American
Clinical Laboratory
Association

May 30, 2001

01D-0044
C21

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

01 MAY 30 P3:48

Re: Docket No. 01D-0044

Dear Sir or Madam:

Attached are the comments of the American Clinical Laboratory Association on the above referenced docket, Medical Devices Draft Guidance for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Criteria for Waiver. Our comments are the testimony we presented at the FDA open workshop on CLIA criteria for waiver held on August 14 and 15, 2000. Our position has not changed.

Sincerely,

David Sundwall

David N. Sundwall, M.D.
President

Attachment

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STATEMENT
OF THE
AMERICAN CLINICAL LABORATORY ASSOCIATION
ON CRITERIA FOR WAIVED TESTS

On behalf of the American Clinical Laboratory Association (ACLA), we are pleased to submit this testimony today on the criteria for obtaining waived status under the Clinical Laboratory Improvement Amendments of 1988 (CLIA). ACLA is an association representing independent clinical laboratories throughout the United States including local, regional and national laboratories. ACLA members perform a wide variety of laboratory testing and have a strong interest in ensuring that all laboratory testing is as safe and accurate as possible.

Waived tests are exempt from the CLIA health and safety standards, including personnel, patient test management, quality control, proficiency testing, quality assurance, and routine inspections requirements. Determining which tests qualify for waived status, and how those tests are assessed to ensure their safety and accuracy has historically been both an issue of concern to the laboratory community and a somewhat ambiguous issue.

The CLIA statute initially identified waived tests as simple laboratory examinations and procedures which have an insignificant risk of erroneous result, including those which --

> (A) have been approved by the Food and Drug Administration for home use;
> (B) employ methodologies that are so simple and accurate so as to render the likelihood of erroneous results negligible; or
> (C) the Secretary has determined pose no reasonable risk of harm to the patient if performed incorrectly.

42 USC/253a(3).

Thus, the statute initially suggested that tests approved for home use were one example of tests that are simple and that have an insignificant risk of an erroneous result. However, in the preamble of the CLIA regulations published in 1992, the Health Care Financing Administration (HCFA) stated that FDA clearance of a test for home use could not be used as a sole criterion for qualifying as a waived test. *See* 57 FED. REG. 7002 (February 28, 1992).

After evaluating the public comments on the 1992 rule concerning waived tests, many of which requested clearer guidance on these waived test criteria, HCFA approached the Clinical Laboratory Improvement Advisory Committee (CLIAC) about the need to more clearly define the criteria and process for categorizing waived tests. In 1993, the CLIAC agreed that the criteria should be better defined, and suggested that a moratorium be placed on adding tests to the waived category until then. The moratorium was imposed, but was lifted shortly thereafter in 1994 without the desired regulatory clarification.

In 1995, HCFA issued a proposed rule in which it stated that [a] ny test system cleared by the FDA for home use will, *upon receipt of a request for waiver* from the manufacturer, be waived under CLIA. (emphasis added). With regard to the other criteria for waiver, the 1995 proposed rule sought to add clarity by specifying performance characteristics and studies designed to demonstrate that any test system categorized as waived should be simple, easy to perform, and essentially error-free. To that end, HCFA proposed that tests not approved for home use by FDA meet the requirements in CLIA to ensure that the test procedure is simple and not prone to error.

In most respects, ACLA agrees with the clarified waived criteria in the 1995 proposed rule, and with HCFA s basic position that test systems not cleared for home use by FDA must possess certain characteristics that would make them easier to use and must be able to demonstrate a level of accuracy and precision that ensures that the correct test result is generated regardless of the user s level of expertise. 60 FED. REG. 47534, 47536. ACLA believes that application of the 1995 proposed rule and its quality standards to <u>all</u> waived tests (including those cleared by the FDA for home use) is appropriate. Waived tests should meet the same level of accuracy and predictability as tests performed in moderate and high complexity laboratories. Importantly, performance criteria should include an evaluation of the test that examines test performance when performed by a control group of untrained or lay users when compared to the same test when performed by certified laboratory personnel. ACLA further agrees with the proposed standard that test systems be designed for use by those with no more than a seventh grade comprehension level to ensure that the test system instructions will be easily understood.

Unfortunately, the 1995 proposals were never finalized. However, in 1997, the Food and Drug Administration Modernization Act amended the Public Health Service Act, and, in so doing, changed the CLIA statute by modifying the definition of waived test to include

> examinations and procedures 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 correctly.

42 USC/263a(3). This change created a unique, and extremely broad, exception that allows manufacturers to submit tests for home use clearance, and upon approval, automatically obtain waived status under CLIA. While this process includes an assessment of the test s substantial equivalence as compared to a predicate test, it gives no consideration to varying degrees of accuracy nor to the specific criteria for waived tests considered in 42 CFR/493.17.

