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AdvaMed
Advanced Medical Technology Association

May 25, 2001

Dockets Management Branch (HFA –305)
Food and Drug Administration
5630 Fishers Lane - Room 1061
Rockville, MD 20857

Re: Docket No. 01D-0044 – Guidance for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Criteria for Waiver; Draft Guidance for Industry and FDA

Dear Dr. Hackett:

These comments are submitted by the Advanced Medical Technology Association (AdvaMed), on FDA's "Guidance for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Criteria for Waiver: Draft Guidance for Industry and FDA". AdvaMed is a Washington D.C. based trade association and the largest medical technology association in the world. AdvaMed represents more than 800 manufacturers of medical devices, diagnostic products, and medical information systems. AdvaMed's members manufacture more than 90 percent of the $58 billion of health care technology products purchased annually in the United States, and more than 50 percent of the 137 billion purchased annually in the world.

General Comments

AdvaMed commends FDA on providing a guidance document that is flexible in its approach for obtaining waiver status. The draft guidance document clearly outlines an alternative approach to obtaining waiver status, which more closely meets the original intent of Congress as compared to prior waiver assessments. However, we believe that FDA must also clearly address the public perception that the waiver review process is a stand-alone event. If not addressed, such a perception will generate comments on this document that recommend additional and unnecessary testing, labeling, etc., that is duplicative of the 510(k)/PMA submission. Adding additional language to the draft guidance to highlight that these tests have been evaluated and been shown to be appropriate to be marketed would clarify this issue. In that regard, it would be helpful to specifically cross-reference the most important in vitro diagnostic 510(k) guidance documents to show what these other requirements are, and how the two processes and

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two sets of criteria (i.e. waiver and 510(k)) relate to each other. Indeed, whenever FDA publishes the CLIA guidance, the agency may wish to make the 510(k) guidances available in tandem.

In a related vein, we believe that some of the criteria/requirements stated in the draft CLIA guidance actually fit under the authority of section 510(k) of the Federal Food, Drug & Cosmetic Act, rather than under CLIA. (See comments in attached table.)

We also note that the proposed draft guidance document presumes that every test submitted to the FDA for consideration for waived status is "new". The current document does not make any mention of how the FDA should consider a test that is added onto a platform that has analytes already waived. A manufacturer should not be required to continually perform the same untrained versus professional user studies for a test that is added-on a previously waived platform. We would like to work with FDA to develop a reasonable approach to this situation.

Section III/ Section IV

We recognize that FDA's adoption of criteria that allow "simple and accurate, as to render the likelihood of erroneous results by the user negligible" as an evaluation of the comparison between the trained and the untrained users is a somewhat different focus from the prior system employed by the CDC. We strongly believe that the FDA approach is consistent with Congressional intent for waived tests, which is to provide testing in non-clinical laboratory settings by non-laboratorians in non-clinical settings. To this end, AdvaMed recommends combining Sections III and IV. The new title would be "Agreement Studies" and would contain the "Untrained/Professional Agreement Study for Quantitative Tests" and the "Untrained/Professional Agreement Study for Qualitative Tests". We believe that both "accuracy" and "demonstrating risk of erroneous results" would be accomplished by performing the agreement study between the untrained and the professional user.

If the manufacturer recommends alternative Quality Control approaches, then this should be included in the 510(k)/PMA review process using the approaches suggested in the NCCLS EP18-P *Quality Management for Unit-Use Testing* or the harmonized standard ISO/DIS15198 *Validation of manufacturer's recommendations for user quality control.* We believe that these suggested modification meet Congressional intent.

Closing

In closing, the effort FDA has put into developing this guidance document is commendable. If the guidance document is to serve as the basis of the Final Rule on waiver criteria, FDA must also consider the impact of unnecessary additional requirements on innovation in IVD testing in the near-patient environment. We

encourage FDA to continue to work with its stakeholders to adapt the waiver criteria to the new technologies yet to be developed.

