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Performance Goals for the Internal Quality Control of Multichannel Hematology Analyzers; Approved Standard

This document addresses performance goals for analytical accuracy and precision for multichannel hematology analyzers; the relationship of these goals to quality control systems and medical decisions; and recommendations for minimum calibrator performance and the detection of measurement errors.

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Performance Goals for the Internal Quality Control of Multichannel Hematology Analyzers; Approved Standard

Abstract

Performance Goals for the Internal Quality Control of Multichannel Hematology Analyzers; Approved Standard (NCCLS document H26-A) provides recommendations for performance goals for the internal quality control of multichannel hematology analyzers on the basis of the use of physical and chemical standards, accepted reference methods, subcommittee recommendations on what is currently achievable, and the concept of medical usefulness. Critical performance characteristics of quality control systems (i.e., the probabilities of error detection and false rejection) also are considered. A well-designed internal quality control program must achieve the level of error detection specified in this standard; yet it should not be so sensitive as to falsely reject valid results.

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Contents

Foreword

The primary objective of quality control in the clinical laboratory is to ensure that the analytical values are sufficiently reliable to be used in the care of patients. Once quality goals are established for an assay, their results can be evaluated in terms of clinical usefulness. This approach can have distinct advantages in the quality control of multichannel hematology analyzers.

This standard examines the effects of the following variables on performance goals:

- Calibration of the instruments
- Imprecision of the analytical measurements
- Analyte variations within an individual
- Inherent differences in values among persons.

The first two of these sources of variation define opportunities for improvement in analyzer design. The second two define irreducible biological variables.

In this document, the Subcommittee on the Blood Count provides goals for standards of performance that are useful for diagnosis, patient monitoring and control of therapeutic regimens. These performance goals set the stage for a review of quality control options that are intended to provide a framework for ensuring that patients' assays are made as precisely and accurately as the analyzer allows. To this end, the production of a companion document is planned that will address the principles and methods of quality control that will help users and makers of automated hematology analyzers achieve these goals. This approach should stimulate improvements in analyzer design and interpretation of assay results. One goal is that manufacturers will recognize the need to coordinate the performance of different analytical methods so that assay results from different analyzers will have a reasonable degree of interchangeability. A further goal in this context is for designers to strive to minimize some of the existing disparities between analyzer and reference assays.

Universal Precautions

Because it is often impossible to know which might be infectious, all patient blood specimens are to be treated with universal precautions. Guidelines for specimen handling are available from the U.S. Centers for Disease Control and Prevention [MMWR 1987; 36 (Suppl 2S) 2S–18S]. NCCLS document M29-T2, *Protection of Laboratory Workers from Infectious Disease Transmitted by Blood, Body Fluids and Tissue—Second Edition; Tentative Guideline*, deals specifically with this issue.

Key Words

Accuracy, analytical bias, calibration, calibrator, imprecision, linearity, quality control, sensitivity, specificity, value.

Performance Goals for the Internal Quality Control of Multichannel Hematology Analyzers; Approved Standard

1 Introduction

The elements of the complete blood cell count (CBC) included in this standard are the measurement of hemoglobin concentration (Hb), hematocrit (Hct), erythrocyte count (RBC), mean cell volume (MCV), leukocyte count (WBC), and platelet count (Plt). Goals for the derived red cell indices, mean cell hemoglobin (MCH), and mean cell hemoglobin concentration (MCHC) are not included.

The widespread acceptance of automated whole blood analyzers and concomitant improvements in calibrators and control materials has had a major effect on the efficiency of laboratory operation. Also, a marked improvement in intralaboratory and interlaboratory precision and accuracy has occurred. For values in the adult reference range, within-laboratory coefficients of variation (CV) of less than 1.0% for RBC, Hb and MCV are readily achieved on the newest generation of analyzers, while WBC counts show CVs less than 2% and Plt counts CVs less than 3%.[1-5] However, maintaining accuracy by preventing or predicting drift during routine operation remains a problem with some types of analyzers.

2 Scope

This document presents performance goals for analytical accuracy and precision of multichannel hematology analyzers capable of being calibrated. These clinical performance goals relate the majority of routinely produced analytical values to reference populations and to action limits established by the laboratory.

Goals for standards for specimen handling, equipment operation, electronic checking, preventive maintenance, and reagent quality are not included in this document, but their effect on performance is discussed where relevant.

This standard will be useful to laboratory directors, supervisors, quality control officers, and others who have responsibilities for ongoing quality control in hematology laboratories, particularly in the light of current regulatory pressures. It is a starting point for national and international discussion of the issues surrounding the design of quality control systems for multichannel hematology analyzers and as an aid to manufacturers who seek to improve the performance of their products.

3 Definitions

Within this document, terms are defined as follows:*

Accuracy: A measure of agreement between the estimate of a value and a "true" value; quantifiable in terms of departure from accuracy; expressed as systematic error or bias.

- *Accuracy, of an analytic process*: Expressed as the difference between the average result obtainable by a method under specified conditions and the result accepted as true or standard; expressed in the same units as the result, or as a percentage of the standard result (relative accuracy).

  NOTE: The lower the difference, the higher the accuracy (the lower the inaccuracy). Conventionally, this difference includes only process inaccuracy (process bias or systematic error) because the contribution of process imprecision (random error) is minimized by the averaging of multiple determinations.

- *Accuracy, of a result*: Expressed as the difference between a result and the "true" value.

*References include ICSH, *Rules and Operating Procedures*, 1991; ISO, *International Vocabulary of Basic and General Terms in Metrology, 2nd Edition*, 1993; NCCLS, NRSCL8-P2, *Nomenclature and Definitions for Use in NRSCL and Other NCCLS Documents—2nd Edition; Proposed Guideline*.

NOTE: This difference includes contributions not only from process inaccuracy but also from process imprecision, especially when one determination per specimen is the rule. It is expressed in the same units as the result.

- *Accuracy, of a control result*: Same as for a result.

  NOTE: In this case, because the accepted mean and standard deviation of the population are known, the bias can be expressed alternatively as a Z-score, the signed difference between the result and known mean divided by the known standard deviation. The Z-score is unitless and is a uniform expression for all analytes.

Bias (synonym for "systematic error"): A quantitative measure of inaccuracy or systematic departure from accuracy under specified conditions of analysis. A signed difference (+, –) between two values.

NOTE: In general, the difference between the true or expected value obtained using an accepted method and the observed value from the method being tested is typically based on replicate measurements. Bias is expressed in the units of the measurement or as a percentage.

Calibration: The determination of a bias conversion factor of an analytical process under specified conditions, in order to obtain accurate measurement results. The accuracy over the operating range must be established by the appropriate use of reference methods, reference materials, or calibrators, or any combination of these.

Calibrator: A (reference) material (e.g., solution) or device of known quantitative/qualitative characteristics (e.g., concentration, activity, intensity, reactivity) used to calibrate, graduate, or adjust a measurement procedure or to compare the response obtained with the response of a test specimen/sample.

NOTE: The quantities of the analytes of interest in the calibrator are known within limits ascertained during its preparation and may be used to establish the relationship of an analytical method's response to the character-istic measured for all methods or restricted to some. The calibrator must be traceable to a national or international reference preparation or reference material when these are available. Calibrators with different quantities of analyte may be used to establish a quantity/response curve over a range of interest.

(Quality) control material: A substance used in routine practice for checking the concurrent performance of an analytical process.

NOTE: It should be similar to, and is analyzed along with, patients' specimens. Control materials may or may not have known analyte concentrations (i.e., assigned values) within specified limits (e.g., target value +/– standard deviation). Control materials must not be used for calibration purposes.

Derived red cell indices: Quantities that may be calculated from the measurement of hemoglobin (Hb) concentration, packed (red) cell volume and erythrocyte (RBC) concentration (see the definitions for PCV, MCH, MCHC, MCV).

