STATE OF WASHINGTON

DEPARTMENT OF HEALTH

Office of Laboratory Quality Assurance
1610 N.E. 150th Street
Seattle, Washington 98155-9701

DATE: May 25, 2001

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

FROM: Gail V. Neuenschwander, Program Manager
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Office of Laboratory Quality Assurance
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RE: Comments on Docket No. 01D-0044

Copies of comments that were previously submitted on Docket No. 00N-1394, are included with this submittal. In addition to what was previously submitted, the following comments are added in regard to the "Guidance Document".

Page 3: Step 3
If FDA determines that the test is simple (step 1), has an insignificant risk of erroneous result (step 2), but is NOT ACCURATE – it then falls unto the Secretary to determine whether it should be waived. When it is determined that a test is not accurate, it has no value. There should be no question as to whether or not it should be categorized as waived. Instead it should not even be cleared for market availability.

Page 3: Step 4
The statement "Then we will issue a notification of waiver and we will notify HCFA to ensure timely and proper CLIA survey reviews" infers that waived tests are reviewed during CLIA surveys. Waived tests are NOT routinely reviewed during CLIA surveys.

Page 4: Definition of "untrained user" and "laboratory professional"
"Laboratory professional" is defined in this document as an individual who meets the qualifications to perform *moderate* complexity testing. Under CLIA, this can be an individual who has the minimum qualifications of a high school diploma and on the job training. In physician office laboratories, moderate complexity testing personnel commonly seen are medical assistants, licensed practical nurses and registered nurses - not medical technologists or medical laboratory technicians. Therefore, individuals that are called "laboratory professionals" in this

document could be on the job trained personnel with no formal laboratory training. They would differ very little in practical laboratory experience from the "untrained user". We recommend that "laboratory professional" be defined as someone with **formal laboratory training**.

Page 5: Demonstrating "Insignificant Risk of Erroneous Result"
If a device has to rely on external controls to ensure that it is not producing erroneous results, it should not be waived. Since there are no inspection requirements for waived laboratories, there is no assurance that external controls will be run. This has already been demonstrated by the surveys of waived laboratories conducted under CLIA. Our experience inspecting moderate complexity laboratories shows that first time operators often fail to run external controls and/or do not take appropriate action when external controls fall outside acceptable limits. External controls should be relied on only if the device has lockout capability when the controls are either not run or the controls are outside acceptable limits.

Page 6: First Paragraph, Last Sentence
If external controls are required, labeling must say "MUST" perform and pass quality control prior to patient testing. Throughout this guidance document it must be clear in what is required by using the word "must", and avoidance of the word "should".

Page 7: Hardware and electronics integrity
Expand the statement regarding physical trauma to the unit to include dropping from a height from 1 to 4 feet.

Page 9: QC Materials
Recommending QC gives the user the option of deciding whether or not to follow the recommendation. If the quality control mechanism is going to ensure that there's an insignificant risk of an erroneous result, than the quality control **must** be a requirement versus a recommendation.

Page 10: "Demonstrating "Accurate"
The proposed CDC criteria (FR Vol. 60, No. 177, 9/13/95) required demonstration of accuracy with reference materials, patient samples, and patient samples containing interfering substances. In the Federal Register notice that transferred the clinical laboratory complexity categorization responsibility from CDC to FDA (FR Vol. 64, No. 250, 12/30/99) it is stated, "The criteria for categorization under CLIA will not change". However the guidance document does change the criteria for categorization.

The criteria for accuracy in the guidance document uses comparison of results of untrained users and laboratory professionals as a means of demonstrating accuracy. We feel this is more a demonstration of reproducibility rather than accuracy. Webster's dictionary defines accuracy as "adhering closely to a standard". Accuracy should be determined by comparing the method against a reference method. Many people equate a waived test with a highly accurate test since it "poses no unreasonable risk of harm to the patient". If the accuracy of the test is not measured

against a reference method, patients, insurance companies and the federal government will be paying for tests that offer very little clinical usefulness for the patient.

