Executive Summary – Overview of the FDA Waiver Process

In the United States, the "waiver" concept affects both laboratories and the tests that they use for clinical purposes. First, the Clinical Laboratory Improvement Amendments of 1988 (CLIA) provided for three categories of laboratories: high complexity, moderate complexity and waived. Waived laboratories are subject to minimum regulatory oversight including requirements to obtain a certificate of waiver from the Centers for Medicare and Medicaid Services (CMS), to use only laboratory tests categorized by the Department of Health and Human Services (DHHS) as waived, and to follow manufacturer's instructions. There are no explicit regulatory requirements for CLIA inspections, for specific training or experience on the part of laboratory personnel, for specific measures of day-to-day control over testing environments or operators doing testing, for use of proficiency testing or quality assurance programs in the provision of waived tests, or for physician oversight in the ordering or use of test results.

Second, CLIA, 42 U.S.C. 263a(d)(3) Examinations and Procedures, as modified by the Food and Drug Administration Modernization Act, reads as follows regarding tests that may be performed by laboratories with a Certificate of Waiver:

> The examinations and procedures … 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 examination and procedures that have an insignificant risk of an erroneous result, including those that – (a) employ methodologies that are so simple and accurate as 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.

From 1995 to 2008, most CLIA waiver decisions were based on this statutory language and on information provided in a draft proposed regulation published in 1995 by the Centers for Disease Control (CDC) (FR 60(177):47534-47543).

In January 2008, based on input from the Clinical Laboratory Improvement Amendments Committee (CLIAC) and from numerous outside parties, FDA published a guidance entitled "Guidance for Industry and FDA Staff: Recommendation for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices."

The 2008 guidance requires the following components in a CLIA waiver application:

A description of the device to demonstrate it is simple. To meet this requirement the device should be designed in a manner that assures use of unprocessed specimens and reagents/equipment that do not entail any skilled manipulation, no operator intervention, no need for technical or specialized training, and only simple operational steps that can easily be followed using provided instructions. The guidance includes some examples of what would be considered simple.

The results of risk analysis including the identification of potential sources of error for the device. The sponsor of the test is expected to demonstrate that (1) the test system design is robust and insensitive to environmental and usage variation and (2) that all known sources of error are effectively controlled using lock-out (fail-safe features) or failure alert features. The guidance includes a comprehensive list of 34 elements under four categories (operator error/human factors, specimen integrity and handling, reagent integrity, and hardware/software/electronic integrity) to be considered in the waiver process.

The results of risk evaluation and control including a description of (1) measures implemented to mitigate the risk of errors and (2) validation and/or verification of these measures. Studies to demonstrate risk mitigation should be conducted under conditions that stress the device to show how fail-safe and failure alert mechanisms work. These should be linked to recommendations for external quality control and confirmed by clinical studies performed to demonstrate device performance.

A description of the design and results of clinical studies conducted to demonstrate that the device has an insignificant risk of erroneous results in the hands of the intended user. Sponsors must demonstrate that a waived device will provide accurate and reliable results in the hands of intended users (non-laboratory trained health care professionals) in real world settings under real world intended use.

Proposed labeling with instructions for use consistent with a device that is "simple." To accommodate the wide variety of potential operators, device labeling should be written at a 7th grade reading level or lower and to be accompanied by Quick Reference Instructions. FDA encourages use of educational programming and proficiency testing as mechanisms to assure quality in waived settings.

FDA recognizes that a critical issue to be addressed in waiver decision making is the trade-off between increased access and the potential for poor device performance or incorrect results in an unregulated use setting. Unfortunately, to date, little outcome information is available on the course of this trade-off in routine clinical use.

