AMERICAN ASSOCIATION OF BIOANALYSTS

917 LOCUST STREET • SUITE 1100 • ST. LOUIS, MISSOURI 63101-1413
TELEPHONE: (314) 241-1445 FACSIMILE: (314) 241-1449 E-MAIL: aab1445@aol.com

September 15, 2003

Ms. Rhonda Whalen
Chief, Laboratory Practice Standards Branch
Division of Laboratory Systems
Public Health Practice Program Office
Centers for Disease Control
4770 Buford Highway, N.E., Mailstop F-11
Atlanta, Georgia 30341-3717

RE: Comments to the Clinical Laboratory Improvement Advisory Committee (CLIAC) on the AdvaMed Clinical Laboratory Improvement Amendments of 1988 (CLIA) Criteria for Waiver; Industry Proposal

Dear Ms. Whalen:

The American Association of Bioanalysts (AAB) -- a national professional association whose members are directors, owners, managers, supervisors and medical technologists within community clinical laboratories -- respectfully submits the following comments relating to the Criteria for Waiver that will be discussed at the Clinical Laboratory Improvement Advisory Committee (CLIAC) meeting on September 17th and 18th, 2003. AAB members serve communities throughout the nation and provide integral laboratory services that assist in the diagnosis, treatment, and management of disease.

AAB's major concern is that the criteria and processes being used by the Food and Drug Administration (FDA), Centers for Disease Control (CDC), and Centers for Medicare and Medicaid Services (CMS) to waive tests under CLIA are unclear and have never been properly promulgated.

In 1992, the Department of Health and Human Services (HHS) used its own interpretation of the CLIA statute as the basis for decision-making about the status of waived tests. That policy led to so much controversy that HHS, **at the urging of CLIAC**, instituted a moratorium on waiver decisions until appropriate regulations were promulgated. The moratorium was lifted in 1995 when it was assumed (incorrectly) that the publication of CDC's 1995 proposed rule on waiver criteria presaged the prompt publication of a final rule. The final rule was never published.

AAB believes that a moratorium on waiving tests should be reinstituted immediately. We have no problem discussing proposals, such as AdvaMed's, as to what the criteria for waiver ought to be, but not while the HHS continues to waive tests based on the criteria that have

never been vetted through formal rulemaking and that may even be at odds with the CLIA statute.

The following are a few of AAB's concerns about the proposal of AdvaMed, the trade association for manufacturers of clinical laboratory testing equipment, supplies, and kits. Remember, though, that AAB believes a full discussion of AdvaMed's proposal is appropriate **ONLY IF** a moratorium on waiving tests is adopted until the criteria for waiving tests is legally promulgated through the publication of a Final Rule in the *Federal Register*.

Attached please find as background to AAB's position on these important public health issues, the May 2001 comments the Association submitted to the FDA on the draft criteria for CLIA waiver guidance that was circulated at the time for public input.

AdvaMed Industry Proposal

AAB has carefully reviewed AdvaMed's "Trade Industry Proposal" for revising the CLIA waiver criteria. This proposal, if adopted, will reduce the quality of laboratory testing conducted within the United States and will substantially increase the health risk to patients as more tests are inappropriately moved into the waived category. For these reasons we strongly urge CLIAC to reject the Trade Industry Proposal. Our primary concerns with the Trade Industry Proposal are set out below:

First and foremost, the AdvaMed proposal does not meet the statutory requirements for "waived" testing. The statute requires that in order to be designated as waived the test or procedure must either "have been approved by the Food and Drug Administration for home use" or "are simple laboratory procedures that have an insignificant risk of an erroneous result..."

The AdvaMed proposal would broaden the definition of "simple" testing well beyond the statutory framework. The AdvaMed proposal states that:

> "Risk mitigation and error detection methods cannot be 100 percent effective, however. Therefore, FDA must consider the unavoidable remaining risk versus the expected patient care benefit of having rapid access to a test..."

In effect, AdvaMed acknowledges that there are very few tests that can meet the CLIA requirement of "an insignificant risk of erroneous result." In order to circumvent this problem, the Trade Industry Proposal introduces a new standard that has no statutory basis. Under AdvaMed's proposal, regulators are supposed to weigh the risks associated with erroneous results against the "expected" benefits of making the test widely available.

This type of balancing provision is simply not contained in the CLIA statute. The statute protects consumers by placing certain minimal personnel and quality control (QC) requirements over all laboratory testing with two narrow exceptions: "home use" tests and "simple laboratory procedures that have an insignificant risk of erroneous result." If there is a significant risk that the test could be performed inaccurately it must be done in a professional -

and regulated - environment that is designed to minimize that risk. Thus, such tests should not be eligible for waiver.

An inaccurate test can have devastating consequences for individual patients and for the public health. Patients who have tests performed in clinical laboratories, hospitals, or physician's offices must be assured that there are minimal quality standards and that they can have the same degree of confidence in the results irrespective of the environment/location of where the testing was conducted. Establishing this set of safeguards was the whole purpose for the enactment of CLIA.

