference Instructions

| **Contains:** | **Check here** |
|---|---|
| Warning to read the test procedure first | |
| Contraindications and other pertinent warnings and limitations | |
| Safety considerations on safe test operation that particularly apply to untrained users | |
| Step-by-step operating instructions that include instructions for reading/reporting results | |
| Non-technical maintenance, such as cleaning | |
| Preparation of reagents and control materials | |
| Storage of reagents and control materials | |
| QC procedures, frequencies and acceptable ranges | |
| Electronic and other calibration procedures | |
| Action to be taken if QC results are out of range | |
| Action to be taken when electronic or other calibration fails | |
| Action to be taken when system becomes inoperable | |
| Interpretation of results, including | |
| • Action to be taken when the result is not obtained or is out of the reportable range (quantitative test), and who to call | |
| • Action to be taken when the result is in an equivocal range (qualitative test) | |
| • When appropriate, warnings about clinical errors that can occur even when the test result is analytically correct | |
| • When appropriate, additional testing that should be done | |
| • When appropriate, a statement similar to: "This device provides a presumptive result and should be used in conjunction with culture and/or other methods of diagnosis." | |