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May 29, 2001

Docket No. 01D-0044
Dockets Management Branch
Division of Management Systems and Policy
Office of Human Resources and Management Services
Food and Drug Administration
5630 Fishers Lane - Room 1061, (HFA –305)
Rockville, MD 20852

Subject: Docket No. 01D-0044 - Comments on Medical Devices Draft Guidance for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Criteria for Waiver

Dear Dr. Hackett:

On behalf of CARESIDE, Inc., I wish to submit in duplicate comments on Docket No. 01D-0044 Medical Devices Draft Guidance for Clinical Laboratory Improvement Amendments of 1988 (CLIA).

Our comments are in two parts. In the first part, we comment on how the draft guidance is being implemented by FDA during the comment period. In the second part, we comment on the guidance document itself.

Careside commends FDA on providing this guidance document that clearly outlines an alterative approach to obtaining waiver status. However, the entire guidance seems to be written based upon the assumption a waived test is a single test for home use. The guidance should be written in terms that consider all existing testing technologies as well as those that can be reasonably anticipated in the near future. Many waived devices are intended for use by healthcare workers and are not intended for home use. There is already FDA guidance available for home use devices and precedent for FDA in clearing devices for home use. The CLIA waiver criteria guidance document must be flexible enough to address the situation of test systems that serve as a platform to perform multiple waived tests.

Waived devices that are platforms for multiple tests can have multiple advantages for waived testing. Such waived devices, however, require a different approach to demonstrating simplicity and accuracy. These systems tend to be larger and thus they can have larger user interfaces that are easier to use with more powerful quality control functions. In addition, these systems have the inherent benefit of using the same procedure to test many different analytes rather than learning many different procedures for individual analyte waived test systems.

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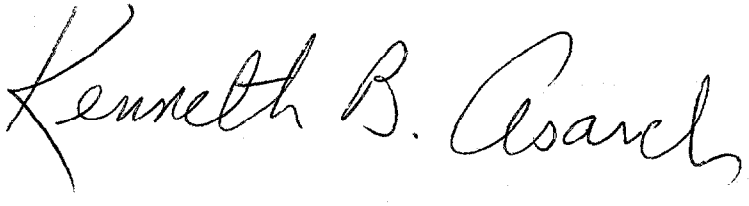
FDA should consider the various ways in which waived testing is currently implemented in clinical practice and how it is likely to be implemented in the near term future. Physicians frequently need multiple test results to care for their patients. As a result, physicians will be performing more and more tests near the patient at the time of care. Even with the extremely limited menu of available waived tests for use at the point-of-care, the data from investigators from the CDC and Washington State Department of Health[1] indicate that more than half of physicians performing waived testing perform 4 or more different waived tests in their offices. More than 10% of the physicians surveyed currently perform more than 7 different waived tests. This number will certainly grow. Is it simpler to expect an untrained user to learn and remember the proper use of 7 different test systems, or to remember one or two test systems? Three platform test systems that are already categorized as CLIA waived or that meet CLIA waiver simplicity criteria are capable of performing a very large proportion of the tests generally ordered by physicians. FDA should recognize that a platform waived test system is easier to use to obtain all of test results needed even if it is not as easy to use as the simplest single test system. Those platform systems that already have 510(k) clearance should not require additional data on the test for each and every analyte if there is no significant difference in the usability of these tests.

If you have would like to discuss any of these comments, please contact me at (310) 436-7171. I may also be reached via e-mail at kasarch@careside.com.

Sincerely,



Kenneth Asarch, Pharm.D., Ph.D.
Vice-President, Regulatory, Clinical, and Quality Systems

[1] K.M. LaBeau, M. Simon, S. Granade, and S.J. Steindel. The Pacific Northwest Laboratory Medicine Sentienel monitoring Network Final Rpoert of the Findings of Questionnarie 1- Waived and PPMP Sites Training on Waived Test Systems. April, 2000.
http://www.phppo.cdc.gov/mlp/pdf/pnwsmn/reportw1.pdf

I. COMMENTS BASED ON CURRENT IMPLEMTATION OF CLIA

Although CLIA regulations do not specify a timeline for categorization of waived candidate tests, the FDA should nevertheless specify goals for the length of the waiver review process including timelines for the determination of "simple" and the determination of "insignificant risk of erroneous result", for the review of the proposed waiver study protocol, and for the waiver application itself. The complexity of these reviews is no greater than for most 510(k) submissions that are routinely reviewed within 90 days. When submitted together, the 90 day timeline should apply to all pre-waiver application determinations as a whole (not 90 days for each). As well, the number of waiver submissions is likely to be a small fraction of the total number of 510(k) applications submitted to FDA's Division of Clinical Laboratory Devices.

