David N. Sundwall, M.D.
620 Hawkesbury Terrace
Silver Springs, MD 20904

April 8, 2004

Ms. Carolyn D. Jones
Associate Vice President
Technology and Regulatory Affairs
Advanced Medical Technology Association
1200 G Street NW, Suite 400
Washington, DC 20005-3814

Dear Ms. Jones:

We appreciate the Advanced Medical Technology Association's (AdvaMed) participation in the Clinical Laboratory Improvement Advisory Committee (CLIAC) Waiver Workgroup. AdvaMed's contributions to the Workgroup discussion and subsequent CLIAC deliberations provided valuable insight into the laboratory device industry's perspective on the criteria for the Clinical Laboratory Improvement Amendments of 1988 (CLIA) waiver approval and the review process.

Although CLIAC is charged with providing advice to the Department of Health and Human Services (HHS) regarding issues relevant to CLIA, in discussing the waiver issues at the February 2004 CLIAC meeting, it was suggested that several of the Committee's recommendations were more appropriately directed to the laboratory device industry than to the government. These recommendations pertained to fail-safe mechanisms, or alternate failure-alert mechanisms including external quality control (QC) testing, and waived test labeling.

In order to meet the CLIA statutory requirement that waived tests have an insignificant risk of an erroneous result, CLIAC strongly supported the inclusion of fail-safe mechanisms (lock-out features) as part of a waived test system. The Committee recommended that, whenever possible, manufacturers incorporate lock-out features that ensure a waived test system does not provide a result if the result exceeds the reportable range or any component of the test system malfunctions. If fail-safe mechanisms (lock-outs) are not feasible, CLIAC noted that failure-alert mechanisms such as external QC testing are critical, and recommended manufacturers provide built-in checks or QC materials if possible. In designing future test systems, the Committee encouraged manufacturers, whenever possible, to find ways to incorporate internal fail-safe or failure-alert mechanisms to prevent erroneous results.

With respect to external QC testing, CLIAC recommended that manufacturers determine the minimum testing frequency based on risk assessment and risk mitigation. Part of this would include stress studies that evaluate points in the testing process where errors could occur. Once the frequency is determined, manufacturers should specify the minimum frequency in the test system instructions, as well as including recommended levels of QC materials appropriate for medical decisions. CLIAC also suggested that QC testing and evaluation instructions should be

integrated with the test performance instructions. To facilitate the performance of external QC testing, the Committee recommended that QC materials be provided with, preferably in, test system kits. The materials should be ready-to-use or require only simple preparation. If it is not feasible to package QC materials with the test system, the two should be shipped together when possible. If the test system manufacturer does not provide external QC materials, recommended sources for these materials need to be included in the package insert. Overall, CLIAC stressed the importance of external QC testing as a failure-alert mechanism, and noted that the measures listed above are ways to increase the likelihood that this testing will be performed.

In discussing waived test labeling, CLIAC addressed several recommendations to test system manufacturers. The Committee emphasized the importance of a standardized format for waived test labeling, and recommended that this include a warning that failure to adhere to manufacturer's instructions is off-label use of the test, resulting in the test being uncategorized, high complexity, and subject to all CLIA regulations. CLIAC also recommended that newly waived test systems include a quick reference guide in addition to the package insert, and that labeling include risk assessment/risk mitigation information and the results of waiver studies. Labeling should identify the test system as waived, and needs to notify users that when testing is performed, CLIA certification is required. Indicating a test is CLIA waived without including this notification could be confusing for users who may misinterpret what waived status means. For tests waived based on home-use approval, CLIAC recommended that labeling include a cautionary statement that the test has not been evaluated for use in clinical settings, unless this evaluation has been performed.