We also recommend that until final rulemaking on criteria for waiver is completed, FDA continue to review **all** waiver petitions based on the assessment of the technology and on the CLIA statute.

We offer our assistance as FDA attempts to reconcile the diverse opinions that will undoubtedly be expressed. Thank you for the opportunity to provide these comments.

Comments on specific areas of the guidance document are presented in the attached table.

Sincerely

Carolyn D. Jones
Associate Vice President
Technology and Regulatory Affairs

Section	Suggested Change	Rationale
Introduction step 1, Page 3	Revise as follows: If possible, sample(s) of the test system should may be included at the discretion of the manufacturer..."	While it may be practical for manufacturers of single-use devices to send samples of their devices to the FDA as part of the waiver petition, it is not practical for manufacturers of systems that include a permanent component (i.e., small instrument) with disposable units (cassettes, cartridges, strips) to likewise comply.
Introduction, Page 4	Clarify FDA's definition of term "untrained user."	This definition is not entirely consistent with the recommendation in Section IV, under Demographic Data, that individuals who represent anticipated users should be enrolled in the study. In which case, the anticipated users could include nurses who have had laboratory courses. An untrained user could be defined as a study participant who has not had formal laboratory training or specific experience in clinical laboratory testing and who represents the anticipated user of the device. This would allow persons who have taken college biology courses to participate in the study.
Introduction, Page 4	Suggest the following change to the "laboratory professional" definition: "an individual who meets the qualification to perform moderate or high complexity testing, as indicated in the CLIA regulation."	This provides a more concise definition of a trained individual and allows broader discretion in the selection of the "professional" which could be helpful in selecting study sites.
Section II, Demonstrating Simple, Page 4	Add the following language "No electronic or mechanical maintenance beyond simple cleaning, changing of batteries, setting of codes, checking the screen, etc."	The requirement is very general and thus excludes general maintenance procedures. The addition of examples will clarify FDA's intent.
Section II, Demonstrating Simple, Page 5	Add the following clarifying language " Produces a direct readout of result that requires no calibration (outside of calibration set by the manufacturer, simple entering of a code or performing a procedure similar to what is expected by the user to perform a test), interpretation, or calculations."	The addition clarifies that it is not the intent of the document to indicate that a test cannot be waived if it has to be calibrated, but it is the intent that the calibration should not be one that is manually adjustable by the user (i.e., the user does not control the calibration parameters).

Section	Suggested Change	Rationale
Section III, Demonstrating Insignificant Risk of Erroneous result, Page 5	Suggest the following revision: Preferably, waived test systems should contain failure alert mechanisms that produce no result when a test system malfunctions. Alternatively the test system must provide feedback to the user on the validity of the result and provide warnings when the result may need to be verified.	It may be advantageous in some circumstances to provide a result with a warning to alert the patient/user. The sentence as written does not allow for other alternatives that may be ultimately better for the user.
Section III, Demonstrating Insignificant Risk of Erroneous result, Page 5-9	Merge Sections III and IV and re-title "Agreement Studies."	Both "accuracy" and "demonstrating risk of erroneous results" are accomplished by performing the agreement study between the untrained and the professional user.
Section III, Demonstrating Insignificant Risk of Erroneous result, Page 5	Delete the following statement: "In some instances, it is necessary for the operator to run external controls at regular intervals."	This statement is providing a conclusion and a solution to the hazard analysis before the analysis has been performed. A test system that requires external controls at regular intervals may not be the best candidate for waiver. External controls are not the ultimate mechanism for Quality Assurance. External QC should not be required if it does not add value to the quality system for the device.

