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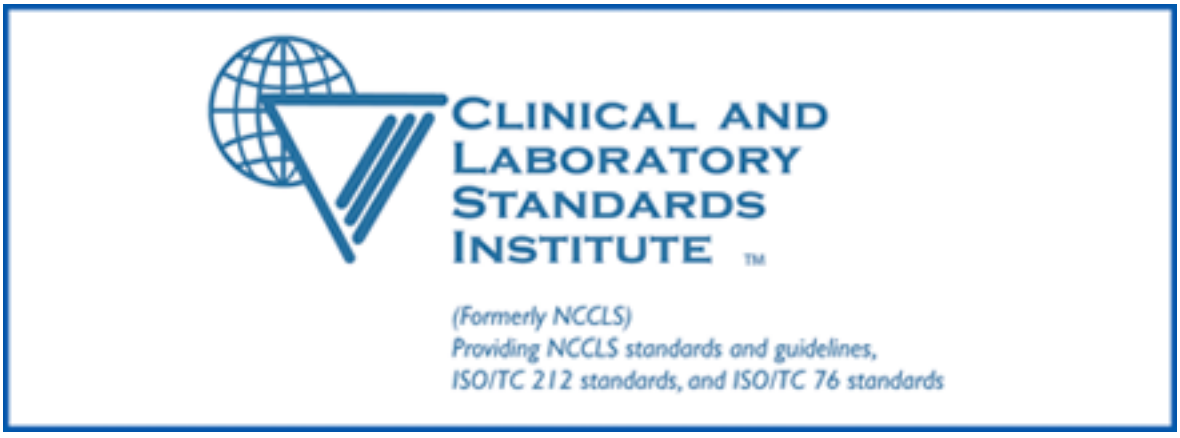
Blood Gas and pH Analysis and Related Measurements; Approved Guideline



This document provides clear definitions of the quantities in current use, and provides a single source of information on appropriate specimen collection, preanalytical variables, calibration, and quality control for blood pH and gas analysis and related measurements.

A guideline for global application developed through the NCCLS consensus process.

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Serving the World's Medical Science Community Through Voluntary Consensus

NCCLS is an international, interdisciplinary, nonprofit, standards-developing, and educational organization that promotes the development and use of voluntary consensus standards and guidelines within the healthcare community. It is recognized worldwide for the application of its unique consensus process in the development of standards and guidelines for patient testing and related healthcare issues. NCCLS is based on the principle that consensus is an effective and cost-effective way to improve patient testing and healthcare services.

In addition to developing and promoting the use of voluntary consensus standards and guidelines, NCCLS provides an open and unbiased forum to address critical issues affecting the quality of patient testing and health care.

PUBLICATIONS

An NCCLS document is published as a standard, guideline, or committee report.

Standard A document developed through the consensus process that clearly identifies specific, essential requirements for materials, methods, or practices for use in an unmodified form. A standard may, in addition, contain discretionary elements, which are clearly identified.

Guideline A document developed through the consensus process describing criteria for a general operating practice, procedure, or material for voluntary use. A guideline may be used as written or modified by the user to fit specific needs.

Report A document that has not been subjected to consensus review and is released by the Board of Directors.

CONSENSUS PROCESS

The NCCLS voluntary consensus process is a protocol establishing formal criteria for:

- the authorization of a project
- the development and open review of documents
- the revision of documents in response to comments by users
- the acceptance of a document as a consensus standard or guideline.

Most NCCLS documents are subject to two levels of consensus—"proposed" and "approved." Depending on the need for field evaluation or data collection, documents may also be made available for review at an intermediate (i.e., "tentative") consensus level.

Proposed An NCCLS consensus document undergoes the first stage of review by the healthcare community as a proposed standard or guideline. The document should receive a wide and thorough technical review, including an overall review of its scope, approach, and utility, and a line-by-line review of its technical and editorial content.

