ABBOTT LABORATORIES

Corporate Regulatory and Quality Science

Douglas L. Sporn
Divisional Vice President
Corporate Regulatory Affairs
D-387, AP6C-1
Telephone: (847) 937-7986

100 Abbott Park Road
Abbott Park, Illinois 60064-6091
Facsimile: (847) 938-3106
E-mail: doug.sporn@abbott.com

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Dockets Management Branch (HFA –305)
Food and Drug Administration
5630 Fishers Lane - Room 1061
Rockville, MD 20857

RE: Guidance for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Criteria for Waiver; Draft Guidance for Industry and FDA [Docket No. 01D-0044]

Dear Sir or Madam:

Abbott Laboratories (Abbott) submits the following comments in response to the Agency's request for comments on the FDA "Guidance for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Criteria for Waiver: Draft Guidance for Industry and FDA," published in the Federal Register on March 1, 2001 at 66 FR 12939.

Abbott commends FDA on providing a guidance document that is flexible in its approach for obtaining waiver status. We recognize that FDA's adoption of criteria that allow comparison between the trained and untrained users is controversial. We agree that this approach is consistent with the CLIA statute requiring criteria that focus on test performance by the user. In addition, we strongly believe that this approach is consistent with the original intent of waived tests, which is to provide access to testing in non-clinical laboratory settings by non-laboratorians.

The draft guidance document clearly outlines an alternative approach to obtaining wavier status; we believe that FDA must also clearly address the public perception that the waiver review process is an isolated event. If not addressed, such a perception will generate comments on this document that recommend additional testing, labeling, etc. that is duplicative of the 510(k)/PMA submission. Adding additional language to the draft guidance to highlight the fact that these tests have been evaluated and shown to be appropriate for marketing would clarify this issue.

Comments on specific areas of the guidance document follow in the order in which they appear in the guidance document. Underlined text is used to indicate proposed text insertions to the guidance document.

01D-0044 C17

1. Section I, Introduction step 1, page 3

The document states, "whenever possible, sample(s) of the test system should be included with your request for waiver..." Please clarify that the intent of this item recognizes that it is not always practical for manufacturers to send samples, and that in such cases FDA would not expect sample(s) of the test system. For example, it is not practical for manufacturers of systems that include a permanent component (i.e., small instrument) with disposable units (cassettes, cartridges, and strips) to provide sample(s) test systems.

2. Section I, Introduction, page 4

Clarify FDA's definition of the term "untrained user." When this definition is considered alongside the definition of "laboratory professional" there is a gray area that is not addressed. This area includes anticipated device users who may have had some exposure to laboratory testing or, for example, anticipated users could include nurses who have had laboratory courses. Additionally, the definition of "untrained user" is not entirely consistent with the recommendation in Section IV, under Demographic Data (page 10), to enroll in the studies individuals who represent anticipated users. Therefore, we suggest defining "untrained user" as a study participant who has not had formal laboratory training or specific experience in clinical laboratory testing and who represents the anticipated users of the device.

3. Section I, Introduction, page 4

We suggest modifying the definition of laboratory professional to "an individual who meets the qualification to perform moderate or high complexity testing, as indicated in the CLIA regulation, for example a medical technologist (MT) or medical laboratory technician (MLT)." This modification provides a more concise definition of a trained individual and allows broader discretion in the selection of professionals when selecting study sites.

4. Section II, Demonstrating Simple, page 4

Delete "uses direct unprocessed specimens" from the list of characteristics of a simple test. In defining "laboratory," under CLIA regulation 42 CFR § 493.2, facilities "only collecting or ***preparing*** specimens" (emphasis added) are specifically exempted from the definition of laboratory. This indicates that activities such as drawing and spinning down a specimen were not considered a difficult task. Therefore, specimen processing should not be used in defining a simple test.

5. Section II, Demonstrating Simple, page 4

Modify the seventh bullet point by adding "requires no electrical or mechanical maintenance beyond simple cleaning, changing of batteries, setting of codes, checking the screen, etc." The requirement is very general and thus excludes general maintenance procedures. The addition of examples will clarify FDA's intent.

6. Section II, Demonstrating Simple, page 5

Modify the eighth bullet point by adding, "produces a direct readout of result that requires no user calibration, interpretation, or calculations." This addition clarifies that it is not the intent of the document to indicate that a test cannot be waived, if it includes calibration, but rather it is

intended that the calibration should not be one that requires the user to manually adjust the test system (i.e., the user does not control the calibration parameters).

