

## INFORMATION

### Regulation:

#### [PART 864 -- HEMATOLOGY AND PATHOLOGY DEVICES](#)

##### Subpart F--Automated and Semi-Automated Hematology Devices

###### Sec. 864.5200 Automated cell counter.

(a) *Identification.* An automated cell counter is a fully automated or semi-automated device used to count red blood cells, white blood cells, or blood platelets using a sample of the patient's peripheral blood (blood circulating in one of the body's extremities, such as the arm). These devices may also measure hemoglobin or hematocrit and may also calculate or measure one or more of the red cell indices (the erythrocyte mean corpuscular volume, the mean corpuscular hemoglobin, or the mean corpuscular hemoglobin concentration). These devices may use either an electronic particle counting method or an optical counting method.

(b) *Classification.* Class II (performance standards).

###### Sec. 864.5220 Automated differential cell counter.

(a) *Identification.* An automated differential cell counter is a device used to identify one or more of the formed elements of the blood. The device may also have the capability to flag, count, or classify immature or abnormal hematopoietic cells of the blood, bone marrow, or other body fluids. These devices may combine an electronic particle counting method, optical method, or a flow cytometric method utilizing monoclonal CD (cluster designation) markers. The device includes accessory CD markers.

(b) *Classification.* Class II (special controls). The special control for this device is the FDA document entitled "Class II Special Controls Guidance Document: Premarket Notifications for Automated Differential Cell Counters for Immature or Abnormal Blood Cells; Final Guidance for Industry and FDA."

[67 FR 1607, Jan. 14, 2002]

## Background:

Taken together, the test systems under the two regulations cited above account for the great preponderance of testing to distinguish and count the formed elements in blood (complete blood count, CBC and WBC differential count, Diff). Traditionally, clearance for these devices has been limited to use in laboratories staffed by laboratory professionals and qualified for moderate or complex testing. With the increase in point-of-care and waived testing, manufacturers are requesting clearance of devices for use in these non-traditional testing facilities.

Clinical concerns include issues of operators' interpretation and reporting of abnormal or unusual results. In the laboratory, technologists are trained to verify and interpret abnormal and unusual results such as cold agglutinins, clumped platelets, clotted specimen, nucleated red cells, lipemic interference, differences in hemoglobin and hematocrit, etc., which are common occurrences in the laboratory. The means of providing such insight by operators in a waived test setting, or the impact of dispensing with it, needs to be considered.

Other concerns include fail safe issues that may not be detected due to the less frequent testing of quality control material. These devices will also be used in areas that may not be supported by healthcare professionals to provide technical guidance for resolving discrepancies and interpreting critical results.

In a 510(k) submission, a sponsor needs to demonstrate substantial equivalence to a previously cleared device with the same intended use. In a CLIA waiver submission, a sponsor is required to demonstrate accuracy and negligible error in the hands of the intended users.

About half of the sites that are licensed to use only CLIA waived devices are not doctor's offices but may be nursing homes and other settings with minimal or no laboratory supervision. Once a device is waived, it is not possible to restrict the use of the device to a specific waived setting (e.g. only in a doctor's office).

## Concerns Related to Demonstrating Insignificant Risk of An Erroneous Result – “Accuracy”:

The 2008 FDA CLIA Waiver guidance “Guidance for Industry and FDA Staff: Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices” includes criteria for demonstrating the waiver device is “accurate” in the hands of intended operators. According to the guidance, it should be demonstrated that the test being waived, in the hands of intended operators in the waived setting, is comparable to tests whose results of measurements are traceable to designated references of higher order.