AdvaMed's proposal for determining whether a test is "accurate" is particularly problematic. AdvaMed is proposing to move tests into the waiver category if it can be demonstrated that:

> 1)...data from lay-user studies show that the performance of the test system is comparable to test results obtained with a high-order laboratory method, and
>
> 2) a lay-user, working only with manufacturers' instructions for use can reasonably expect to obtain substantially equivalent test results as a professional laboratorian using the same instructions for use.

Once again, these proposed standards are far weaker than the current CLIA statutory requirements and there is no legal basis for their adoption. Congress determined that testing conducted in an unregulated environment must meet very rigid standards. Waived tests must "have an insignificant risk of an erroneous result." Otherwise, the statute requires that they be performed under the protections and quality controls governing non-waived testing.

The AdvaMed proposal also substantially expands the definition of "simple" test. The Trade Industry Proposal states that in order to qualify as "simple" a test must have certain characteristics. While the proposal lists examples of simple tests that would - theoretically - meet these criteria, the initial criteria set out by AdvaMed for "simple" are incomplete. Moreover, we are even more troubled by AdvaMed's examples, many which are associated with testing procedures that clearly are not simple and therefore pose substantial likelihood that the laboratory collection and testing process could result in a significant risk of error. We fear that if the Trade Industry Proposal is adopted these "examples" subsequently will be utilized by manufacturers to seek waiver for an even broader list of tests that would not otherwise be waived even by rigorous application of the criteria stated in the document.

For these reasons, we strongly urge CLIAC to reject the Trade Industry Proposal. Perhaps most telling is the AdvaMed summary, which states that the policies advanced in the proposal are designed to promote accessibility for innovators by "allowing innovators to prove accuracy as defined in this document, which will permit all analytes become eligible for waiver, so long as the other criteria set out here are met." AAB believes that AdvaMed's objective is to thwart the CLIA regulatory program by eventually categorizing all tests as "waived." We believe that the AdvaMed waiver criteria proposal suggests a dangerous oversimplification of a process already lacking QC and proficiency testing (PT) requirements. AAB maintains that the tremendous growth in the waived testing arena necessitates additional standards instead of a more streamlined, "one-size-fits-all" treatment. AAB agrees with a CLIAC observation that

laboratory technology is developing faster than policy to regulate it, and concurs with the recommendation that waiver reviews strongly consider the ways in which these tests will be used.

Recommendations

AAB urges CLIAC to revisit the idea of a moratorium on waived tests until both FDA and the CMS are able to resolve issues relating to how tests can be considered and qualified for waived status.

Errors, test failures, and erroneous results only can be detected when mandatory QC, quality assurance (QA), and PT programs are in place with CMS oversight, just as traditional laboratory service is regulated. In many cases where waived testing errors have been identified, the test failures and errors were detected due to the presence of QC and PT programs. FDA and CMS should work collaboratively to develop new and innovative approaches to QC and PT as well as initiatives to ensure operator competence and test/instrument performance in the field. Such efforts would work to ensure that waived testing is accurate and reliable over time. In addition, CMS should develop and implement programs and processes to identify and address non-compliance issues when providers performing waived testing do not comply with manufacturers' instructions. Oversight by CMS on a continuing mandatory basis is needed. The QC and QA could be a self-report format but performed on a regular basis. The PT should be a mandatory requirement with regular review of results by CMS and would provide a scientific basis for evaluating the accuracy of waived testing. On-site inspection by CMS should be mandatory for problem resolution. The PT program should be an independent, objective, CLIA-approved PT program.[1] FDA should not categorize tests as waived if the PT data do not support the accuracy of the test. For additional recommendations, please see the attached document.

Summary

Laboratory testing clearly plays a critical role in appropriate diagnosis, treatment, early detection, prevention, and follow-up care. Therefore, accuracy in laboratory testing is essential to reducing medical errors and ensuring that patients receive proper care. Reducing risk, ensuring safety, and minimizing extraneous health care costs require greater attention to systems that help prevent and mitigate errors. AAB has serious concerns that the AdvaMed proposal would be a movement toward less protection.

Contrary to what the Trade Industry Proposal would achieve, AAB believes that FDA should be judicious in its review and approval of waived tests as these tests are conducted in unregulated environments and therefore inherently cannot provide patients and health care professionals the same degree of assurances as those tests conducted in environments subject to QC and PT.

---

[1] Manufacturers' PT programs are subject to potential bias as they inherently are testing their own products.

While certain segments of industry may desire to move all tests into an unregulated environment, that is not why CLIA was enacted. CLIA was not created to accommodate manufacturers, laboratories, or physicians - it was enacted to safeguard patients' health and well-being. The focus of CLIA and oversight of laboratory testing in all environments - CLIA regulated and waived - should be on reducing and preventing errors and protecting patients. AAB agrees with the Institute of Medicine (IOM) that "preventing errors means designing the health care system at all levels to make it safer. Building safety into processes of care is a more effective way to reduce errors."[2]

AAB believes that the adoption of our aforementioned recommendations - including implementing a moratorium on the waiver of any additional laboratory tests until a formal process and criteria can be established - would strengthen the health care system, bolster the quality of waived laboratory testing and oversight, work to reduce further the likelihood of medical errors associated with waived testing, and help to safeguard patient care and well-being. AAB appreciates the chance to share its comments with you on this issue and welcomes the opportunity to work with CLIAC on this important public health matter.