7. Section III, Demonstrating Insignificant Risk of Erroneous Result, page 5

We suggest the following modification; "waived test systems should contain failure alert mechanisms, which preferably produce no result when a test system malfunctions." This allows for the circumstances in which it is better for the user to receive a result with a warning to alert the patient/user (e.g., it may be useful for a diabetic to receive information that the glucose result is above or below the linear range of the assay rather than no result appearing at all).

8. Section III, Demonstrating Insignificant Risk of Erroneous Result, page 6, ¶ 2

We recommend modifying the second sentence to read, "first, conduct a hazard analysis to identify potential test system failures by the untrained user. " This modification is consistent with the CLIA statute to focus on test performance "by the user," rather than inherent device performance.

9. Section III, Demonstrating Insignificant Risk of Erroneous Result, page 6, ¶ 2

Modify the last sentence by replacing "validated" with "verified" to read, "results of stress testing should be clearly described in your request for waiver, and the necessity of recommended QC to address system failures should be verified." Having to verify the mitigation of a certain hazard is reasonable to expect. However, having to validate mitigations in customer sites would be difficult if not impossible, since it would be necessary to artificially induce most of the failures in order to test the mechanism of protection against the failure. We also recommend replacing the term validated with verified in subsequent areas in this section for clarity and consistency.

10. Section III, Demonstrating Insignificant Risk of Erroneous Result, page 9, ¶ 2

We suggest the following revision to the last sentence of the paragraph, "the calibration of the system should be traceable to a higher order internationally recognized reference material and/or method whenever possible." Calibration materials, not quality control materials, should be traceable to a higher order material or method when available. However, it is often necessary for a manufacturer to develop calibration and QC material that function only with the specific test for which it was designed.

11. Section III, Demonstrating Insignificant Risk of Erroneous Result, page 9, ¶ 3

We request deletion of this paragraph because matrix and QC materials will have already been considered in the premarket notification or preapproval application. It should not be necessary to duplicate this information.

12. Section III. Demonstrating Insignificant Risk of Erroneous Result, page 9 last ¶

In the last sentence of the last paragraph, delete the word "consecutive" when describing the three lots. The use of "consecutive" lots appears arbitrary with no apparent clinical value.

13. Section IV, Demonstrating Accurate, page 10, ¶ 1 and pages 11-13

We recommend deleting the requirement to conduct a precision study and the subsequent precision study protocol. Only an agreement study is needed. Precision testing is included as part of the premarket notification or preapproval application. Conducting an additional study does not add value to the analysis of showing accuracy or comparability between an untrained user and a professional.

14. Section IV, Demonstrating Accurate, page 10, ¶ 4

We recommend modifying the "instructions for use section" as follows, "you should provide the untrained users with any training materials routinely included with the purchase of the test system. Untrained users should receive no additional training, coaching, prompting or written or verbal instructions beyond what is routinely provided." Manufacturers often include several types of training materials: manuals, package inserts, quick reference instructions and videos. It is not representative of actual use to provide the untrained user with only the written test procedure when other materials would be routinely available.

15. Section IV, Demonstrating Accurate, page 13, ¶ 4

Under the untrained/professional agreement study for quantitative tests, we recommend replacing the use of "300 matrix-specific specimens" with "a number of matrix-specific specimens that reflects a statistically valid number and appropriate levels." The requirement for 300 specimens seems arbitrary and excessive. The number of samples and levels should be part of the study design and should be statistically justified.

16. Section IV, Demonstrating Accurate, pages 13-14

Requiring 300 untrained users and 3 professionals for the study is arbitrary and may not be statistically valid in all situations. Rather than defining a specific study in the guidance document, we suggest the manufacturer determine the appropriate statistics and study protocol that is statistically justified.

17. Section IV, Demonstrating Accurate, page 14

Under the "performance target for quantitative test," we suggest stating the results from the untrained users should be compared to the professionals by using a valid statistical method, for example Deming regression and analysis of differences. Although the Deming regression may be useful in some circumstances, its use should not be required.

18. Section IV, Demonstrating Accurate, page 15-16

Tables 4, 5 and 6 should be deleted and the instructions replaced with a statement that the "manufacturer is responsible for setting up statistically valid protocols showing adequate agreement between the untrained and the professional user."

19. Section IV, Demonstrating Accurate, page 16

Under "performance target for qualitative tests," we recommend replacing the second sentence as follows: "As a suggestion, the manufacturer may apply logistic regression, which estimates positivity probability as a function of a continuous output (concentration)." Such an approach will make use of all the specimen data, including the 100 samples (strong negatives and strong positives) not formally evaluated.

20. Section V, Waiver Labeling, page 17

We recommend updating the instructions for writing Quick Reference Instructions from a 7th grade reading level to an 8th grade reading level, so the CLIA guidance is consistent with appendix A of FDA's recently released guidance document "Guidance on Medical Device Patient Labeling" (66 FR 20149, April 19, 2001).

