

ISSUE SUMMARY: Rapid HIV Tests and CLIA Waiver

Blood Products Advisory Committee, June 14, 2001

The Clinical Laboratory Improvement Amendments (CLIA) law of 1988 and the CLIA regulations at 42 CFR 493 published on 2/28/92 require laboratory oversight to ensure quality testing and are based on test complexity. The regulations identify three categories of tests: waived, moderate and high complexity. Waived tests are exempt from quality standards and are defined as simple tests having an insignificant risk of an erroneous result. All laboratories must be certified. Laboratories conducting moderate complexity and/or high complexity tests are subject to specific requirements for quality control, quality assurance, personnel qualifications and responsibilities, and proficiency testing with routine biennial inspections. These laboratories may choose whether they wish to be surveyed by the Health Care Finance Administration (HCFA) or by a HCFA-approved private accreditation organization. Waived laboratories are required only to enroll in the CLIA program, become certified, pay applicable certificate fees biennially, and follow manufacturers' test instructions. The regulations exempt laboratories performing only waived tests from personnel, proficiency testing, quality control, and quality assurance standards and from routine inspections. The CLIA program is entirely user fee funded; therefore, all laboratories must pay biennial certificate fees to HCFA with those laboratories surveyed by HCFA also paying for the cost of their surveys. Accredited laboratories pay their accrediting organization for their survey directly.

The CLIA regulations contain a certificate application exception for laboratories performing only limited public health testing. Not for profit or Federal, state or local government laboratories that engage in limited (no more than a combination of 15 moderate and waived complexity tests) public health testing may complete only one application for all of their testing sites. This provision, when exercised, can save enrollment, certificate, proficiency testing and survey costs if the laboratory meets the above criteria.

In the 1992 CLIA regulations, FDA was assigned responsibility for test categorization and waiver determinations of *in vitro* diagnostic devices. Shortly thereafter, the Secretary, DHHS, assigned that responsibility to the Centers for Disease Control and Prevention (CDC).

In 1995, CDC and HCFA published a proposed rule to clarify the statutory criteria for waiver as recommended by the Department's Clinical Laboratory Improvement Advisory Committee (CLIAC). The proposed rule defined simplicity and low risk, and described accuracy and precision studies to show that the test has an insignificant risk of an erroneous result. Accuracy studies were based on comparison to reference materials and precision was to be demonstrated using field studies. Waiver determinations were primarily made on the basis of inherent test performance. In addition, to meet the low risk criterion, the proposed rule required that tests be robust and have a fail-safe mechanism that would render no result when the test system malfunctions or the result is outside of the reportable range.

The Food and Drug Modernization Act (FDAMA) (1997) revised the statutory criteria for waiver to clarify that waived tests are cleared or approved by the FDA either for home use (and therefore automatically waived) or are simple tests that, as determined by HHS, have an insignificant risk of an erroneous result. FDAMA also added the phrase "by the user" to the waiver provision regarding the simplicity and accuracy of testing methodologies ("employ methodologies that are so simple and accurate as to render the likelihood of erroneous results by the user negligible"). This clarifying language was intended to focus the waiver criteria on verifying test performance by the user rather than on inherent test performance.

In 1999, an interagency agreement transferred the responsibility for CLIA complexity from CDC to FDA, and FDA held a public waiver workshop in August 2000 to obtain comments on the criteria and process used to determine waiver. Following the waiver workshop, FDA developed a draft guidance document, which was issued for public comment on March 1, 2001 with a 90-day public comment period. The comment period ended on May 30, 2001 and comments are being evaluated. Four alternative routes to waiver approval are listed in the FDA draft guidance. They include FDA approval for home use, tests meeting the criteria specified in the 1992 regulations, tests meeting the 1995 CDC proposed rule criteria, or tests meeting the alternative criteria proposed in the FDA draft guidance. The draft guidance addresses the waiver criteria as clarified in FDAMA, and describes a mechanism for tests to meet these criteria. The guidance addresses simplicity (met through defined characteristics), insignificant risk of an erroneous result (addressed through a hazard analysis and failure alert mechanism through quality control procedures and materials), and low likelihood of erroneous results by the user (addressed through precision and agreement studies comparing professional and untrained users). The draft guidance also specifies waiver labeling and voluntary post-market safeguards to monitor test performance after waiver approval.

The key differences between the CDC/HCFA 1995 proposed rule and the FDA draft guidance are:

- CDC requires determination of accuracy by comparing product performance to reference methods, materials, or well-established procedures, whereas FDA requires a demonstration of comparability of results between lay and professional users as an accuracy surrogate.
- CDC requires manufacturers to specify in labeling when users must perform QC as a failsafe mechanism, whereas FDA requires only that the label recommend that QC be performed.
- FDA proposes a voluntary post-approval surveillance process, whereas CDC requires no post-approval surveillance.

In the past, FDA has discussed the public health need for rapid HIV tests with BPAC. For neonates delivered from at-risk women of unknown HIV status and for health-care workers with needle-stick injuries, the results from rapid HIV tests will permit initiation of anti-retroviral therapy within the narrow window of opportunity for effectiveness. In addition, data presented by CDC have shown that approximately one third of individuals tested in clinics and 25% of individuals testing positive for HIV do not return for their conventional test results, which require hours to days to be completed. Therefore, it has been argued that it is in the interest of the public health to maximize the availability of these tests to reach the populations that need HIV testing. Waiver under CLIA of HIV rapid tests that meet the criteria for simplicity and accuracy/performance would widen their market availability by enabling their use in outreach and point-of-care settings. FDA therefore expects manufacturers of rapid HIV tests to apply for CLIA waivers.

Relaxation of controls under CLIA waiver is very significant, however, and raises some concerns. CLIA waiver under either the CDC proposed rule or the FDA draft guidance simply allows a waived laboratory to acquire and perform a waived test. There are no restrictions regarding location or which individuals may perform or oversee these tests. With regard to the potential waiver of rapid HIV tests, FDA is concerned about the interpretation of test results, the ability to have appropriate follow-up testing performed, and the ability to provide pre- and post-test counseling. Therefore, limiting access to medical professionals is desirable, but CLIA waiver does not permit this distinction to be made. A waived test can be performed by anyone,

anywhere, in clinical or lay facilities with no direct oversight. In addition, limitation of test use through labeling is ineffective.

FDA will bring the issue of CLIA waiver for rapid HIV tests before BPAC in the following manner:

1. CDC will present an historical overview of CLIA waivers.
2. FDA will present an overview of its draft CLIA waiver guidance.
3. CDC will discuss public health strategic goals for increasing the number of persons who receive testing and know their HIV infection status.
4. HCFA, the HHS agency responsible for administering CLIA, will discuss requirements for moderate complexity tests, and its experience with CLIA waived tests in the laboratory setting. A HCFA representative will also comment on the CLIA provision for exceptions for categorized tests based on limited public health use.
5. FDA will present questions to the committee.

Questions for the committee

1. Considering the known benefits and risks of rapid HIV testing, should FDA consider the possibility of removing all CLIA quality assurance oversight for such tests (*i.e.* waive simple and accurate HIV testing from CLIA) under its proposed criteria?
2. If not, what are the criteria that should be applied in making waiver decisions for these tests?
3. If rapid HIV tests are not waived, is it appropriate to pursue other approaches under CLIA (e.g. limited public health use) to promote wider access to rapid HIV testing?