

Comparison of CLIA’s 1995 Proposed Waiver Rule to AdvaMed’s Proposal for Waiver and Previous CLIAC Waiver Recommendations

Note: Waiver provisions in the CLIA Law at the end of the table

1995 Proposed Rule (NPRM)	AdvaMed’s Proposal	Previous CLIAC Waiver Recommendations
Demonstrating Simple		
Proposes that, to be simple, a test system must be fully automated or self-contained; require no operator intervention during the analytic phase; provide direct readout of results (quantitative tests); and provide distinct positive or negative endpoint (qualitative tests).	Proposal includes the NPRM test system characteristics to demonstrate simple. Also includes tests with results determined by obvious color gradations.	
Stipulates that only direct, unprocessed specimens are to be used, requiring no manipulation before the analytic phase of testing.	Proposes allowing basic, non-technique-dependent <i>specimen</i> manipulation. “Basic, non-technique-dependent specimen manipulation” is not defined. Proposes allowing “capillary whole blood, plasma, serum, urine, and swabs from a variety of locations” as specimens.	
States that, to be simple, a test should not require testing personnel to perform any invasive test system troubleshooting nor electronic or mechanical maintenance.	Proposes that troubleshooting not require technical or specialized training. Test systems should not require electronic or mechanical maintenance.	
Test system <i>instructions</i> need to include step-by-step protocols for the <i>preparation</i> and storage of reagents, calibrators, controls, or other materials used in testing, but does not specifically address the degree of reagent preparation allowable. Qualitative tests are limited to the addition of a specimen to a reagent-impregnated device.	Proposes allowing basic, non-technique-dependent <i>reagent</i> manipulation and simple <i>reagent</i> mixing steps, such as “mix reagent A and reagent B.”	To document untrained user ability to follow the package insert and perform the test correctly, the manufacturer should test the ability of the user to understand QC and test a patient sample.
Specifies that test system instructions be written at no higher than a 7 th grade level, and address analytical skills required of testing personnel; limitations of the physical environment or conditions for test performance; requirements for specimen collection, handling, storage and preservation; reportable range for patient results; and reference range. Test system instructions should also include step-by-step protocols that address, as appropriate, instrument or test system operation and test performance instructions; action(s) to be taken when calibration or control results do not meet the acceptable range of values; and description of course of action to be taken when the test system becomes inoperable.	Refers to FDA’s role in assuring that clinicians and lay-users of waived test systems are provided easy-to-read and easy-to-follow (“simple”) instructions for use of IVD products. Proposal lists instructions written at no higher than a 7 th grade level as an example of a characteristic of a simple test. Proposal does not address specific items to be included in the test system instructions, other than the inclusion of the statistical analysis of the “accuracy” studies in the product labeling.	Waived test instructions should be clear, easy to read and understand. Recommend inclusion of step-by-step instructions and visual aids. Also include performance and prevalence data in labeling, as well as test limitations.