Section	Suggested Change	Rationale
Section III, Demonstrating Insignificant Risk of Erroneous result, Page 6 ¶ 2	Recommend the following revision: "Results of stress testing should be clearly described in your request for waiver, and the ability of recommended QC to address system failures should be verified."	The term "validation" vs. "verification" should be carefully considered throughout this section. These two terms have different meanings. The QSR is very specific about the use of these two terms. Having to verify the mitigation of a certain hazard is reasonable to expect, having to validate mitigation in a customer site would be difficult if not impossible, since most of the failures would have to be artificially induced in order to test the mechanism of protection against the failure. There are certain hazards and mitigation that a manufacturer would want to test in the user's environment to validate that it works as intended but not all hazard mitigation is best tested in this way. Validating all hazards would not provide the outcomes necessary while adding tremendous expense. **This is a product performance issue that should be addressed in the 510(k) review of the device. Unless the risk analysis identifies hazards specific to the waived operator, these issues should be addressed during the 510(k) review, and not during the waiver petition process.**
	Change title to "*Developing a Quality Assurance System.*"	QC alone cannot address many of the issues listed in this section. Care should be taken throughout the document to use the terms quality control and quality assurance appropriately.
Developing QC Procedures, Page 6	**Use of Hazard Analysis: Recommend that FDA require only those sections dealing with recommendations for QC to be submitted with waiver request.**	The items listed are certainly among the risk elements that need consideration. When evaluating the hazard analysis findings, FDA should keep in mind that waived tests are usually point-of-care tests. Health care professionals benefit by having test results quickly, while the patient is still present. **Unless the hazard analysis identifies hazards specific to the waived operator, these issues should be addressed during the 510(k) review, and not during the waiver petition process.**

Section	Suggested Change	Rationale
Hazard Analysis, Page 6	**All hazard analysis issues should be addressed within the 510(k) review, unless the hazard analysis identifies hazards specific to the waived operator.**	The test itself benefits by the presence of the patient – if the test results do not match the patient's condition, then the results can be questioned, repeated, or confirmed. POC tests do not stand-alone. Certain risks that may be identified during the hazard analysis process will be mitigated by the presence of the patient and the signs and symptoms, or lack thereof. It should be sufficient to provide the sections of the hazard analysis that refer to QC recommendations for the waiver review. The entire hazard analysis is available to FDA through the Design Control process.
Hazard Analysis, Page 6	Add statement; *See NCCLS EP 18-P for list of possible hazards (errors) to consider.* Then it is possible to delete the examples in the guidance.	The list in NCCLS EP18-P is more extensive and complete and could easily be cited in this section. This hazard analysis should only consider those items specific to the waived operator. **All other potential hazards should be considered during the 510(k) review.**
Validating QC Procedures, Page 7	Change title to: "*Verifying the Quality Assurance System*"	This allows the manufacturer to perform the best analysis to test the mitigation of the hazard. Restricting testing to only validation testing in a customer site is not necessary and would not allow for stress limit testing or repeated opportunities of failure testing.
QC Materials, Page 9 ¶ 2,	Delete the paragraph requiring the calibration of the system to be traceable to a higher order reference material. Note: For analytes that do not have a consensus reference material or method available, it is not necessary as a prerequisite for waiver.	**This issue should only be addressed in the 510(k) review process. This is not a waived operator issue.** Calibration materials should be traceable to a higher order material or method when available; however, many companies have needed to develop their own calibration and QC material that functions only with the specific test for which it was designed. This is especially true for systems that use a whole blood matrix. The value of external QC is to confirm that the test system is performing within specifications at the moment of testing and it is not necessary for the QC material to be traceable to a reference material. In addition, "higher order reference material" is a key term if it is retained and should be fully defined by the agency.

