

**COMMENTS TO DRAFT GUIDANCE:
RECOMMENATIONS FOR CLIA WAIVER APPLICATIONS**

1. I am pleased to see that the technological characteristics that define waived tests (“demonstrating simple”) have not undergone a material change.
2. I am pleased that hazard analysis, already a requirement for design controls and most quality systems, can be leveraged for another purpose- CLIA waiver. The stated approach is also consistent with the manner in which CLIA waiver petitions have been handled over the past several years.
3. It is excellent to see that a sanctioned reference method is no longer mandatory; other traceability links are acceptable.
4. Page 8 of the document states that a test could not be considered simple if results need to be reported to a public health department. Is this consistent in light of the fact that an HIV test is waived?
5. I disagree with the recommendation that control material be traceable to a reference material. There is no magic in the traceability of controls, but rather it is more important that controls behave in a predictable manner. Control materials are often prepared and optimized for a variety of test systems, and that is why surrogates are commonly used. As long as the operators achieve results in the assigned control ranges when the system is functioning properly, that is all that is required.

Along these lines, there should no recommendation that the control materials mimic patient samples. For many POC waived tests, the matrix is whole blood, and we all know that control materials do not behave like whole blood. Any matrix differences between clinical samples and controls are beyond the scope of CLIA waiver.

6. It is evident that the regulators have decided to modify the paradigm for how POC devices are to be evaluated in the field studies. The original model (CDC '95) targeted the “lowest common denominator,” and therefore the POC tests underwent testing in non-technical, lay user environments. Now it is clear that the focus has switched to the intended environment (doctors’ offices), and therefore the request is that these devices are evaluated by office assistants, nurses, and related personnel.

There are philosophical pros and cons to both systems, but there must be consistency within one approach. In the “old” system, training of the testers was not allowed, and this was sound because the primary purpose of the evaluation was to see how the totally novice user would perform “cold.” Now, if we wish to mimic real life, it is unreasonable that no “training, coaching, or prompting” is allowed (Page 16), because that at is NOT representative of the end user environment. Sales representatives do not drop off test kits and/or equipment, and leave the customer unsupported. They do not do this, because doing so would be bad business. If the petition process will now require “real-life” field studies, then minimal training must be allowed.

7. RE: Operator questionnaire: This is admittedly a minor point in practice, but it is unbelievable that, after 10 years of CLIA waiver petitions, there is still a lack of understanding regarding the basic difference between POC CLIA waived testing in the office,

and home testing. On Page 17 of the Document, there is a recommendation that the questionnaire include the interpretation as to whether a test is intended as a screening test or a confirmatory test. This is relevant for home testing where result interpretation is a part of the test system, but NOT for professional use. In the office environment, the doctor orders the test, the operator performs the test and records the answer, and then delivers the result to the doctor. This is a number, or a pos/neg result, and it is beyond the scope of the operator's education, experience, or state licensure to interpret the result and make a judgment as to the nature of the test result. In fact, this recommendation is in direct conflict with the 8th bulleted point under "II. Demonstrating Simple," where it is stated, "produces results that require no operator calibration, *interpretation*, or calculations." The distinction between a screening test or a diagnostic (confirmatory) test is an interpretation.

8. Comments related to the field studies:

- What is the statistical basis for n = 120 at 3 sites (for quantitative tests)? This number seems arbitrary and not grounded in science. The document cites CLSI C28-A2 as a reference (Ref 5), but that Guideline is for establishing a reference range for a new analyte, or for transferring an existing analyte to a new system, and therefore citing CLSI C28 is a bastardization of the Guidance's intent. Reference range questions were addressed in the 510(k) for the POC device, and they have nothing to do with ease-of-use issues, nor method comparisons. CLSI EP-9, on the other hand, states that 40 samples can be sufficient for method comparison; even allowing for the need to evaluate a greater range of potential procedural errors, 360 is nine times 40.
- If actual patient samples are to be used, with comparative analyses between the POC device and the routine lab, how will sample handling for the lab be controlled? Who will decide which lab tests are the comparators? What if the three sites use different labs with different instruments- can those data be pooled?
- Even if the comparative methods problem described above can be resolved, the suggested model for field testing poses a logistical nightmare. So much so, that the canned statement of Least Burdensome on Page 7 is an embarrassment.
- Issues include:
 - The suggestion of consecutive patients over a month's time is an incredible intrusion to the doctor's office and the patients. When setting up POC IVD clinical trials for 510(k) submissions, companies work with office staff so as to be as unobtrusive as possible, and this usually requires that site study coordinators contact patients ahead of time and make the necessary arrangements. Using a random approach catches everyone off-guard, and study uptake is likely to be very low.
 - How can the office work flow be managed effectively? Who will take responsibility for approaching and consenting the patient? When will the POC testing be done in relationship to the office visit? When will the venous blood sample be drawn, and by whom? Who will process the venous blood sample and take responsibility for sending the sample to the lab? When the lab results are returned, who will be responsible to matching that result to the POC result?

- For this plan to work, the POC company will need to dedicate at least one person per site for the 2-4 week time span to make sure the logistics are covered correctly. Since many companies cannot spare more than one person (if even one person can be spared), that same person will need to support all three sites in successive time spans. This means that the CLIA testing time interval is 6-12 weeks. This model will be exorbitantly expensive and overly time-consuming, and in no way could be considered “least burdensome.”
- We all know that if the test results between the POC device and the lab do not agree, the POC device will be assumed wrong. Since sample handling to the lab will be largely uncontrolled, this is an unfair assessment.
- Who will pay for the IRB approvals, since Informed Consent alone is no longer customary, due to liability issues.
- Will doctors ever agree to this? In my experience, doctor appointments are scheduled 10 minutes apart, and they are usually running 40 minutes behind. Now we wish to add a new component to their daily routine?
- Why would a patient agree to participate? Their appointments are already running late, and reading a multi-page consent form, having the study explained to them, and having to wait for a fingerstick and venous draw is not reasonable.

My recommendation for field studies: If there is now a desire to perform POC field testing in the intended environment, this can be done with prepared samples- either natural or artificial. Patients do not need to be involved, and they should not be involved, due to the logistical issues raised above. Further, the assessment of accurate and easy-to-use can be made with far fewer than 360 results. This exceeds the scope of most 510(k)s.

Also further to the use of prepared samples, the continued moaning of potential matrix differences is unwarranted, because matrix effects are not relevant. The CAP and other proficiency providers have been supplying artificial samples that do not behave as clinical samples to labs for decades, and no one seems to have a problem with that. If the nurse or office assistant can get the same “right” or “wrong” answer as the trained professional regardless of any matrix effects of an artificial sample as compared to a natural sample, then CLIA waiver field testing has been satisfied.

Lastly (and we should not lose sight of this), it is not clear how imposing ridiculously onerous rules for CLIA field studies will improve office testing with waived test systems. When CMS discusses the problems with noncompliance in the doctors’ offices, the problems are primarily due to the lack of following the directions for use. Should not the focus of any changes to the CLIA waiver program concentrate on compliance vs the method itself?

9. QC Testing: On Page 30, I do not believe that the suggested text for QC labeling is written to the 7th grade reading level.
10. Further to Page 30: where are the data to support that a 2-week lapse in testing represents a new operator? Has it been shown the medical staff have 2-week memories?
11. It is evident the site-to-site precision is no longer an issue for quantitative tests. I am just curious as to why this was decided.