As part of the waived test labeling recommendations, CLIAC also provided advice relevant to test limitations/intended use, and test system instructions. They recommended that limitations, restrictions, and special considerations (including a warning when color-blindness could affect test results) be specified in test system instructions and quick reference instructions, and added that major limitations need to be prominently displayed on the outside of test packaging. For test system instructions, CLIAC emphasized that these should be clear, easy to understand, written at no higher than a 7th grade reading level, and printed in a readable font.

I am enclosing a copy of the complete set of CLIAC waiver recommendations with this letter. I hope that AdvaMed will continue to work with CLIAC and HHS in the future on the criteria for waiver approval, the waiver review process and surveillance of waived testing, as well as other issues relevant to laboratory device manufacturers.

Sincerely yours,

David N. Sundwall

David N. Sundwall, M.D.
Chairperson
Clinical Laboratory Improvement Advisory Committee

Enclosure

CLINICAL LABORATORY IMPROVEMENT ADVISORY COMMITTEE (CLIAC) RECOMMENDATIONS FOR WAIVER CRITERIA, PROCESS AND OVERSIGHT

On February 11-12, 2004, the CLIAC provided recommendations for waiver of tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA). By law, a waived test must either be approved for home use or be simple and have an insignificant risk of an erroneous result. The CLIAC recommendations are intended to provide clarifications for meeting the statutory criteria for waiver, and suggestions for oversight of waived testing.

Demonstrating Simple

Test System Characteristics

- Waived test systems should be fully automated, unitized, or self-contained and should provide direct read-out of results (quantitative tests) or distinct positive/negative endpoint (qualitative tests)
- Test systems with distinct color gradations should be considered for waiver only when studies demonstrate test performance by intended users is comparable to a traceable reference method
- The adequacy of any test system should be based on valid, empirical data

Specimen Characteristics

- Waived test specimens are currently limited to direct unprocessed specimens, including capillary whole blood, urine, throat swabs, saliva/oral fluid, stool, and tissue biopsies. Although expansion of waived test specimens may be considered, CLIAC does not support specimen types that require significant pre-analytic manipulation/processing such as centrifugation and/or assessment of specimen quality and integrity
- At this time, the use of plasma and serum for waived testing are not recommended because the manipulation and centrifugation steps in processing increase the likelihood of errors. Future technology may reduce the degree of manipulation required for these specimens, warranting reconsideration

Demonstrating Insignificant Risk of an Erroneous Result

Flex Studies

- Waived tests may need to be more robust than non-waived tests
- Potential sources of error need to be identified and studies should demonstrate that sources of error are controlled or mitigated
- As part of the waiver submission, manufacturers should include information on
    - Risk assessment (risk of erroneous results)
    - Likelihood of erroneous results
    - Measures provided or incorporated to mitigate risk

Fail-safe (Lock-out)/Failure-alert Mechanisms

- Fail-safe mechanisms should ensure that a waived test system does not provide a result (lock-out) if the result exceeds the reportable range or any component malfunctions
- Lock-out features are the ideal fail-safe mechanism, but may not always be feasible
- When fail-safe mechanisms are not feasible, failure-alert mechanisms are critical and may serve as risk mitigation tools by notifying the operator of test system problems
- Manufacturers should provide built-in checks or quality control (QC) materials whenever feasible
- If some components of waived test systems are not monitored internally
    - Electronic checks, when available, should be performed and evaluated at specified intervals
    - External QC should be tested at regular intervals and evaluated over time to monitor
        - Operator performance
        - Test system operation
        - Environmental conditions (e.g., temperature, humidity)

