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*Advancing Excellence*

Direct Response To:

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December 1, 2005

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

Re: Docket Number 2001D-0044

Dear Sir/Madam:

The College of American Pathologists (CAP) is providing the following written response to the Food and Drug Administration's (FDA) request for public comment on the Draft Guidance for Industry and FDA Staff: Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications. The College of American Pathologists is a national medical specialty society representing more than 16,000 pathologists who practice pathology and laboratory medicine. The College's Commission on Laboratory Accreditation is responsible for accrediting more than 6,000 laboratories worldwide. College members have extensive expertise in providing and directing laboratory services and serve as inspectors in the accreditation program. In addition, the College provides laboratories with a wide variety of proficiency testing programs and educational solutions to assist in the improvement of the laboratory's performance and its positive impact on patient care. 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.

It is the College's 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 College believes that all test procedures used for the diagnosis, prevention, treatment and assessment of human disease regardless of designated CLIA test complexity, should be subject to a documented quality control program and to proficiency testing when available. We stand in support of 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. In this regard, the College is submitting the following comments.

The College recognizes the work of the FDA in developing a guidance document that reflects many of the comments the College previously submitted to the original "Guidance for Clinical

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Laboratory Improvement Amendments of 1988 (CLIA) Criteria for Waiver,” Draft Guidance for Industry and FDA issued March 1, 2001. The guidance also responds to the recommendations of the Clinical Laboratory Improvement Advisory Committee (CLIAC) calling for a more demanding waived test evaluation standard supported by the College. The specific changes include greater emphasis on scientifically based flex studies and validation studies linked to hazard analysis for each device, additional emphasis on use of quality control procedures, and updated study recommendations with emphasis on use of patient specimens in an intended-use environment.

### **DEMONSTRATING "SIMPLE"**

The College agrees with the list of characteristics that designate a test as “simple” outlined in the waiver guidance. In particular, the College supports characteristics that would include devices that:

- Need no operator intervention during the analysis steps
- Need no electronic or mechanical maintenance
- Produce results that require no operator calibration, interpretation, or calculations
- Produce results that are clear to read, a direct readout of numerical values, the clear presence or absence of a line, or obvious color gradations
- Provide instructions and materials for obtaining and shipping specimens for confirmation testing, in cases where such testing is clinically advisable
- Have test performance comparable to a traceable reference method, as demonstrated by studies in which intended operators perform the test

Unless it is otherwise covered, the College recommends adding the following to the list of characteristics:

- Requires no precise timing in any step of the procedure

The College also supports the list of characteristics that a test designated as “simple should not have, including devices where:

- Sample manipulation is required to perform the assay including 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
- Results need to be reported to a public health department at the state or local level

### **DEMONSTRATING "INSIGNIFICANT RISK OF AN ERRONEOUS RESULT" Failure Alerts and Fail-Safe Mechanisms**

The College agrees with language in the document that states waived tests should be more robust than non-waived tests. The College also supports language in the draft guidance requiring waived tests to contain failure-alert mechanisms that do not report a result when a test system malfunctions or when analyte concentrations are outside of the range of accurate measurements for the device. We further agree with the stipulation that manufacturers must present information

that demonstrates the failure-alert mechanisms contained in a device are based on valid scientific evidence. The FDA provides a relevant list of examples of potential sources of error to consider for the hazard analysis and flex studies. In performing a hazard analysis to identify potential test system failures, the College agrees that there should be an evaluation of expected sources of problems, failures, and/or interference with a specific test. Clinical and Laboratory Standards Institute (CLSI) document *Quality Management for Unit-Use Testing; Approved Guideline (EP18-A)* recommends a quality management system for unit-use devices that will aid in the identification, understanding, and management of sources of error and help to ensure correct results. It provides valuable information to manufacturers and users alike on identification of "Source of Error" analysis. We agree further, after identification of potential problems, there should be an analysis of how a potential problem affects a test. Based on the results of the hazard analysis, flex studies should be conducted. As the document indicates, flex studies should be designed to challenge the system under conditions of stress to identify potential device failures and determine the robustness of the test system. The College, however, 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 emphasize that any erroneous result carries the potential for the very real risk of patient harm.

