

DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Medicare & Medicaid Services
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Center for Medicaid and State Operations

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

Dear Sirs:

The Centers for Medicare & Medicaid Services (CMS), Division of Laboratory Services, is pleased to offer comments to the Food and Drug Administration (FDA) Draft Guidance for Industry and FDA Staff: Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications. We applaud the FDA for its efforts to suggest improved guidance to manufacturers who are applying for waived status under CLIA for certain test systems.

CMS has a significant general concern that pervades the entire document: there appears to be an assumption on FDA'S part that test systems requesting waived status will be used principally, if not exclusively, in physician directed/operated facilities. There are references to "intended clinical settings" – physician's office, out-patient clinic; "intended operators" – individuals employed in these clinical settings, to be used as study sites and study participants, respectively. CMS data presents a different picture of waived test system (WTS) users. Currently, there are 111,338 Certificate of Waiver laboratories, of which 51,792 are in physician's offices. Therefore, only 46.5% of facilities operating under a Certificate of Waiver function with physician oversight whereas 53.5% do not. Because of the extensive use of WTS by non-medical, non-clinical individuals, CMS requests the FDA to consider re-directing the recommendations in the document to include only the least knowledgeable, least educated, least experienced individuals to perform testing for study data collection of the system requesting waived status. Sites should NOT be clinical/medical settings. This approach would legitimately stress the test system under the least ideal conditions using the least proficient individuals, conditions that occur frequently in over half of the Certificate of Waiver facilities.

CMS has received a large number of inquiries from the public asking when the test systems categorized as waived since 2000 will be published in the *Federal Register* for public comment. The CLIA regulations at §493.15(d) require "Revisions to the list of waived tests approved by HHS will be published in the *Federal Register* in a notice with opportunity for comment." FDA has been delegated by the Department to perform all functions relating to test categorizations. Without the periodic publications specified, FDA is in violation of this CLIA regulatory requirement and is not fulfilling its responsibility to the public. CMS requests the FDA to bring the public up to date by publishing for comment all test systems waived since 2000.

Specific Recommendations to FDA:

1. Reinstate the post surveillance language into this document. CMS may not inspect Certificate of Waiver laboratories routinely. (Those we have visited have shown significant quality problems.) Because of this limitation, it seems logical to include post surveillance recommendations from the manufacturer in the package insert. Users and manufacturers should notify the FDA of any test system problems. We anticipate the FDA would then notify CMS of such test system faults.
2. Laboratories using WTS must be notified that any change to the manufacturer's test kit instructions for use will automatically change the categorization of the test system to high complexity. Ideally, this notice should be prominently placed in the package insert.
3. Page 3 of the document discusses failure alert mechanisms that should be included in the device when a fail-safe mechanism is not feasible. We believe that some procedural or electronic controls may not provide sufficient control mechanisms to function as failure alert mechanisms. They may be function checks that provide only limited problem detection. They do not alert the operator with sufficient information necessary to indicate a system failure. We request this option be reconsidered as a single failure alert mechanism that would replace the need for external quality control materials, particularly when these "controls" do not generate useful system monitoring information.
4. The "External control materials" section, pp.13-14 is well written and would be of significant assistance to users. We suggest all of the information in the section be included in the package insert.
5. We suggest that the FDA specify to manufacturers that the least experienced, least knowledgeable, least educated individuals be selected to perform testing for study data collection. It seems logical that manufacturers will use individuals who will present data favorable to making the waiver decision. This bias should be eliminated.
6. Page 18, the last paragraph under "Clinical study reports" seems to allow the removal of outliers under certain circumstances. Outliers must never be omitted from test data. If they happen, it is usually for good reason and must be included in the data calculations.
7. CMS believes that a test system requesting waived status should be evaluated using either a reference method or a comparative method (Types A and B on page 19). Systems that cannot be evaluated using either of these methods should not be eligible for waiver. Solid method comparisons should be performed to demonstrate the dependability and accuracy of the system.
8. The least experienced, least educated users should collect all specimens that are to be used in the studies. Specimen collection and handling frequently influences the quality of a test, many times negatively. The same individuals who will be performing the testing should also collect the specimens mimicking what occurs frequently in the facilities.
9. Pages 19-20, Clinical study design and statistical analysis:
 - CMS recommends more than 3 sites (at least 6) and more than a total of one to three operators at each site (at least five operators per site). One operator per site is unacceptable.

- Using at least 6 sites, 120 specimens/patients per site would be more exemplary of the performance of requested WTS. We recommend this increase in both sites and specimens.
 - “If the order in which the samples are collected impacts the results of testing, we strongly encourage you to consult OIVD concerning your clinical study”. If a test is negatively impacted simply by the order of sample collection, it cannot be eligible for waiver. That negative impact WILL happen in the field.
10. Labeling for Waived Devices, page 29 – CMS finds the recommendation for manufacturers to write the package insert/labeling “at a level appropriate for the intended user” too vague and non-specific. A manufacturer may consider physician office or other medical facility personnel as their “intended users” when waived test systems can be and are used at sites that are not at all medically oriented. We recommend the language be written in language easily understood by individuals educated to a 6th grade or lower level. Unfortunately, there is no guarantee testing personnel in facilities performing waived testing are literate. We also suggest that the information and language included in the labeling be standardized for consistency for all manufacturers’ devices, wherever possible.

Judy Yost

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