- *MCH; mean cell (corpuscular) hemoglobin*: the average amount of hemoglobin within the red blood cell in a given blood sample.

$$MCH(pg) = \frac{Hb(g/L)}{RBC(x10^{12}/L)}$$

- *MCHC; mean cell (corpuscular) hemoglobin concentration*: the average hemoglobin concentration within the red blood cells of a given blood sample.

$$MCHC(g/L) = \frac{Hb(g/L)}{PCV(L/L)}$$

- MCV; Mean cell volume: the average volume of the red blood cell in a given blood sample

$$MCV(fL) = \frac{PCV(L/L)}{RBC\ (x10^{12}/L)}$$

Linearity: The ability of an analytical process to provide a measurement proportional to the analyte being measured over a defined concentration or counting range.

NOTE: Linearity refers to overall system response (i.e., the final analytical answer rather than the instrument output). When analytical results are plotted against concentration or counts, the degree to which the plotted curve conforms to a straight line is a measure of system linearity. Criteria for linearity should be based on appropriate slope, intercept, standard deviation of *y* about *x*, as well as the linear range.

Packed (red) cell volume, (PCV): The measure of the ratio of the volume occupied by the red blood cells to the volume of whole blood, expressed as a fraction (L/L).

NOTE: The term "hematocrit" has been, and often is, used for this quantity.

Precision: Agreement between replicate measurements. It has no numerical value, but it is expressed in terms of imprecision.

NOTE: Generally, the degree of imprecision is reflected by the standard deviation, which is the measure of random error. For repeated measurement of any given analyte, the random errors are generally assumed to be distributed normally around the observed mean.

Quality control (internal): The set of procedures undertaken in a laboratory for the continual assessment of work carried out in the laboratory and the evaluation of tests to decide whether the results are reliable enough to be released to the requesting physician.

NOTE: The procedures should include tests on control material, results of which may be plotted on a control chart showing upper and/or lower control limits and may include statistical analysis of patient data. The main objective is to ensure day-to-day consistency of measurements or observations, if possible in agreement with an agreed-on indicator of truth, such as a control material with assigned values.

Quantity (measurable): Attribute of a phenomenon, body, or substance that can be distinguished qualitatively and determined quantitatively.

Reference material: A material or substance with one or more property values that are sufficiently homogeneous and well established to be used for the calibration of an apparatus, the assessment of a measurement method, or for assigning values to materials.

NOTE: The term “reference material(s)” should be used generically. They form a class of materials to which "reference" can be made. They include certified reference materials (CRM), standard reference materials (SRM), calibrators and standards (see also definitions for CRM, calibrators, and standards). A reference material, together with appropriate and well-defined systems for measurement, makes possible the transfer of the value of a measured quantity (physical, chemical, biological, or technological) between two places. A reference material may be a pure or mixed gas, a liquid or solid of biological origin, or a manufactured object.

Reference material, certified (CRM): A reference material, accompanied by a certificate, with one or more property values that are certified by a procedure that establishes traceability to an accurate realization of the unit in which the property values are expressed, and for which each certified value is accompanied by an uncertainty at a stated level of confidence.

Reference population: A group of *N* persons in a described state of health or disease.

Sensitivity:

- *Sensitivity, analytical*: The change in the response of a measuring instrument divided by the corresponding change in the stimulus. The sensitivity may depend on the value of the stimulus.

  NOTE: The term analytical sensitivity has also been used synonymous for detection limit, i.e., the smallest quantity of analyte that can be reproducibly distinguished from background noise in a given assay

system. It is usually defined at the 0.95 (95%) confidence level (+/- 2 SD).

- *Sensitivity, clinical*: The proportion of patients with a well-defined clinical disorder whose test values exceed a defined decision limit (i.e., a positive result and identification of the patients who have the disorder).

  NOTE: The clinical disorder must be defined by criteria independent of the test under consideration.

Set point: The level (i.e., analyte concentration) at which an instrument is calibrated.

Specificity:

- *Specificity, analytical*: Freedom from measurement interference, i.e., the ability of an analytical method to determine only the component it purports to measure.

- *Specificity, clinical*: The proportion of patients who do not have a well-defined clinical disorder and whose test values do not exceed a defined decision limit (i.e., a negative result and identification of patients who do not have the disease).

Standard (measurement): (1) Material measure, measuring instrument, reference material, or measuring system intended to define, realize, conserve, or reproduce a unit, or one or more values of a quantity, to serve as a reference; or (2) (preferred) an authoritative document that sets forth criteria for performance and characteristics.

- *Standard, primary*: A standard that is designated, or widely acknowledged as having the highest metrological qualities and its value is accepted without reference to other standards of the same quantity.

- *Standard, secondary*: A standard, the value of which is assigned by comparison with a primary standard of the same quantity.

- *Standard, working*: A standard that is used routinely to calibrate or check material measures, measuring instruments, or reference materials.

4 Performance Goals

Performance goals for accuracy and precision of multichannel hematology analyzers represent a compromise between what would be ideal for clinical practice and what is realistically attainable with modern instrumentation. Bias and imprecision are the major analytical causes of assay error. Some aspects of the perform-ance of an analyzer may vary as a function of analyte concentration. The effect of analyte concentration on imprecision and bias are discussed in relation to critical decision levels, such as reference intervals and clinical action limits.

4.1 Analytical Error: Inaccuracy

Accuracy is a measure of agreement between the estimate of a value and its "true" value. Inaccuracy is a statement of disagreement between these parameters. Numerical statements about degrees of inaccuracy should take into account the imprecision of its estimate and the imprecision of the value with which it is compared. This helps to determine whether a disagreement between the methods is nonsystematic and random (imprecision) or systematic, unidirectional, and nonrandom (bias).

Bias or inaccuracy can be evaluated relative to the impact it would have on clinical decisions. Biased assays pose major problems by shifting patients' values relative to fixed decision levels. For analytes with well-defined upper and lower decision limits, shifts in test values decrease or increase clinical specificity and sensitivity. These changes depend on the direction of the shift and the altered positions of the values from patients with disease compared with the reference populations. This is illustrated by examples given in Section 5.

Bias can take one form or a combination of three forms.

- It can be proportional to analyte level; multiplication by a single factor can bring all values of the propositus assays into agreement with reference assays. This condition is a linear *slope* error.

- It can be a constant additive error, independent of analyte level; the addition or subtraction of a constant will bring the assay values into agreement with reference assays. This condition is a linear *offset* error.

- It can reflect a complex, but well-defined, relationship to analyte level. This is a special case of *nonlinear response*. One example is the non-linear effect of coincident cells within the count-sensing zone.

The first form of bias can be caused by incorrectly-assigned calibrator values, but, in addition, the accuracy of clinical assays can be adversely affected by improper use of the calibrator. See Section 4.3 for a further discussion of this aspect of bias. Additional information on bias appears in NCCLS document EP9-A, *Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline*.

Total bias is the greatest possible deviation from truth of a single assay. It is a statement of the theoretical degree of error that would occur in the extremely improbable event that all the components of bias, listed above, operated at full magnitude in the same direction at the same time. It is calculated as the linear sum of the limits for set point error, maximum allowable drift error of 2SD, and the single-tailed 95% confidence limit of a single assay rather than the square root of the combination of the individual variances. This is because, for this purpose, it is assumed that the individual error sources are independently controlled. The concept of total bias is of more value to analyzer designers than to analyzer users.