#### **DEMONSTRATING INSIGNIFICANT RISK OF AN ERRONEOUS RESULT "ACCURACY"**

In order for manufacturers to demonstrate that their device is "accurate" in the hands of the intended operator, the guidance document recommends that prospective clinical studies be conducted using patient samples collected in the intended testing environment. In this way, the studies will demonstrate, as closely as possible, how the device performs on actual clinical specimens by intended operators under the conditions of intended use.

These requirements reflect The College's previous comments. Additionally, statistical analysis of comparison studies to reference methods and validation of the analytical reportable range should be required. Performance should be evaluated at medical decision points and include confidence intervals. The manufacturer should also consider sensitivity and specificity for target population(s) with the appropriate and inappropriate target population(s) to 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.

The number of samples needed to evaluate accuracy of waived tests should be at a minimum the same as those for non-waived 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 CLSI Publication *EP9-A2 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. Variation in user technique and competence represents one of the common problems associated with waived tests. Manufacturers should evaluate test performance by intended users 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.

### **Quality Control Labeling Recommendations**

The College supports the concept that Quality Control (QC) requirements for waived tests should be modeled on standard laboratory QC devised for laboratory-based methodologies. The College agrees that the FDA should hold manufacturers 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 language that recommends the types of information that should be included such as, 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, etc.

### **Educational Information**

We agree with the recommendation that manufacturers should develop innovative mechanisms to provide technical assistance to laboratories and to ensure they understand the labeling information. We also agree with the recommendation that manufacturers assist laboratories performing waived tests to become better educated on proper laboratory techniques. For example, the College agrees with the specific recommendation that manufacturers develop and promote good laboratory practices by developing training and education programs for end operators and promote laboratory participation in proficiency testing programs. (See attached November 11, 2005 Morbidity and Mortality Weekly Report, *Good Laboratory Practices for Waived Testing Sites*). In addition, we agree that good laboratory practice information should be included in the package insert, in accessory educational or technical material, and through the development of formal educational training programs. The document provides a recommended list of topics of information that manufacturers should provide to operators. The College recommends requiring manufacturers to provide information on the consequences of an incorrect result to this list of topics.

### **Safeguards for Waived Tests**

The College supports the concepts in this section that recommend manufacturers:

- Provide information about the Med Watch medical products reporting program in the package insert so that failures can be reported
- Maintain and implement medical device reporting procedures, establish and maintain medical device report (MDR) event files, and submit MDRs of individual adverse events as required by federal regulations
- Notify CMS when device failures are reported.

### **Miscellaneous**

The College is providing the following miscellaneous comments to the guidance document:

- FDA should consider a requirement that test kits 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.
- FDA should require that waived test packaging include any special patient preparation information, taking into consideration, for example, the need for the patient to fast for a specified period of time prior to administering the test.
- Manufacturers instructions should be provided in multiple languages. This would include any information that needs to be given to the patient for either preparation or follow up.
- In the case of unit use tests, the test label should have markings to clearly indicate it as a unit use test to prevent any attempt to reuse the kit.
- Manufacturers should design their products so they are distinct and easy to differentiate. For example, if a manufacturer sells a rapid strep cassette and an H. pylori cassette, it should package these two cassettes differently so that the wrong cassette is not used accidentally.

### **Conclusion**

The College would like to reiterate its strong support for language throughout this document that would build in mandatory requirements for these functions. 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 College strongly supports the need to ensure that laboratory test devices and kits are as robust and failure-proof as possible.

Thank you for the opportunity to present the College's views. Please feel free to contact me or Phil Bongiorno, Assistant Director of Public Health and Scientific Affairs at (202) 354-7113 or pbongio@cap.org with any comments or questions.

Sincerely,



Thomas Sodeman, MD, FCAP  
President