

# Panel Question #1

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## Pre-analytical

In performing CBC/Diff tests, laboratory professionals traditionally control for a variety of pre-analytical variables such as hemolysis, gross presence of interfering substances (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 to the question is yes,*

- a. Should submissions address pre-analytical errors specifically in the waived setting? If so, how?**
- b. Please identify any pre-analytical sources of error for CBC/Diff that will be particularly difficult to control, and how they might be addressed.**

*If the answer is no, please explain why.*

# Panel Question #2

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## Analytical

In performing CBC/Diff testing, laboratory professionals traditionally control for a variety of biological factors that produce 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.

- 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.**

# Panel Questions #3, #4, #5

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## Post-analytical

Depending on the particular test system involved, CBC/Diff testing can report results for a wide range of hematologic analytes and in a wide variety of use settings. Operators in moderate or high complexity labs are trained to control potential post-analytical sources of error using a variety of techniques, including evaluation of microscopic slides.

- 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?**

# Panel Question #6a

## Performance

According to the 2008 FDA CLIA Waiver Guidance, for analytes that have existing performance limits for professional use (i.e., those listed in the CLIA 88 regulations), the published limits should be used to define boundaries of the allowable total error (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:

<b>Analyte</b>	<b>CLIA 88 acceptable limits</b>
Hemoglobin	$\pm 7\%$
Hematocrit	$\pm 6\%$
WBC	$\pm 15\%$
RBC	$\pm 6\%$
Platelet count	$\pm 25\%$

**6a. Do these appear to be the correct ATE target values? Please discuss.**

# Panel Question #6b

Limits for Erroneous Results (LER) represent results for which error is large enough to present harm to a patient.

Analyte	Limits of Erroneous Results (Maximum Error; 0% of waiver results exceed these limits.)
Hemoglobin	??
Hematocrit	??
WBC	??
RBC	??
Platelet Count	??

**6b. For each analyte, what is the maximum error that would not endanger a patient's health?**

# Panel Question #6c

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In the CLIA 88 regulation, there are no ATE criteria (either as percentages or as absolute counts) 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  $0.4 \times 10^9/L$

Lymphocytes  $0.2 \times 10^9/L$

Monocytes  $0.2 \times 10^9/L$

Eosinophils  $0.2 \times 10^9/L$

Basophils  $0.2 \times 10^9/L$ .

You may wish to define ATE limits that vary by ranges within analytes (e.g., across cut-off values that drive various medical decisions). For purposes of discussion, we suggest analyte-specific ranges in the following two slides. FDA requests ATE recommendations for three-part and five-part differential counts.

# Panel Question #6c (Cont'd)

**6c. To assure clinically relevant performance, what ATE do you recommend for 3-part differentials and (in the following slide) 5-part differentials? You may specify limits as a percentage or in absolute numerical counts.**

Analyte	Reference Interval*	Allowable Total Error (95% of waiver results in these limits)	
		Ranges	ATE
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)	??

\*Reference Intervals and Ranges are in SI units  $10^9/L$

# Panel Question #6c (Cont'd)

**6c (cont'd) Please recommend ATE here for 5-part differential counts, in which granulocytes are further differentiated as neutrophils, eosinophils and basophils. You may specify limits as a percentage or in absolute numerical counts.**

Analyte	Reference Interval*	Allowable Total Error (95% of waiver results in these limits)	
		Ranges*	ATE
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)	??

\*Reference Intervals and Ranges are in SI units  $10^9/L$

# Panel Question #6d

Limits for Erroneous Results represent results for which error is large enough to represent harm to a patient.

**6d. For each analyte, 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.)
Lymphocytes	??
Monocytes	??
Granulocytes	??
The following three analytes are for 5-part differential only	
Basophils	??
Eosinophils	??
Neutrophils	??

# Panel Question 7

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## Quality Control

- 7. What frequency of Quality Control (QC) should be performed for these analytes in the waived setting? With what circumstances or events should additional QC measurements be performed (e.g., every new lot, every new operator)?**