4.2 Analytical Error: Calibrator Bias

Error in the assigned values of the calibrator is propagated to clinical assays. Therefore, the goal of the process of assigning calibrator values should be to achieve zero bias. The process should allow measurement of the errors contributed by each of its stages [6,7]. The propagation of these errors through the assigned value provides a statement of the calibrator confidence limits. Errors should be controlled in a manner that prevents the calibrator from contributing bias except through accumulation of random error. However, improper use, deterioration as a result of improper storage, shipping, or use beyond the specified shelf life can cause calibrator-induced bias. Demonstration of the use of red cell indices for assessing the accuracy of hematology calibrators, using the argument that the principles of the methods yielding negligible bias for those components would also produce a similar standard of accuracy for other analytes, has been shown.[8]

4.3 Analytical Error: Calibrator Use

Manufacturers have made progress in minimizing the human element in calibration by automating set- point adjustment. The calibra-tion set point in an instrument with this feature is free from human error and its accuracy depends only on the number of measurements contributing to the mean recovered value of the calibrator. Fewer iterations will result in higher set-point variation and a higher likelihood of bias. For a single assay of an unknown blood specimen, the random error (imprecision) of the instrument must be combined with the estimate of bias range to give the probable analytical error range.

The 95% bias range of an analyzer should be measured and recorded each time calibration is performed. It is calculated by combining the 95% confidence limits (CL) of the assigned calibrator value with the standard error of the mean (SEM) for the number of times the calibrator is assayed. SEM is defined as the range over which the means of *n* iterations is expected to vary. It is described by the following equation:

$$SEM = \frac{SD}{\sqrt{n}}$$

For example, the mean of 10 replicate assays of the calibrator has a standard error of ($SD_{analyzer} \div \sqrt{10}$) or ($SD_{analyzer} \div 3.16$). To com-bine the analyzer SEM with the 95% CL of the calibrator, the SEM is raised to 95% CL by multiplying it by the appropriate t factor taken from the Appendix. Select the t factor for n – 1 (one less than the number of iterations actually used). Thus, t for 10 iterations will be row 9 in the table or 2.2622. The formula for bias limits then becomes:

$$95\%\ Bias = \sqrt{(CL^2_{analyzer} + CL^2_{calibrator})}$$

It is convenient to express assay bias as percent because this error is propagated proportionately throughout the reportable (linear) range of the instrument. Thus, if the 95% bias limits for Hb set point of 125.0 g/L is ± 2.0 g/L, all assays within the reportable range will have a percentage bias range of (2.0 ÷ 125.0 · 100) or 1.6%.

4.4 Analytical Error: Nonlinearity

Nonlinearity of an assay has an effect similar to that of assay bias, but the magnitude of the error depends on the value of the measurement. Typically, nonlinearity produces greater changes with measurements beyond the limits of the reportable range. Values close to the calibration set point are least affected. Because clinical decision limits and reference range limits are usually located away from the set point, nonlinearity can cause changes in assay sensitivity and specificity. The goals for nonlinearity, shown in Table 1, are implicitly defined by the assay bias goals when these goals are stated for a reportable range of test values.

Table 1. Recommended Minimum Ranges for Analytic Linearity

Analyte	Units	Low Limit	High Limit
WBC	10^9/L	0.1	100.0
RBC	10^{12}/L	1.50	7.0
Hb	g/L	20.0	200.0
Hct	L/L	0.33	0.54
MCV	fL	50.0	130.0
Plt	10^9/L	5.0	1,500

Manufacturers should include claims of linearity limits in their product labeling. This allows the user to estimate the magnitude of this error by interpolation between the stated linearity limit and the reported result. Whenever nonlinearity is algorithmically corrected, e.g., for the correction of coincidence error, manufacturers should reveal this to the user and provide an outline of the corrective method and a statement of its limitations.

This standard discourages the suppression of results that exceed the upper linearity limit. Results that fall above this limit should be available to the laboratory, but not for the patient's record, and they should be flagged, either through laboratory action limit rules or by signals from the analyzer. In most cases, quantitative dilution of the specimen with the analyzer diluent reagent will bring the result into the linear range of the analyzer.

4.5 Analytical Error: Imprecision

Analyzer imprecision is important in regard to both the processes of calibration and quality control, and the clinical interpretation of measurements on patients' specimens. The principal stages at which random error plays a part are shown in Table 2. The calibration process involves transferring assigned values from the calibrator to the analyzer. The better the precision of the analyzer, the more exact is the estimate of set-point error for a given number of iterations of calibrator assays. Also, the more precise an analyzer, the easier it is to detect instrument drift away from the set point. Therefore, it requires fewer assays of control material to decide whether it is performing within specified limits. A clinician might not perceive the imprecision of measurements when interpreting an isolated test result because test value**s** include a combination of both analytical and biological variation. When one of these components of variation is much larger than the other, it becomes a limiting factor. For instance, changes in analytical precision less than 25% of the within-person biological variation might not be perceptible without performing replicate tests.[9,10] Comparison of these components of variation can thus be used to define bounds for analytical precision.

The analytical imprecision component contains two subsets:

- The combination of the multiplicity of variable physical events that take place during an analysis. All these events are essentially independent and not gen-erally related to analyte concentration. They combine according to the square root of the sum of their individual variances.

- The irreducible error attached to sampling a finite number of randomly distributed cells or particles that are independent (not interacting). This is the Poisson error[11] where under-reporting or over-reporting of a count is due to the fact that the actual number of detected cells is randomly variable as a function of the square root of the number of cells counted.

Higher counts have proportionately less Poisson error than lower counts. Its contribution to the overall imprecision of the assay, expressed as CV, can be stated as follows:

$$CV = \frac{\sqrt{N}}{N} \cdot 100$$

Where *N* is the number of cells counted (not the number reported).

It is tempting to reduce the Poisson effect on the error of the calibration set point by using calibrators with high values. However, the hoped-for benefit from high cell concentration might not be realized because of the counterbalancing effect of increased viscosity and coincidence error.

By using the mean of iterative (for example 10) calibrator assays, the 95% confidence limit (or 2.2622 · SD) of the set point is reduced to one-third the standard deviation of a single assay. See Section 4.3.

Table 2. The Contribution of Random Error Components to the Confidence Limits (CL) of Calibration

Stage	Random error components
Assign reference values*	Dilution imprecision Reference analyzer imprecision (Poisson)
Calibrate automated analyzer*	Automated analyzer imprecision Stability of calibrator material
Assign calibrator values*	Automated analyzer imprecision Stability of calibrator material
Use of calibrator	Error of assigned values User's analyzer imprecision Stability of calibrator material

*Components associated with assigning calibrator values.

4.6 Analytical Error: Interferences

The third cause of analytical error is the response of the analyzer to the presence of interfering substances that mimic an analyte without being a true part of it. This leads to reduced analytical specificity. An example is the influence of lipemic or leukocytic turbidity on hemoglobin measurement. This is described in NCCLS document, H15-A2, *Reference and Selected Procedures for the Quantitative Determination of Hemoglobin in Blood–Second Edition; Approved Standard*, and is one of the reasons why some commercial calibrators are system-specific and not usable with all types of automated analyzers. It is the responsibility of the manufacturers of both the analyzer and the calibrator to document such phenomena and caution users as to their effects on analytical accuracy.

The phenomenon of interference is important in the process of assigning values to calibrators. During this process, accurate transfer of reference values to the automated analyzer depends on both systems reacting in the same way to the analyte. If this is not so, that is, if the analytical specificities of the systems differ, significant bias can be introduced. Detection of interference depends on the principle that the imprecision of differences of paired reference assays versus the imprecision of paired analyzer assays should, lacking interference, be nearly equal to the combined imprecisions of the reference and analyzer assays. In the presence of interference, the imprecision of the combined differences is greater.

The manufacturer of a calibrator must choose between incorporating an "interference allowance" in the assigned values or selecting reference specimens that are free of interference. In the former case, the calibrator carries a bias for all specimens equal to the mean frequency of the interference in the reference population. In the latter case, clinical specimens that contain the interference will have an error; others will not.