ACLA is concerned that the 1997 changes to the Public Health Service Act allowing test manufacturers to obtain waived status for tests approved for home use may lead to waivers being granted for some tests that might otherwise not qualify for waived status when taking into account the accuracy and precision of the test itself. ACLA is troubled by that potential outcome, and suggests that the statutory change be reexamined as a result or that the FDA apply criteria similar to those in the September 1995 proposed rule before it grants FDA approval for home use tests.

Our fundamental concern is that all testing--regardless of whether it will be performed in a patient s home, a physician office, or a moderate or high complexity laboratory--should be safe, reliable and accurate. The current system, which allows each test that is approved for home use to automatically become a waived test that can be performed without any quality control requirements or other controls, simply does not offer sufficient protection that the test will be performed correctly.

Further, these concerns become especially serious when that waived test is being performed in a physician s office or other clinical location, where the patient justifiably expects that the test will have a high degree of accuracy. Because there will be no quality control or other performance testing requirements applied to that test, it must be clear that the test will produce a result that can be relied upon in making clinical decisions, and that the person performing that test will do so correctly. However, if a test was granted waived status based upon its approval for home use, then no such assurances are present, because the criteria applied for home use clearance measure only safety and efficacy, often in comparison to a test that was previously approved. Thus, there is no assessment of criteria such as those in the 1995 rule that evaluated the accuracy of the test and the ease of performance by a lay person.

In sum, it is not permissible to assume that, because a test is simple, it will be done correctly and yield an accurate result--regardless of where the test is being performed. Accordingly, ACLA believes that no test should be approved for home use unless the test is subject to the same criteria for accuracy and precision as a test performed in a moderate or highly complex laboratory, and the test includes mechanisms to assess both the accuracy of the test and the untrained user s ability to correctly perform and interpret the test.

Subjecting tests approved for home use to the same accuracy and performance standards currently imposed on other waived laboratory testing is a necessary and proper means of ensuring both test quality and the public health.

RESPONSE
OF THE
AMERICAN CLINICAL LABORATORY ASSOCIATION
TO QUESTIONS ON WAIVED TESTING

In response to the Federal Food and Drug Administration s request for public input on all issues regarding the classification of laboratory tests as waived, the American Clinical Laboratory Association submits the following responses, designed to address both the general and specific concerns raised in the FEDERAL REGISTER notice issued July 21, 2000.

1. What criteria should be used to demonstrate that a waived test is a simple laboratory examination and procedure with an insignificant risk of an erroneous result? For example:

> A. Should a waived test, when performed by untrained users, provide an accurate result with no significant clinical or statistical error when compared to a measure of truth? This requires availability of well-characterized reference methods and/or materials as part of the waived test assessment. The current threshold for waiver as established by CDC is no significant inaccuracy and no significant imprecision.

Response: A waived test, when performed by untrained users, should provide at least as high a degree of accuracy as a well-characterized reference method, a designated comparative method, or a laboratory method used by a moderate or high complexity laboratory.

> B. Should a waived test, when performed by untrained users, provide a test result that shows no user error when compared to the same test performed in a CLIA-certified lab by a trained user? This requires comparison of the test in a lay-user setting with performance of the test in a CLIA-certified lab by a trained user. The threshold for waiver would be no difference in performance in the two settings.

Response: The results of a waived test, when performed by untrained users, should be within the statistical limits of error when compared to the same test performed in a CLIA-certified laboratory by a trained user.

> C. Should FDA apply a different model to determine the waived status of a test?

Response: No, the model does not need to be changed, but the criteria in the proposed rule should be adopted to assure the accuracy of a proposed waived test.

2. What criteria should FDA use to determine if a methodology is so simple and accurate to render the likelihood of erroneous results by the user negligible?

A. Should a waived test be so accurate when performed by untrained users that inaccurate results will not occur?

Response: A waived test should be so accurate that there is little likelihood that inaccurate results will occur when untrained users perform the test. Although it is virtually impossible to guarantee that inaccurate results will not occur when untrained users perform the test, a waived test should provide at least as high a degree of accuracy as a well-characterized reference method, a designated comparative method, or a laboratory method used by a moderate or high complexity laboratory.

B. Should a waived test have variable accuracy if used adjunctively; is it acceptable to waive tests that have inaccurate results but do not have any major negative clinical impact? How should FDA make this assessment?

Response: It is not beneficial to the public health, appropriate, or acceptable to waive tests that have inaccurate results even if it is perceived that inaccurate results will not cause major negative clinical impact.

3. What criteria should FDA use in determining that a test will pose no unreasonable risk of harm to the patient if performed incorrectly?

Response: FDA should not rely on the criterion of whether a test will pose no unreasonable risk of harm to the patient if performed incorrectly. If FDA requires proof that the test meets the proposed simplicity and accuracy criteria, the test will by definition pose no unreasonable risk of harm to the patient if performed incorrectly.

