



AMERICAN ASSOCIATION OF BIOANALYSTS

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SEP 14 10 24 '00

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00N-1394

Clara Sliva
Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20850

Dear Ms. Sliva:

Following are comments submitted by the American Association of Bioanalysts (AAB) relating to the August 14-15, 2000, public workshop on CLIA Waiver Criteria, the notice for which was published in the July 21, 2000, *Federal Register*, Vol. 65, No. 141, p.p. 45384-45385.

The American Association of Bioanalysts is a national professional association whose members are directors, owners, managers, and supervisors of community clinical laboratories.

Below are general comments concerning the quality of laboratory testing produced by clinical laboratories operating with CLIA "certificates of waiver," followed by AAB's responses to the specific questions listed in the July 21, 2000, *Federal Register* notice.

The Performance of CLIA "Certificate of Waiver" Laboratories

At the August 14-15, 2000, Public Workshop on Clinical Laboratory Devices, Judy Yost, HCFA's CLIA Administrator, released and explained the findings of a pilot study conducted by HCFA in Ohio and Colorado of 80-100 CLIA "certificate of waiver" laboratories.

The pilot study indicates that more than 50% of these laboratories have testing problems. The problems range from obsolete instructions, to no instructions, to failure to follow manufacturers instructions, to instructions for the wrong analyte. Seven to ten percent of the labs were testing beyond the scope of waived tests, and fifty percent of waived laboratories in Ohio had quality control problems. Thirty percent of the laboratories in Colorado had quality control problems.

C18

These findings were reinforced, at this meeting, by a representative from the New York State Department of Health who conducted a similar survey in New York and found similar deficiencies.

A study by the Centers for Disease Control and Prevention (CDC) (JAMA 1998; 279:463-7) shows that POLs and ancillary health care providers do not achieve the level of test quality found in traditional sites, which fall under the purview of CLIA '67.

In another study performed by the California Department of Health's Laboratory Field Services (JAMA 1998; 279:498-72) researchers noted proficiency testing discrepancies among POLs, POLs that employ licensed clinical laboratory scientists, and non-POLs. California's Laboratory Field Services found that the unsatisfactory PT failure rate among POLs was nearly three times that of non-POLs (21.5% vs. 8.1%) and about 1.5 times greater than POLs that employ laboratory professionals as testing or supervisory personnel.

In view of these studies and the fact that 74% of all laboratories in this country have CLIA "certificates of waiver," it is clear that more governmental oversight of CLIA certificate-of-waiver laboratories is needed to assure that quality testing is performed at these sites. AAB suggests that, at a minimum, these sites be subject to inspection and that an ongoing proficiency testing program be mandatory for these laboratories in order to achieve a balance between access and quality of health care.

AAB wishes to point out that a major Congressional objective in the CLIA statute is to establish site neutrality, so that the patient public can be assured of quality laboratory results from any laboratory. AAB urges the FDA to adopt criteria for waived tests that meet this important Congressional objective.

General Questions for Public Input

1. *What criteria should be used to demonstrate that a waived test is a simple laboratory examination and procedure with "an insignificant risk of an erroneous result?"*

A. *Should a waived test, when performed by untrained users, provide an accurate result with no significant clinical or statistical error when compared to a measure of truth?*

Test results on patient samples should be compared to results obtained by an established reference method on the same samples. The criteria for acceptance should be no statistically significant inaccuracy or imprecision.

B. *Should a waived test, when performed by untrained users, provide a test result that shows no user error when compared to the same test performed in a CLIA-certified lab by a trained user?*

Compare test results from untrained users to those from CLIA-certified lab personnel on the same samples. No statistically significant difference should be present for accuracy or precision.

- C. *Should FDA apply a different model to determine the waived status of a test?*

No, the strict adherence to the criteria should be sufficient.

2. *What criteria should FDA use to determine if a methodology is "so simple and accurate to render the likelihood of erroneous results by the user negligible?"*

- A. *Should a waived test be so accurate when performed by untrained users that inaccurate results will not occur?*

As written, this is an unattainable goal since inaccurate results are obtained by all methods regardless of the user's level of expertise. It should probably be rewritten as "A waived test should be so accurate that when performed by untrained users, the likelihood of obtaining an inaccurate result is not significantly different from that obtained when performed by trained users."