Page 11: Untrained/Professional Precision Study for Quantitative Tests
In addition to testing the low, medium, and high concentrations of specimens, include specimens that exceed the upper and lower reportable ranges of the instrument to test operator reactions under such crucial situations.

Page 18: Quality Control Labeling Recommendations
This whole section should be changed to read Quality Control Labeling ***Requirements*** versus ***Recommendations***. The labeling must be strong and clear. Quality control requirements should be in bold print and/or underlined. The instructions must clearly state that patient results must not be reported if quality control is not run or is outside of acceptable limits.

- Page 18 states that quality control instructions "should emphasize the value of repeat external quality control testing". However on pages 19 and 20, this becomes diluted when you *"suggest possible* minimum frequency *recommendations"*.
- Studies [1,2] have shown that the rate at which sites test external liquid controls is significantly higher when quality control is required ("must") versus recommended ("should"). Manufacturers must be required to use definitive language in their quality control instructions such that use of external controls are required, not just recommended. As the CLIA regulations currently stand, we cannot assure good laboratory practices for waived tests by requiring training, inspections or proficiency testing, since the regulations do not require waived laboratories to comply with these requirements. However the user of a waived device has to follow manufacturer's instructions for performance of the test, and this is where requirements can be clearly spelled out.

  [1. LaBeau KM. Final Report of the Findings of Questionnaire 3- Waived & PPMP Sites – Quality Assessment Activities. December 2000. 2. LaBeau KM. Final Report of the Findings of Questionnaire 15 – Quality Assessment of Waived Test Systems. January 2001. Pacific Northwest Laboratory Medicine Sentinel Monitoring Network. (www.phppo.cdc.gov/dls/mlp/pnlmsmn.asp).]

- The following reflects some of our experiences with sites adopting "creative" interpretations of product insert instructions for quality control recommendations/ requirements. In particular, deeming their waived device as a "moderate" complexity" device to avoid what they perceive as more stringent quality control recommendations/ requirements. It also appears that manufacturers are finding creative ways to allow laboratories not to follow the quality control instructions that were approved when the device was initially granted waived status. Instructions in the guidance document must be clear to manufacturers as to what type of FDA review is required when product or package inserts are modified from what was originally submitted for categorization as a waived test.

- Roche CoaguChek
  The product insert identifies this device as a CLIA-waived system. Quality control is clearly written, requiring the testing of two liquid controls with each new test kit and each operator. To avoid the expense of testing controls with multiple operators, a moderate complexity test site decided to call this device "moderate complexity" and run 2 levels of electronic controls daily. By doing so, they do not follow the manufacturer's instructions, since nothing in the product insert that they have describes handling this instrument as a moderate complexity device.
- Roche CoaguChek S
  This device is categorized as a CLIA-waived system yet the product insert instructions for the electronic controls allow the user the option of running it as a waived test or as a moderate complexity test. Waiver status was granted (by CDC) based upon the failsafe provision that instructions require that positive and negative external controls be tested with each new lot and operator. The subsequent re-wording of the product insert (reviewed by FDA???), to allow users an option to consider it moderate complexity (to avoid the use of external control materials) appears to go around the intent of assuring that the device meet the provisions for failsafe operation.

  On a practical basis, since this test is technically "waived", laboratory surveyors will not know to review the device for compliance with all applicable requirements for moderately complex testing, unless the testing site volunteers information about how they use the test. If the site subscribes to proficiency testing (as required for moderately complex tests), the proficiency testing data will not be posted electronically for monitoring by the state agency since this is a "waived test" versus a "regulated analyte".

  There is also a concern that individuals will translate this practice (of arbitrarily calling a waived test moderate) to other waived tests, where the product insert does not give such an option and provisions for failsafe operations require testing liquid control materials.