Section	Suggested Change	Rationale
QC Materials, Page 9 ¶ 3,	Delete the following: "When the matrix effect of the QC material differs from that of the specimen, define how these differences might affect or limit the information provided by the QC result... This testing will identify matrix differences that may impact QC results."	QC materials and matrix effects will have already been considered in the 510(k). **This issue should only be addressed in the 510(k) review process. This is not a waived operator issue.**
QC Materials, Page 9, ¶ 4	Delete the paragraph: "For quantitative tests, set external quality control tolerance limits according to the precision of the device..."	It is unclear if this paragraph is meant to deal with setting tolerance limits in QC or goes beyond that to requiring that these simple devices have some kind of sophisticated built in QC trending analysis systems to monitor QC values. Tolerance limits are usually addressed in the 510(k). A sophisticated QC analysis software package within these devices could be a solution to a hazard for a particular device, but should not be required of all quantitative devices since it may or may not provide a solution to a failure mode. **This issue should only be addressed in the 510(k) review process. This is not a waived operator issue.**
Other QC Concerns Page 9, ¶ 4	Delete the sentence requiring lot-to-lot reproducibility studies should be conducted on at least three consecutive lots.	**This issue should only be addressed in the 510(k) review process. This is not a waived operator issue.**
Section IV. Demonstrating Accurate, Page 10	Change title to "Agreement Studies" and merge this section with Section III. See comment above under Section III.	The section outlines studies intended to compare test performance in the hands of trained and untrained users. The proposed title clearly states the intent of this section.
Section IV. Demonstrating Accurate, Page 10, ¶ 1	Reword sentence beginning with "To address the accurate issue..." as follows: "To address the accurate issue, we recommend conducting a study of the agreement between untrained and professional users."	We recommend deleting the requirement to conduct a precision study; only an agreement study is needed. Precision testing is done as part of the premarket submission process and does not add value to the analysis of showing accuracy or comparability between an untrained user and a professional. If the untrained user can run a test and obtain equivalent results to those obtained by the professional, no additional precision information is needed.

Section	Suggested Change	Rationale
Financial Disclosure, Page 10, ¶ 1	Suggest changing title to *Clinical Investigators* and rewording the section as follows: "If clinical investigators are involved in the study, please refer to the CDRH guidance, Guidance for Industry: Financial Disclosure by Clinical Investigators...as well as other guidance documents on performing clinical studies."	If clinical investigators are used, there may be much more required of them than just the financial disclosure.
Instructions for Use, Page 10	Suggest the following wording: You should provide the untrained user with any training materials routinely included with the purchase of a system. Untrained users should receive no additional training, coaching, or prompting than what is routinely provided.	Manufacturers often include several types of training materials: manuals, package inserts, quick reference guides, and videos. It is not representative of actual use to provide the untrained user with only the written test procedure, if all of these other materials would be routinely available.
Precision Study, Page 11-13	Delete study.	The precision study should be deleted. **All precision information should be reviewed during the 510(k) submission, not the CLIA waiver petition.** Further, the precision components listed in Table 2 cannot be obtained from the study design presented in Table 1. In order to get within-run precision estimates, replicate analyses in a single run must be performed. The study presented has only singlecate analysis by one lay user and one professional each day. Between-run and Between-day precision estimates are confounded. With only one run per day, these cannot be separated. If FDA wishes to have each of the listed components of precision estimated, then a different study design is needed. Also, the requirements to include "appropriate . . .day-to-day variation in the study design" and spread testing over multiple days seems arbitrary and adds considerable cost.

Section	Suggested Change	Rationale
Precision Target for Quantitative Tests, Page 13	Clarify whether the criterion in the table applies to the overall SD. If it does not, it should be modified for application to individual sites.	This precision target standard deviation is very tight. How is this justified? One number may not be appropriate for all tests/analytes. Performance criteria should be weighed with clinical utility and access to health care. If the criterion in the table does not apply to the overall SD the table should modified for application to individual sites, because the sample size for any one site will be much less than the combined sample size.
Agreement Study for Quantitative Tests, Page 13, ¶ 1	We recommend that the sentence beginning with "You should conduct your trained/professional agreement study on at least 300 ..." be revised as follows: "The number of matrix specific specimens required for your trained/professional agreement study should reflect a statistically valid number and appropriate levels.	The requirement for 300 specimens seems arbitrary and excessive. The number of samples and levels should be part of the design of the study and should be statistically justified.
Untrained/ Professional Agreement Study for Quantitative Tests, Table 3, Page 14	Delete table.	Requiring 300 participants and 3 professionals is arbitrary and may not be statistically valid in all situations for all products. 300 samples would be an appropriate sample size if it were necessary to detect extremely small difference between the two systems. Without set criteria it is difficult to discuss an appropriate sample size. This study is overall too proscriptive and may not fit for all products. It should be up to the manufacturer to determine appropriate statistics and study protocol to be used with consultation of the FDA.
Performance Target for Quantitative Tests, Page 14, ¶ 1	Reword the sentence beginning with "You should compare results from untrained users..." as follows: "You should compare results from untrained users with results from the professionals by a valid statistical method, for example, Deming regression and an analysis of differences."	Although the Deming regression may be useful in some circumstances, the FDA should not require the use of it.

