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Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20850

October 12, 2000
CLIA Waiver Criteria

Dear Sir / Madam,

The attached document represents Roche Diagnostics Corporation's responses to the questions posed by FDA at the August 14-15, 2000 CLIA Waiver workshop. If anyone at the agency needs clarification or additional information, please do not hesitate to contact me.

Best regards,

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CLIA Waiver Criteria

Roche Diagnostics Corporation
Response to FDA's CLIA Workshop Questions

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Purpose

The purpose of this document is to provide Roche Diagnostics Corporation's response to the CLIA Waiver criteria questions posed by FDA at their August 14-15, 2000 workshop. In the sections below, the question is repeated, and then the response to each question is provided.

In moving forward, Roche Diagnostics will be happy to work with FDA in further development of guidance or regulations regarding CLIA waiver. Please let us know how we can be of service.

Question 1

Criteria for waived tests under the Public Health Service Act were amended by FDAMA to read: 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 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..."

What criteria should be used to demonstrate that a waived test is a simple laboratory examination and procedure with "an insignificant risk of an erroneous result?" For example:

- A) Should a waived test, when performed by untrained users, provide an accurate result with no significant clinical or statistical error when compared to a measure of truth? This requires availability of well-characterized reference methods and/or materials as part of the waived test assessment. The current threshold for waiver as established by CDC is no significant inaccuracy and no significant imprecision.*
- B) Should a waived test, when performed by untrained users, provide a test result that shows no user error when compared to the same test performed in a CLIA-certified lab by a trained user? This requires comparison of the test in a lay-user setting with performance of the test in a CLIA-certified lab by a trained user. The threshold for waiver would be no difference in performance in the two settings.*

Should FDA apply a different model to determine the waived status of a test?

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CLIA Waiver Criteria, Continued

Response 1

FDA determines that tests are appropriate for their intended use and their intended user during the premarket review process. If a test is intended for use in a physician's office lab (POL), then all issues associated with the use of that test in that facility should be addressed by the 510(k) or PMA submission. Once a test's performance has been determined by FDA to be suitable for use in a POL, then the question of waiver can be considered.

The preamble of the CLIA '88 Final Rule states that the intent of the regulation is to ensure the quality of testing no matter where the procedures are performed. Therefore, we agree that the threshold for achieving waiver should be based on the premise of demonstrating equivalent performance between trained laboratory professionals and untrained users. However, we do not agree that a test performed by untrained users cannot show "user error" when compared to the same test performed in a CLIA-certified laboratory.

User errors can and do occur in both traditional and non-traditional lab settings. For example, waived urine dipsticks and spun hematocrits performed manually are equally susceptible to user error in both settings due to tester-to-tester differences in visual interpretation. Therefore, it is clear that the intent of Congress is not to waive only devices that provide perfect results all the time. Instead, Congress was looking for a low error rate and for the regulating agency to weigh the public health benefit of the availability of the waived test outside laboratories regulated by moderate or highly complex CLIA rules.

Recommendation for Guidance on Waiver: FDA should grant waiver based on a comparison between lab professionals and non-lab professionals that demonstrates equivalent performance between the two groups.

Question 2

What criteria should FDA use to determine if a methodology is "so simple and accurate to render the likelihood of erroneous results by the user negligible?"

- A. *Should a waived test be so accurate when performed by untrained users that inaccurate results will not occur?*
 - B. *Should a waived test have variable accuracy if used adjunctively; is it acceptable to waive tests that have inaccurate results but do not have any major negative clinical impact? How should FDA make this assessment?*
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CLIA Waiver Criteria, Continued

Response 2

Again, inaccuracies in test results occur in all laboratories, regardless of the CLIA categorization. Errors made by highly trained laboratory technologists working in CLIA highly complex labs, or by untrained users working in waived labs can cause erroneous results. FDA should not, and do not expect tests to be error free. Within the 510(k) or PMA process, FDA determines if tests are accurate enough for their intended use, by the intended user. This information appears in the product labeling. Criteria for accuracy does not now, and should not in the future, depend upon the CLIA classification.