Tentative A tentative standard or guideline is made available for review and comment only when a recommended method has a well-defined need for a field evaluation or when a recommended protocol requires that specific data be collected. It should be reviewed to ensure its utility.

Approved An approved standard or guideline has achieved consensus within the healthcare community. It should be reviewed to assess the utility of the final document, to ensure attainment of consensus (i.e., that comments on earlier versions have been satisfactorily addressed), and to identify the need for additional consensus documents.

NCCLS standards and guidelines represent a consensus opinion on good practices and reflect the substantial agreement by materially affected, competent, and interested parties obtained by following NCCLS's established consensus procedures. Provisions in NCCLS standards and guidelines may be more or less stringent than applicable regulations. Consequently, conformance to this voluntary consensus document does not relieve the user of responsibility for compliance with applicable regulations.

COMMENTS

The comments of users are essential to the consensus process. Anyone may submit a comment, and all comments are addressed, according to the consensus process, by the NCCLS committee that wrote the document. All comments, including those that result in a change to the document when published at the next consensus level and those that do not result in a change, are responded to by the committee in an appendix to the document. Readers are strongly encouraged to comment in any form and at any time on any NCCLS document. Address comments to the NCCLS Executive Offices, 940 West Valley Road, Suite 1400, Wayne, PA 19087, USA.

VOLUNTEER PARTICIPATION

Healthcare professionals in all specialties are urged to volunteer for participation in NCCLS projects. Please contact the NCCLS Executive Offices for additional information on committee participation.

Blood Gas and pH Analysis and Related Measurements; Approved Guideline

Abstract

This guideline is a consolidation of six NCCLS documents and projects. The Area Committee on Clinical Chemistry and Toxicology concluded that NCCLS's constituencies (professions, government, and industry) would be better served with the production of a single document that retains the essential information from the six original documents while making it even more relevant and useful. It addresses blood gas, pH, and related measurements (e.g., fractional oxyhemoglobin, oxygen content, hemoglobin-oxygen saturation, and selected electrolytes as measured in whole blood). It defines terminology and discusses performance characteristics as well as preanalytical variables and analytical considerations. It also addresses quality control issues.

This guideline consolidates and updates:

- C12-A— *Definitions of Quantities and Conventions Related to Blood pH and Gas Analysis*; *Approved Standard;*
- C21-A— *Performance Characteristics for Devices Measuring pO_2 and pCO_2 in Blood Samples*; *Approved Standard;*
- C25-A— *Fractional Oxyhemoglobin, Oxygen Content and Saturation, and Related Quantities in Blood: Terminology, Measurement and Reporting*; *Approved Guideline;*
- C27-A—*Blood Gas Pre-Analytical Considerations: Specimen Collection and Controls*; *Approved Guideline;*
- C32-P—*Considerations in the Simultaneous Measurement of Blood Gases, Electrolytes and Related Analytes in Whole Blood; Proposed Guideline;* and
- C33— *Practical Blood Gas and pH Quality Control* (unpublished).

Sections of another NCCLS document, H11— *Procedures for the Collection of Arterial Blood Specimens*, have also been included; however, H11 will remain a separate document, because its content is of interest to a broader audience.

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Blood Gas and pH Analysis and Related Measurements; Approved Guideline

Volume 21 Number 14

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Many others have generously contributed their time and efforts as advisors and observers to these subcommittees. Their participation has been extremely important to the satisfactory completion of these documents.

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Contents

Contents (Continued)

Foreword

This guideline is the result of the decision of the Area Committee on Clinical Chemistry and Toxicology to combine and update four approved-level documents, one proposed-level document, and one unpublished document. The intent is for this document to serve more effectively the three major constituents (professions, government, and industry) of NCCLS. The challenge for the working group was to retain the essential elements of each document while making the content current and increasing its relevance for the users.

This guideline consolidates and updates:

- C12-A—*Definitions of Quantities and Conventions Related to Blood pH and Gas Analysis*; *Approved Standard;*
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- C33— *Practical Blood Gas and pH Quality Control* (Unpublished).