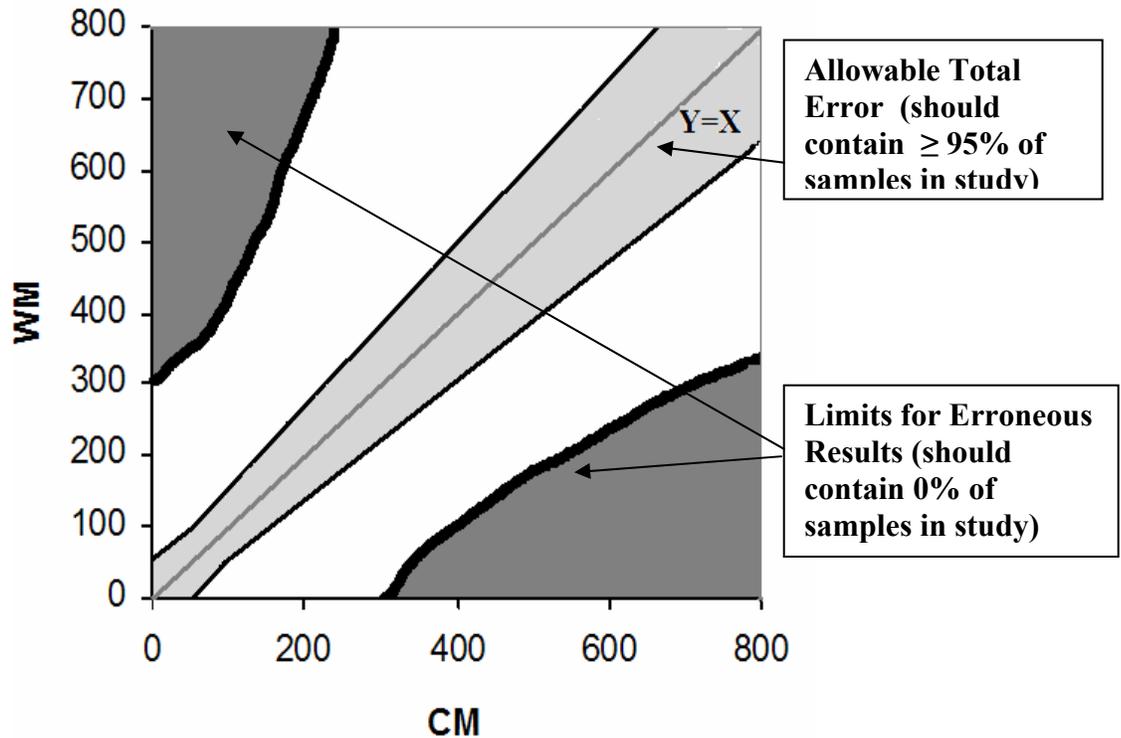
There is a need to define accuracy, which can be a challenge for a hematology device with either a 3 part WBC differential (lymphocytes (LYM), granulocytes (GRN) and monocytes (MON)) or a 5-part WBC differential (LYM, MON and Neutrophils (NEU), Eosinophils (EOS) and Basophils (BAS)). A reference method based on manual counts has a high degree of measurement error, but a sponsor does have the option of doing 2 or more measurements via a reference method and averaging the results to obtain final results for comparison.

The 2008 FDA CLIA Waiver Guidance allows comparison to a well characterized (e.g. automatic system) which has traceability to a reference method (or reference materials), has at most a small amount of bias and also has low imprecision.

Under the 2008 FDA CLIA Waiver Guidance, sponsors can provide documentation for an Allowable Total Error for each analyte reported. The Allowable Total Error is the amount of error one can tolerate without compromising clinical management of the patient. In addition to using a reference method for comparison, the sponsor may elect to compare their device to a traceable method with low variability and almost no systematic bias (because a traceable method is calibrated using a reference method or reference materials). Real samples with real intended users in a setting comparable to waived settings are strongly recommended under this new guidance.

The new guidance calls for 360 specimens tested using at least 9 operators over three typical waiver settings. Results from the samples must span the measurement range of the device. Some samples may be “spiked” with the analyte or retrieved from archives. According to the 2008 FDA CLIA waiver guidance, 95% of the 360 observations must fall within the limits defined by the Allowable Total Error (ATE). None of the 360 results should be in a range thought to put the patient at risk for harm due to the results (zones of Limits of Erroneous Results (LER)).

A hypothetical example of Allowable Total Error (ATE) and Limits for Erroneous Results (LER) is diagramed below.



**Figure 1. Example of ATE and LER zones**

Several sources of information can be used to establish criteria for ATE and LER zones for the analyte measured by the Waiver device.

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 fixed criteria based on the percentage difference from the target value (not the number of standard deviations).

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.  $10^9/L$ ).

The limits can be used in the following way. Let a value %R be the allowable percent of deviation (e.g., as described in the CLIA regulations cited above) in the waived method

(WM) result from the target value of a comparative method (CM). For example, the value of %R equals 7% for hemoglobin. Once the value of %R is defined, the zone of ATE is bounded by  $CM \pm \%R * CM$ . If, when values of the CM and WM are both low, one can tolerate a larger value of  $\%R * CM$  without invalidating the medical usefulness of the WM results, then the zone of ATE for these low values might be established as  $CM \pm D$ , where D is a fixed number. Thus, the ATE zone can be defined as  $CM \pm D$  for low CM values (i.e., below a defined threshold value) and  $CM \pm \%R * CM$ , for high CM values that exceed the threshold.

There are no criteria for ATE (in the form of fixed percent or fixed number) for WBC differentials cited in the CLIA 88 regulation. Criteria for the ATE for Diff results is one area in which FDA seeks recommendations from the panel.

As noted in the graph above, none of the observations from the WM vs CM study should fall in a region called Limits of Erroneous Results (LER). When a value falls within the LER, patient care may be compromised. Criteria for the LER are not given in regulation either for CBC results or for Diff results. Recommendations for these criteria are also sought from the panel.