Section	Suggested Change	Rationale
Performance Target for Quantitative Tests, Page 14, ¶ 1	Add the following sentence: "These are examples of statistics that the manufacturer may consider using; however, other statistics may be used that are statistically justified."	Examining percent change can obscure the meaning of the data. For an example, should one be reassured by a small percent change if the universe of likely measurements ranges from 100 units to 110 units? A difference between Untrained and Professional users of 1 unit, on average, signifies a 1% difference, yet this is 10% of the likely range of measurement, comprising an extremely significant difference. Percent change is one way to deal with constant CV (standard deviation increasing with the mean, and at the same rate). However, data transformations can also address this situation (e.g. Box-Cox procedure). The transformed data is then amenable to any statistical analysis appropriate for normally distributed data, such as linear regression, plots, t-tests, etc.
Performance Target for Qualitative Tests, Page 16	Remove table 5, replace with the statement: "Samples need to be spread across the assay range."	This amount of detail in the table is not necessary. The distribution of the levels should be determined by the manufacturer to be statistically significant over the range of the assay.
Agreement Study, Page 16, ¶ 1	Reword the sentence beginning with "The professional should also be masked..." as follows: "The aliquots tested by the professional should also be masked..."	Clarification purposes only.

Section	Suggested Change	Rationale
Performance Target for Qualitative Tests Page 16, ¶ 1	Replace paragraph with the following language: "As a suggestion, the manufacturer may apply logistic regression, which estimates positivity probability as a function of a continuous input (concentration). This analysis approach would make use of all the data, including the 100 samples not currently evaluated formally, and would both quantify differences and allow for hypothesis testing."	The sample size of 300 is large relative to the amount of information gleaned from it. This is because at least four different concentrations are checked, yet they are checked independently, with no effort to combine the results into an overall performance comparison. Two of the concentrations (weak negative and weak positive) are checked with specific criteria applied to 100 observations for each operator type. 100 may not be adequate. Considering one concentration, a perfect system has about a 7% chance to fail the criterion. Since the criterion is actually fairly broad-an odds ratio of 4 or ¼ is pretty extreme. In addition, the criteria are then applied to two concentrations. However, collecting data on the second concentration does not really augment what we may have learned from the first concentration. In fact, the manufacturer is taking additional risk, because in the case of a perfect system, it has to pass another hurdle with a 7% chance of failure. The chance of simultaneously passing both criteria is $(100\% - 7\%)^2 = 86.49\%$. So the manufacturer with a perfect system has approximately 15% chance of failure. Finally, the manufacturer is asked to test an additional 100 samples for which no formal criterion will be applied.
Section V. Waiver Labeling, Page 17	At the end of the first paragraph, add a sentence, "Note: It is more important that the information be readily available to the user rather than in a specific order as required in 21 CFR 809.10."	AdvaMed agrees that a Quick Reference Guide (QRG) is appropriate for waived tests. Industry is concerned that providing a QRG is repetitive with what is already required in the package insert. 21 CFR 809.10 requires elements be in a specific order. FDA should acknowledge that for ease of use these elements might need to be rearranged. The manufacturer should not be required to provide the same information in a QRG and then duplicate it in the package insert per 809.10. Some agreement should be made that the QRG include certain elements and be separate, but considered part of the package insert, or that the identified areas of importance for the QRG be brought to the beginning of the package insert.

