



December 5, 2005

**RE: COMMENTS ON FDA DRAFT GUIDANCE FOR INDUSTRY AND FDA
STAFF: RECOMMENDATIONS FOR CLINICAL LABORATORY
IMPROVEMENT AMENDMENTS OF 1988 (CLIA) WAIVER APPLICATIONS**

Cholestech appreciates the considerable effort the Agencies have dedicated to creating the draft guidance document. We are pleased the Agencies are reevaluating and clarifying the expectations for CLIA waiver applications; however, we have several serious concerns with the draft guidance.

CLIA waiver is an important part of improving the delivery of healthcare. Almost all waived testing (93%) occurs in physicians' offices. CLIA waiver of diagnostic tests puts the test in the physician's office where the patient gets the results and lifestyle counseling and or drug therapy as appropriate. CLIA waiver is a very effective means of ensuring that testing is conducted and used to aide the physician in timely diagnosis and treatment of patients.

Medicare claims demonstrate the underutilization of approved, necessary testing when patient testing is referred to traditional moderately complex test sites. For example, Medicare reimbursed lipid testing only increased 11% in the moderately complex labs from 2001 to 2003 versus a 51% increase in the CLIA waived physician office lab for the same period.

Unfortunately, several aspects of the draft guidance would be so burdensome that many tests, particularly the innovative tests developed by smaller firms such as Cholestech, would never make it to market. While we believe it is the Agency's intent to clarify and improve the CLIA waiver application process, we fear that this draft guidance imposes greater requirements, far beyond Congress' intent, at great expense both to the developer/manufacturer and to the detriment of public health.

Of greatest concern are the expanded clinical study requirements and the concomitant manufacturer responsibility to develop allowable total error models. It appears that the objective of the studies in the draft guidance is to demonstrate inherent performance characteristics which have already been demonstrated via the pre-market clearance process. These requirements are not just redundant, they exceed those required for pre-market clearance or approval.

We concur with the direction Congress gave the Agency in 1997 – the CLIA waiver application is not to demonstrate the product's inherent performance characteristics. Rather, the objective of the CLIA waiver study should be to demonstrate that the waived user can operate the test in accordance with the product instructions for use.



Fortunately, the more onerous clinical study requirements in this draft guidance document were not in place when existing lipid tests became CLIA waived. If they had been, small firms, such as Cholestech, would not be able to provide these tests to the physician's office lab. Would public health be better served by removing lipid testing from the physician's office? Would public health be better served by eliminating the smaller firms specializing in addressing the unique needs of the underserved physician office laboratories?

The following are specific comments on sections of the draft guidance.

Hazard Analysis and Risk Management

We are pleased to see the use of hazard analysis and the application of risk management based on ISO 14971:2000 – Application of Risk Management to Medical Devices.

The use of these tools in the section III, Tier 1: Hazard Analysis is apropos; however, ISO 14971 should not be limited to this section of the document. Hazard analysis and risk management should be applied throughout the CLIA waiver application process starting with the assessment of what is "simple" all the way through the clinical studies.

We recommend risk management be addressed at the beginning of the document as a guiding principle to be applied throughout the document. Examples of the application of hazard analysis and risk management can then be provided within the various sections of the document.

External Controls

Requiring the use of external controls in CLIA waived tests is a good practice and we agree this is appropriate and necessary. Rather than prescribe a set frequency for running external controls, we recommend the frequency be established independently for each product based on the risk of generating erroneous results that could negatively impact patient well being.

Laboratory Compliance Issues

It appears that the unduly burdensome clinical study requirements in the draft guidance document stem from a desire to resolve compliance issues in CLIA waived labs. The cause of the most common compliance issues will not be identified or resolved in these clinical studies, nor is that the purpose of the CLIA clinical studies.

Compliance problems exist in all types of laboratories, non-waived and waived. The purpose of the CLIA waiver clinical studies is not to prove compliance. It is to test the understandability of the manufacturer's instructions and to test whether the product's design is simple enough to produce results consistent with a moderately complex lab. The compliance issues found in CLIA waived sites are frequently found in moderately complex labs as well. Increasing the number of clinical samples nine-fold will not resolve compliance issues such as not maintaining a current version of the product instructions.

CLIA waiver Application More Burdensome than Home Use 510(k)

The clinical study requirements for a CLIA waiver application are far greater than those required to attain a CLIA waiver via a 510(k) for home use. Does this mean that professional users in the waived lab are less capable of running the test than the lay consumer? This is not logical, and is evidence that the new clinical studies section is overly burdensome and inconsistent with the Agency's current requirements for test clearance and waiver via home use. For example, most OTC (home-use) IVDs are cleared with data from 80-100 patients at each of three sites, and data requirements are not as prescriptive as those described in the current draft guidance document. Please see below for further comments regarding the number of patients needed and the data requirements to show the "goodness" of the POC test in the hands of the nontraditional operators.

Section II. Demonstrating "Simple"

We are pleased to see no significant changes here. We are concerned, however, with the use of absolute language in this section defining "simple". This language is too restrictive and unrealistic. For example:

"Needs no technical or specialized training..." Many in the industry provide operator training/overview of the new product. This training typically includes an overview of the system's troubleshooting, error codes, etc. We recommend adding a sentence: "Standard operator set/up and product orientation is permitted and may include an overview of the system's troubleshooting and error codes."

"Needs no electronic or mechanical maintenance." Strictly interpreted, this could mean the operator cannot replace a battery or power cord. We suggest replacing the word "no" with the word "minimal".

"Produces results that require no operator calibration, interpretation or calculations." Operators interpret results when discerning whether they are conducting a screening or confirmatory test. If a reagent set includes an internal standard or calibrator and the operator loads this on the instrument, does that constitute calibration and cause the device to not meet this requirement for being simple? We recommend replacing the word "no" with "minimal".

