Potential Waiver of Complete Blood Count/Differential Testing

Clinical Laboratory Improvement Advisory Committee

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CLIA Waiver for Automated Cell Counters and Automated Differential Cell Counters

- Contacts from industry for waiver of various devices intended to identify and count cells in peripheral blood.
- FDA concerns about suitability for waiver
- Meeting of the FDA Hematology and Pathology Devices Panel, 18 July 2008
- Dr. Valerie Ng as one panelist

Panel Question #1

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.

Question #1 Panel Summary

- “CBC testing as it is currently performed with known instrumentation is not simple and there is the potential for erroneous results.”
- “This may change should there be instrumentation developed that can properly identify the pre-analytical variables that we are concerned about and should an instrument be able to demonstrate such in an effective manner, then the panel generally believes that waived testing may be applicable to such instrumentation.”

Question #1 Additional Points

- “Long list of flagging issues”
- Much discussion about the need for “…some sort of training requirements, even if they’re fairly minimal, on the people who are going to operate…”
- Stipulations about operator training are not part of the waiver context.

Panel Question #2

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.

Question #2 Panel Summary

- "…there are many issues that would face an instrument pertinent to its proper analysis of a CBC sample…"
- "very secure fail-safe mechanisms" needed
- "significant issue" about how account for the issues in reporting; which results "reportable" for problem samples?
- Concern that study of 360 samples "would not be adequate to exemplify … potential analytical interferences"

Panel Questions #3

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?**

Question #3 Panel Summary

- "…the Committee generally believes that the combination of perhaps hemoglobin with total white cell count might be the most appropriate for a waived submission, possibly to include a percent neutrophil count, but wants to make note that omission of other results may be problematic because of the assumption that those results that are not reported may be normal."

Panel Questions #4

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.

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.**

Question #4 Panel Summary

- "…there would have to be specific provisions for some result because the instrument can generate critical or panic results. In addition to that, there would also be the potential for erroneous results, and these would require follow-up. "

Panel Questions #5

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.

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

Question #5 Panel Summary

- "…given the current instrumentation as we know it, we don't feel it would be possible to have untrained personnel that could identify the post-analytical problems or that could identify the problems, but if the instrumentation were to be advanced such that there would be fewer inherent errors, then it would be potentially possible to have untrained personnel or not formally trained personnel."

Panel Question #6a

Performance

According to the 2008 FDA CLIA Waiver Guidance, for analytes that have existing performance limits for proficiency testing (PT) (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 PT performance:

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

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

Question 6a Panel Summary

- “the Panel generally feels that these allowable errors should be stringent and perhaps more stringent than CLIA 88 regulations, but there are some very important caveats to that, that the FDA consider the physiological variation and perhaps consider another method for evaluating the error, and it's been proposed that the locally smoothed median absolute difference curve analysis be considered.”

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?

Question 6b Panel Summary

- "…if I can summarize the Panel's opinion, in regard to determining how the LERs should be obtained, or determined for each of these analytes, there was significant discussion and perhaps no real consensus. There's some thought that perhaps the LER should be redefined, that perhaps we should look at clinically relevant zones and, for each of the ranges that we're measuring, determine when clinical decision-making occurs, and if results should vary in a significant manner, to change clinical decision making and that would be different along each of the analytes and along the range."

Panel Question #6c

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 $0.4x10^9/L$
Lymphocytes $0.2x10^9/L$
Monocytes $0.2x10^9/L$
Eosinophils $0.2x10^9/L$
Basophils $0.2x10^9/L$.

You may wish to define ATE limits that vary by ranges within analytes (e.g., acoss 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

Question 6c Panel Summary

- "…the Panel generally feels that the accuracy standards as they are currently available would be the minimum and that the Panel would recommend perhaps more stringent numbers."
- FDA notes value and welcome for any additional information about appropriate ATE limits to set for differential counts.

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	**??**

Question 6d Panel Summary

- Specific recommendations defining the Limits of Erroneous Results for differential cell counts were deferred, in light of the previous discussion of LER for usual CBC analytes alone.

Panel Question 7

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)?

Question #7 Panel Summary

- "…the Panel generally feels that QC is a important component of the testing and that it be offered at multiple levels in a manner to mimic patient samples with a QC lockout option of the instrument or portion of the instrument -- function of the instrument."