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



Re: Docket No. 00N-1394 – CLIA Waiver Criteria

Dear Sir or Madam:

These comments are submitted by the Advanced Medical Technology Association (AdvaMed), formerly the Health Industry Manufacturers Association, in response to FDA's queries regarding issues related to the criteria and process the agency should use to determine whether a particular test is waived. AdvaMed is a Washington D.C. based trade association and the largest medical technology association in the world. AdvaMed represents more than 800 manufacturers of medical devices, diagnostic products, and medical information systems. AdvaMed's members manufacture more than 90 percent of the \$68 billion of health care technology products purchased annually in the United States, and more than 50 percent of the 159 billion purchased annually in the world. Although a very small percentage of products fall under CLIA Waiver criteria or will, our members have an intense interest in CLIA as it impacts the development and use of their products and the potential positive benefit of these products on public health.

On July 21, 2000, the FDA published the above referenced document and requested responses to a series of questions. These comments supplement the comments made at FDA's August 14-15, 2000 Public Workshop. For convenience of the readers, the questions have been transcribed.

General Questions

- 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?" For example:**
 - 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? This requires availability of well-characterized reference methods and/or materials as part of the waived test assessment. The current threshold for waiver as established by CDC is no significant inaccuracy and no significant imprecision.**

Response: Every aspect of the CLIA debate, drafting and subsequent rulemaking makes it clear that Congressional intent is that CLIA regulates laboratories, not medical devices. For purposes of categorization for waiver status, this means that CLIA implementation should assure that personnel without formal laboratory training who run tests in waived laboratories can

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produce the same test results as a trained laboratorian using the same test. Such a comparative result should be the baseline qualification for waiver categorization. The risk of consequences must be negligible when performed by either party to have the test meet the "safety and effectiveness" standard of FDA clearance. Therefore, if the product is 510(k)-cleared and an untrained person can perform it with the same success as a trained person, the safety and effectiveness are the same. Congress did not intend that a "clinical or statistical error when compared to a measure of truth" be an entry criterion for waiver categorization. The concept of a reference method comparison to prove accuracy under CLIA is a recent and inappropriate proposal, and should be replaced with the operator or user performance accuracy comparison as the proof.

- 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? This requires comparison of the test in a lay-user setting with performance of the test in a CLIA-certified lab by a trained user. The threshold for waiver would be no difference in performance in the two settings.**

Response: Demonstration of the test in a controlled setting of users with no formal laboratory training or users with formal laboratory training should show very low error rates. It is possible for errors to occur regardless of the skill level of the user, but as long as the rate is low, this is tolerable.

We note that certain specific products were originally listed as waived. Some errors can occur with some of the listed technologies. Therefore, it is clear that the intent of the Act and original regulation is not to waive only devices that provide perfect results all the time. Instead, the public health was and is served by expecting a low error rate by users and for the regulating agencies to recognize the public health benefit of having timely waived tests available outside laboratories regulated by moderate or high complexity CLIA rules.

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

Response: The model should be a comparison of the performance of the test when performed by a person with no formal laboratory training to the performance of the test by a person with formal laboratory training.

- 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?"**

Response: For an in vitro diagnostic product to be cleared by the FDA for distribution in interstate commerce, it must be "safe and effective for its intended use." If persons with no formal laboratory training can use a "test that is safe and effective for its intended use" and obtain results that are comparable to test results obtained by persons with formal laboratory training, the CLIA criteria for waived status are met. FDA should keep in mind that results of waived tests are reported back to the health care professional who ordered the test. It is the responsibility of that person to interpret the test results in conjunction with the patient's other medical information.

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

Response: No, see previous response.

- 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?**

Response: The majority of diagnostic tests are adjunctive. It would be very difficult to say otherwise since most of the tests under consideration would not be used alone to make a diagnosis. For a test that is not adjunctive to be waived, there should be a weighting given to the public benefit of having access to the test via laboratories holding a Certificate of Waiver.

In regard to variable accuracy, the inherent accuracy of the test should be the same whether a laboratory professional or a person with no formal laboratory training performs it. If the results of correctly performed tests are variable as an inherent limitation of the test, the labeling should explain the limitation and any hazards this may raise. This puts all users of the test on notice in clinical decision-making.