Sincerely,

Mark S. Birenbaum, Ph.D.
Administrator

[2] To Err is Human: Building a Safer Health System," Institute of Medicine (IOM), National Academy of Sciences, 2000.

AMERICAN ASSOCIATION OF BIOANALYSTS

917 Locust Street, Suite 1100 • St. Louis, Missouri 63101-1419
Phone: (314) 241-1445 • Fax: (314) 241-1449 • E-Mail: aab@aab.org • Web Site: www.aab.org

2000-2001
Officers & Board of Directors

President
Pennell C. Painter, PhD, BCLD(ABB)

President Elect
James E. Prier, PhD, HCLD(ABB)

Vice President
Melvin Bishop, HCLD(ABB)

Vice President
Patrick Quinn, PhD, HCLD(ABB)

Secretary/Treasurer
Helen Lewis, MCLD(ABB)

Regional Administrative Secretaries

Southern Region
Nicholas T. Serafy Jr.

Eastern Region
George Mitilenes, PhD, HCLD(ABB)

Midwestern Region
John F. Halsey, PhD, HCLD(ABB)

Western Region
Robert Footlik, HCLD(ABB)

Regional Manager Representatives

Eastern Region
Annette Iacono

Western Region
Elizabeth Lowe, BLM(ABB)

Regional Supervisor Representative

Eastern Region
Shawn J. Hartley

AAB Associate Member Section (AMS) Liaison
Sheryl Jensen, MT(AAB)

College of Reproductive Biology (CRB) Liaison
Thomas B. Pool, PhD, HCLD(ABB), Chairman

Committees

Government & Professional Relations
Alvin M. Salton, HCLD(ABB), Chairman

Proficiency Testing Service Co-Chairmen:
Nicholas T. Serafy Sr., HCLD(ABB)
Nicholas T. Serafy Jr.

Continuing Education
Brooks A. Keel, PhD, HCLD(ABB), Chairman

Constitution & Bylaws
Alvin M. Salton, HCLD(ABB), Chairman

Board of Scientific Advisors
J. Douglas Hutchison, PhD, HCLD(ABB), Chairman

Administrator
Mark S. Birenbaum, PhD

May 30, 2001

Clara Sliva
Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852
Docket No. 01D-0044

RE: Medical Devices Draft Guidance for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Criteria for Waiver

Dear Ms. Sliva:

The American Association of Bioanalysts (AAB) - a national professional association whose members are directors, owners, managers, and supervisors of community clinical laboratories - respectfully submits the following comments relating to the Food and Drug Administration's (FDA) medical devices draft guidance for Clinical Laboratory Improvement Amendments of 1988 (CLIA) criteria for waiver. AAB members serve communities throughout the nation and provide integral laboratory services that assist in the diagnosis, treatment, and management of disease.

General Comments

As part of its mission, AAB has long-standing policy advocating policies and programs to ensure access to quality laboratory testing for all Americans. As part of AAB's commitment to this goal, the Association maintains that the quality of a laboratory test must be assured irrespective of the environment in which it is performed and regardless of the type of test. AAB asserts that no incorrect laboratory test result is free of health care risk to a consumer, no matter how simple the test procedure. The Association believes that a test whose erroneous result cannot harm a patient does not have value to help a patient.

Moreover, the Association believes that all laboratory tests used for diagnosis, treatment, and disease monitoring should be subject to quality control (QC) and proficiency testing (PT). With more than seventy-four percent of the nation's laboratories falling outside the purview of government oversight, it is essential that steps be taken to ensure that testing

conducted in these unregulated environments is valid, reliable, and meaningful for patients and health care providers.[1]

Last year, the Institute of Medicine (IOM) reported 44,000 to 98,000 deaths annually as a result of medical errors. Medical errors rank as the eighth leading cause of death in the United States. The IOM report specifically lists the kinds of errors that result in medical injury; they are characterized as diagnostic, treatment, preventive, or other errors. As erroneous laboratory testing can lead to adverse events and/or exacerbate an existing problem, many of the types of errors in the four error categories relate directly or indirectly to laboratory testing. Types of errors related to laboratory testing include:

- Error or delay in diagnosis
- Use of outmoded tests or therapy
- Failure to act on results of monitoring or testing
- Error in the performance of an operation, procedure, or test
- Error in the dose or method or using a drug
- Avoidable delay in treatment or in responding to an abnormal test
- Equipment failure.[2]

Laboratory testing clearly plays a critical role in appropriate diagnosis, treatment, early detection, prevention, and follow-up care. Therefore, laboratory testing accuracy proves essential to reducing medical errors and ensuring that patients receive proper care.

Since the release of the IOM report, renewed attention has been paid to reducing the risk of medical errors. The IOM recommended that health care providers develop methods of preventing, identifying, and analyzing errors and integrate competency certification and re-certification in the delivery of health care services. Thus, as health-related private, non-profit, and government entities seek to identify and implement such policies and programs to reduce and prevent medical errors, AAB upholds ensuring the validity and reliability of all laboratory testing as integral to minimizing and preventing medical errors.