The basis for the choice between these decisions depends on the frequency and magnitude of the interference in the reference population versus its frequency and magnitude in the clinical population and the sensitivity of the analyzer to the interfering substance.

4.7 Analytical Error: Drift

Drift is an unintended, unanticipated change of analyzer response. The change may be gradual, reaching a detectable magnitude only over a period, or it may be step-wise. In either case it can cause bias of assays during an analysis run so that an unknown proportion of results that preceded its detection might be in error. Drift occurring in an instrument that is normally drift-free can be an early symptom of a serious malfunction. Instruments that are prone to drift in ordinary use, to a degree that has a clinical significance, should have this propensity specified by the manufacturer. Currently, there is no information available from manufacturers to permit a generalized, predictive estimate of how much drift, its probable direction, or how often it might occur in any given analyzer. It is proposed that the goal for the permissible range of variation of results due to drift should be ± twice the instrument SD. This limit is selected as conforming to the usual action limit of the laboratory internal quality control system. Calibration bias limits (see above) are not affected by drift because drift, by definition, occurs after calibration has taken place and is assumed not to occur during calibration.

Drift can affect the analyzer response such that its error is proportionate throughout the reportable range (slope change), or it can take the form of an offset (constant error) that adds or subtracts a fixed quantity. Sometimes both factors are at work. The possibility of drift, and the need for its detection, must be a key factor in the design of internal quality control systems.

Drift detection should encompass the following factors:

- The sensitivity of drift detection should be within limits that permit the clinical use of results that precede its discovery when no other errors are present.
- The laboratory workflow rules must allow results to be quarantined after drift detection, pending an analysis of causes.
- There should be provision for the release of selected results based on a careful review of medical need.

5 Relating Performance Goals to Medical Decisions

It is useful to relate performance goals, as applied to medical decisions, to the terms "specificity" and "sensitivity." According to Galen and Gambino,[12**] "The sensitivity of a test is the incidence of true-positive results obtained in patients who are known to have the disease".[12] It is often expressed as its complement. That is, the more untrue (false-negative) results, the less the sensitivity. "The specificity of a test is the incidence of true-negative results obtained in patients who are known to be free of the disease".[12] It is

** See also Section 3 of this document.

often expressed as its complement. That is, the more untrue (false-positive) results, the less the specificity.

The term "patients who are known to have the disease" is redefined for this standard as *patients with true assay values that either violate the reference limit or the clinical action limits*. The term "patients who are free of the disease" is redefined as *patients with true assay values that are within reference limits or do not violate the clinical action limits.*

Both bias and imprecision can affect specificity and sensitivity. Following are examples of both situations.

5.1 Effect of Assay Bias

5.1.1 Effect on Reference Limits

The distribution of analyte values in a healthy population may only approximately follow a normal or Gaussian curve. The normal range or reference interval is taken to be the center 95% of the distribution. Assay results that fall above the upper reference limit or below the lower reference limit are considered "non-normal" or, in Fisher's terminology,[13] "formally significant."

Laboratories should establish their own reference limits that are appropriate for their local populations. NCCLS document C28-A, *How to Define, Determine, and Utilize Reference Intervals in the Clinical Laboratory; Approved Guideline*, provides methods for establishing reference limits.

Figure 1 is a Gaussian model of the distribution of hemoglobin assay results in a healthy population (heavy line).[***] The lighter lines model the effects of calibration 3.75 g/L (3%) and 6.23 g/L (5%) below an unbiased set point. Figure 2 is an enlargement of the lower reference limit of this dispersion.

[***] The data on which this and other figures in Section 5 are based wereprovided by a member of the subcommittee. This information is intended to illustrate only the concepts discussed in this section.

Figure 1
Gaussian model for normal Hb distribution

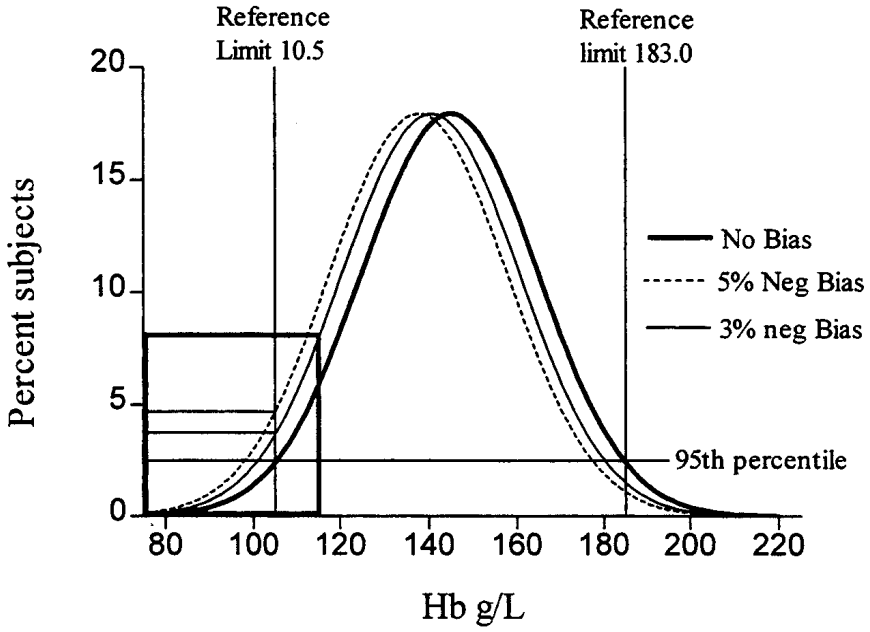
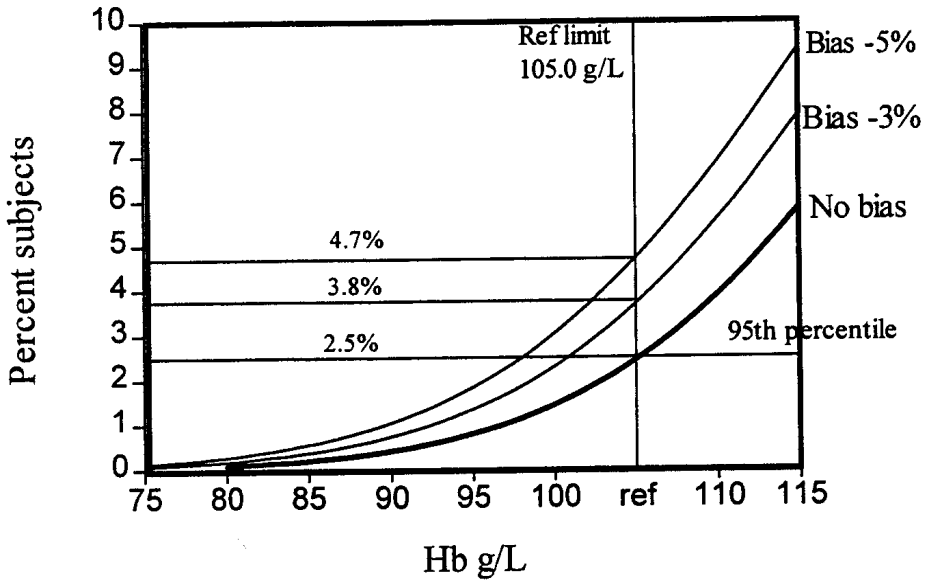


Figure 2
Gaussian model for normal Hb distribution
Enlarged from Figure 1



Assuming the unbiased set point to be 125.0 g/L and linear propagation of error through the reportable range, Table 3 shows the effect of two magnitudes of bias at the lower reference limit of 105.0 g/L and the proportion of false-positive results that would be engendered by these errors. A false-positive result is one that is incorrectly placed outside the reference limit. The effect of bias on the upper reference limit of 185.0 g/L is the inverse of this situation.