In Careside's case, a waiver petition was submitted on December 22, 2000 near the time of the initial release of this guidance. The device was demonstrated to FDA on January 25, 2001, and as of this time (over 5 months), we still have not received any specific feedback. Both the determination of waiver candidacy/waiver study proposal adequacy and the actual waiver application should be handled as in the case with any 510(k), within 90 days of receipt unless there is a substantial deficiency in the filing. A product that is deemed not to be a candidate for waiver should have the basis for the preliminary denial specified in detail. The sponsor of the device should have an opportunity to provide information or evidence to reverse the preliminary denial. Alternatively, the sponsor should be allowed to make modifications to the device, user interface, or labeling to address the concerns upon which the preliminary denial was based without returning to the beginning of the review queue.

II. SPECIFIC COMMENTS ON DRAFT GUIDANCE

Item	Section	Comment/Suggestion/Rationale
1	I.	Careside supports the overall intent of the guidance to provide an open, consistent, and reliable process for industry and FDA to follow to assure that qualifying tests meet the waiver criteria. In addition, FDA should include a mechanism for an efficient and expeditious review process that is consistent both with providing access to valuable point of care test results and protecting public health by providing waived tests that pose no unreasonable risk of harm to the patient if performed incorrectly.
2	I.	Since it is likely that the review of comments for the draft guidance will take months, if not years, it is imperative that FDA allow this guidance document to serve as "an interim waiver review process that may continue until a re-proposal of the regulations to clarify the statutory criteria for waiver is published."
3	I.	FDA should publish a list of all analytes, which are suitable for waiver (that meet the criteria of no unreasonable risk of harm to the patient if performed incorrectly should be on this list). All class 1 and class 2 in vitro diagnostic devices should be on the list based upon the tests that have already been waived and used for the benefit of patients. FDA should also review class 3 in vitro diagnostic devices and place any that are suitable on the list.
4	I.	The qualifications for inclusion of personnel in waived test studies should include personnel qualified by experience in addition to by license. A lab technician who is qualified by experience should be allowed as a suitable comparison subject to an untrained user. For example, a trained, experienced lab technician who has worked with a device in a manufacturer's laboratory should be qualified as a comparator to an untrained lay user.
5	II.	The criteria for the "simplicity" determination are ostensibly objective, but there is no provision for assuring that the criteria are applied objectively. **The ultimate measure of simplicity is whether an untrained user can use the device based only on the product's labeling (manuals, tutorials, etc.) and get comparable results to a trained user.** In fact, a manufacturer should to be able to make a self-assessment of their conformance to the "simplicity" criteria. For example, there might be a scoring system similar to that proposed in the 1999 Federal Register (42 CFR 493.15, Oct. 1, 1999) with a numerical limit to objectively determine whether or not a device meets the waiver criteria. The fact that FDA does not provide for this self-assessment is worrisome – the determination of "simplicity" should itself be "simple."

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6	II.	FDA's criteria for demonstrating "simple" must be reconciled with FDA's other recommendations. The FDA guidance document recommends many quality assurance activities that are not supported by most, if any, of the currently waived test systems. It is possible to have a simple test system that supports these quality assurance activities. However, such a system will be less simple due to the embedded quality assurance features, than a system that does not have these features. Nevertheless, the waived system that stores and manages quality assurance records will most likely encourage the user to perform quality assurance activities. Whereas a system that requires all quality assurance to be performed externally and manually, does not encourage the use of a quality assurance system.

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7	III	CLIA currently does not require a QA/QC review by FDA beyond the QA/QC review performed during the 510(k) for a device. In the event that FDA authorizes a separate QA/QC review, FDA should only set QC goals rather than suggesting specific ways of achieving a solution. For example, the recommendation that manufacturers provide QC materials in the test kit may not be the best way of providing QC material. Not all waived tests are in the form of "kits." Providing QC materials as part of the "kit" reflects a bias towards home use tests. For tests that are not intended as home use tests, it is much more efficient to provide QC materials as a separate item within a waived testing system. Providing QC materials as separate products is more efficient. Additionally, some healthcare facilities prefer to use QC materials from another manufacturer.
9	IV.	The number of untrained users proposed for the Untrained/professional Agreement Study for Quantitative Tests (300) is excessive. Usability engineers rarely require more than 20 subjects. If more data is needed, it should be based on each subject testing more samples, and not more untrained users. In addition, it is more important and more realistic to observe the repeated performance of a test by an untrained user. Waived tests are not necessarily home use tests which may be performed only once by a user. Guidance already exists for the approval of home use tests. It is important that an untrained user of a "waived" device, designed for use in a healthcare setting, be able to quickly learn how to use the device. Learning proper use of the device may require more than one trial. If the untrained user can demonstrate the ability to learn how to use the device in 2 trials, then this is more important than trying to show that 300 different users can use the device ONE time. Furthermore, a study published by the Washington State Office of Laboratory Quality Assurance and the CDC indicate that in the majority of healthcare facilities that use waived tests, there are usually only 2 people that perform the test.[1] A different person is not performing the test everyday.