Patients should be safe from injury caused by the health care system. As the IOM notes, "errors can be prevented by designing systems that make it hard for people to do the wrong thing and easy for people to do the right thing."[3] The IOM goes on to state that

---

[1] Fifty-two percent of the nation's laboratories perform only waived tests and twenty-two percent are limited to performing waived and/or microscopy tests.

[2] "To Err is Human: Building a Safer Heath System," Institute of Medicine (IOM), National Academy of Sciences, 2000.

[3] IOM Report, 2000.

Errors are also costly in terms of opportunity costs. Dollars spent on having to repeat diagnostic tests or counteract drug events are dollars unavailable for other purposes. Purchasers and patients pay for errors when insurance costs and co-payments are inflated by services that would not have been necessary had proper care been provided. It is impossible for the nation to achieve the greatest value possible from the billions of dollars spent on medical care if the care contains errors.[4]

Thus, reducing risk, ensuring safety, and minimizing extraneous health care costs require greater attention to systems that help prevent and mitigate errors - not a movement toward less protection. To that end, AAB believes that a waived test when performed by an untrained user should provide as high a degree of accuracy as when the test is performed by trained personnel in a moderate or high complexity laboratory.

The Association recognizes that generally there is a lack of data relating to adverse outcomes associated with waived testing and therefore urges FDA and the Health Care Financing Administration (HCFA) to conduct pilot studies to assess the impact of waived testing on patient outcomes. The danger of incorrect waiver test results is a principal issue to which we urge the government's attention. AAB believes that some governmental oversight of CLIA Certificate of Waiver Laboratories should be instituted to assure that quality testing is performed in these sites and the likelihood of medical errors is reduced.

Troubling Performance of CLIA "Certificate of Waiver" Laboratories

Recent government studies have found that serious problems exist in waived laboratories. AAB believes that these studies suggest widespread problems in waived laboratories and indicate that the standards of practice in such environments are substandard. Thus, the use of waived tests in these laboratories poses potential threats to quality care for patients.

A pilot study conducted by HCFA in Ohio and Colorado studied 80 to 100 CLIA "Certificate of Waiver Laboratories" and found that fifty percent of those examined had testing problems. The problems ranged from obsolete instructions to no instructions at all to the combination of instructions being used with the wrong analyte. Seven to ten percent of the laboratories were testing beyond the scope of their CLIA certificates. Moreover, fifty percent of waived laboratories in Ohio and thirty percent in Colorado had quality control problems.

---

[4] IOM Report, 2000.

Preliminary findings of an extended study of waived laboratories in eight additional states corroborate the initial study results. Additional problems uncovered through the pilot study of Certificate of Waiver laboratories include:

- Failure to meet the Centers for Disease Control and Prevention's (CDC) additional quality control requirements.
- Absence of calibration function checks as required by manufacturers' instructions.
- Lack of training for testing personnel.
- Deficiency of CLIA information - laboratories do not know whom to contact for general CLIA information, such as which tests are waived. Laboratory/office personnel relied principally on manufacturers' sales representatives.

Further, CDC conducted a study that demonstrates that physician office laboratories (POLs) and ancillary health care providers do not achieve the level of test quality found in traditional sites that fall under the jurisdiction of CLIA. In addition, the California Department of Health's Laboratory Field Services researchers noted PT discrepancies among POLs, POLs that employ licensed clinical laboratory scientists, and non-POLs. Further, they found that the unsatisfactory PT failure rate among POLs was nearly three times that of non-POLs - 21.5 percent vs. 8.11 percent - and approximately one-and-a-half times greater than POLs that employ laboratory professionals as testing or supervisory personnel.[5,6]

---

[5] Further corroborating these findings, the Departments of Health of Arkansas, Idaho, New York, Oregon, and Washington have collected information on waived testing practices. The results of a QC study in waived and PPMP laboratories uncovered the following:

- QC measures are not used consistently in waived laboratories.
- Explicit guidelines for CLIA compliance for each test were not present.
- Test classes with high rates of non-performance of QC primarily are those that have a non-automated configuration (e.g. dipstick tests, ESR, $CuSO_4$, Hgb, etc.).

[6] The Pacific Northwest Laboratory Medicine Sentinel Monitoring Network reported data for waived testing that indicated the following:

- Forty-six percent of waived tests are used for diagnoses with no result confirmation.
- Confusion exists about what QC is needed.
- Some laboratories developed their own QC protocol based on perceptions of regulations and accreditation standards.
- Tests often are used not as intended.
- Employed personnel are untrained.
- Absence of availability of reference materials.

Given these disturbing findings, AAB remains concerned with the trend of laboratories moving away from oversight and accountability rather than increasing efforts to comply with federal safeguards. For example, the federal government currently surveys only 26,000 laboratories - a number that reflects a decrease of 20,000 laboratories that are surveyed by HCFA under CLIA. AAB is concerned that this number may drop further if more laboratories move to waived status. This migration of laboratories away from oversight serves to erode the intent and power of CLIA and could result in lower quality of laboratory services for Medicare beneficiaries and the general public. Waived and Physician Performed Microscopy Procedure (PPMP) level laboratories are less likely to use QC measures to ensure data quality which impacts the quality of patient results. Further, AAB urges that HCFA and FDA consider granting certificates of waiver from CLIA only to physicians' offices in which testing is performed for immediate needs of the physicians' own patients.