Table 3. Effect of Calibration Bias on Hb Accuracy at the Lower Reference Limit of 105.0 g/L

Bias %	Error g/L	False Positive %
3.0	-3.2	52
5.0	-5.3	88

The percentage proportion of false values is calculated as follows:

Subjects at unbiased limit = 2.5%
Subjects at 3% biased limit = 3.8%
Incremental change = (3.8 - 2.5) = 1.3
Increment % = (1.3 ÷ 2.5) · 100 = 52%

This example shows that biased reference limits can lead to diagnostic error. Assay results that fall near the reference limits can be falsely labeled "normal" (FN) or falsely labeled "abnormal" (FP), depending on the direction and magnitude of the bias. Bias that affects both reference limits and clinical assays gives the appearance of mutual consistency, but distinctions between normal and abnormal and the recognition of cases that transgress clinical action limits might not be consistent with results obtained in another institution where like bias is not present.

If reference limits are established by a biased analyzer and the bias is subsequently corrected, the proper recognition of specimens that violate the reference limits is jeopardized in a similar way.

5.1.2 Effect on Action Limits

Generally, action limits used in the clinical interpretation of test results depend on the reference ranges established for the test. If the analyzer response changes, the test values do not correspond to the clinician's reference points and this can result in incorrect interpretation. The specific action limit used for each clinical decision depends

on the clinical problem and the circumstances involved for that specific patient, but these action limits can also be related to the (normal) reference intervals of the pertinent analyte(s) and are not based on the assumption that these are not biased.

The relationship between the magnitude of analytical bias and the clinical sensitivity and specificity of the assay depends on where the decision values lie on the curve of the distribution of test values and the slope of the distribution curve at that position. The distribution of hemoglobin test values in a major primary care institution differs significantly from the distribution of test values in a healthy population. This is illustrated in Figure 3. The institutional population is skew-ed in the direction of the most frequently encountered types of pathology (anemias) and practically uninfluenced by rarely encountered diseases (polycythemia). From this example, it is clear that the dispersion of clinical values cannot be treated as Gaussian with a simple downward-shifted mean. Because of the variability of patient populations, estimates of changes of analytical sensitivity and specificity as a function of bias should be made from the data base of each institution.

The effect of calibration bias on the rate of false-positive and/or false-negative results in leukocyte counting is demonstrated by modeling a common clinical situation as shown in Figure 4. Let it be assumed that a WBC value of 3.0 x 10^9/L is the clinical decision level for a chemotherapy regimen. A WBC value above the decision level permits continuation of therapy. A WBC value below that level suggests that therapy should be discontinued. For the purposes of analysis, it is assumed that bias induced at the calibration set point (8.0 x 10^9/L) is linearly propagated to the decision level.

Figure 3
Hb distribution in a clinical population

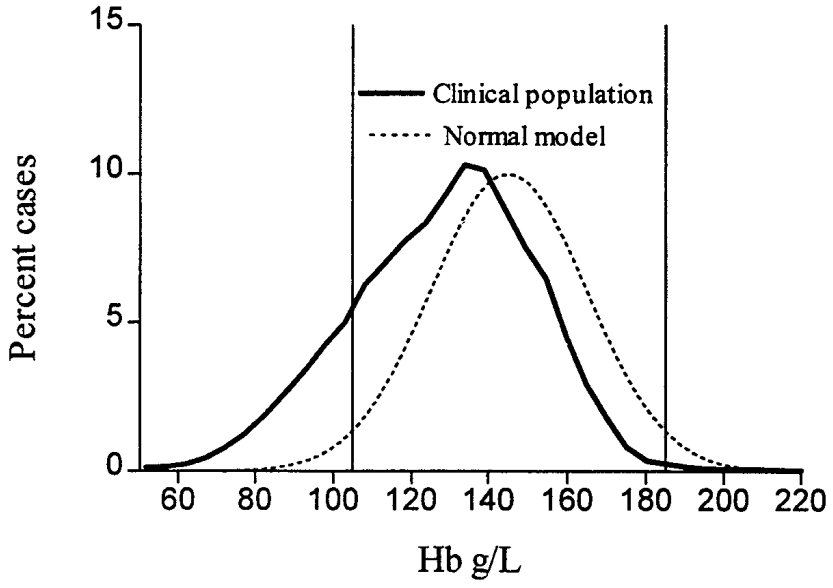
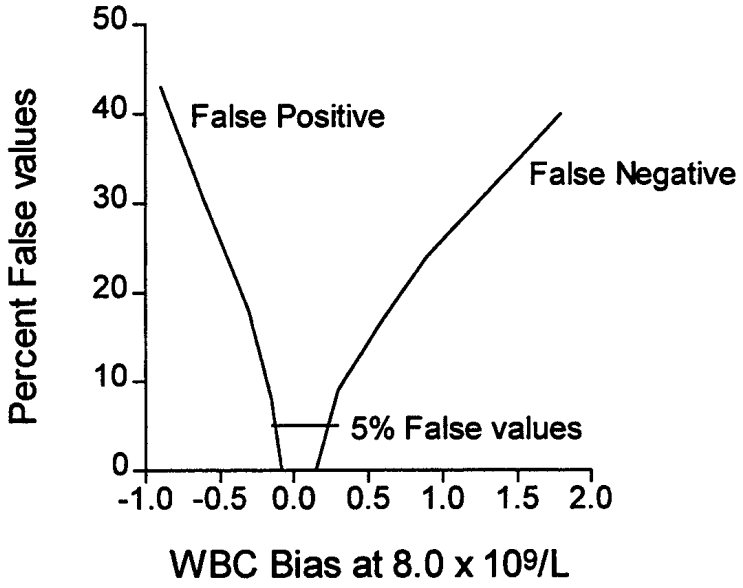


Figure 4
Effect of WBC bias on
Frequency % FP or FN at
3.0 x 10^9



A false-positive result is one that makes the WBC level fall falsely below 3.0 x 10^9/L, leading to an unnecessary cessation of therapy. A false-negative result is one that makes the WBC result rise falsely above 3.0 x 10^9/L, leading to continuation of therapy in the face of true depressed leukopoiesis. Figure 4 shows the relationship between bias at the calibration set point and the percentage of false results at the clinical decision level. Expressed in this manner, it appears that negative calibration bias shouldnot exceed 0.10 x 10^9/L and positivecalibration bias should not exceed 0.20 x 10^9/L.

5.1.3 Tabulation of Action Limits

Table 4 provides a subcommittee consensus of action limits or quantitative flags. These decision values are also supported by Kost.[14] They are given here to enhance the understanding of the effect of imprecision and inaccuracy on the reliability of diagnostic criteria. These proposed values are for guidance only. The unique needs and experience of each institution will exert a modifying influence.

Different criteria are needed for children or neonates. For example, normal MCV in children ages 3 to 10 may be as low as 70 fL and as high as 120 fL in neonates. Populations resident above 1,000 m may require upward adjustment of Hb and RBC action values. Consideration should be given to the hemodilution effect of pregnancy where appropriate.

Examination of a stained blood film may be useful in cases that violate these limits.

