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May 10, 2001

Dockets Management Branch
Division of Management Systems and Policy
Office of Human Resources and Management Services
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852

Docket Number: 1147

Dear Sir or Madam:

Please find enclosed comments on the proposed draft guidance document " Guidance for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Criteria for Waiver; Draft Guidance for Industry and FDA Applications.

Introduction:

Page 3. Step 1. While it may be practical for manufacturers of single-use devices to send samples of their devices to the FDA as part of the waiver petition, it is not practical for manufacturers of systems that include a permanent component (i.e., small instrument) with disposable units (cassettes, cartridges, strips) to likewise comply. This request creates a two-tiered system that is subject to criticism.

Page 4. Terms used in this document. It may be useful to expand the definition of Laboratory professional to include R&D scientists.

1 Page 4. Untrained user vs intended user.
The term untrained user is technically inaccurate. They are really minimally trained. This user should refer to a study participant that represents the intended user of the device under study.

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III. Demonstrating "Insignificant risk of erroneous result":

Page 9. Second complete paragraph. The document states that QC material should be traceable to a reference material whenever possible. Many companies have needed to develop their own QC material that functions only with the specific test it was designed for. This is especially true for systems that use a whole blood matrix. The value of external QC is to confirm that the test system is performing within specifications. What is the value of tracing the control material to a reference preparation?

IV. Demonstrating "Accurate":

Page 11. First paragraph. The suggestion that day-to-day variability should be assessed by one untrained/trained paired test per day is totally impractical. This study would require 60 days to perform. Since each of the three sites will likely perform the testing on separate days, the study design already has day-to-day variability built in.

Page 12. Table 2. Within run precision cannot be calculated for the untrained users since they will only be performing a single test for each of the "A", "B" and "C" samples. The table should be redesigned to clearly identify which components of total estimate of precision are germane for untrained users and professionals, respectively.

Page 14. "Untrained/Professional Agreement Study for Quantitative tests. Instead of accepting the arbitrary number of 300 matrix-specific specimens for use in the Agreement study, a statistician should calculate the minimum number of samples that are required to reach statistical significance and then recommend that that number replace the arbitrary number of 300 samples. Alternatively, the manufacturer should recommend the appropriate sample size based on a statistically valid approach.

Page 14. Table 3. In some instances more than three professionals could be used in the testing. The table should be modified to say "at least three" professional testers.

Page 14. "Performance Target for Quantitative Tests". Are all of these statistics useful?

Page 14. Next to last paragraph. Either a definition (and equation) for "95% tolerance interval for 95% of the distribution of the differences" should be included or the calculation should be eliminated.

V. Waiver Labeling:

Page 17. Quick Reference Instructions. The quick reference instructions should be a "cheat sheet" that a user can refer to without going back to either the package insert or operator manual. The proposed components of the quick reference instructions are too detailed and too many. It effectively recapitulates the package insert. If it is not easy and quick to refer to, then the operator will not use it and it fails in its purpose. Items that would not be appropriate for the quick reference instructions would include: maintenance, QC frequency, acceptable ranges for QC, calibration procedures, and troubleshooting and clinical interpretation. (Perhaps it would be enlightening to ask users what information would be most valuable and useful to them).

Page 19. Quality Control Labeling Recommendations. What value is added by requiring that QC testing should be performed by each new operator (with the definition as an individual that has not performed the test within the past two weeks)? Since there is a requirement for waiver to satisfactorily perform the Untrained/Professional Agreement Study without ever been trained on the test, what value does this requirement add?

VI. Voluntary Safeguards for Waived Tests.

Page 20. General. This section is a thinly veiled attempt to get IVD Manufacturers to address the issues identified by the HCFA study of waived labs that was presented at the August 2000 Public Workshop on CLIA waived tests. It is arguable if it is the manufacturers responsibility to perform surveillance of their customers - - that is the job of the HCFA inspectors or the state authorities.