AAB believes that FDA should seek to restrict the number of waived tests as these tests are conducted in unregulated environments and therefore inherently cannot provide patients and health care professionals the same degree of assurances as those tests conducted in environments subject to QC and PT. In addition, AAB believes that tests intended for use in the following situations should not be granted CLIA waived status: (a) the test result is entirely or substantially the basis for clinical decision-making, (b) the consequences of the clinical decision create a risk of significant physical or emotional harm to the patient, other individuals, or public health, (c) a physical examination and/or other tests do not offer a prompt and accurate means to confirm or reject the test result in question, and (d) the test results require confirmation with a second or follow-up test. [7], [8] AAB seeks to

[7] In many cases, screening tests require a second test to be conducted for confirmation of results. Waived screening tests only provide primary information and do not serve as replacements for a conventional test. Therefore, AAB asserts that the waiver process for these tests should be more rigorous since there can be no assurance that confirmatory testing will be conducted. Just as with other tests, waived tests for screening must be validated and there must be assurances of quality results and operator competency. One problem is that some physicians presume a result of a waived laboratory test is equivalent to a traditional laboratory assay. However, many are not. Some of these tests are being used in triage, diagnosis, and treatment of patients and unfortunately, some clinicians do not distinguish different reference ranges or different performance characteristics from the traditional laboratory. Given the nature of waived testing and the lack of QC and PT, it is unlikely that the untrained user will seek a confirmatory test to verify the results of a screening test. Therefore, the need for confirmatory testing should raise the threshold for a waiver decision.

[8] Misuse of tests poses a significant problem and is related to mislabeling of waived tests. An example of this is the use of a waived blood sugar test for a diagnosis of diabetes. Waived blood sugar tests should not be performed on a patient who has not been diagnosed as a diabetic with a traditional diabetic diagnostic laboratory test procedure. The waived tests only should be used to monitor diagnosed diabetic patients.

ensure that all laboratory testing and the associated results are safe, efficacious, and accurate for all patients and health care providers involved.

FDA Categorization of OTC/Home-Use Tests as Waived

AAB understands that by law any test system approved for home-use or cleared for over the counter (OTC) use by FDA also is approved for waiver. The statutory language directing FDA automatically to categorize home-use tests as waived tests is of significant concern to AAB because currently FDA OTC/home-use criteria outlined in guidance regulation set a lower standard for testing, only consider safety and efficacy, and fail to require any form of QC. Further, the approval for OTC/home-use process fails to take into consideration varying degrees of accuracy or any of the specific criteria by which other waived tests are evaluated currently. This creates a two-tiered system within the waived category with two very different sets of standards for tests being conducted in the same environment without any scientific rationale for the differential.

This automatic waiving of OTC/home-use tests may lead to waivers being granted for some tests that otherwise might not qualify for waived status when held to accuracy and precision standards. As such, this regulatory loophole must be closed to ensure patients and providers that all testing in CLIA waived laboratories is held to the same basic standard and is safe, reliable, and accurate. While AAB believes that the availability of OTC, home-use, and prescription-home-use tests provide benefits to patients, the Association remains concerned about the wholesale categorization of these tests as waived and therefore available for use in POLs – environments without trained laboratory personnel and for whom these tests were not designed nor intended.

For example, Lifescan, Inc. recently pled guilty to federal criminal charges based on its failure to inform FDA of two serious faults in its Sure Stop product - an instrument that reads blood glucose levels. These two defects - a software problem that caused the device to display an error message instead of a "HI" at blood glucose levels above 500mg/dl and a mechanical glitch that caused the meter to display inaccurate readings if the monitor's test strip was not inserted fully - produced serious instrument malfunction and problematic readings. Many of these invalid test outcomes resulted in complaints to Lifescan about illness and hospitalization - possibly attributable to the erroneous testing associated with the device flaws.

While this device was approved for OTC/home-use, under current law it received automatic categorization as waived so therefore was available for use in physicians' offices. The adverse events associated with some of the erroneous test results provide tangible evidence of what can go wrong with a testing procedure that receives de facto waiver through its FDA approval for home-use. Moreover, the existence of such serious flaws in an OTC/home-use device demonstrates the need for stronger standards for OTC/home-use approval to ensure that when such devices are utilized in POLs that patients can be assured of the validity and reliability of the test results and medical errors can be minimized.[9]

Since a majority of the tests currently in the waived category automatically receive waived status as OTC/home-use devices, more and more tests are moving to waived status. Therefore tests are moving from a regulated setting to an environment usually staffed by highly variable personnel and laboratory testing occurring without any PT or QC programs. This shift results in a circumventing of the intent of CLIA and the waiver process and undermines the goal of CLIA to provide oversight, accountability, and regulation of laboratory tests to ensure quality testing.

AAB believes that this current system of allowing all OTC/home-use tests to become waived and therefore performed without any QC requirements does

[9] AAB has concerns that the Lifescan situation is not unique. For example, the Cholestech LDX alanine aminotransferase - which received waived status in April 2001 - shows poor performance in both the AAB and American Academy of Family Physicians proficiency testing programs. When contacted, the company admits that there are problems with this assay, however the test remains on the market and in use.

not offer adequate protection of public health or provide any assurance to patients or providers that the test will be performed correctly. As no QC will be required, it is essential that the test be designed to ensure a result that can be relied upon for clinical decision-making and that the test operator correctly perform the test.