Section	Suggested Change	Rationale
Quick Reference Instructions Pages 17-18	We recommend that the Quick Reference Guide (QRG) be limited to the following: • Warning to read the test procedure first • Warnings and limitations • Safety considerations on safe test operation that particularly apply to untrained users • Step-by-step operating instructions that include instructions for reading/reporting results • Storage of reagents and control materials	The proposed list of elements to be included in a QRG is too extensive and may negate any benefits derived from providing a QRG. QRGs typically include only the procedural steps for running the test on a patient sample/and or a quality control sample.
Quality Control Labeling Recommendations, Page 19, ¶ 2	We recommend that FDA delete the following sentence: "FDA recommends that quality control instructions be based on data generated through actual field studies of each device."	This is contrary to FDA's requirement to verify the use of quality control in conjunction with the hazard analysis. In the hazard analysis, the manufacturer determines the failure modes that are mitigated by quality control. That mitigation is verified. The frequency of control testing needed is tied to that verification and is addressed in the original 510(k).
	We recommend the following change to the sentence beginning with "In the absence of specific data..." "The manufacturer, using the hazard analysis as a basis, should provide recommendations to the user for quality control testing."	The manufacturer should be addressing these issues in the hazard analysis. In the hazard analysis, the manufacturer determines the failure modes that are mitigated by quality control. That mitigation is verified. The frequency of control testing needed is tied to that verification.
Quality Control labeling Recommendations, ¶ 2, 3rd bullet	We recommend changing the following bullet to read, "each new operator (defined as an individual who has not shown competence in running the test."	A new user should not be defined as an individual who has not run the test in the past two weeks, but as an individual who has not shown competence in running the test.
Section VI. Voluntary Safeguards for Waived Tests, Page 20, item 2	We recommend deleting reference to FDA's MedWatch program (item 2).	The manufacturer should provide appropriate training and technical support so that the products are used correctly, safely and effectively. It is not appropriate to require a description of the MedWatch program along with the telephone number in the package insert. This is not a requirement for labeling of either moderately or highly complex tests where the potential is greater that an incorrect result will have an adverse impact on a patient.

Section	Suggested Change	Rationale
Section VI. Voluntary Safeguards for Waived Tests, Page 20, item 3	We recommend deleting reference to a manufacturers surveillance plan (item 3).	Maintaining customer complaint files is a Quality Systems Requirement. All manufacturers monitor product function in the field and the data are tracked and trended and the information made available to FDA during inspections. Additional requirements to submit surveillance plans are redundant and burdensome. This is also redundant with adverse event reporting requirements. In addition, this level of oversight not only far exceeds what Congress intended for waived tests, but also exceeds that oversight imposed on moderate and high complexity tests.
Section VI. Voluntary Safeguards for Waived Tests, Page 21, item 4	We recommend deleting reference to submission of analysis of the surveillance data (item 4).	The add-to-file is overly burdensome for industry and for FDA. • MDR records – manufacturers currently submit MDR records per 21 CFR 803. • Recalls – manufacturers currently submit recall information per 21 CFR 806 and 810. • Lists of common errors are included in the complaint handling databases. • Real world (field) QC results –many of these products are sold through distribution, and the manufacturers do not know who the specific customers are so it would be impossible to obtain this information. • Proficiency testing – proficiency testing is not required for waived devices. • Design control validation is complete at the time of launch of the product. If there is a change to the product that impacts the 510(k) or PMA the change is evaluated and submitted to FDA as needed. QSR requires the use of risk analysis to determine how a change can affect the need for a new submission and the impact on operator and patient. • All published reports associated with the device – what is the purpose of this request? This requirement is burdensome for both the manufacturer and the FDA reviewer. • Waived tests do not require proficiency testing, or other quality control besides that recommended by the

Section	Suggested Change	Rationale
		quality control besides that recommended by the manufacturer so there is no need to report on external QC results. (See comment above for QC). Also, providing this add-to-file has little or no value, while increasing the burden on the manufacturer.
Appendix A and B, Waiver checklist		This checklist is a useful tool for the manufacturer to use. Suggest changes to reflect the comments above.