



*Advancing Excellence*

**College of American Pathologists  
Statement to the  
Clinical Laboratory Improvement Advisory Committee (CLIAC)**

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The College of American Pathologists (CAP) is pleased to submit the following comments to the Clinical Laboratory Improvement Advisory Committee (CLIAC) regarding criteria for obtaining waived status under the Clinical Laboratory Improvement Amendments of 1988. The College is a national medical specialty society representing over 16,000 pathologists who practice clinical and/or anatomic pathology in laboratories across the country. The College's Laboratory Accreditation Program is a Centers for Medicare and Medicaid Services (CMS) approved accrediting organization as specified in CLIA regulations. The College's Commission on Laboratory Accreditation is responsible for the accreditation of over 6,000 laboratories worldwide. CAP members have extensive expertise in providing and directing laboratory services and serve as inspectors in the accreditation program. These programs are designed to improve the quality of laboratory services and to ensure the accuracy and reliability of test results. Therefore, the College has a profound interest and extensive experience in this topic.

At the September 17-18, 2003 CLIAC meeting the committee was presented with a proposal to address the CLIA Waiver Test Categorization process that resulted in the creation of the CLIAC Waiver Workgroup. The purpose of the workgroup was to address stakeholder concerns regarding the performance of waived tests and the process to determine the waiver categorization in the best interests of public health and safety.

### **Fundamental Principles**

The College continues to believe that all test procedures used for the diagnosis, prevention, treatment and assessment of human disease regardless of complexity, including those that are waived, should be subject to a documented quality control program and to proficiency testing when such is available. We stand in support of the efforts to move forward to develop new and innovative approaches to quality control (QC), proficiency testing (PT), performer competence and test/instrument performance in the field, which will ensure that waived tests are accurate and reliable over the life of the instrument/kit. It is our belief that no test is so simple and straightforward to perform that erroneous results cannot occur and that no incorrect test result is "risk free" or inconsequential with regard to potential harm. The fact that the Secretary of the U.S. Department of Health and Human Services (HHS) would designate certain laboratory tests as "exempt" from the requirements of the CLIA 88 regulations conflicts with the fundamental principle that documented quality control activities, participation in proficiency testing where available or some alternative means of external monitoring are in the best interests of patient care and safety.

### **Food and Drug Administration Modernization Act**

The 1997 Food and Drug Administration Modernization Act amended the Public Health Service Act, and thus modified 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.

This change essentially allows manufacturers to submit tests for home use clearance, and upon approval, automatically obtain waived status under CLIA.

The College is concerned with the impact of language in the 1997 Food and Drug Administration Modernization Act that revised CLIA waiver provisions to allow tests approved for over-the-counter use to automatically qualify for CLIA waiver status. The over-the-counter test approval process is generally less rigorous than the CLIA waived test approval process. This is of particular concern when over-the-counter tests are used to make medical decisions in the clinical setting. As an example, the medical consequences of home testing for pregnancy are much different than the medical consequences of testing for pregnancy in a doctor's office before ordering X-rays or prescribing medication that could harm the fetus. The College recommends that HHS should harmonize approval processes for over-the-counter tests and waived laboratory tests and seek remedies to correct this "back door" that allows for tests intended for home use to be used in the clinical care setting.

### **Demonstrating Insignificant Risk of Erroneous Result –Failure Alert Mechanisms**

The College supports requirements instructing waived test systems to contain failure-alert mechanisms that do not render a result when a test system malfunctions or when analyte concentrations are outside of the range of accurate measurements for the test system.

We further support stipulations that manufacturers present information that demonstrates the failure-alert mechanisms contained in a device are based on valid scientific evidence.

### **Demonstrating Accuracy**

The term "accurate" has been interpreted to mean that the test performs the same in the hands of the untrained users as it does in the hands of laboratory professionals when using the test under realistic conditions. The College recommends that "Accuracy" should be determined by comparison to well-characterized reference methods and/or materials and to appropriate clinical endpoints. Furthermore, we recommend that the criteria should minimally require the same performance criteria as those for moderate complexity tests. Statistical analysis of comparison studies to reference methods and validation of the analytical reportable range should be required. We feel that performance should be evaluated at medical decision points and include confidence intervals. The manufacturer should also consider sensitivity and specificity for target population(s). Appropriate and inappropriate target population(s) should be identified. To ensure accuracy of results, principles of quality assurance such as quality control and proficiency testing at an appropriate interval should be used to assess the accuracy of these methods in the hands of untrained personnel.

