



**Medical Products Group**

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

**RE:** *Draft Guidance for Industry and FDA Staff: Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Application [Docket 2001D-0044]*

Dear Sir or Madam:

Abbott Laboratories submits the following comments regarding FDA draft guidance document "Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Application," published in the Federal Register on September 7, 2005 at 70 FR 53231.

Abbott submitted comments on the previous draft guidance issued on March 1, 2001, and we appreciate the opportunity to provide these comments on the revised draft guidance document. Generally, we are pleased with the guidance FDA has provided to demonstrate that tests are "simple" and have "an insignificant risk of an erroneous result." Our comments on specific sections of the guidance document follow in the order in which they appear in the guidance document.

1. Section II, Demonstrating "Simple," pages 7-8

Abbott agrees with the agency's identification of the characteristics of a simple test. We would, however, appreciate FDA confirmation that the second bulleted item listing specimen types is intended as a list of examples, and not an all-inclusive list. The guidance lists the characteristic as "uses direct unprocessed specimens," and then proceeds to list specific specimen types. It is our understanding that other direct unprocessed specimens, such as arterial whole blood, would also meet the characteristic, "uses direct unprocessed specimens."

2. Section II, Demonstrating "Simple," page 8 (Footnote 2)

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We are pleased that FDA has adopted the term "intended user," as opposed to "untrained user" as initially proposed in the draft 2001 guidance document, and modified the definition to reflect anticipated users of the test system.

3. Section II, Demonstrating "Simple," page 9

We appreciate that the current draft guidance document has clarified when FDA would expect to see device samples.

4. Section III, Demonstrating "Insignificant Risk of an Erroneous Result" – Failure Alerts and Fail-Safe Mechanisms, pages 9-15

Generally, we are pleased with the guidance that FDA has provided to demonstrate that a test system has appropriate fail-safe and failure alert mechanisms. Further, we are pleased to see FDA's recommendation to use a hazard (risk) analysis in accordance with ISO 14971, flex studies, identification of mitigation measures, and the use of studies to test the mitigations. Although the document specifies validation studies as the mechanism to test mitigations, for the reasons described in the following paragraphs, we recommend replacing "validation" with "validation and/or verification" throughout section III to reflect that certain mitigation measures may be effectively studied through verification studies.

We note that, in accordance with ISO 14971, risk control measures are verified as to their implementation and verified as to their ability to mitigate the severity or probability of occurrence of the risk. Verification of the risk mitigation can take place as a verification study (i.e., meeting requirements) or a validation study (i.e., meeting user needs and intended uses). Thus, ISO 14971:2000 allows for the use of verification or validation studies to mitigate identified risks.

Further, we recognize that the term "flex studies," described under Tier 1 of the document, could be considered verification or characterization of a product's ability to meet requirements. Design verification, however, can also be used effectively to show that risk mitigation has occurred.

This is especially true when the controls are imbedded into the design of the product, and only through working outside the normal range of user conditions, can the errors be produced or seen. For example, results outside of the reportable range are flagged. To test this fail-safe measure, an artificially created specimen must be used. It is not related to the user's interface, but more to the specimen concentration, therefore verification is appropriate.

In summary, we note that validation studies are appropriate to address measures associated with how the user interacts with the test system. However, not all mitigation measures can or should be addressed through validation studies, and that for certain mitigation measures verification studies are appropriate to test the mitigation. Thus, we recommend replacing "validation" with "validation and/or verification" throughout section III to reflect the use of verification studies.

5. Section III, Demonstrating "Insignificant Risk of an Erroneous Result" – Failure Alerts and Fail-Safe Mechanisms, pages 13-14



Under the section “External control materials,” we recommend deleting the statement “[t]he control material should be traceable to a reference material whenever possible.” Controls are designed to ensure the test system behaves in a predictable manner, allowing the user to assess that the test system is functioning properly. It is important for calibrators, not controls, to be traceable to a reference material as they are responsible for the accuracy of the assay, while the controls are used to determine systematic errors of the entire analytical process. Thus, traceability to a reference material is not necessary for controls to function properly.

6. Demonstrating Insignificant Risk of an Erroneous Result – Accuracy page 16

Under “Clinical Study Sites and Participants” - Instructions for use the guidance document states:

You should provide the intended operators who participate in the study with only the proposed package insert and/or Quick Reference Instructions. Study participants should receive no training, coaching prompting, or written or verbal instructions beyond the written test procedure.

This statement appears to be in conflict with the overall intent of the clinical study, which is to “evaluate test performance in a setting designed to *replicate, as closely as possible, the actual intended clinical use setting* (emphasis added).”

Rather than restricting the intended operators to the proposed package insert and/or Quick Reference Instructions, which does not reflect the actual intended clinical use setting, we recommend modifying the guidance document to reflect the lowest level of training materials that the manufacturer intends to provide to the intended operators in the intended clinical use setting when the product is marketed. For example, if the manufacturer plans to provide intended operators with a user guide, training manual, video, customer phone number, and/or other materials, the intended operators should receive these materials as part of the clinical study to replicate as closely as possible, the actual intended clinical use setting.

7. Section IV, Demonstrating Insignificant Risk of an Erroneous Result – Accuracy page 19

In the section “Selection of the Comparative Method (CM), we are pleased to see that FDA, consistent with its least burdensome approach to regulations, is willing to discuss with a manufacturer alternative comparative methods, and has not limited the comparative methods to those described as CM of type A and B.

8. Section IV, Demonstrating Insignificant Risk of an Erroneous Result – Accuracy pages 19-20

We have the following comments regarding the section specimen collection and sample preparation:



- Because the use of a minimum of 360 specimens at a minimum of 3 clinical sites, with a minimum of 9 operators provides for robust testing conditions we question the need for additional limitations on the study, specifically obtaining specimens from consecutive patients over a specified time frame of two to four weeks, and recommend deleting these two items from the guidance. Obtaining samples from consecutive patients presents a host of issues, such as patient will not consent or insufficient specimen volume, requiring extensive documentation to explain each instance when consecutive patient specimens were not collected. Additionally, given the number of samples, users, and sites, a two to four week collection time frame seems unnecessary.
- To allow for situations in which there is statistical rationale for testing less than 360 specimens we recommend the guidance include a statement recommending consultation with FDA to discuss the use of fewer specimens.
- Rather than obtaining 360 patient specimens that span the measuring range of the device, we recommend the manufacturer obtain 360 patient specimens that span the range expected at the intended use sites. As part of the submission clearance/approval process, the manufacturer will have already studied specimens that span the measuring range of the device. Rather than repeat a study that is already part of the clearance/approval process, we recommend focusing on the intended use site.

9. Section IV, Demonstrating Insignificant Risk of an Erroneous Result – Accuracy page 24

For analytes that have existing performance limits for professional use, we agree with the approach outlined in the guidance document in regards to how to use these limits to establish Allowable Total Error (ATE).

10. Safeguards for Waived Tests page 32

We recommend deleting the following statement, “[w]e recommend manufacturers also notify CMS when device failures are reported.” As noted in the previous sentence, adverse events are to be reported in accordance with the MDR regulations. Thus, such information will have already been reported to the FDA, and the need to report duplicative information to an additional Health and Human Services (HHS) agency is unclear. Additionally, there is no process for reporting such information to CMS.

Should you have any questions, please contact me at (847) 937-8197 or by facsimile at (847) 938-4422.

Sincerely,

April Veoukas, J.D.  
Director, Regulatory Affairs  
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Abbott Laboratories