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

Response: This is the third of three alternative routes to waived status. Because the interpretation of this provision has never been clarified, waiver petitions have generally been premised on one of the other provisions. If a petitioner chooses to use this provision, the question that must be asked is, “Does the benefit outweigh the risk as seen by the physician, not by regulators?” FDA’s public health goal under both the Food Drug and Cosmetic Act and CLIA is to inform users of potential hazards with tests, not to bar access to any test in a particular setting because that test is not “perfect” in its performance. The FDA has the ability to balance this question within the wording of the Act.

It should be up to the applicant to document the benefit and risk of a false negative or false positive. The level of documentation will depend on the test and the action taken when a test is a valid positive, valid negative, or false result.

- 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?**

Response: The need for confirmatory testing should have no impact on the waiver determination.

A laboratory that operates on a Certificate of Waiver is required to only perform waived tests and to follow manufacturers instructions for use. A laboratory that operates under a Moderately Complex Certificate can perform waived and moderately complex tests within the specialties identified on the certificate. A laboratory that operates on a High Complexity Certificate can perform waived, moderate and highly complex tests in the specialties on the certificate. Moderate and High Complexity laboratories must comply with CLIA requirements for reporting results. It is the laboratory's responsibility to inform the person ordering the test when a confirmatory test is required and how to go about getting the confirmation test performed. There is no requirement that a laboratory be authorized to perform both an initial test and a confirmatory test, or to assure that a confirmatory test is performed unless so ordered. Companies must include information in their labeling when follow-up confirmatory testing is required. Any laboratory, no matter what type of certificate it possesses, that chooses to ignore the manufacturer's recommendations, regarding confirmatory testing, is violating CLIA requirements. Enforcement of applicable CLIA requirements is not the responsibility of the FDA.

Specific Questions

- 5. Should accuracy be determined using comparison of the waiver 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?**

Response: None of the above. Accuracy should be compared between the user with no formal laboratory training and the user with formal laboratory training. If the product has been determined to be safe and effective for its intended use per the FD&C Act, the accuracy of a waived test should be the same regardless of the professional status of the user. Testing must be consistent with the 'Intended Use' of the product.

- 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.)**

Response: It is the responsibility of the manufacturer to provide valid statistical data to support the intended use and intended users of the product. Because of this, each product may have different requirements. Any data should be statistically supportable.

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

Response: Within a waived laboratory environment, the employees have varying levels of education and experience. It is appropriate to include users who represent these varying levels, including users who have no prior laboratory experience, LPNs, and RNs, for example. The manufacturer should identify the criteria used to select the participants in the use study.

- 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)?**

Response: Simply equivalence between persons with no professional laboratory training and persons with formal laboratory training. That is, statistical only. Sponsors should be allowed to choose and justify the appropriate statistical test depending upon the assay characteristics. The device's clinical sensitivity and specificity will not change by granting a waiver if persons with no formal laboratory training can perform the test with the same accuracy.

- 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 participants testing three levels representing appropriate decision points, to be tested at each of three sites by lay users using materials in either artificial and/or real matrices depending on availability and biohazard issues.**

Response: It is important to show that the precision of the assay is not significantly impacted when used by persons with no formal laboratory training at three different assay levels. Within run precision can be assessed either by having a few users run many replicates, or by having many users run a few replicates. The choice of study should be made by the sponsor and be statistically justifiable. Other variables may need to be considered in making the choice, for example, sample stability. In the case that the question assumes a quantitative result, it should be clarified that the three levels should be a low negative (not zero), a low positive, and a high positive. These three areas will be sufficient to compare the user's results.

- 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)?**

Response: This should be up to the statisticians and may be different based on the test, test format, whether it's qualitative or quantitative. The results of the statistical analysis should show that the precision is not significantly different between persons with formal laboratory training and persons with no formal laboratory training.

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

Response: None, this has been addressed as part of the premarket clearance process and is covered in the labeling.

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

Response: None, this has been addressed as part of the premarket clearance process and is

covered in the labeling.

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

Response: This was described above: low negative; low positive; and high positive.

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

Response: Same as the previous answer.

Summary

As stated in the comments above, accuracy under CLIA should be interpreted to be a comparison of results obtained between the user with no laboratory experience and the laboratory professional user. Other performance studies, for example, for precision, clinical sensitivity and specificity, etc, are already included in the FDA premarket review and they are not regulated under CLIA. Factors like the need for confirmatory testing should have no impact on a waiver determination. All laboratories, waived, moderate and high complexity, are and should be required to follow the manufacturer's instructions for use.

Thank you again for the opportunity to submit these comments.

Sincerely



Carolyn D. Jones
Associate Vice President
Technology and Regulatory Affairs