Table 4. Suggested Action Limits

Analyte (Units)	Action Limits	Clinical Relevance: Abnormal Results May Reflect the Following Conditions
WBC (10^9/L)	< 3	Sepsis, chemotherapy, radiotherapy, agranulocytosis, marrow hypoplasia, cobalamin, folate, iron deficiency.
	>12	Acute stress (including surgery), infection, malignancy, lymphoma, leukemia.
RBC (10^{12}/L)	>6.2♂ >5.2♀	Dehydration, polycythemia, shock, chronic hypoxia.
Hb (g/L)	>180♂ >160♀	
Hct L/L	>0.54♂ >0.48♀	
RBC (10^{12}/L)	<4.4♂ <3.9♀	Anemia from blood loss, cobalamin, folate, iron deficiency, malignancy, chronic inflammation, chronic liver disease, renal disease, marrow hypoplasia, chemotherapy, radiotherapy, hemolysis, hemoglobinopathy, thalassemia.
Hb (g/L)	<120♂ <110♀	
Hct L/L	<0.39♂ <0.30♀	
MCV (fL)	<80	Microcytosis from iron deficiency, chronic blood loss, chronic inflammation, hemoglobinopathy, thalassemia, sideroblastic anemia.
	>100	Macrocytosis from chronic liver disease, cobalamin or folate deficiency, sprue, smoking, hemolysis.
Plt (10^9/L)	<50	Risk of bleeding. Idiopathic, chemotherapy, radiotherapy.
	>800	Risk of thrombosis. Polycythemia, post splenectomy, thrombocythemia.

♂, men.
♀, women.

5.2 Effect of Assay Imprecision

5.2.1 Effect of Analytical Imprecision

Clinical interpretation of assay results is influenced by two forms of imprecision. One is analytical imprecision as discussed in Section 4.5. Apart from its influence on the calibration set point, this form of imprecision determines the degree to which the results of repeated assays of the same specimen may randomly disagree. The clinician should be aware of the possible range of results (confidence limits) that can be given by a single assay and the clinician should relate this range to diagnostic requirements.

Analytical imprecision affects two types of decisions:

- Is the value above or below the reference interval limit?
- Does the value violate the clinical decision action limit?

It is customary to assume that the reported value falls on the mode of all possible values for that assay. In fact, there is a diminishing probability that the value will fall to one or the other side of the mode. In the event that a clinical decision requires a more exact statement of analyte concentration than is given by a single assay, the mean of multiple assays can be used. Figure 5 uses hemoglobin assay as an example of the way in which replicate assays can reduce interpretive error due to analytical imprecision. This example assumes a "true" or mean value of 125.0 g/dL and the 95% confidence limits of a single assay to be ± 3.0 g/L. Because the confidence limits shrink as a function of the square root of the number of assays contributing to the mean, little benefit is to be gained by performing more than four replications. However, the mean of duplicate assays improves the confidence limits of the result to ± 2.0 g/L (3.0 ÷ √2).

The laboratory should publish its observed 95% confidence limits for all analytes so that clinicians can relate the imprecision of a reported result to the diagnostic problem. Manufacturers' claims of analytical imprecision should not be used for this purpose unless they have been confirmed by test results obtained under actual conditions of use.

5.2.2 Effect of Biological Variability

Short-term variation of analyte concentration within an individual person (biological variability or diurnal variation) was introduced in Section 4.5. It can provide a useful yardstick against which to set goals for analytical imprecision. Ideally, analytical imprecision should not exceed 25% of biological variability. A ratio of diurnal to analytical variation that does not meet this criterion can blur the distinction between these two causes of change when making repeated assays on an individual person.

Figure 5
Reduction of 95% CL with increasing iteration

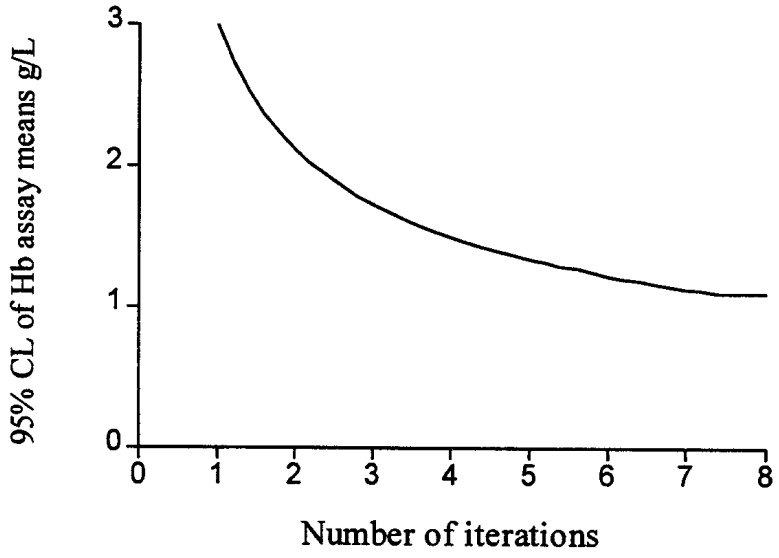


Table 5 describes the diurnal variation of CBC analytes in healthy subjects from data provided by three major institutions.**** Diurnal SD (SD_{diurn}) is calculated by subtracting the analytical variation ($SD_{analytic}$) from the total 24-hour variation (SD_{total}) as follows:

$$SD_{diurn} = \sqrt{SD^2_{total} - SD^2_{analytic}}$$

Diurnal CV was calculated as (SD_{diurn} ÷ *Population Mean)* ▯ *100.*

The column headed "Ratio" provides a figure-of-merit that relates diurnal to analytical variation. Values below 0.25 indicate that the criterion for analytical precision has been met. Manufacturers should consider within-person variability to be immutable and should relate their design goals for analytical imprecision to it. For CBC analytes, the simplistic goal of analytical SD being 0.25 of the diurnal SD might not be appropriate. The physiological rate of change of the analyte, as well as the clinical implications of measurement error, must be taken into account. For example, the time required for the detection of a significant change of MCV in a patient being monitored for response to cobalamin therapy is measured in days. The time required for the detection of a significant WBC change in a patient being monitored for response to antibiotic therapy is measured in hours. Considering these extenuating conditions, only Plt measurement exhibits unsatisfactory performance. Plt measurement at critical values, such as 50 x 10^9/L, should, ideally, have an analytical SD of the order of 3.0 x 10^9/L.[15]

Within-person variability should be taken into account when evaluating violation of reference intervals and action limits.

The effect of diurnal variation on the measurement of reference intervals has been raised.[16] It will contribute uncertainty (but not bias) in the tails of distribution histograms. This is most likely for WBC and least likely for MCV.

_____

****Data provided by University of California, San Francisco General Hospital; Veterans Affairs Medical Center, Minneapolis; and the University of Miami Hospitals and Clinics.

Table 5. Population Mean Assay Values, Coefficients of Variation of Diurnal Changes, and the Ratios of Within-Person Variation, S_{diurn}, to Analytical Imprecision, S_{anal}.

Analyte	Units	Population Mean	Diurnal CV%	Ratio $S_{anal} \div S_{diurn}$
WBC	10^9/L	7.0	14	0.12
RBC	10^{12}/L	4.8	3.5	0.29
Hgb	g/L	142.0	3.0	0.31
Hct	L/L	0.425	3.7	0.4
MCV	fL	89.2	0.5	1.9
Plt	10^9/L	257	5	0.53

Appendix

Values of t for n Iterations at $P_{.05}$ (95% Confidence)

n	t	n	t
2	4.3027	17	2.1098
3	3.1824	18	2.1009
4	2.7764	19	2.0930
5	2.5706	20	2.0860
6	2.4469	21	2.0796
7	2.3646	22	2.0739
8	2.3060	23	2.0687
9	2.2622	24	2.0639
10	2.2281	25	2.0595
11	2.2010	26	2.0555
12	2.1788	27	2.0518
13	2.1604	28	2.0484
14	2.1448	29	2.0452
15	2.1315	30	2.0432
16	2.1199	31	2.0395

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Summary of Comments and Subcommittee Responses

H26-P: *Performance Goals for the Internal Quality Control of Multichannel Hematology Analyzers; Proposed Standard*

General Comments

1. The issue of repeat testing of a specimen over an extended time period should be addressed. For example, a doctor asks us to repeat a CBC that we ran yesterday and the specimen is now 24 hours older. What we need to know are the precision goals that relate to biological degradation.