The IOM notes in its report that "there are two opportunities for FDA to ensure and enhance patient safety: during its approval process for drugs and devices, and through post-marketing surveillance."[10] Therefore, AAB urges FDA and Congress to consider changes to the OTC/home-use approval process so as to ensure patients will be protected when such tests are employed in a waived environment. As patients expect the tests performed by physicians in their offices to be higher quality than those that can be performed at home - and often seek such testing believing it to be superior to home-use tests - it follows that the accuracy and quality of POL testing should be held to a higher standard than those tests performed by consumers at home.

AAB believes strongly that all tests granted CLIA waiver should be held to the same stringent standards for accuracy and precision and meet the same requirements for design, labeling, QC, PT, and training and monitoring of field users. One way to achieve uniform standards would be to incorporate the CLIA waiver process into the FDA process for review and approval of OTC/home-use devices. Moreover, once FDA has established final criteria for waiver, all tests with existing waiver status should be reevaluated by the new standards to ensure that all waived tests available in the marketplace meet the same level of accuracy and precision.

As part of ongoing monitoring efforts, FDA should consider comparing performance of waived tests in different test settings after waiver status has been granted. Specifically, AAB suggests that FDA conduct a study of the impact that the automatic waiver for OTC/home-use devices has had on testing and patient outcomes, including an evaluation of how these devices are used by waived laboratory personnel in the field. Further, until uniform standards are adopted and applied, AAB urges FDA - when considering approval for devices to be marketed OTC/home-use - to be aware of the de facto result of the test becoming waived and available widely in POLs.

Simplicity, Accuracy, and Precision of Waived Tests

AAB urges FDA to consider carefully the definitions and requirements for simplicity, accuracy, and precision and believes that simplicity should be considered separately from accuracy and precision. The Association has serious concerns related to the disparity between the statutory definition and

[10] IOM Report, 2000.

intent associated with "simplicity" and "accuracy" and FDA's current use and application of the concepts.

Specifically, AAB maintains that within the original CLIA statute, Congress employed "simple" to mean the type of testing itself and did not intend to refer to or include operation of the test. The original statute specifies nine types of tests that are exempt from CLIA regulation - eight of which are non-automated tests. Thus, AAB believes that Congressional intent was to provide waiver from CLIA regulation to only the most simple and basic testing mechanisms such as those specifically detailed in the statute. However, as FDA has expanded the waiver category to include numerous tests that are "simple" as it relates to operator function but complex in terms of the actual test process/methodology, AAB believes the agency has failed to uphold Congressional intent in this regard.

Therefore, AAB proposes the following changes to Section II of the Draft Guidance, *Demonstrating Simple,* that details all of the characteristics that a test must posses in order to be considered simple:

- Add the following to the list of characteristics - "Does not rely on complex electronic or mechanical devices or processes" - many tests while simple in their outward operation indeed involve complex and involved internal testing methodologies that when malfunction require a trained professional to interpret the error code and/or troubleshoot the situation[11]
- Delete the parenthetic remark "interpreting error codes does not constitute troubleshooting" - error codes and problematic test results inherently require troubleshooting by the operator and such troubleshooting requires experience, deductive reasoning, and a greater degree of skill than that of a lay-person.

AAB maintains that there is a clear distinction between accuracy as it relates to the performance of the test itself as opposed to the performance of the test operator. Despite this critical difference, it appears in the draft guidance that FDA currently focuses principally on demonstrating operator accuracy and not the test instrument itself. This approach really encapsulates performance comparability - not accuracy - and focuses on ease-of-use not result veracity.

Therefore, AAB believes both analytical and clinical accuracy should be assessed and test performance standards should be defined and developed. Test performance should be evaluated both by assessing reliability of results and performance comparability. Analytical accuracy should be determined

[11] AAB maintains that FDA's current interpretation of Congressional intent related to the definition of "simple" to mean testing that is "simple" to operate (as in pressing buttons on the apparatus) but could be internally or inherently complex is erroneous. Testing that operates by internal processing and circuitry should not fall within the definition of "simple methodology."

by comparison of the test to a well-characterized reference method and/or materials where available. If a reference method is unavailable, comparison should be made to a well-characterized comparative method and/or materials. The method also should be subjected to PT and demonstrate acceptable performance. Clinical accuracy should be determined by comparing test results to clinical outcomes as established by a well-accepted clinical algorithm. Similarly, qualitative methods should be evaluated by agreement to an accepted reference of comparative method. Discrepant values should be evaluated based on clinical outcomes.

Test results from untrained users should be compared to those from CLIA-certified laboratory personnel on the same samples. No statistically significant difference should be present for accuracy or precision. If allowances are to be made for variable accuracy, the consequences of an inaccurate result must be viewed in the light of all possible clinical outcomes. Representatives of the populations to which the test will be marketed should evaluate waived tests in the myriad settings of intended use. In general, such users should have a seventh grade education level. Users of the comparative method should be trained laboratory personnel.

