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

Re: Docket No. 2001D-0044: Draft Guidance for Industry and FDA Staff: Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications

Dear Sir or Madam:

AdvaMed provides this submission in response to the Food and Drug Administration's (FDA's) request for comments on its draft guidance titled Draft Guidance for Industry and FDA Staff: Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications (Draft Guidance). AdvaMed is the world's largest association representing manufacturers of medical devices, diagnostic products, and medical information systems. AdvaMed's more than 1,300 members and subsidiaries manufacture nearly 90 percent of the $75 billion of health care technology products purchased annually in the United States, and more than 50 percent of the $175 billion purchased annually around the world. AdvaMed members range from the largest to the smallest medical technology innovators and companies. More than 70 percent of our members have less than $30 million in domestic sales annually. AdvaMed member companies have assumed a key role in developing many novel diagnostic tests for use in waived laboratories. Our companies, thus, have a significant interest in FDA's CLIA waiver policy.

AdvaMed acknowledges that FDA put a great deal of time and effort into the creation of this document. We do, however, have serious concerns about several aspects of this Draft Guidance. The most important concerns are described in this letter. Because the study requirements outlined in the Draft Guidance go well beyond what Congress intended CLIA waiver requirements to be and beyond requirements previously imposed on petitioners for waiver, we ask that FDA withdraw it and work with AdvaMed and other stakeholders to develop waiver criteria that are consistent with Congressional intent. Our collective goal is to meet clinicians' and patients' needs for rapid and reliable point-of-care test systems without placing undue burdens on the developers of these essential technologies.

AdvaMed is concerned that there are fundamental CLIA principles that were missed in this Draft Guidance. Our major concern centers on FDA's philosophy and objectives when creating this guidance document. Consistent with the Act and with Congressional intent, industry does not agree with FDA – and the CLIAC – that waived tests need to perform "better" when placed in the hands of CLIA waived laboratory operators. Inherent performance characteristics of a test should not be the focus of a CLIA waiver review; this objective is met with premarket clearance or approval.

Congress expressly stated this in House Report 105-310, the report of the House Committee on Commerce (on H.R. 1411) when it amended the CLIA waiver section of the law in 1997 to direct reviewing agencies to consider *only* "likelihood" of error "*by the user*" [Emphasis added.]:

> "In addition to waiving CLIA requirements for tests approved by the FDA for home use, current law also provides that the Secretary may determine that other products are simple and have an insignificant risk of erroneous results. Subparagraphs (A) and (B) provide examples of product types that could satisfy this criteria. **The bill clarifies, in subparagraph (A) that *this criteria should focus on test performance "by the user" and the potential for operator error in performing the test.*** The purpose of CLIA quality control, proficiency testing, and personnel requirements is to ensure consistent, reliable, and appropriate use of a test system by users of the test. **Without the clarifying "by the user", interpretations of "erroneous result" and "accurate" could include the inherent clinical sensitivity/specificity of a test system, parameters that are properly reviewed by the FDA in its process of determining whether to approve or clear product for marketing**. CLIA controls would not meaningfully affect a product's inherent sensitivity/specificity profile, and would provide no assurances of proper test performance by users. This "by the user" clarification is intended only to specify the focus of subparagraph (A) and is not meant in any way to change the acceptable level of user error. [Emphasis added.]"

Clearly, Congress intends for the CLIA waiver process and criteria to be independent of the FDA clearance or approval process establishing safety and effectiveness of a device. Congress intends for the CLIA waiver process to focus only on the ability of the foreseeable users to operate the test as it is cleared by the FDA under its Federal Food, Drug & Cosmetic Act requirements. The report language also shows that Congress clearly intends that the waiver review shall not focus on the inherent performance characteristics of the test. When treating a patient, it does not matter to a clinician whether the test result comes from a user performing the test from a waived laboratory test or from a central clinical laboratory method (and it is even less likely to come from a designated reference method), so long as the test result is as reliable as each test system manufacturer says it is in its FDA-cleared or approved product labeling. In this way, the clinician can assess the relevance of the test for meeting medical needs.