Executive Summary – Assessment of the Complete Blood Count and Differential Cell Count for the FDA Waiver Process

The complete blood count (CBC) and differential cell count (Diff) is a group of assays used in various combinations to detect or assess a broad spectrum of disorders. Among these are anemia, bacterial and viral infections, leukemia, some clotting disorders, vitamin deficiencies, and congenital disorders. The CBC or CBC/Diff is also used to monitor drug treatment and patient response to varied treatment regimens. Although these assays are frequently performed and usually highly automated, they require professional knowledge to interpret and troubleshoot the many variables associated with the results. In practice, only laboratory professionals have been charged with assuring

the quality of CBC or CBC/Diff results. This is due to the complexity of knowledge required to detect and resolve many analytical issues for assuring quality results.[1]

With the advent of testing facilities outside of the traditional centralized laboratory, many assays have been developed to allow for testing that is performed at the point of care or by non-laboratorians. Although it is commonly believed that testing in a waived laboratory increases access to useful results in some clinical settings, it is extremely important that patient care is not compromised by the quality of test results. Therefore, it is crucial that waiver be granted only to tests that (a) employ methodologies that are sufficiently simple and accurate as 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. Until now, the CBC and CBC/Diff have not been approved for waiver because there has not been an analyzer that is capable of successfully controlling the many sources of analytical error than can result from lack of oversight by a laboratory professional. Furthermore, it is unclear what fail-safe features are needed to exclude an unreasonable risk of harm to the patient from incorrect test results.

[1] Measurements of hemoglobin and spun hematocrit, two components of the CBC, were waived in the 1992 publication of the CLIA regulation.

Panel Questions

Pre-analytical

Hematology parameters with automated differential cell counts have traditionally required technical and interpretative skills from a laboratory professional to assure proper results and quality control. Laboratory professionals typically control a variety of pre-analytical variables that can affect the accuracy of CBC/Diff results including hemolysis, gross presence of interferents (e.g., bilirubin, lipid), short or long sampling, or partial clotting (e.g., fibrin strands).

1. Considering the pre-analytical issues, can CBC/Diff testing meet the waiver criteria that the test is "simple" and shall "have an insignificant risk of erroneous result"?

   If the answer is yes,
   (a) Do you have suggestions on how a waiver submission could address pre-analytical error sources? In particular, can these be addressed adequately by extrapolation from the professional use setting, or do they require assessment specifically in the waived setting?

   (b) Are there any pre-analytical sources of error for CBC/Diff that will be particularly difficult to control; and if so, do you have suggestions on how to address these?

   If the answer is no, please explain why.

Analytical

Incorrect results can also occur as a result of a large number of biologically common phenomena causing analytical variation. These include cold agglutinins, rouleaux, osmotic matrix effects, platelet agglutination, giant platelets, unlysed erythrocytes, nucleated erythrocytes, megakaryocytes, red cell inclusions, cryoproteins, circulating mucin, leukocytosis, in vitro hemolysis, extreme microcytosis, bilirubinemia, lipemia, etc. The user in the waived setting will not likely understand these potential sources of error; will not be able to perform studies to confirm site specific user metrics such as reference ranges or limits of operation; and will not be able to perform microscopic quality control of results using blood smears.

2. Please explain what data/information a waiver submission should include to address these or other analytical issues; or if these issues cannot be adequately addressed in a submission for waiver categorization, please explain why.

Post-analytical

Depending on the particular test system involved, CBC/Diff testing can report results for a wide range of hematologic analytes. The clinical uses of CBC/Diff testing range from non-specific screening, to time-critical and clinically important diagnostic decision-

making. When unexpected or problematic results are generated, operators in moderate or high complexity labs are trained to identify these potential sources of error, and can use a variety of techniques including evaluation of microscopic smears to control the quality of results. This is obviously not possible in the waived setting.

3. In order to ensure that there is no unreasonable risk to the patient from incorrect test results, are there particular CBC/Diff analytes or combinations of analytes that are more appropriate than others for use in a waived test setting?

4. Should there be specific provisions for follow-up of some results (e.g., "critical/panic values"), or other post-analytical measures that should be considered for waived CBC/Diff testing? Please explain.

5. How should the lack of trained operators in identifying post-analytical anomalous or incorrect results be addressed?

Performance

6. Total analytical error (a composite of bias and imprecision) represents the interval that contains 95% of waived test results compared to an established comparative method. Assuming that the issues discussed above do not preclude CLIA waiver, what level of Allowable Total Error (ATE) should be considered?

   a) According to the 2008 FDA CLIA Waiver Guidance, for analytes that have existing performance limits for professional use (those listed in the CLIA 88 regulations), these limits should be used to define boundaries of the ATE zones. These limits are expressed in CLIA 88 as criteria based on the fixed percentage difference from the target value.