### **Quality Control**

The College believes that any erroneous test result presents a risk to patient safety. Therefore, CAP does not think that criteria can be developed to determine that a test will "pose no unreasonable risk if performed incorrectly." The College supports the concept that Quality Control (QC) requirements for waived tests be modeled on standard laboratory QC that is

devised for laboratory-based methodologies. In the previously issued FDA Draft Guidance for Waiver Criteria, the FDA provided manufacturers the option of “alternative QC practices and modalities.” In this regard, we asked that this term be clarified. In performing a hazard analysis to identify potential test system failures, there should be an evaluation of expected sources of problems, failures, and/or interference with a specific test. The NCCLS document *Quality Management for Unit-Use Testing* (EP18 - A) provides valuable information to manufacturers and users alike on identification of "Source of Error" analysis. After identification of potential problems, there should be an analysis of how a potential problem affects a test. Necessary resources for support of users such as manufacturer hotlines should be identified to address expected user problems. It would be desirable for test kits to have internal controls or indicators that would identify when a test had been stored improperly, sustained packaging leaks, or when test reagents no longer have full reactivity. The College does not believe that it is appropriate to waive tests that have inaccurate results even if it might be perceived that inaccurate results would not have a negative clinical impact. We would again like to emphasize that any erroneous result carries the potential for very real risks to patient safety.

## **Studies**

### Number of Samples

The number of samples needed to evaluate accuracy of waived tests should be at a minimum the same as those for moderate or high complexity tests. Samples should be evenly dispersed over the clinically relevant range of the test. Evaluation should occur in multiple settings in which this testing will be performed. The number of samples tested should be determined by statistical methods in order to detect clinically relevant inaccuracy. Experiments presented in the NCCLS Publication EP9-A *Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline*, can be used to determine and evaluate accuracy of method or device against a reference method or comparative method. The recommendation for method comparison is at least 40 patient samples analyzed over at least 5 operating days. Analysis of each patient sample in duplicate for both reference/comparative method and waived test is recommended. If possible, at least 50% of the sample run should be outside the reference intervals. Evaluation of bias may be of limited value depending on specimen type for reference vs. waived test method.

### Users

Users should have a high school education at minimum and appropriate training to perform the test including quality control and external monitoring when appropriate. Variation in user technique and competence represents one of the common problems associated with waived tests. There should be evaluation of variation of test performance by non-laboratory personnel with specimens at or near assay threshold or medical decision levels. For tests requiring visual interpretation, the necessary level of visual acuity should be determined. Furthermore, it is important to evaluate the effects of color blindness on the ability to obtain an accurate result on tests that require the interpretation of colors. Users should also consist of trained laboratory personnel to provide a benchmark with which to compare non-laboratory user results.

## **Labeling**

Manufacturers should be held accountable for incorporating the necessary QC into waived test device design and instructions for use so as to ensure that the performance of the test is reliable and accurate over the life of the instrument and/or reagents. The College supports quality control labeling recommendations that 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. Specifically, the College supports requirements that would recommend including information such as, the general purpose of quality control, the value of using quality control within a broader system of quality assurance, and the need for proper operator training, etc.

## **Safeguards for Waived Tests**

The College recommends that manufacturers should:

- Take responsibility for ensuring their products are used correctly and educate laboratories on proper laboratory techniques
- Provide information about the Med Watch medical products reporting program in the package insert so that failures can be reported
- Submit to FDA a detailed surveillance plan for how they will monitor performance of their waived test device under conditions of actual use including providing assurance of proper and consistent use of the device in the waived setting. Mechanisms for monitoring performance include collection of quality control data from waived laboratories and proficiency testing.

Because waived testing takes place in a largely unregulated and unmonitored environment and is performed by individuals with little or no previous experience in laboratory testing, the CAP strongly supports the need to ensure that laboratory test devices and kits are as robust and failure-proof as is possible. We look forward to the CLIAC Waiver Workgroup recommendations and the possibility of providing further comments.