Page 20. Number 2. It is not appropriate to add a brief description of the MedWatch medical products reporting program and telephone number on the package insert. This is not a requirement for labeling for either moderate or highly complex tests where the likelihood of failure may have significantly greater adverse impact to the patient. To require only waived tests to comply with this request inappropriately singles out waived tests.

Page 20. Number 3. The described surveillance plan adds significant cost to the marketing of waived tests and it is arguable that it would be unworkable. Further, what is the benefit? All these issues were addressed via the original 510(k) clinical studies or the CLIA waiver studies. Explicit on-going surveillance is not a manufacturer's responsibility for moderate and high-complexity tests, and it should not be for waived tests.

Page 21. Number 4. An annual submission of an analysis of the results of the surveillance plan as an add-to-file to the 510(k) added cost and would be burdensome to manufacturers. If the intent is to insert into a file without any review then it has little or no value to either the manufacturer or the FDA. Again, you are suggesting a 2-tiered arrangement between waived tests and nonwaived tests. What is more bewildering, is that now waived tests would be regulated more stringently than nonwaived tests.

The proposed draft guidance document in its current form makes an erroneous presumption; namely, that every product submitted to the FDA for consideration for waived status is a new stand-alone product. The current document does not make any mention of how the FDA should consider Add-On Tests to currently waived test systems. Since CLIA waiver studies evaluate user technique and compliance with procedural steps, what is the value to the manufacturer, the FDA or the intended user of repeating user studies where the procedural steps do not change from analyte to analyte? It would seem to be of little use to any of the stakeholders since it adds no new useful information and is burdensome to the manufacturer.

A reasonable approach to this problem is for the FDA and the manufacturer to jointly develop a set of criteria unique to the Add On test under consideration that uses the guidance document as a check list. Information for certain sections could be referenced from previous petitions. Critical studies would be defined and agreed upon. For example, if a new test is added to a waived test system that is the same as the previously waived system except for a different chemistry, then Section II." Simple" is addressed by the previous submission(s) and there is no value or need to re-address the subject in the new submission. Similarly, under the example above, the hazard analysis would be identical and that part of Section III. "Demonstrating Insignificant Risk of an Erroneous Result" would not change and could therefore be referenced to the original waiver petition.

Studies that should be submitted would address specific issues from the Hazard Analysis. For example, any identified operator dependent source of error should be specifically addressed in a petition for an Add-On test. Also data should be included (if it had not been submitted as part of the 510(k)) to address Quality Control material, open and closed vial stability, as well as lot to lot variability of the QC material.

The key studies that a petition for an Add-On test should focus on are in Section IV. "Demonstrating Accurate". In this section, the key study is the Untrained vs Professional Agreement Study and an appropriately designed and mutually agreed upon study should be submitted. It is not so clear that the precision study is of value since:

a. Precision data is available from the 510(k).
b. In specific test systems, the only operator dependent source of imprecision is the addition of sample to the device; all other sources of imprecision are beyond

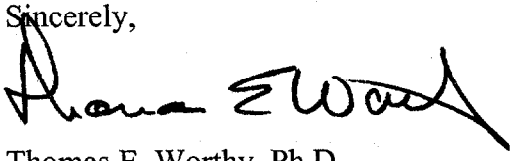
the control or influence of the operator. In this case, addressing the operator dependent source of imprecision via Section III - Hazard Analysis addresses the issue of precision.

c. The Untrained vs Professional Agreement study also generates data relative to precision. For example, if that data is analyzed with a two-tailed T test and it passes the test for not significantly different, then the untrained and Professional participants have been shown to perform the test with equivalent precision since the T test is comparing replicate values of samples.

The remaining sections dealing with labeling, etc., would be germane to all submissions.

Please contact me at (510) 293-8002 or by email at tworthy@Cholestech.com if you have any questions or would like clarification of any of the points raised in this letter. Thank you for the opportunity to provide comment on this important document.

Sincerely,



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