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Demonstrating Insignificant Risk of Erroneous Result		
<p>Test systems are to have a fail-safe mechanism that renders no result when the test system malfunctions, the test system is out of calibration, or the result is outside the reportable range. In lieu of a fail-safe mechanism, waiver review guidelines permit external QC as a failure-alert mechanism, when a fail-safe mechanism is not feasible.</p>	<p>Advocates risk assessment of test performance. Suggestions for risk mitigation mechanisms are: error detection mechanisms, training programs, quality control checks, or modified instructions for use. Proposal states the manufacturer is responsible for providing evidence that the risk mitigation mechanisms are effective.</p>	<p>Require lockout features, when feasible, to ensure QC performance and accurate results.</p>
	<p>Proposal states, "since risk mitigation and error detection mechanisms cannot be 100% effective, FDA must consider the unavoidable remaining risk versus the expected patient care benefit of having rapid access to a test, with appropriate labeling to guide physician decision-making in the waived testing environment."</p>	<p>Concerns about access should not outweigh issues of maintaining waived test quality.</p>
<p>Test system instructions are to include step-by-step protocols for control procedures, including the type of control materials, suggested concentrations, and frequency of assay.</p> <p>If external QC is used as a failure-alert mechanism (in lieu of a fail-safe mechanism), waiver review guidelines specify frequencies for running controls for some test systems. In general, testing external controls is needed at least once per operator per kit, depending on test kit size.</p>	<p>Proposal states, "It is each manufacturer's responsibility to recommend quality control mechanisms, according to a risk analysis for an individual product, to reduce the risk of test system failure. The manufacturer is required to assure that the recommended QC measures employed to evaluate test kit integrity are clear to end-users."</p>	<p>Require QC, rather than recommend, especially if used in lieu of a fail-safe mechanism. Manufacturer should specify QC frequency and levels/concentrations in claims to FDA.</p>
<p>The test system needs to be simple and field studies are to be conducted to demonstrate performance by untrained users.</p> <p>By law, waived tests are exempt from CLIA standards, including the evaluation of testing personnel competency.</p>	<p>Proposal states, "It is the laboratory director's (or supervising physician's) responsibility to establish competency assessment measures for test system users. Manufacturers cannot be expected to assure end user competency."</p>	<p>Measures should be taken to ensure that personnel are knowledgeable regarding test performance and understand the importance of following test instructions. One suggestion is to require testing personnel obtain a certificate of competence following completion of a course of instruction on a specific test system.</p>
<p>Proposes that laboratories notify the manufacturer or producer of the test system of any performance, perceived or validated, that does not meet the performance specifications as outlined in the test system instructions.</p>	<p>"It is the physician's responsibility to determine whether an individual test system, whether waived or not, performs adequately for use with his or her population of patients."</p>	<p>Strongly support post-approval surveillance of test performance. Recommend re-evaluation of waived tests based on field performance 3-5 years after initial waiver determination, and development of a mechanism for withdrawal of waiver approval, if post-approval performance data shows substantive variance from the original waiver approval data.</p>

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Accuracy		
<p>Studies are used to demonstrate that the results of a test are traceable to recognized reference materials; results are not affected by specimen matrix; errors are not introduced due to the presence of substances commonly causing interference within a patient sample; and errors are not introduced due to environmental influences.</p> <p>There should be no statistically significant difference between test results and the value of the reference materials.</p>	<p>Proposes "accurate," for purposes of CLIA waiver, to mean the following:</p> <p>(1) data from lay-user studies (to include anticipated test users) demonstrate the performance of the test system is comparable and traceable to test results obtained with a higher-order laboratory method (as described in prEN ISO 17511), and</p> <p>(2) a lay-user, working only with a manufacturer's test instructions can reasonably be expected to obtain substantially equivalent test results as a professional laboratorian using the same set of test instructions.</p> <p>Suggests that <u>one or more</u> lay-user studies are needed to demonstrate the product meets both of their waiver accuracy criteria. Proposal also states, "Manufacturers should determine the appropriate number of subjects on a case-by-case basis through a statistical approach. It is the responsibility of each manufacturer to design the proper study to assure that the number of samples reaches statistical significance."</p> <p>(Lay users should receive no training, coaching, or prompting, and should have no opportunity to discuss testing or observe each other.)</p>	<p>Use the terms "accuracy," "precision," and "comparability" appropriately.</p> <p>To ensure accuracy for a waived test, it may be necessary to meet a higher threshold than what is required for 510(k) clearance of moderate or high complexity tests.</p> <p>Evaluate accuracy by comparing test performance to a measure of truth. Measures of truth include reference methods, designated comparative methods, well characterized working methods, and may include clinical evidence.</p> <p>Determine accuracy using laboratory professionals in a laboratory setting.</p>
	<p>Proposes that each lay user test one sample, and results from lay-users are compared to the results of higher-order laboratory methods using a statistically appropriate method such as Deming regression. Specimens for these studies should be equally distributed across the reportable range of the test. Proposes that, for data analysis, the manufacturer provide a scatter plot of the results, descriptive statistics, and regression estimates of slope and intercept, including the respective 95% confidence intervals. Also states "the manufacturer should provide an annotated line listing of the data, and be prepared to provide electronic versions of the data sets." No minimum criteria for the study are given.</p>	