Tests of analytical accuracy may vary according to the method being evaluated. Quantitative methods should be evaluated statistically by regression methods (Passing-Bablok or Deming) and by difference plots (Bland-Altman). Thresholds for performance will vary from method to method, but acceptability should be judged based on reasonable guidelines established and accepted by the scientific community.

AAB agrees that specimens used for testing should represent the expected range of clinical specimens and include some specimens at a level near important medical decision levels as well as some samples close to the thresholds of assay sensitivity. Precision performance thresholds should be based on predefined performance goals such as Tonk's formula or any other suitable formula as accepted by the clinical scientific community.[12]

The practical reporting limits of the test should be evaluated. The functional sensitivity of the test should be reported as well as the upper limit of accurate recovery. The suggested reference range should be submitted and should be based on data from at least 100 patients from defined populations. Generally, all testing conducted to assess untrained/professional precision and untrained/professional agreement should model real field circumstances as much as possible.

---

[12] At a minimum, the current CDC recommendation of 20 samples at three levels representing appropriate decision points to be tested at three sites by lay users is acceptable. However, the materials used should be limited to actual samples/specimens for which the test is intended.

AAB believes that with each waived test an evaluation of expected sources of problems, failures, and/or interference should be conducted. Specifically, the fashion in which potential problems, failures, and interferents affect a test should be analyzed. Interference studies should include those interferents that will be encountered commonly in the routine performance of the test. Interferents should include hemolysis, lipemia, bilirubin, and commonly encountered drugs. Other endogenous or exogenous interferents, such as hormones, or compounds known to interfere with other similar tests, would be appropriate. In addition, AAB concurs that environmental stress studies should be suitable for the nature of the test. All conditions commonly encountered in the routine performance of the test should be tested. The hazard analysis should address the full range of possible sources of error including specimen handling, operator error, reagent integrity, hardware and electronics integrity, environmental factors, and calibration stability.

Manufacturers should be directed to build in internal controls and indicators that identify when a test has been stored improperly, experienced packaging leaks, or its reagents no longer have full reactivity. In addition, AAB agrees that lockout functions should be incorporated to ensure that testing cannot proceed if QC is not performed, results are unexpected, or if something with the test is out of control. The waived device also should have operator lock-out so that only individuals who are trained and certified on the instrument and associated procedures can perform the test analyses. Further, reagents should be in self-contained packages or pre-prepared reagent should be provided and manipulation of controls, calibration, or other tests components should be minimized, but preferably eliminated, from product design.

In addition, manufacturers should be required to incorporate the necessary QC and PT into waived test devices and instructions for use so performance of the test is valid and reliable throughout the course of the instrument or reagents' life. Manufacturers should include clear instructions for the reporting of test system/instrument failures in the user procedure manual. FDA should take steps to encourage and enforce the reporting of this information and make it available to users and the public. AAB agrees that the provision of a toll-free number for technical assistance on QC and test operation would help to improve the quality of waived testing and work to ensure that QC is conducted as appropriate.

AAB agrees with FDA that the package insert should include identification of the tests as CLIA waived but believes that this information should provide further explanation at to what that means. For tests receiving waived status through OTC/home-use approval, these tests should have specific labeling since they do not contain QC or other protections to ensure accuracy. As most patients receiving testing in a waived POL are unaware that they are receiving tests results from an unregulated environment, informing test operators and patients provides a greater degree of informed consent.

AAB supports the requirement that manufacturers reapply for waived status should they make any changes to their products that could affect accuracy and reliability. Manufacturers should develop and implement a post-market surveillance plan to monitor the accuracy of their waived tests in the field and collect and analyze data to improve product design and QC efforts. Such data should be made available to providers, consumers, and FDA.

Oversight of Certificate of Waiver Laboratories

FDA and HCFA should work collaboratively to develop new and innovative approaches to QC and PT as well as initiatives to ensure operator competence and test/instrument performance in the field. Such initiatives would work to ensure that waived testing is accurate and reliable over time.

Measurement of outcomes is needed on a mandatory and regular basis. Mandatory PT would provide a scientific basis for evaluating the accuracy of waived testing and should be a requirement on a quarterly basis for waived testing sites. The PT program should be an independent, objective, CLIA-approved PT program.[13] FDA should not categorize tests as waived if the PT data do not support the accuracy of the test.

Errors, test failures, and erroneous results only can be detected when mandatory QC, quality assurance (QA), and PT programs are in place with HCFA oversight, just as traditional laboratory service is regulated. In many cases where waived testing errors were identified, the test failures and errors were detected due to the presence of QC and PT programs. HCFA should develop and implement programs and processes to identify and address non-compliance issues when providers performing waived testing do not comply with manufacturers' instructions. Oversight by HCFA on a continuing mandatory basis is needed. The QC and QA could be a self-report format but performed on a regular basis. The PT should be a mandatory requirement with regular review of results by HCFA. On-site inspection by HCFA should be mandatory for problem resolution.

