

**Comments on
Draft Guidance for Industry and FDA Staff:
Recommendations for Clinical Laboratory Improvement Amendments of
1988 (CLIA) Waiver Applications**

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Dear Sir/Madam:

Having reviewed the draft document named above, I would like to make a few comments on it:

1. Precise, accurate, and error-free diagnostic test results are vital to patients and to the physicians who treat them. Medical staff, clinical laboratory professionals, and diagnostic industry personnel are very concerned with the quality of medical testing. I realize and appreciate that at the core of the draft guidance is the goal to insure quality.
2. In general, I believe it is important to remember that “waived tests” are not designed or sold for “home use.” So, while the waived tests might be simple and may be able to be preformed by very unskilled workers, the results of these tests will be reviewed by trained medical personnel—not by the patients. Certainly, the results of these tests will be combined with the overall condition of the patient in making diagnoses, as would results coming from the clinical laboratory.
3. At the '04 CLIAC Meeting, CMS described that the primary deficiency they observed for “waived tests” during their survey was lack of compliance by staff of the instructions provided by the manufacturers and/or not having the manufacturer’s instructions even available. Most of the revisions in this guidance document emphasize additional testing by the manufactures. However, that didn’t seem the primary problem when issues occurred at the sites visited by CMS. The problem was with the staff disregarding the simple instructions provided. We don’t see how the proposed revisions and extensive additional testing by manufacturers will reduce the compliance issue.
4. Currently, a significant amount of data is provided with our 510(k) submissions on our physician’s office or point-of-care medical tests. This data does not seem to be included in consideration of the quality and utility of these products.
5. Most reference methods are “manual methods” and require, essentially, “home brew” reagents. At least the manufacturers of large laboratory analyzers and their reagents possess Quality Systems to insure the quality and consistency of their products. Relying on “home brew” methods will always have quite a bit of uncertainty about them. Waived tests should provide values that correspond to the values that would be obtained in the clinical laboratory, not in the research lab. That’s the essence of the “substantially equivalent” requirements for most of these test methods.

6. Reference methods and even reference materials are not available for some analytes from any source.
7. Most reference methods are very labor-intensive and there are few sites in the United States who even do reference method testing. Studies requiring 360 patient samples done by reference methods would be impractical, if not impossible.
8. Current, CRMLN Certification of Total Cholesterol and HDL, where the reference methods are very labor-intensive, only 40 samples are required across the dynamic ranges of each. Re-certification of Total Cholesterol, completed every two years, requires only 10 samples.
9. Further, most reference methods cannot be done on whole blood. That would mean that whole blood would be tested by the proposed waived test and a separate serum tube would have to be collected to provide a sample to analyze them. This will add some level of error.
10. If one examines the results of CAP surveys or other proficiency surveys, one notices differences among even tried-and-true clinical laboratory methods. In many cases, the results have to be defined by methodology or reaction mechanism. In these surveys reference methods are not even included.
11. Many existing reference methods for serum enzymes, for instance, as described by the IFCC, are supposed to be done 30° C. However, in the United States most test methods for enzymes are done at 37°C. Enzyme measurements will never be the same at those two temperatures.
12. Currently, large mainframe clinical laboratory analyzers are not required to compare their results with “reference methods.”
13. In the environments in which waived tests would be done, for instance in a physician’s office, it will be nearly impossible to obtain samples with extremes of values to cover the dynamic ranges of most test methods. Most patients will be “normal.” For the average physician to obtain samples to cover the dynamic range will take a very long time—if ever. Spiking analytes into whole blood for “contrived” samples is not easily done and sometimes not at all feasible.
14. Waived tests must be done on unprocessed whole blood—fresh blood. In order for lab methods or reference methods to be done on them, they will have to be processed. This will have an effect on the results in correlation studies on analytes. For instance, glucose measurements on whole blood will change very quickly unless they are processed to remove the red blood cells (metabolism of the glucose while awaiting analysis) from the plasma. Many physician’s offices will not be equipped to prepare the samples to insure equality between tests on the whole blood versus plasma.
15. Who in a busy physician’s office, for instance, will coordinate this “clinical research” being done in his/her site? A clinical trial coordinator will be required on site for weeks.

16. For many simple systems that get waived, subsequent tests use identical procedures. So, if the protocol for a subsequent analyte test method is identical in every way to the original one, why would waiver applications have to started from scratch for every additional test method using that system to demonstrate that it is simple?
17. Including external quality control materials will typically not be possible for waived tests. Many analytes are not stable at room temperature or even stored 2-8° C. They must typically be supplied frozen to insure stability. Lyophilization has already been ruled out because of the requirement not to have to do precise measurements—it wouldn't be ready to use.

Please consider my comments in your review of this draft document.

Sincerely,

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