This guidance document is not viable because it does not focus *exclusively* on the two criteria set out in the statute: (1) prove that the test is "simple," and (2) prove that there is little "likelihood" of

"operator error" when an operator is using only the test kit and directions for use cleared by the FDA. Therefore, the criteria can be demonstrated in studies showing that personnel who perform testing in Certificate of Waiver laboratories can obtain substantially equivalent results as trained laboratory professionals using methods available in centralized clinical laboratories. This is true for both qualitative and quantitative test systems. With these clear requirements in mind, AdvaMed offers the following comments to illustrate how overreaching the Draft Guidance requirements are:

1. The accuracy study, as described, is overly burdensome and inflexible. Several manufacturers determined that for seasonally-related infectious diseases (such as influenza) the study described by FDA would cost well over $1 million. Such a burden on companies, especially small start-up firms that are often responsible for development of the most unique technologies, would inhibit current innovations in waived testing from getting to clinicians. These include the rapid influenza tests that are emerging as frontline tools during both ordinary and extraordinary flu seasons. We do not believe that it is FDA's intent to inhibit such innovation in laboratory medicine nor to limit the availability of point-of-care tests by raising the regulatory bar to obtain waived status. To the contrary, FDA leaders have publicly stated that they favor increased access to testing, and allowing more simple and accurate tests to be waived. To accomplish this objective, FDA should withdraw this Draft Guidance and rigorously reconsider the waiver application requirements for determining that a test is "simple" and presents little "likelihood" of error "by the user" as the Secretary has been directed to do by Congress.

   In line with this clear Congressional intent, the purpose of the waiver study should be to establish the waived user's ability to operate the test using only a manufacturer's directions for use, and not include any requirements to prove any of the inherent performance characteristics of the test being evaluated. The "total allowable error" concept included in this Draft Guidance is not appropriate. Likewise, it is not appropriate to require the manufacturer to prove the "traceability" of a test to a higher-order laboratory method. Both of these concepts are and should continue to be addressed in the premarket submission.

   The "accuracy" study for waiver should *only* be required to demonstrate that the waived user can operate the device as well as a professional user. This can be done in a number of ways, using both native and contrived specimens. The number of specimens should be statistically justified. FDA more closely recognized this concept in the original draft guidance for waiver, released in March 2001. That guidance described "agreement studies" that are more appropriate for evaluating waived devices and meet Congressional intent.

2. As proposed by AdvaMed, the Draft Guidance does include the concept of risk management. Manufacturers use risk management techniques to determine where errors may occur in their test systems. The guidance needs to clarify that, for the purposes of CLIA waiver, the risk management considerations need to focus on "likelihood" of user error and understanding of the instructions. The waiver application should be expected to identify areas of potential risk that can be caused by the user, and

how such risks of error are mitigated. FDA should recognize that there are many ways of mitigating the risk of user error, including design, lockouts, alerts, quality control testing, and labeling instructions. AdvaMed agrees that the manufacturer should demonstrate that the risk mitigations are effective.

FDA should also not prescribe in the guidance many of the product details included in this version, e.g., test kit size, since laboratories vary greatly in size and number of specimens they analyze each week with correspondingly different purchasing needs to be efficient.

3. Manufacturers do not agree that the MedWatch information should be provided in the waived package insert. Such a new labeling requirement needs a proposed regulation with an opportunity for comment. It is most appropriate, as is now done, for manufacturers to provide access to 24-hour help lines, and then to report any adverse events through the Medical Device Reporting system already in place with FDA. Additionally, most waived tests do not constitute an immediate danger to patients or users that would involve death or serious injury. To add this requirement would also overburden FDA's vigilance monitoring system, which is already overwhelmed with MDR submissions. Finally, including this information will lead to confusion for the user regarding whom to call when they have a concern, issue, or problem. In the best case, it would delay the user from getting the expert advice needed to use the device correctly, and in the worse case, the user would not make the second call to the manufacturer in order to obtain the expert advice they need.

With any future guidance development for achieving waived status under CLIA, FDA needs to remain sensitive to criteria included in the statute and the intent of Congress. We remain hopeful that FDA leadership and its counterparts in the CDC and CMS will develop clear, consistent, and reasonable pathways to waived status. Any future guidance needs to be flexible to accommodate the many variations in technology that waived test system manufacturers are employing. The guidance needs to fulfill Congress' mandate that "likelihood" of error "by the user" be demonstrated and allow reasonable risk mitigation techniques to be employed.

AdvaMed is willing to work with the agency to develop a guidance document that is consistent with Congressional intent and that meets the needs of all stakeholders: FDA, CMS, CDC, the clinical community, and industry. In this process, we must remind ourselves that our collective responsibility as stakeholders is to every patient whose physician is seeking reliable and timely information to guide diagnostic and treatment decisions. We look forward to meeting and working with all of the agencies involved in CLIA implementation next year to start anew the development of CLIA waiver criteria and processes.

Respectfully Submitted;

Carolyn D. Jones

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