Sections of H11— *Procedures for the Collection of Arterial Blood Specimens*, also have been included; however, H11 will remain a separate document, because its content includes greater detail and is of interest to a broader audience.

In the process of consolidating and updating, several factors were considered. Because regulations exist regarding record keeping, quality control, calibration, and other operational practices, it is no longer necessary to include or explain some aspects of these in this guideline. In addition, some of the originally discussed quantities are no longer considered appropriate, and these have been omitted. When C21 was developed, whole blood tonometry was considered the reference for assessing quality. This guideline discusses tonometry as one means to assess quality, but omits the detailed instructions that are more appropriate for manufacturers' manuals. The reader is referred to the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) document on whole blood tonometry.[1] C25 was developed before many of the principles and applications of multicomponent spectrophotometry were readily available in a single source. The educational and descriptive text and figures once necessary are now included in manufacturers' information. The unique preanalytical, analytical, and postanalytical considerations and how this information relates to the patient's sample are included. C32 includes considerations when measuring electrolytes simultaneously with blood gases. The necessary elements for these measurements are in this guideline.

Foreword (Continued)

With this consolidation and update, the working group believes the guideline is more laboratory-focused. Yet, the essential information found in the original six documents and important to manufacturers and government agencies remains.

Standard Precautions

Because it is often impossible to know what might be infectious, all human blood specimens are to be treated as infectious and handled according to "standard precautions." Standard precautions are new guidelines that combine the major features of "universal precautions and body substance isolation" practices. Standard precautions cover the transmission of any pathogen and thus are more comprehensive than universal precautions which are intended to apply only to transmission of blood-borne pathogens. Standard precaution and universal precaution guidelines are available from the U.S. Centers for Disease Control and Prevention (*Guideline for Isolation Precautions in Hospitals*. Infection Control and Hospital Epidemiology. CDC. 1996;Vol 17;1:53-80.), [MMWR 1987;36(suppl 2S):2S-18S] and (MMWR 1988;37:377-382, 387-388). For specific precautions for preventing the laboratory transmission of blood-borne infection from laboratory instruments and materials; and recommendations for the management of blood-borne exposure, refer to NCCLS document M29—*Protection of Laboratory Workers from Instrument Biohazards and Infectious Disease Transmitted by Blood, Body Fluids, and Tissue*.

Key Words

Blood gas, carbon dioxide, fractional oxyhemoglobin, hemoglobin-oxygen saturation, oxygen content, pH

Blood Gas and pH Analysis and Related Measurements; Approved Guideline

1 Introduction

There are several aspects of blood pH and gas analysis that are unique among clinical laboratory determinations, and, at the same time, no other test results have more immediate impact on patient care. This area of laboratory medicine also has the reputation of being somewhat confusing and difficult to understand, partly because of the many different measured and derived quantities that have been used over the years. This document provides clear definitions of the several quantities in current use and includes information on appropriate specimen collection, preanalytical variables, and quality control. There is also a section containing a list of performance characteristics pertinent to blood gas analyzers which can be used by manufacturers to provide operational specifications in a uniform way, to facilitate comparison by potential customers of different instruments.

This guideline is primarily intended for laboratory technologists, respiratory and critical care practitioners, and others responsible for obtaining and analyzing blood for pH, oxygen, carbon dioxide, and related measurements. It will also be useful to manufacturers and those responsible for teaching this subject to medical students, residents, and allied health personnel.

2 Scope

This guideline addresses blood gas, pH, and related measurements (e.g., fractional oxyhemoglobin, oxygen content, hemoglobin-oxygen saturation, and selected electrolytes as measured in whole blood).

This document defines terminology and discusses performance characteristics as well as preanalytical variables, analytical considerations, and quality control issues.