- Waived Strep tests where manufacturer's instructions say "positive and negative controls *should* be tested with each new kit or shipment and each change in operator...".

  The testing personnel in one lab interpreted "should" for "must" and wanted to change from a certificate of waiver to a moderate complexity testing license to avoid excessive testing of liquid controls by multiple operators. This creates confusion and a perception that even though a test is waived, a user can call it moderately complex to avoid more stringent quality control. Again the individuals may translate this practice to other waived tests, where the product insert may require testing of liquid control materials.

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DATE: October 9, 2000

TO: Dockets Management Branch (HFA-305)
Food and Drug Administration
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FROM: Gail V. Neuenschwander, Program Manager
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RE: Comments on Docket No. 00N-1394

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1. Criteria used to demonstrate that a test is a simple laboratory examination with "an insignificant risk of an erroneous result".
   - The test should demonstrate no significant inaccuracy and no significant imprecision (CDC criteria) when tested by untrained users;
   - Waived tests run by untrained users should be compared with tests run in certified labs by trained personnel. As long as the test result is being used in the same manner by the clinician, there should be no difference in the threshold of performance.
   - **The model should also include the criteria that the test must pose no reasonable risk of harm to the patient if performed incorrectly**. Certain analytes (e.g. glucose, prothrombin time) should not be considered for waived status because the risk of harm is too high if the test result is inaccurate.

2. Criteria to determine if a methodology is "so simple and accurate to render the likelihood of erroneous results by the user negligible".
   - Since the test can be performed by personnel that are untrained in laboratory procedures and do not have the necessary knowledge to judge when the testing system is not working properly, the system must be failsafe or foolproof to not allow a test result that could be inaccurate. This would

require validation of the manufacturer's data in a setting using untrained users. The test results should be accurate at least 95% of the time.

- Certainly the accuracy becomes less important if the test does not have any major clinical impact, but then the question arises of why the test is being performed, and why is the test available on the market if it can not demonstrate accurate test results. The patient is certainly expecting a valid test result, and has no idea that the test might have only 75% sensitivity or specificity and could be performed by untrained laboratory personnel, with no oversight of the testing.

- One of the reasons that CLIA came into being was so that we could go to any laboratory, be it the hospital or POL, and get the same accuracy of testing. If the accuracy of the test is not considered when a test is approved as waived, we will be back where we started prior to CLIA. This is already true with many of the tests that have already been granted waived status.

- Laboratorians and other scientists will have widely varying opinions about what should be done to demonstrate "accuracy" (comparison to well-characterized reference methods or some other criteria). The accuracy of the test should be tested using untrained users, and the manufacturer's data should be validated to some degree. Regardless of the criteria, a reasonable degree of accuracy must be expected for all waived tests prior to market release. But "accuracy" must also be put into perspective with clinical usefulness. Clinical requirements for accuracy will differ, depending on the test (glucose, prothrombin time vs. urine dipstick, fecal occult blood), the setting (intensive care ward, physician's office, health fair) and the intended use of the test result (screening vs. diagnosis vs. adjustment of medication dosage).

- An area of major concern is the number of tests that are being waived simply because they can be sold over-the-counter (OTC). Many manufacturers are placing new tests in that OTC category simply because it doesn't require that the consumer be subject to QC requirements. It should not be allowed to be waived simply because it gets OTC status. These tests basically have no safeguards built in, as there are no QC requirements.

There is a very different expectation of accuracy when a test is performed at home by a patient and when it is performed in a professional setting, particularly when the patient is paying for a professional result. If tests are used in the professional setting, they must meet more stringent accuracy requirements than those approved for patient self-testing.

In the many years we have surveyed laboratories we have encountered situations where personnel with no laboratory training perform "simple" tests such as glucose on meters that are approved by FDA for home use. There have been many instances where the devices were not checked with quality

control material to ensure that they were working properly. There were also many instances when the devices were checked with quality control material and the results showed that something was wrong, yet the patient tests were still performed on the instrument and no investigative action was done to see what was wrong with the procedure. The nonlaboratorians performing the test expected that if the device gave an answer, it must be working properly.