In order to attain these quality testing goals, manufacturers must be required to provide training for all testing personnel, at a comprehensible level, for instrumentation and test procedure qualification by performance. This training must be documented and certified by the manufacturer for every operator/tester and his/her replacement who performs the test procedures. Manufacturers' operator/tester training should include proper collection procedures for all tests. As part of this effort, manufacturers should create self-assessment tools for waived devices to assist laboratories in determining

[13] Manufacturers' PT programs are subject to potential bias as they inherently are testing their own products.

their ongoing compliance with the manufacturers' instructions for both QC and PT. The laboratory director should be involved in this effort, as it would help assess and ensure performer competence for all personnel performing tests.

Since a significant number of the personnel performing waived tests are not formally trained laboratorians, programs to provide non-laboratorians with a basic level of understanding of the scientific method as well as educate them on the value and performance of QC and PT for accuracy and reliability of results would help ensure compliance. HCFA, working in collaboration with FDA, should develop a pilot program to identify methods for educating waived laboratory personnel in these areas.

AAB supports the concept of scientific clinical study to evaluate the performance of untrained users vs. laboratory personnel. The results of the study should be made available to consumers as well as the entire laboratory community.

Compliance and operational problems could result in inaccurate and erroneous test results that adversely could impact patient care and well-being. Only with these requirements in place can the public be assured of ongoing quality health care delivery irrespective of where the laboratory test is performed.

Development of "Low Complexity" Category

AAB remains concerned about the lack of QC and PT for waived testing and the impact that increasing testing in unregulated environments will have on patient care and well-being. Allowing dozens of tests whose accuracy has not been established definitively in the field into the untrained hands of lay users does not provide patients or health care professionals with the assurances they need that the medical decisions based on these test results can be relied upon. Therefore, AAB believes that FDA should consider establishing a "low complexity" test category that would be appropriate for tests whose simplicity, accuracy, and precision have not been proven yet in the field.

The low complexity category could be a "pass-through" category in that once tests have shown consistency in their performance as it relates to accuracy and manufacturers provide FDA with longitudinal "real-world" data on performance in lay-users' hands, tests could be moved into the waived category. AAB recognizes that currently a majority of waived tests achieve their exemption from regulation either because they are one of the nine types of tests detailed in CLIA or they are approved by FDA for OTC/home-use. However, AAB believes that by strengthening the process by which tests receive OTC/home-use approval coupled with the creation of a low

complexity category that the tests ultimately used in a waived environment will be only those that meet stringent standards and satisfy necessary uniform safeguards.

As the IOM notes, "errors can happen in all stages in the process of care, from diagnosis, to treatment, to preventive care."[14] Waived tests increasingly are used to inform the full range of health care decisions and subsequently, the chance of such tests leading to medical errors also increases. By requiring all new tests seeking waived status to first be categorized in a "low complexity" category for an established period of time and then - once validated as accurate - moved into the waived category, the accuracy and precision of such tests as used in unregulated environments will be enhanced.[15]

General Guidance Requirements

The Association urges FDA to consider strengthening the guidance by including language that makes it clear that manufacturers must meet the guidelines and standards set forth in the document. The guidance document includes many uses of "may" or "should" as opposed to making a clear statement that the manufacturer is required to fulfill a particular instruction. Therefore, AAB recommends the use of "shall," "will," and "must" to communicate clearly to manufacturers the requirements and expectations to meet in their entirety. Strengthening the instruction language, standards, and substantive content in the guidance documents for both FDA waiver and the OTC/home-use labeling ultimately will help ensure the accuracy of those tests when used in CLIA-exempt laboratories.

Summary

AAB appreciates the opportunity to comment on the draft guidance and stands ready to work with FDA, HCFA, Congress, and other stakeholders to ensure that all laboratory testing is valid, reliable, and meaningful for patients and health care providers. The Association recognizes that FDA is limited in its ability to institute many of these recommendations and therefore avails itself to Congress to work collaboratively to see that all laboratory testing is safe, efficacious, and accurate.

Given the current problems and challenges facing waived laboratory environments coupled with the growing need to implement efforts to

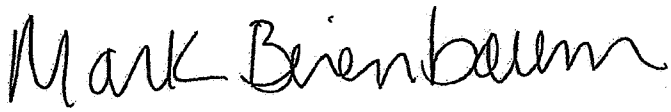
[14] IOM Report, 2000.

[15] AAB also has concerns about the effect waived tests might have on public health and the ability of CDC and other public health entities to collect and analyze data about infectious disease. By developing a "low complexity" category that includes post-market surveillance of tests and proof of accuracy in the field, the waiving of tests for infectious disease, such as influenza, will occur only when the test sensitivity is rigorous enough to justify its use in CLIA-exempt environments.

minimize medical errors, AAB cautions FDA against rapid expansion of waived testing and urges additional oversight for waived laboratories. AAB maintains that errors associated with waived testing can pose potential risks to patients and every step to minimize such threats should be undertaken.

The Association agrees with the IOM that "preventing errors means designing the health care system at all levels to make it safer. Building safety into processes of care is a more effective way to reduce errors."[16] AAB believes that the adoption of our aforementioned recommendations would strengthen the health care system, bolster the quality of waived laboratory testing and oversight, work to reduce further the likelihood of medical errors associated with waived testing, and help to safeguard patient care and well-being.

Sincerely,



Mark Birenbaum, Ph.D.
Administrator

[16] IOM Report, 2000.