During the product design process, and as required by quality system design control, manufacturers perform risk analyses on their products. These risk analyses typically may consider findings from human factors studies of the new product or existing similar products. In the process of risk mitigation, manufacturers may design in product failsafes, so that products have a very low likelihood of producing an erroneous result. The risk analysis process considers both usual use of the product, as well as reasonably foreseeable misuse.

Recommendation: FDA can request a summary of the risk analysis. The risk analysis should detail the risks associated with the testing procedure and the steps taken to reduce user error (e.g., built-in features that monitor the testing process and/or labeling instructions).

Question 3

What criteria should FDA use in determining that a test will “pose no unreasonable risk of harm to the patient if performed incorrectly?”

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CLIA Waiver Criteria, Continued

Response 3

Performing the test incorrectly may or may not produce an erroneous result. Manufacturers should perform a risk analysis addressing the potential of performing tests incorrectly and obtaining an erroneous result. FDA should consider the output of the risk analysis. How severe is the risk? How is the risk mitigated? If the risks are low, then the benefits of providing the particular test at the point of care may outweigh any potential risks.

FDA should also consider that for waived tests, the patient is present when the test is performed and interpreted. The health care provider can immediately assess whether the test results are consistent with the patient's condition, and then determine the appropriate follow-up actions, in real time.

Recommendations: FDA should review the risk analysis for objective evidence regarding the risks associated with use of the test. Many products contain features, sometimes referred to as failsafes, that prevent results from being obtained if the test is performed incorrectly. In addition, FDA should consider the test results are often, if not always, reported in real time while the patient is available for further testing. Certainly, these tests should be eligible for waiver.

Question 4

Should the waiver process be different for screening tests that require a second test for confirmation? Since there are no CLIA standards for performance of waived testing, except instructions to follow the manufacturer's package insert, what is the assurance that confirmatory testing will be performed? Should the need for confirmatory testing raise, lower, or have no impact on the threshold for a waiver decision?

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Response 4

Screening tests that contain instructions for performing confirmatory testing before making treatment decisions should by definition pose little risk of harm if the user follows instructions. Of course, it is possible that users may not always perform confirmatory testing but this is the practice of medicine, and FDA does not regulate the practice of medicine. By CLIA regulation, those labs that choose to deviate from the manufacturers' instructions are considered to be highly complex laboratories, and must validate the "off-label" usage of the system. HCFA already has mechanisms in place to impose punitive measures on laboratories that are performing tests of a higher complexity than the laboratory's certification.

Recommendation: A test used for screening purposes that requires further confirmation before the patient is treated should reduce the threshold for granting a waiver decision.

Question 5

Should accuracy be determined using comparison of the waiver test to a well-characterized reference method and/or materials, to a designated comparative method and/or materials, to a working laboratory method and/or materials, to a clinical algorithm for diagnosis and/or to other endpoints?

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CLIA Waiver Criteria, Continued

Response 5

This question is not pertinent to CLIA waiver. Through the 510(k) or PMA processes, FDA has already determined that tests are safe and effective for their intended use and their intended user.

Roche is concerned that this question arises from the CDC view that FDA's 510(k) requirements for determining substantial equivalence are not as rigorous as the waiver determination. This is nonsense and is not supported by FDA law, regulation, and current premarket review requirements.

First, the law of substantial equivalence is based on the requirement that manufacturers must demonstrate that a new device is similar in terms of performance to an existing device that was already in use prior to enactment of the 1976 amendments. FDA classification panels determined that enough was known about the safety and effectiveness of most pre-76 devices to classify them as either Class I or II. Therefore, when a manufacturer demonstrates substantial equivalence to a predicate device, this is objective evidence that performance is as good or better than another device already determined to be safe and effective for its intended use.