3. Criteria used to determine that a test will "pose no unreasonable risk to the patient if performed incorrectly".
   - From our experience of looking at regulated labs that theoretically know something about QC and QA, we have seen circumstance where there is potentially great harm that can be done to patients with waived tests. Many times when labs are asked if they are running controls for their waived prothrombin times, glucoses, and lipid panels they are not even aware that there is quality control available because their "rep never explained that to them". Recently reviewing some proficiency testing that one of our labs was taking for their waived prothrombin time test showed that they had gotten a high prothrombin time result in seconds, but when they calculated the INR, which is what gets reported to the doctor, they reported it out as a normal INR. Even after they had been running this test for quite some time, being untrained laboratory personnel, they did not realize that this was an erroneous result. If this had been a patient, it could have had serious consequences.

   - The consequences of an erroneous result should be considered when granting waived status to any test by getting input from laboratory experts, clinicians and patients.

4. Screening tests that require a second test for confirmation.
   - It would be difficult to ensure that a confirmatory test would be done in each case, since there is no oversight of labs only performing waived testing. If the thresholds were to be lowered for these tests, it would be of utmost importance that the manufacturers label such tests in **LARGE BOLD PRINT** that a confirmatory test is mandatory, and that this information must be relayed to the patient as well.

   - Many people equate a waived test with a highly accurate test since it "poses no unreasonable risk of harm to the patient". In many cases manufacturers will have different versions of a test and when asked will say that the waived test is not their most sensitive or specific assay. The regulated versions of these tests require a few more testing steps, which increases the sensitivity and specificity. A test that gives false positive or negative results, or an erroneous result because it needs to be so simple to get waived status, certainly isn't serving the patients' well being. It potentially also increases healthcare costs to Medicare, the patient, or insurance company for a test that has little or negative value to the patient and may need to be repeated by a more accurate

method. If you had to chose between a test that was only 50% accurate and one that was 90% accurate, which one would you want to pay for or use to diagnose your illness?

General comments

The CLIA law states that tests, which are to be categorized as, waived are simple laboratory examinations and procedures, which have an insignificant risk of an erroneous result including tests:

- Approved by FDA for home use;
- Employ methodologies that are so simple and accurate as to render the likelihood of erroneous results negligible; or
- Pose no reasonable risk of harm to the patient if performed incorrectly.

Concern arises when a test is classified as waived based on **only one** of the criteria above, without taking into consideration the risk of harm to the patient if performed incorrectly. Since there are no personnel requirements for persons performing waived tests they can be performed by someone with no clinical laboratory training. If a test is performed incorrectly for such analytes as glucose or prothrombin time (both with methods that are currently waived) the risk of harm is immense.

How many true patient outcome studies have been done to demonstrate whether the "likelihood of erroneous results is negligible" for a particular waived test device? Who has demonstrated how often patients get the correct diagnosis or obtain appropriate treatment when testing is performed with a waived test device? Who has demonstrated how often patients are misdiagnosed or obtain inappropriate treatment?

How much does the clinical environment contribute to the usefulness of the test result and overcome any shortcomings in meeting some arbitrary "accuracy" limits or agreement with a "well-characterized reference method"? When waived testing is done in conjunction with the patient's visit, the patient and the clinician do have the unique ability to judge the reliability of the results that traditional laboratories do not have. Does that capability outweigh the need for overly strict accuracy requirements when used in that setting? For example, what would the accuracy expectations be for a prothrombin time result, where the patient and clinician know the patient's coumadin dose, other medications, diet, and the range of values deemed appropriate for that patient, considering their unique diagnosis and history?

Patient outcome studies must be done. Without data on patient outcomes, it is difficult to determine whether the "likelihood of erroneous results" for a particular waived test device is negligible or not.