21. Section V, Waiver Labeling, page 17

We agree that Quick Reference Instructions are appropriate for waived tests. However, we are concerned that much of the information will duplicate that contained in the package insert, and that too much information will negate the purpose of the Quick Reference Instructions. We suggest modifying the elements contained in the Quick Reference Guide to: 1) warning to read the test procedure first, 2) warnings and limitations, 3) safety considerations on safe test operation that particularly apply to untrained users, 4) step-by-step operating instructions that include instructions for reading/reporting results, and 5) storage of reagents and control materials.

22. Section V, Waiver Labeling, page 19, ¶ 2

We recommend deleting the following sentence, "FDA recommends that quality control instructions be based on data generated through actual field studies of each device." This statement is inconsistent with earlier requirements to verify the use of quality control in conjunction with the hazard analysis. In the hazard analysis, the manufacturer determines the failure modes that are mitigated by quality control and subsequently verifies such mitigation.

23. Section V, Waiver Labeling, page 19, ¶ 2

We recommend replacing the current text describing how to address quality control instructions in the absence of data with the following, "the manufacturer, using the hazard analysis, should provide recommendations to the user for quality control testing." In conducting a hazard analysis the manufacturer determines the failure modes that are mitigated by quality control and subsequently verifies such mitigation. The frequency of control testing is then tied to this verification.

24. Section VI, Voluntary Safeguards for Waived Tests, page 20

We recommend deleting item number two, which references FDA's MedWatch program. It is not appropriate to require a description of the MedWatch program and telephone number in the package insert. This not a labeling requirement nor is it requested for either moderately or highly complex tests. Furthermore, it is not an element in FDA's recently released guidance document "Guidance on Medical Device Patient Labeling" (66 FR 20149, April 19, 2001).

25. Section VI, Voluntary Safeguards for Waived Tests, page 21

We recommend deleting item number three, which references a surveillance plan. Product surveillance (maintaining complaint files) is a Quality Systems requirement. Manufacturers monitor product function in the field through these complaints. These data become part of the Corrective and Preventive Action system as required by 21 CFR § 820.100, and are available to FDA during inspections. Additionally, this level of oversight not only far exceeds Congressional

intent for waived tests; it also exceeds the oversight imposed on moderate and high complexity tests.

26. Section VI, Voluntary Safeguards for Waived Tests, page 20

We recommend deleting item number four, which references analyses of surveillance data as a 510(k) add-to-file or PMA annual report item. This item is overly burdensome for both FDA and industry with no apparent patient benefit. A number of mechanisms currently exist, which eliminate the need for additional surveillance and annual submission of data analyses.

The following examples are illustrative:

a. Medical Device Reporting (MDR) requirements (21 CFR § 803),
b. Correction & Removal requirements (21 CFR § 806)
c. FDA mandatory recall authority (21 CFR § 810)
d. Complaint handling (21 CFR § 820.198).

In addition, some of the listed elements are duplicative of other systems or difficult, if not impossible, to obtain. For example, common errors (bullet point 3) are captured through complaint handling. Real world (field) QC results of the device in use (bullet point 4) becomes complicated because many products are sold through distribution making it almost impossible for the manufacturer to obtain such information. Proficiency testing (bullet point 5) is not required for waived tests. Design control information (bullet point 6) occurs prior to market launch. Subsequent product changes are evaluated for impact to the product premarket notification or premarket approval applications, and submitted to FDA as needed. We are concerned with the overly burdensome task of providing all published reports associated with the device (bullet point 7) especially when the purpose of this item is unclear and imposes substantial time on both FDA and industry. For these reasons, we request deletion of item four, which requires the submission of 510(k) add-to-file reports and PMA annual report items.

27. We recommend updating the waiver checklists contained in appendices A and B to reflect the comments above.

In closing, the effort FDA has put into developing this guidance document is commendable. As FDA considers the comments on the guidance document it is important to focus on the CLIA statute and its requirements for waiver. If the guidance document is to serve as the basis of the Final Rule on waiver criteria, FDA must also consider the impact of unnecessary additional requirements on innovation in IVD testing. It is also extremely important that FDA work with its stakeholders to adapt the waiver criteria to new technologies that are yet to be developed.

Thank you for the opportunity to provide these comments and for your consideration of our comments. Should you have any questions, please contact April Veoukas at (847) 937-8197 or by facsimile at (847) 938-3106.

Sincerely,

Douglas L. Sporn
Divisional Vice President
Corporate Regulatory Affairs, Abbott Laboratories

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