Second, the 510(k) requirements for products submitted today far exceed the requirements of 1976. FDA has generated hundreds of guidance documents, memos, and regulations that specify expectations for performance of products today. FDA has hired medical officers with MD degrees to assist reviewers in understanding the safety and efficacy impact of products on clinical medicine. FDA is doing a very good job in determining that products are safe for their intended use by their intended user. Whenever any doubt remains, post market surveillance studies are mandated. FDA is not allowing unsafe products to enter the marketplace. Health care providers can rely upon laboratory test results.

Recommendation: It is totally inappropriate that the CLIA waiver criteria would impose more burdensome requirements for determination of accuracy. The same criteria for accuracy should apply regardless of the CLIA status of the test.

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CLIA Waiver Criteria, Continued

Question 6 *How many samples, what types of samples (real or artificial) by how many users and how many sites are appropriate to evaluate accuracy? (Current guidelines being followed by FDA are for performance to be demonstrated by laboratory users at a minimum of one site.)*

Response 6 The manufacturer should perform a statistically sound study. The study site(s) should reflect a typical user site, and the operators should reflect typical users. The number of samples should be dictated by statistical rationale. If this number of samples can be reasonably and conveniently collected at one site, then this is reasonable. If there are geographic reasons for multiple sites, e.g. disease prevalency varies, then appropriate multiple sites should be used.

Question 7 *What should be the background of these users?*

Response 7 The users should be typical intended users that are representative of individuals that could reasonably be expected to work at non-traditional test sites. It is not essential that users be 7th graders. Users for waived test studies should be adults who are not laboratory professionals, and should cover a broad range of educational backgrounds. The 7th grade reading level criterion can be proven through word processor language checks.

Question 8 *What performance criteria (statistical or clinical) should FDA apply to the accuracy threshold for a waived test (e.g., t- test or McNemar test at key decision points, description of performance with confidence intervals at key decision points, use of set performance standards using a receiver operator curve —80%, 90%, 95%, or other—at key decision points, and/or others)?*

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Response 8

It is not appropriate to establish a blanket performance criteria. Different tests (or different intended uses) require different levels of performance to be efficacious. This question is not particularly germane to the CLIA discussion, as these tests are being considered for clearance or approval for the particular intended use during the 510(k) or PMA process. An acceptable performance level for any test in any given intended use is determined by FDA during their premarket reviews (either explicitly or implicitly). If a test is found to be safe and effective for an intended use by an intended user, then the performance is acceptable no matter whether the operator is in a CLIA moderate lab or a CLIA waived lab.

When testing whether lay persons and health care professionals can perform a test equally well, it is appropriate to use statistical procedures of equivalence determination. These can include t-tests and McNemar's test.

Question 9

How should FDA define precision for purposes of waiver determination, what types of samples, how many and what types of operators/sites are appropriate? Current CDC recommendation is for 20 participants testing three levels representing appropriate decision points, to be tested at each of three sites by lay users using materials in either artificial and/or real matrices depending on availability and biohazard issues.

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Response 9

Precision testing, whether for waiver or claims validation, should be performed at levels representing relevant decision points. The precision tests should always have the greatest sample size for the variable under investigation. In the case of CLIA waiver studies, the variable under question is the operator, as the performance of other precision variables has been established within the 510(k). A statistically robust study should be designed in order to determine operator to operator variability. This amount of variability should be compared for lay users and for health care professionals. It should be proven that precision achieved by lay users is not significantly different than precision achieved by professional users (either within the study itself, or as compared to professional product labeling claims). The use of artificial and / or real matrices depending on available and biohazard issues is appropriate.

The sample size chosen is dependent upon the performance characteristics of the product. A statistician must determine an appropriate sample size, considering the hypothesis (that the lay-user results are not significantly different than the professional results), as well as the precision of the test, and the amount of difference in results that would not be significantly different. If a test has very good precision (low standard deviation), then the sample size needed to prove no statistical difference will be small. If a test has higher imprecision (higher standard deviation), then the sample size to prove no statistical difference will be higher. For example, for several of the Roche qualitative point of care tests, a sample size of around 40 – 45 can be statistically defended. Whatever sample size is chosen, the manufacturer should be prepared to explain and defend it.