- B. *Should a waived test have variable accuracy if used adjunctively; is it acceptable to waive tests that have inaccurate results but do not have any major negative clinical impact? How should FDA make this assessment?*

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. This would require medical expertise and would best be accomplished by a panel of at least three physicians with expertise in the area applicable to the test.

3. *What criteria should FDA use in determining that a test will "pose no unreasonable risk of harm to the patient if performed incorrectly?"*

See 2.B.

4. *Should the waiver process be different for screening tests that require a second test for confirmation? Since there are no CLIA standards for performance of waived testing, except instructions to follow the manufacturer's package insert, what is the assurance that confirmatory testing will be performed? Should the need for confirmatory testing raise, lower, or have no impact on the threshold for a waiver decision?*

Since waived testing is not under CLIA regulation, it is less likely that the untrained user will seek a confirmatory test to verify the results of a screening

test. The need for confirmatory testing should raise the threshold for a waiver decision.

Specific Questions for Public Input

5. *Should accuracy be determined using comparison of the waive[d] test to a well-characterized reference method and/or materials, to a designated comparative method and/or materials, to a working laboratory method and/or materials, to a clinical algorithm for diagnosis, and/or to other endpoints?*

Two types of accuracy should be assessed -- analytical and clinical. Analytical accuracy should be determined 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 should also be subjected to proficiency testing and demonstrate acceptable performance.

Clinical accuracy should be determined by comparing test results to clinical outcomes as established by a well accepted clinical algorithm.

6. *How many samples, what types of samples (real or artificial) by how many users and how many sites are appropriate to evaluate accuracy? (Current guidelines being followed by FDA are for performance to be demonstrated by laboratory users at a minimum of one site.)*

Accuracy should be established by using at least 40 patient samples performed by as many users as are available at a minimum of three sites.

7. *What should be the background of these users?*

The users of the test to be evaluated should be representative of the population to which the test will be marketed. Users of the comparative method should be trained laboratory personnel.

8. *What performance criteria (statistical or clinical) should FDA apply to the accuracy threshold for a waived test (e.g., t-test or McNemar test at key decision points, description of performance with confidence intervals at key decision points, use of set performance standards using a receiver operator curve -- 80%, 90%, 95%, or other -- at key decision points, and/or others)?*

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. Qualitative methods should be evaluated by agreement to an accepted

reference of comparative method. Discrepant values should be evaluated based on clinical outcomes.

Clinical accuracy should be determined by comparing test results to clinical outcomes as established by a well accepted clinical algorithm.

9. *How should FDA define precision for purposes of waiver determination, what types of samples, how many and what types of operators/sites are appropriate? Current CDC recommendation is for 20 samples at three levels representing appropriate decision points to be tested at three sites by lay users using materials in either artificial and/or real matrices depending on availability and biohazard issues.*

The current CDC recommendation is acceptable, however the materials used should be limited to actual samples for which the test is intended.

10. *What performance thresholds should FDA use to determine whether the precision studies are appropriate for waiver status (e.g., ANOVA analysis, use of predefined performance goals such as Tonks' formula, or percent agreement out of total repeat runs)?*

Precision performance thresholds should be based on predefined performance goals such as Tonks' formula or any other suitable formula as accepted by the clinical scientific community.

11. *What interference studies are appropriate to establish performance of waived tests (e.g., effects of hemolysis, lipemia, etc.)?*

Interference studies should include those interferents which will be commonly encountered 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.

12. *What environmental studies or flex (stress) studies are appropriate to establish performance of waived tests (e.g., temperature or humidity stresses, short fills)?*

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.

13. *What additional studies (if any) should be submitted for evaluation of qualitative tests for waiver?*

None.

14. *What additional studies (if any) should be submitted for evaluation of quantitative tests for waiver?*

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.

AAB appreciates the opportunity to comment on the issues posed in the July 21, 2000, *Federal Register* and to participate in the August 14-15 public workshop.

Sincerely yours,

John Boffa, B.S., HCLD
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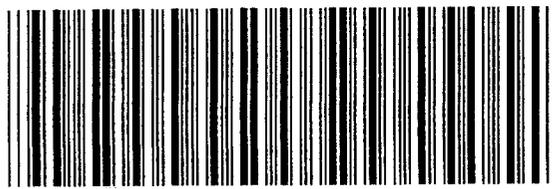
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