      For the analytes listed in the table below, CLIA 88 Regulations provide the following limits for acceptable performance:

Analyte	CLIA 88 acceptable limits*
Hemoglobin	± 7%
Hematocrit	± 6%
WBC	± 15%
RBC	± 6%
Platelet count	± 25%

*In the table above, other than hemoglobin, all results are in SI units (i.e., 10^9/L).

      To assure clinically relevant performance should these values of ATE be considered as the limits of acceptable performance for these analytes as measured by the waived devices, or should other (more/less stringent) criteria be considered? Please discuss.

b) Limits for Erroneous Results (LER) represent results for which error is large enough to present harm to a patient (values falling outside the established total analytical error). To assure results are not harmful to patients, values of the waiver method should not differ too much from the comparative traceable method. For example, if the traceable method indicates severe anemia, it would be inappropriate for the waiver method to produce a normal hemoglobin or hematocrit value. Please provide your best professional opinion on how the LER should be defined for each analyte. [Note that values can fall beyond the ATE but still not fail due to the LER.] What is the maximum error that would not endanger a patient's health?

Analyte	**Limits of Erroneous Results** (maximum error, 0% of Waiver results exceed these limits)
Hemoglobin	
Hematocrit	
WBC	
RBC	
Platelet count	

c) In the CLIA 88 regulation, there are no ATE criteria (criteria in the form of fixed percent or fixed number) for WBC differentials, and consensus recommendations on ATE are not found elsewhere. An example of recommendations for maximum difference between duplicate measurements from the CDC NHANES program is: neutrophils $0.4x10^9$/L, lymphocytes $0.2x10^9$/L, monocytes $0.2x10^9$/L, eosinophils $0.2x10^9$/L, basophils $0.2x10^9$/L. To assure clinically relevant performance, what ATE do you recommend for 3-part differentials and 5-part differentials?

You may wish to define limits that vary by range (e.g., surrounding cut-off values that drive various medical decisions) and, for purposes of discussion, we suggest considering the following sets of ranges for each analyte. You may specify limits as a percentage or in absolute numerical counts.

3-part differentials (absolute values in SI units 10^9/L):

Analyte	**Reference Interval**	**Allowable Total Error** (95% of Waiver results in these limits)	
		Ranges	**Acceptable limits**
Lymphocytes	1.0 -4.8	Low less than 1.0	
		Medium 1.0 -4.8	
		High greater than 4.8	
Monocytes	0.0-0.8	Low 0.0-0.8	
		High greater than 0.8	
Granulocytes	1.8 – 7.5	Low less than 1.8	
		Medium 1.8 -7.5	
		High greater than 7.5	

5-part differentials (absolute values) where granulocytes are further differentiated:

Analyte	**Reference Interval**	**Allowable Total Error**	
		Ranges	**Acceptable limits**
Basophils	0.0-0.2	Low less than 0.2	
		High greater than 0.2	
Eosinophils	0.0-0.8	Low less than 0.8	
		High greater than 0.8	
Neutrophils	1.8 – 7.8	Low less than 1.8	
		Medium 1.8 -7.8	
		High greater than 7.8	

d) Limits for Erroneous Results represent results for which error is large enough to represent harm to a patient (values falling outside the established total analytical error). To assure results are not harmful to patients, values of the waiver method can

not differ too much from the comparative traceable method. For example, if the patient is immunocompromised and the traceable method indicates the presence of very low lymphocyte values, it would be inappropriate for the waiver method to produce a normal lymphocyte value. Please provide your best professional opinion on how the LER should be defined for each analyte. [Note that values can fall beyond the ATE but still not fail due to the LER.] What is the maximum error that would not endanger a patient's health?

3-part differentials (absolute values):

Analyte	**Limits of Erroneous Results** (maximum error, 0% of Waiver results exceed these limits)
Lymphocytes	
Monocytes	
Granulocytes	

5-part differentials (absolute values):

Analyte	**Limits of Erroneous Results** (maximum error, 0% of Waiver results exceed these limits)
Basophils	
Eosinophils	
Neutrophils	

7. If a CBC, with or without differential, is subject to waiver because pre-analytical, analytical and post-analytical issues are addressed in a satisfactory manner and accuracy is demonstrated that meets CLIA requirements, what frequency of Quality Control (QC) should be performed? What are the circumstances or events when additional QC measurements should be performed (e.g., every new lot, every new operator)?