Recommendation: Let the manufacturers determine the appropriate study plan with statistically appropriate sample sizes.

Question 10

What performance thresholds should FDA use to determine whether the precision studies are appropriate for waiver status (e.g., ANOVA analysis, use of predefined performance goals such as Tonks' formula, or percent agreement out of total repeat runs)?

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CLIA Waiver Criteria, Continued

Response 10 As stated above, it should be proven that precision achieved by lay users is not significantly different than precision achieved by professional users (either within the study itself, or as compared to professional product labeling claims). It is up to the manufacturer to design the appropriate study, and defend the statistical approach selected.

Question 11 *What interference studies are appropriate to establish performance of waived tests (e.g., effects of hemolysis, lipemia, etc.)?*

Response 11 No testing above and beyond the premarket claims testing. Interference studies are an important component of premarket reviews, and the need to understand the influence of interferents does not change with the complexity of the laboratory.

Question 12 *What environmental studies or flex (stress) studies are appropriate to establish performance of waived tests (e.g., temperature or humidity stresses, short fills)?*

Response 12 No testing above and beyond the premarket claims testing. These are claims that are addressed in the premarket review. If a product is determined to be safe and effective for use in a POL, then it is. The CLIA categorization does not impact the environmental conditions that the product will be exposed to within that physician's office.

Question 13 *What additional studies (if any) should be submitted for evaluation of qualitative tests for waiver?*

Response 13 Studies providing proof that the lay user can read the instructions, perform the test, and interpret the results to the same level of accuracy and precision as a health care professional user.

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CLIA Waiver Criteria, Continued

Question 14 *What additional studies (if any) should be submitted for evaluation of quantitative tests for waiver?*

Response 14 Studies providing proof that the lay user can read the instructions, perform the test, and interpret the results to the same level of accuracy and precision as a health care professional user.

Other comments

The practice of medicine today demands that patients be monitored or treated on the spot. Patients and their doctors do not want to wait for test results in order to make health care decisions. Doctors must make the best decisions possible in order to provide timely information, while the patient is still in their office. They need as many tools as possible to help make those decisions. Can a less than perfect test provide better information than no test, or a late test? Sometimes yes, sometimes no. The risk versus benefit of each test must be considered.

However, this consideration should be occurring in the premarket review process, not the CLIA waiver process. Doctors are relying on the tests. Either they are appropriate for their intended use, or they are not. It doesn't matter if a doctor has a laboratory professional on staff or not. If it is proven that all operators of a test can achieve equivalent results, then the performance of the test will be the same, no matter who is the operator. The test itself is as good as it is, and FDA already determines if that level of performance is safe and effective for the specific intended use, and the intended user.

CLIA criteria should focus only on the risk analysis of the lay user as the operator. All of the other performance issues must be considered during the premarket review.

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A note about glucose meters

During both the FDA CLIA workshop and the CLIAC meeting, a great deal of concern was raised about the use of home-use glucose meters in professional settings. FDA must be aware that this concern is unfounded. All manufacturers test their glucose meters with hundreds of samples in both professional and home use settings. That data is submitted in the 510(k). FDA has reviewed these data hundreds of times. Claims such as the use of neonatal samples, venous samples, or arterial samples are fully validated in the appropriate sites, by the intended users. These claims would not be allowed in the package inserts if the data were weak or the testing not performed.

Recommendation: We would appreciate it if FDA sets the record straight for CDC and the clinical lab community: all claims in the manufacturers' package inserts are validated by the manufacturer, and reviewed by FDA. FDA has determined that those claims are appropriate during their safety and efficacy evaluation and subsequent substantial equivalence determination. These systems are not entering the professional market through the back door. FDA has consciously and appropriately cleared these systems for use in professional settings.

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