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<p>For qualitative tests, studies are used to demonstrate the test system produces accurate results under the testing conditions when compared to a quantitative result such as the value of a reference material or the presence or absence of a particular biologic component.</p> <p>Waiver review guidelines specify there should be no statistically significant difference between observed and expected values at the cutoff point, and no significant equivocal results at +/- 20% of the cutoff.</p>	<p>“The study should demonstrate that lay-users obtain results that are comparable to the higher-order laboratory method, as defined by the manufacturer’s acceptance criteria.” Study specimens should include negative, positive, and near-cutoff values. At least 10% of the specimens should be near the cut-off.</p> <p>For data analysis, proposes constructing a 2X2 table of lay-user waived test results against results of a higher-order laboratory method, calculating concordant and discordant data, and reporting this data in product labeling.</p> <p>Minimum criteria are not given for these studies. Proposal states, “The manufacturer should be prepared to justify the selected acceptance criteria, based upon statements of clinical need reported in peer-reviewed literature, published by medical specialty groups, or supported by recognized experts in the clinical field.”</p>	<p>For qualitative tests, accuracy assessments should include an evaluation of clinical sensitivity, clinical specificity, and predictive values, and should consider prevalence of disease in a population.</p>
Precision		
<p>Field studies are used to demonstrate that test users can perform the test correctly using only the manufacturer’s written instructions; the test is accurate under testing conditions and defined environmental specifications; and the calibration of the test device is stable over the calibration frequency interval or fail-safe mechanisms render no result when the system is out of calibration.</p> <p>Field studies should demonstrate minimum imprecision of lay-user results among-operators (all study participants), within-sites, and between-sites.</p> <p>For quantitative tests, studies are used to demonstrate performance at all medical decision points, and upper/lower limits of the relevant range, using at least 3 concentrations of the analyte being tested.</p> <p>Under the waiver review guidelines, Tonk’s formula is used for the assessment of total imprecision.</p>	<p>Proposes comparability studies between lay-users and professional laboratorians. (See accuracy studies)</p>	<p>Precision studies should include a representative sample of the intended user population in an intended use setting to provide a valid measure of test performance.</p>

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For qualitative tests, studies should demonstrate that participants are able to read the cut-off and endpoints with the same precision as laboratory professionals.		
Field studies are conducted at a minimum of three independent, non-laboratory sites. The number of study participants needs to be adequate to produce measures of performance that are statistically valid. Waiver review guidelines recommend a minimum of 20 participants per site.		Waiver studies should include a representative sample of intended users to provide a valid comparison of comparability between trained and untrained users.

Other CLIAC Waiver Recommendations

- Base waiver decisions on science, not opinion.
- To offset the inexperience of testing personnel, the quality of waived tests must be high.
- Be conservative in establishing waiver criteria, rather than establishing permissive criteria to be upgraded later.
- Establish a waiver process that is flexible, allowing manufacturers to show why certain criteria may not apply.
- Waiver approval mechanism routes should be equivalent.
- Tests approved for home use should not automatically be waived under CLIA, because home-use-approval criteria are not equivalent to other waiver approval criteria. Need to consider the expanded use of these products in clinical settings when the product is waived. Suggest technical corrections to the statute be considered, where appropriate, to ensure that all waived products are simple and have an insignificant risk of an erroneous result.
- Since risk of harm to patients is difficult, if not impossible, to define, consider the context of testing and clinical impact of waived tests, when making waiver decisions. Also consider all phases of testing (pre-analytic, analytic, and post-analytic) in assessing risk of harm and making waiver decisions.

42 USC Sec 353 of the Public Health Service Act

As amended in 1988 by Section 3 of Public Law 100-578 (Clinical Laboratory Improvement Amendments of 1988) and in 1997 by Subsection (d)(3) of Public Law 105-115 (Food and Drug Administration Modernization Act of 1997)

Waived tests... “are laboratory examinations and procedures that have been approved by the Food and Drug Administration for home use or that, as determined by the Secretary, are simple laboratory examinations and procedures that have an insignificant risk of an erroneous result, including those that -
 (A) employ methodologies that are so simple and accurate as to render the likelihood of erroneous results by the user negligible, or
 (B) the Secretary has determined pose no unreasonable risk of harm to the patient if performed incorrectly.”