[1] K.M. LaBeau, M. Simon, S. Granade, and S.J. Steindel. The Pacific Northwest Laboratory Medicine Sentienel monitoring Network Final Rpoert of the Findings of Questionnarie 1- Waived and PPMP Sites Training on Waived Test Systems. April, 2000.
http://www.phppo.cdc.gov/mlp/pdf/pnwsmn/reportw1.pdf

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10	IV.	Use of 300 untrained users is not appropriate for all tests that could be considered for waiver. A study such as this is again biased towards a single analyte home-use test. Furthermore, the use of 300 untrained users does not conform to the "Least Burdensome" conditions of the 1997 FDAMA. Sample sizes for studies should be based on sound statistical principles that may vary on a case-by-case basis. FDA should explain the statistical basis for any sample sizes that are recommended in the guidance so that each company may determine if the FDA recommendations are applicable in their particular case.
11	IV.	Method comparison studies used to support substantial equivalence between two different methods can be based on 40 samples (NCCLS EP-9A). The same amount of data is adequate and appropriate to demonstrate substantial equivalence (comparability) of results obtained by two different categories of users – trained and previously untrained.
12	IV.	The restriction that untrained users be provided only written training material is unrealistic. This requirement is biased towards home-use devices. Having a test subject work from ONLY written material is unrealistic. In actual clinical situations, users are trained in a variety of ways. The government's own studies[1] indicate that users of waived tests utilize a variety of training modalities. Many manufactures provide hands-on training for their devices. In addition, many tests that are currently waived include training videos. A study performed by the CDC and the state of Washington[1] reported that only 17% of waived test users learned to use the device by reading the package insert, whereas 25% of the users were trained by another employee and an additional 20% were trained by other modalities such as videos. Manufacturers should be able to provide a variety of training modalities for the Waived Study. The optimal learning modality for an individual varies – some learn better visually, and some learn through traditional written instructions.
13	IV.	The appropriate handling of outliers must be clarified. While it is essential that all data be accounted for, it would be inappropriate to include known outliers in an analysis. For example, if a trained user were to accidentally test the wrong sample (i.e. a high control sample instead of a low control sample), it might appear that the trained user had less reproducible results than was the true situation. The trained user might not recall using the wrong control, but the statistical analysis would nevertheless identify the result as an outlier. Leaving the statistical outlier in the analysis would result in the incorrect conclusion.

Item	Section	Comment/Suggestion/Rationale
14	IV.	For simplicity, the optimal specimen for a waived blood test is a whole blood specimen. For purposes of the waiver study, FDA requests a full range of analyte concentrations. This is not realistically achievable for tests using whole blood. FDA should explicitly recognize this dilemma and explicitly sanction the use of native and manipulated serum or plasma specimens for study specimens where appropriate and/or eliminate the requirement to study the entire reportable range. Furthermore, the entire reportable range has been demonstrated within the 510(k) and should not have to be repeated. Demonstrating that the untrained user can test samples over the reportable range is not a usability issue – at least not with the Careside test system.
15	V.	Careside recognizes the importance of providing instructions for use that are written at the appropriate level for the user. The 7th grade reading level is an appropriate goal, but it should not be strictly applied for waived tests that are not intended for home use. Virtually all healthcare workers have at least a high school degree or a GED. Explicit and clear instructions sometimes exceed the 7th grade reading level simply due to the use of a few multi-syllabic words that may be defined within the document and which may be unavoidable. For example, the paragraph on page 19 of the guidance "test (xyz contains....") that was recommended for inclusion within waived package inserts by FDA is written at a 12th grade reading level.
16	VI.	The conditions described for item #3, under the section Voluntary Safeguards for Waived tests, are basic requirements of the Quality Systems Regulations (QSR). There is no need for a special surveillance plan to monitor the performance of the waived device. The requirement is inappropriate and duplicative. All manufacturers use feedback from their customers to ensure the quality of their products and to provide feedback to improve their products. All QSR records are available to the FDA upon inspection of a facility. There should not be an additional requirement for submitting a plan to the FDA as part of a waiver submission. Post-market surveillance is in excess of standard PMA requirements although waived test products in general share little in common with tests that must go through the PMA process. These requirements have not Careside's knowledge been applied to existing waived products or home use products.

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17	VI.	Item #4 under the section Voluntary Safeguards includes requirements for an annual report. The information contained in the annual report is in excess of that required for a PMA annual report. Considering that most CLIA waived tests are either Class I or Class II devices, this requirement is excessively burdensome. In addition, many of these requirements are also part of the QSR and are available to the FDA upon inspection of a facility.
18	VI.	The guidance asserts that manufacturer's should be held responsible that their products are used correctly. Manufacturer's can only be held responsible for what is in their direct control. Correct use of waived testing products is the sum of the cooperative actions of the manufacturer, the physician, or person responsible for the laboratory, the immediate user of the test, as well as the patient and FDA.
19	VI.	All waived test manufacturers are subject to Quality System Regulations that require a complaint handling system. The manufacturer is the best source for information or corrective action, if needed, on a product. To direct user's to call MedWatch is an unnecessary burden on MedWatch and is an inefficient way of getting help when needed. Other systems such as MDR reporting are already in place should there be a serious incident with a waived device.

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