- **The subcommittee recommends that manufacturers provide information on this issue. Different analyzer designs differ as to their sensitivity to degradation of the various analytes in stored specimens, which makes it difficult to give generalized statements.**

2. It would be nice if the committee would prepare a standard method for linearity verification for multichannel hematology analyzers.

- **In the approved-level standard, the committee avoided method descriptions. Another NCCLS document is being developed by the subcommittee that will be a companion document to H26-A, which will include such procedures.**

3. The intended goals of this document are admirable, though many of us concur that the document is overly theoretical. I recommend more emphasis on the more pragmatic aspects of this topic and a more succinct summary of the theoretical basis. The established performance goals are outstanding and long overdue.

- **The subcommittee appreciates the comment and hopes that the approved-level document gives greater clarity.**

4. The discussion of statistical concepts ought to be included as an appendix, rather than a part of the body of this work. I strongly urge the inclusion of the exact definition and aspects of medical usefulness in quality control.

- **The statistical concepts are considered, by the subcommittee, to be inherent to the text. Their relocation would reduce the continuity of the discussion of principles. Section 5, "Relating Performance Goals to Medical Decisions" addresses this comment. A more detailed discussion of quality control aspects will be given in a forthcoming companion document (NCCLS's H38 project on moving averages of red cell indices), which is being developed by the subcommittee.**

5. I recommend numbering the tables for easier reference.

- **The tables are numbered in the approved-level document.**

Section 3.0

6. The terms defined are not used consistently in the document and, apparently, sometimes synonyms are used, or the terms are not defined.

- **Every effort has been made to ensure that terms are used consistently throughout the approved-level document.**

7. Calibration—Replace "a bias conversion factor" with "bias parameters" to account for the more general calibration model where there is more than just one (slope or proportional bias) parameter.

- **The numerous comments dealing with the need to improve the section on definitions (Section 3) and to use terms consistently have been responded to by the subcommittee by rewriting Section 3.**

8. Although "calibrator" is defined and used extensively throughout the document, the term "standard" is never defined or used. Because a primary standard is available for hemoglobin, this term should be included and distinguished from a calibrator.

- **The subcommittee agrees; definitions for standard (measurement) and primary, secondary, and working standard are included in H26-A.**

9. The definition for internal quality control, as written, is not clear.

- **The definition has been revised to address the comment.**

10. "Analytical bias - The numerical difference between the limiting mean." What is a limiting mean?

- **The definition for bias has been revised.**

11. Why isn't there a definition for analytical imprecision. There is one for analytical bias.

- **See the definition for "precision" included in H26-A.**

12. The terms "allowable error" and "error" are undefined. Should this be "analytical allowable error"?

- **See Section 4 for detailed information on analytical errors.**

13. The term "assay bias" is undefined.

- **See the definition for bias included in H26-A.**

14. The terms "assay specificity" and "assay imprecision" are not defined.

- **Section 3 has been revised to include definitions for "specificity" and "imprecision" (see "precision").**

15. The term "instrument precision" is undefined.

- **A definition for precision is now included in Section 3 and a detailed explanation of the concept now appears in Section 4.5.**

Section 4.1.3

16. In Section 4.1.3, it is unclear what is meant by "easier to detect" and "determine statistically." If these refer to the number of controls needed to detect a statically out-of-control condition, the size of the standard deviation is irrelevant. The probabilities are the same because the limits and out-of-control patterns are relative to the SD. If something else is meant, it would be informative to explain what.

- **This comment is pertinent to internal quality control and will be dealt with in the H38 companion document that is being developed by the subcommittee.**

Section 4.1.5

17. The whole section on biological variability and the effect of analytical bias and imprecision is discussed at the end rather than before the setting of analytical performance goals. Thus, it

seems that the effect is not used in deciding what the goals should be. For example, Figure 3 states that a shift of 1 SD will decrease the specificity from 95 to 84%; yet the performance goals are stated at ±3 SDs. Won't the loss of specificity be so great as to make the analytical results useless?

- **Biological variation is of significance in revealing those aspects of analytical precision that might be improved. Section 5.2.2 of the approved-level document clarifies these issues.**

Section 4.2

18. In Section 4.2, Goals for Analytical Bias, there is no reference to hematocrit (hct). This parameter is calibrated and measured on our analyzer; therefore, we need goals for this as well. The hct is calculated on other analyzers, thus, goals are not necessary.

- **Revisions to the document have corrected this omission.**

19. Section 4.2 is confusing and inconsistent with the definitions.

- **This document has been revised to correct this problem.**

Section 4.2.1

20. In Section 4.2.1 the second sentence is not clear. Can it be stated in more detail as to how bias is calculated?

- **This, and other parts of Section 4, have been revised to address this question.**

Section 4.2.2

21. Section 4.2.2 assumes that errors at all levels are linearly proportional. This may not be true, e.g., at high and low levels of platelets.

- **The document has been revised to show that linearly proportional error is limited to the reportable or linear range of the instrument.**

22. There is no discussion of calibration at clinically critical levels. This can be more important than at the normal, midrange, or even ends of the "normal" range.

- **The clinical consequences of calibration-induced bias are considered in depth in various parts of the approved-level standard, particularly in Section 5. It is not within the scope of the document to require calibration at levels other than those recommended by the instrument manufacturer.**

23. "Analytical instrument bias" as defined—low, medium and high range—are arbitrarily defined.

- **It is agreed that low, medium, and high bias limits were arbitrarily defined. Sections 4.1, 4.2, and 4.3 in the approved-level document deal with this issue in detail.**

24. There seems to be some confusion of terms. This section is entitled "Bias," yet it proceeds to talk about variability. This confusion might be because the term "variability" is undefined. Variability typically refers to imprecision. This section discusses the variability of bias, which doesn't make much sense. Biases do not combine in a root mean square manner, so this needs to be explained through the correct use of terms that are defined, and perhaps defining other terms that might be necessary to explain.

- **The approved-level document deals with the effect of confidence limits on bias range. For calculating single-tailed maximum bias limits, linear summing should be used. For predicting probable net bias range, root-mean-square summing of the components of the confidence limits is more appropriate.**

25. As I understand calibration, and using this document's definition, how can there be short-term calibration error? Each calibration produces a bias (it may be zero). Variation or imprecision now results from other factors, but not from that calibration. The stated value has absolutely no uncertainty. Its effect on bias might be uncertain, but that, by no means, indicates that the result is imprecise. Also the equation for SD_{total} seems irrelevant. It is not used anywhere in the document. This whole section on variation of bias is not used in the calculation of performance goals.

- **Revisions to the document address this comment.**

Section 4.2.3

26. As stated in Section 4.2.3, the recommended bias goals for calibrator assignment, instrument calibration, and drift detection are calculated as ± 3 times the estimated error of each process. What happens to the four sources of bias?

- **The subcommittee revised this recommendation. Sections 4.1, 4.2, and 4.3 in H26-A deal with this issue in detail.**

Section 4.2.4

27. As stated in Section 4.2.4, the Poisson counting error adds only to precision. Should this be imprecision?

- **Yes. The effect of Poisson error is discussed at greater length in Section 4.5 of the approved-level document.**

Section 4.2.5

28. Calibrator assignment goals (vial-to-vial maximum difference) would be difficult for the user to monitor, because, in most cases, only two vials are shipped at a time, or, where multiple vials are shipped, only one or two are in use at a time. The document does go on to recommend that manufacturers report "calibration imprecision" on a long-term basis, but either component is of little practical use. The numbers should be available for "comparison shopping" between manufacturers.