External Quality Control

When external QC is needed to monitor test system components

- Regulatory guidance should address minimum frequency based on studies
- Manufacturers should
    - Determine minimum frequency based on risk assessment and risk mitigation. As part of the risk assessment/mitigation, manufacturers should conduct stress studies evaluating
        - Lock-out features
        - Built-in QC
        - Internal process controls
        - Environmental (e.g., temperature) controls
        - Electronic QC
        - Sensitivity of built-in QC to analytical and test system errors
        - Ability to determine mishandling (e.g., dropping) of the device
        - Multiple skill levels of users
        - Stability (e.g., shelf life) of reagents/test systems
        - Lot-to-lot reproducibility
    - Specify minimum frequency in the test system instructions
    - Provide recommended levels of QC materials appropriate for medical decisions
    - Integrate QC instructions (including QC testing and evaluation) within the test system performance instructions
- QC materials should be
    - Provided with, preferably in, test kits to facilitate the performance of QC testing
    - Ready-to-use or require only simple preparation

- If QC materials are not provided, the manufacturer shall recommend sources for QC materials in the package insert

Waiver Studies

- Studies should demonstrate likely test performance in actual clinical use by including
  - Intended clinical testing sites
  - Intended users (e.g., non-laboratorians, waived testing personnel) as study participants
  - Intended sample type/matrix, whenever possible
  - Testing over time as in typical clinical testing
- In lieu of separate studies demonstrating accuracy and precision, one two-armed study that includes split samples, similar to a clinical trial, may be used
  - One arm of the study should demonstrate precision of waived test performance by including multiple intended users in multiple intended sites, with testing performed over several days time
    - Fresh, clinical specimens should be used for the study, whenever possible. Although contrived specimens may sometimes be necessary, studies should not be based solely on contrived specimens
    - The study should demonstrate statistically valid precision within sites, between sites, and among sites
  - The second arm of the study (accuracy) should include a statistically valid comparison of waived test performance to laboratory professional performance of a well-documented, traceable method
- To facilitate waiver studies, guidance should be developed to
  - Address statistically valid sample sizes relative to prevalence. Special considerations may be needed for low prevalence diseases to ensure adequate numbers of positive and negative specimens
  - Include examples of statistical methods appropriate for evaluating study data
  - Include references for evaluating test methodology, such as NCCLS EP-12A: User Protocol for Evaluation of Qualitative Test Performance and NCCLS EP21-A: Estimation of Total Analytical Error for Clinical Laboratory Methods

Labeling

Labeling Elements

- Test system labeling format should be standardized
- Labeling should include a warning that failure to adhere to manufacturer's instructions, including instructions for limitations/intended use and for performing QC testing, is off-label use, resulting in the test being uncategorized, high complexity and subject to all CLIA regulations
- Labeling for newly waived test systems should
  - Include a quick reference guide
  - Identify the test system as waived and notify users that when testing is performed, CLIA certification is required
  - Include risk assessment/mitigation information

- Include results of waiver studies
- For test systems waived based on home-use approval, include a cautionary statement that the test has not been evaluated for use in clinical settings, unless this evaluation has been performed

- Limitations/intended use
  - The context of testing and clinical impact should be considered when making decisions about waived test limitations and intended use
  - Major limitations need to be prominently displayed on the outside of test packaging
  - Limitations, restrictions and special considerations should be included in test system instructions and quick reference instructions
  - Labeling should include a warning when color-blindness could affect reading test results
- Test system instructions need to
  - Be clear
  - Be easy to understand
  - Be in readable font
  - Be written at no higher than 7th grade level
  - Include specific elements concerning quality control, calibration, patient test performance, limitations, and fail-safe/failure-alert mechanisms

Waiver Sales Restrictions/Best Laboratory Practices

- Sales restrictions/recommendations for appropriate use (e.g., selling only to CLIA-certified laboratories or laboratories having an adequate quality assurance program) may need to be considered for some waived tests.
- Guidelines addressing "best laboratory practices" should be developed to promote quality testing and used for the training/education of waived testing personnel
- Consideration should be given to development of training and education programs for the end-user

Post-waiver Reporting/Surveillance

Surveillance of waived test use and performance is needed and is

- Preferable to passive event reporting to FDA by manufacturers
- Especially critical in waived laboratories that have no system of monitoring test performance
- The shared responsibility of manufacturers, laboratories and government