4. Should the waiver process be different for screening tests that require a second test for confirmation? Since there are no CLIA standards for performance of waived testing, except instructions to follow the manufacturer's package insert, what is the assurance that confirmatory testing will be performed? Should the need for confirmatory testing raise, lower, or have no impact on the threshold for a waiver decision?

Response: The presence of a confirmatory test should have no impact. Assuming that the FDA adopts criteria that ensure the accuracy of the testing (including both screening and the confirmatory tests where applicable), FDA need not consider different thresholds for tests that require confirmation.

5. Should accuracy be determined using comparison of the waived test to a well-characterized reference method and/or materials, to a designated comparative method and/or materials, to a working laboratory method and/or materials, to a clinical algorithm for diagnosis, and/or to other endpoints?

Response: Yes. A waived test, when performed by untrained users, should be accurate, which should be verified by comparison to a well-characterized reference method, a designated comparative method, or a working laboratory method used by a moderate or high complexity laboratory. Requirements for accuracy should meet the same criteria as for moderate and high complexity assays for the same analyte.

6. How many samples, what types of samples (real or artificial) by how many users and how many sites are appropriate to evaluate accuracy? (Current guidelines being followed by FDA are for performance to be demonstrated by laboratory users at a minimum of one site.)

Response: The number of samples, users, and sites should be statistically significant. Reference should be made to NCCLS or other standards (*e.g.,* at least 100 samples etc.). Studies should meet the minimum requirements of NCCLS EP9A guideline for Method Comparison and Bias Estimation Using Patient Samples. The minimum number of sites evaluating a new assay proposed for waived status should include two untrained, and two trained sites, with all four sites comparing the proposed waived assay to a routine laboratory assay. The study could be split into two separate 3-way studies, to show reproducibility of the results. Each of these studies should include a minimum of 50 samples distributed over the range of the assay (refer to EP9 for recommendations).

7. What should be the background of these users?

Response: The users in whose hands the test is being evaluated should be lay users having no more than a seventh grade education.

8. What performance criteria (statistical or clinical) should FDA apply to the accuracy threshold for a waived test (*e.g.,* t- test or McNemar test at key decision points, description of performance with confidence intervals at key decision points, use of set performance standards using a receiver operator curve --80%, 90%, 95%, or other-- at key decision points, and/or others)?

Response: Accuracy criteria for waived tests should be the same as those applied to a moderate or high complexity test.

9. How should FDA define precision for purposes of waiver determination, what types of samples, how many and what types of operators/sites are appropriate? Current CDC recommendation is for 20 samples at three levels representing appropriate decision points to be tested at three sites by lay users using materials in either artificial and/or real matrices depending on availability and biohazard issues.

Response: ACLA recommends using the NCCLS EP5A guidelines for determination of precision. At a minimum, this should include one run per day, two tests per run, over

20 days, to determine the short term variation and the long term variation. This should be performed by the same sites that are performing the comparison of methods study (described above at question 6).

10. What performance thresholds should FDA use to determine whether the precision studies are appropriate for waiver status (*e.g.*, ANOVA analysis, use of a predefined performance goals such as Tonks' formula, or percent agreement out of total repeat runs)?

Response: The same criteria for moderate or high complexity tests should be used.

11. What interference studies are appropriate to establish performance of waived tests (*e.g.*, effects of hemolysis, lipemia, etc.)?

Response: The same criteria should be used as is standard for moderate or high complexity testing. Please see the NCCLS guideline EP7P for interference testing.

12. What environmental studies or flex (stress) studies are appropriate to establish performance of waived tests (*e.g.*, temperature or humidity stresses, short fills)?

Response: ACLA supports the following environmental studies as appropriate means to establish the performance of waived tests:

- Effects of various temperature conditions for reagents (freezing, refrigeration, room temperature, and hot).
- Effects of various temperature conditions for the device (warm due to poor air circulation, and cool due to direct exposure to an A/C duct).
- Insufficient sample.
- Too much sample.
- Wrong sample type.
- Impact of inadequate maintenance by the untrained user.
- Physical abuse: impact of dropping the device.
- Impact of lower, or total loss, of power.
- Impact of Radio Frequency Interference (due to proximity of electric motors like the office vacuum cleaner, X-ray machines, radio-dispatch transmitters).

13. What additional studies (if any) should be submitted for evaluation of qualitative tests for waiver?

Response: Stability of color readout before fading.

14. What additional studies (if any) should be submitted for evaluation of quantitative tests for waiver?

Response: Same overall criteria as for a moderate or high complexity device, including such factors as: linearity/reportable range, limit of detection for certain analytes, and adequacy of warning to the untrained user.