- **Error in the assigned values of the calibrator is a significant source of bias. This is discussed in Sections 4.1 and 4.7 of the approved-level document. The H38 document that is being developed by the subcommittee as a companion document to H26-A will deal in depth with this and related matters.**

29. As stated in Section 4.2, the values for the goals are expressed as coefficients of variation; presumably these are goals for analytical bias. Bias is defined as the difference between mean and true value. Why are the goals expressed as CVs and not as limits of allowable differences? If this is not comparing different things, then would explaining why not be informative?

- **The approved-level document addresses this comment. It is often convenient to use CV in cases where error, such as calibration set point bias, is propagated in a linear manner. Expressing this goal as the limit of allowable error in units would require the value of the set point to be stipulated.**

Section 4.2.6

30. The numbers given in the chart are not tight enough for our use. The example given allows a ± 0.4 difference on a WBC of 8.0, whereas the manufacturer of the calibrator we use allows only a 1.25% or 0.1 difference. I would not want as much "play" in an instrument's set point as the document allows.

- **The subcommittee agrees and has revised this section accordingly. See Section 5.**

Section 4.2.7

31. I assume the term "drift detection" refers to a standard QC program of controls every shift, but it is not defined. The numbers are closer to 3 SD than 2 SD. If these are derived from "short-term precision data" from the manufacturers, could they not be customized for each instrument, and in many cases, tightened?

- **The subcommittee has minimized the implication that instrument drift is an inherent characteristic of automated hematology analyzers and has added further discussion on the topic. The goals have been tightened and are now limited to mid-range values**.

32. Two important topics (for us) relevant to short-term (shift-to-shift) drift detection were not discussed: moving averages and within-shift patient/precision verification.

- **These matters will be discussed in detail in the H38 companion document that is being developed by the subcommittee.**

Section 4.2.8

33. The numbers stated in Section 4.2.8 can be tightened only as the individual components are tightened.

- **The subcommittee agrees. Note, however, that standards must attempt to embrace as broad a spectrum of instruments as possible without degrading the practice of medicine.**

34. We are assuming that Section 4.2.8 suggests goals (%) regarding instrument to instrument variation.

- **The standard assumes that automated hematology analyzers, calibrated with the same material will have similar bias. References dealing with comparisons among different manufacturers are cited in Section 1.**

35. Section 4.2.8 says that the goals were set at three times the short-term precision. Should this be "imprecision"? Because, by the definition in this document, precision is measured in CVs and SDs, then three times would still make them CVs or SDs. Are not the values in the table SDs? So instrument drift is comparing a change (difference?) to an SD? Could this be explained more carefully.

- **The subcommittee agrees that this statement needs both clarification and justification. The document has been revised accordingly.**

36. Section 4.2.8 says that errors are combined linearly. Yet, they are the sum of the three goals that are stated as SDs and, in Section 4.2.2, there was an equation for SD_{total} that combined them in a square root manner. Are the goals for the table in SD units?

- **The subcommittee agrees that this statement requires clarification and justification. Therefore, Section 5 in the approved-level document addresses the clinical consequences of imprecision and bias and uses consistent terminology.**

Section 4.2.9

37. I believe that the stated lower limit (recommended) of hemoglobin at 2 g/dL is unrealistically low and a more practical figure of 2.5 or 3 g/dL should be considered.

- **The subcommittee agrees that an assay result of 2.0 g/dL is clinically unlikely. This value is a design goal. Design goals should always exceed the maximum expected clinical range.**

Section 4.3

38. The "goals for precision" are much more liberal than the "analytic imprecision numbers (Section 5.2.2), and it is not clear which set of numbers would be used in practice.

- **The revisions in H26-A in Sections 4.5 and 5.2 address this question.**

39. After having three tables with goals stated on SDs in the section on analytical bias, the document now addresses precision goals. This is confusing.

- **The approved-level document now uses consistent terminology (either SD or confidence limits) in the numerous references to imprecision. In the few cases where CV is more appropriate, its use is explained.**

Section 6.0

40. The section on quality control should be more elaborate. This section could be more useful if it explained how out-of-control rules would help maintain certain minimum true-positive and true-negative rates. I think the section is weak in making a connection between the performance goals recommended in Section 4.2 and the out-of-control rules recommended.

- **To correct this situation, the subcommittee has undertaken the preparation of a companion document (i.e., NCCLS's H38 project on moving averages of red cell indices) that makes recommendations for calibration and quality control that are consistent with performance goals.**

Section 6.2

41. Section 6.2 states that the quality control system for an instrument with good accuracy and precision could be less elaborate than (one) with less ideal performance. The accuracy and precision is irrelevant to whether the quality control system is more or less elaborate, if one is speaking of statistical quality control. The issue of elaborateness depends on the stability of the system and what type of change one wants to detect. Because this section states that the performance goals are the same for all systems, then only the former issue is of concern. However, it is not addressed in the document.

- **See the response to Comment 40.**

Section 6.3

42. Though the recommendations to manufacturers are laudable, I don't believe compliance would be readily forthcoming. Perhaps development of these number sets could come from agencies with access to data, i.e., College of American Pathologists.

- **The subcommittee agrees that manufacturers might find difficulty in complying with the original Section 6.3. This will be addressed in greater depth—within the framework of various regulations with which compliance is required—in the companion document that is being developed by the subcommittee.**

Related NCCLS Documents

C28-A **How to Define, Determine, and Utilize Reference Intervals in the Clinical Laboratory; Approved Guideline (1995).** C28-A provides a protocol for the determination of reference ranges for defined populations as an aid to the interpretation of laboratory data.

EP9-A **Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline (1993).** EP9-T discusses procedures for determining the relative bias between two methods or devices; the design of a method-comparison experiment using split patient samples; and analysis of the data.

H7-A2 **Procedure for Determining Packed Cell Volume by the Microhematocrit Method—Second Edition; Approved Standard (1993).** H7-A2 discusses the standard microhematocrit method for determining packed cell volume, recommended materials, and information on potential sources of error.

H15-A2 **Reference Procedure for the Quantitative Determination of Hemoglobin in Blood—Second Edition; Approved Standard (1994).** H15-A2 describes the internationally accepted reference method for hemoglobin against which all methods should be evaluated. It includes specifications for the accurate measurement of blood hemoglobin content using the hemiglobincyanide method, the construction of standard curves and calibration graphs or tables, and the special characteristics of HiCN solutions suitable for use as secondary calibration material, including the calculation of HiCN content from spectrophotometric measurements.

H20-A **Reference Leukocyte Differential Count (Proportional) and Evaluation of Instrumental Methods; Approved Standard (1992).** H20-A discusses automated differential counters and establishes a reference method based on the visual (or manual) differential count for leukocyte differential counting to which an automated or manual test method can be compared.

H44-P **Reticulocyte Counting by Flow Cytometry; Proposed Guideline (1993).** H44-P offers guidelines to help laboratorians in reticulocyte counting by flow cytometry. It includes factors that affect the accuracy and precision of reticulocyte counting, and a recommended reference procedure.

M29-T2 **Protection of Laboratory Workers from Infectious Disease Transmitted by Blood, Body Fluids, and Tissue—Second Edition; Tentative Guideline (1991).** M29-T2 provides guidance on the risk of transmission of hepatitis B virus and the human immunodeficiency virus in the laboratory. Specific precautions for preventing the transmission of bloodborne infection during clinical and anatomical laboratory procedures are addressed.

NRSCL8-P2 **Nomenclature and Definitions for Use in NRSCL and Other NCCLS Documents—Second Edition; Proposed Guideline (1993).** NRSCL8-P2 provides proposed definitions for use in NCCLS standards and guidelines, and for submitting candidate reference methods and materials to the National Reference System for the Clinical Laboratory.