Section III. Demonstrating "Insignificant Risk of an Erroneous Result" – Failure Alerts and Fail-Safe Mechanisms

On page, 9, first paragraph in the section, last sentence, "We recommend that test system design incorporate fail-safe mechanisms whenever possible."

This does not allow for cost benefit or risk management analysis to establish reasonably achievable controls. What if a fail-safe mechanism is possible, but prohibitively expensive and it only minimally reduces what is already ranked as a low risk? The words "whenever possible" indicate the manufacturer would still be required to put this fail safe mechanism in place.



We support the use of failure alerts and fail-safe mechanisms. However, as worded, the draft guidance does not clearly allow the manufacturer to apply hazard analysis and risk management to determine when fail safe and fail-alert mechanisms are necessary. This apparent excessive reliance on Fail Safe and Fail Alert mechanisms will make products too expensive for the physician's office lab.

We encourage the use of hazard analysis and risk management to determine the extent of flex and validation studies required and to determine when fail alert or fail safe mechanisms are required. It should NOT be presumed that a fail safe or fail alert mechanism will be in place for ALL potential sources of error.

Other examples from the guidance document which should be determined on the basis of risk, not because they are written into the document:

- Lock out functions to prevent output of results if controls or system checks are not completed.
- Lock out mechanisms to prevent output of results if the device was mishandled
- Environmental monitoring mechanisms and user alert system

Section III 2. External Control Materials

In general, we support the use of external control materials; however, certain requirements in the guidance document are unrealistic and/or unnecessary.

Requiring that controls be run if an operator has not run the test in two weeks is excessive and an unnecessary expense for the user. This implies that the operator is at higher risk of not performing the test correctly if more than 2 weeks lapses between uses. By the very definition of "simple", frequent use should not be required to ensure proper operation of the test system.

Expecting controls to mimic patient samples is unrealistic, particularly when whole blood patient samples are used.

The most important aspect of controls is that they perform predictably such that operators can reliably use the control ranges to discern when the system is or is not functioning properly. Requiring the external controls be traceable is unnecessary, and not realistic.

Section IV Demonstrating Insignificant Risk of An Erroneous Result

A. Clinical Study Sites and Participants

The clinical studies section is not least burdensome, but most burdensome. The increase in the number of samples from 180 prepared samples (20 people x 3 sites x 3 samples/person) to 360 clinical (actual) samples will make clinical trials longer and more expensive. The rationale for this additional burden is not evident.

What additional increase in the protection of public health is accomplished by partitioning the clinical study data, thus increasing the number of samples to 120 per site? If the goal is to compare results in the waived user's hands to results in the moderately complex lab, there already is an established standard CLSI EP-9. Per CLSI EP-9, 40 samples are sufficient for method comparison.

The excessive number of samples required for clinical studies appears to be based on CLSI C28-A2. The standard was not intended to be used this way. CLSI C28-A2 is for establishing reference ranges and evaluating the transfer of an analyte to another instrument. This should have already been evaluated and established in the product's 510(k). The purpose of the CLIA waiver clinical study is not to establish analyte performance on a new system, but to compare results obtained by waived users compared to results obtained by moderately complex users. CLSI EP-9 is the more appropriate standard for this situation. It states that only 40 samples are required for method comparison.

Additional concerns with the increased clinical studies requirements are:

- Use of consecutive patient samples is not realistic in the physician's office lab. It will be nearly impossible to recruit representative users to participate in studies requiring 120 consecutive patient samples.
- The 510(k) already addressed product performance with patient samples. The objective of the field studies should focus on difference in tests results generated in a moderately complex lab v. the waived user. Hence, field testing in operators hands would be better controlled using prepared samples rather than patient samples.
- There is no provision for scaling the size and scope of the study. For example, if an analyte is being added to an already CLIA waived system and the new test operates in the same manner as the other CLIA waived analytes on the same system, does it really require the same extensive clinical studies as a brand new analyzer, software and first analyte on the system?

3. Performance Criteria for WM with Quantitative Results

Page 24, second paragraph, "In the cases where the allowable percent of deviation is higher than 20%, the value of %R should be adjusted downwards to 20%."

We are pleased to see the Agency move from the arbitrary application of Tonk's Allowable Limits of Error; however, rather than replace it with another arbitrary number, or require manufacturers to develop a new error model, total error should be removed. This is another example where the proposed CLIA waiver application criteria by far exceeds the pre-market clearance/approval requirements.

The draft guidance only provides one existing error model - the Clarke error grid which is only applicable for glucose tests. Does the Agency expect a manufacturer to create an error model prior to making a CLIA waiver application? This is an enormous additional

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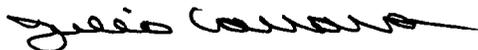
burden, and a potentially significant delay in bringing important tests to the point of care. This is particularly burdensome for smaller manufacturers, who frequently bring important and innovative products into point of care settings supporting the underserved communities.

If allowable total error remains a part of the CLIA waiver application, then risk management and medically important decision points should be applied to establish an appropriate ATE rather than this arbitrary 20% ceiling. The guidance document should describe the process for establishing models for other products.

The statistical approach appears to drive the much larger clinical trial size. Alternative models such as the use of tolerance intervals can provide the same level of confidence in the test result and bring the clinical trial size more in line with current practice.

In closing, we are encouraged by the FDA's efforts to improve the CLIA waiver application process, but feel strongly that the concerns noted above should be addressed prior to changing the process. While we cannot support the draft guidance document as written; we look forward to working with the Agency to truly improve the process and resultantly, the quality of healthcare, particularly for the underserved communities.

Sincerely,



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