3 Concepts and Definitions

This section contains terms and definitions in standard NCCLS format (NRSCL8—*Terminology and Definitions for Use in NCCLS Documents*) integrated with related information and concepts. The formal definitions are accompanied by supplementary information necessary to understand and apply the concepts of blood gases and related quantities. The definitions and supplemental information contained in this section have been developed with the intent of providing maximum clarity for the typical reader of this document. This results in some definitions differing from the full definition as found in NRSCL8. While the definitions reflect the essence of those contained in the NCCLS standard on terminology, they are not, in all cases, word-for-word.

The reader is referred to the definitions and explanatory notes found in NRSCL8—*Terminology and Definitions for Use in NCCLS Documents,* both for related terms and definitions not contained in this document and for a more precise understanding of a term's concept.

3.1 pH

pH, *n* - the symbol for the negative (decadic) logarithm of the relative molal hydrogen ion activity (αH^+), which is a measure of the effective concentration of hydrogen ions in solution; **NOTE:** Historically, pH arose as a symbol for the "power of hydrogen."

$$pH = - \log \alpha H^+ \quad (1)$$

pH is commonly used as both the symbol and the name of the quantity. The concept of pH is unique among physicochemical quantities in that it involves a single-ion activity that is experimentally immeasurable. Because the activity of a single ionic species is a thermodynamically inexact quantity, the International Union of Pure and Applied Chemistry (IUPAC) has adopted a conventional scale of pH. It is defined by reference buffer solutions with pH values assigned using a special electrochemical cell without liquid junction and containing a hydrogen-gas working electrode and a silver/silver chloride reference electrode.[2-4]

3.2 Partial Pressure of CO_2 and O_2

Partial pressure//(Tension), *n - of a gas in a solution* the pressure that would exist in a hypothetical ideal gas phase, in equilibrium with the solution.[5,6]

For carbon dioxide and oxygen, the partial pressures are symbolized as pCO_2 and pO_2, respectively. "Partial" indicates that it is one part of the total ambient pressure.

The customary unit for pCO_2 and pO_2 is millimeter of mercury, represented by the symbol mmHg, and will be used throughout this document. The kilopascal (kPa) is the unit of measure for pressure (partial) in the International System of Units (SI).[7] The relationship between these two units is that 1 mmHg = 0.133 kPa. Kilopascal units will be reported in the text as (kPa).

3.2.1 Symbols

The symbols chosen for use in this document are all compatible with IFCC/IUPAC recommendations.

Quantity Symbols: In this document, each quantity designation, including partial pressure (*p*), saturation (*s*), substance fraction (*F*), and substance concentration (*c*), shall be designated, as shown.

Specimen Type and Source Symbols: If it is necessary, characterize the type of sample (e.g., in whole blood) and its source (e.g., arterial). **NOTE**: whole blood = B; extracellular fluid = ecf; arterial = a; alveolar = A; venous = v; mixed venous = $\bar{v}$; capillary = c.

Composite Symbol: A composite symbol, based on the aforementioned principles, for an arterial blood CO_2 tension would thus be: pCO_2 (a).

3.2.2 Calibrator Gas Tension

When calibration gases for pCO_2 or pO_2 come from a dry gas mixture of accurately known composition, which is then humidified, the following relationships apply:

$$pCO_2 = FCO_2\ (p\text{total} - pH_2O) \quad (2)$$

$$pO_2 = FO_2\ (p\text{total} - pH_2O) \quad (3)$$

where *F* is the mole (substance) fraction of gas in the dry gas mixture, *p*total is the ambient pressure, and pH_2O is the partial pressure of water vapor at the equilibration temperature.

$$pH_2O = 10^{(0.0244T + 0.7655)} + 0.4 \quad (4)$$

(T = temperature in degrees Celsius)

Equations 2 and 3 are derived from Dalton's law of partial pressures and Henry's law of solubility and, although strictly applicable only to ideal gases, also apply to real gases near or below atmospheric pressure. The pH_2O is accurately estimated in Equation 4, which is derived from the Smithsonian

Metrological Table and the Geigy Scientific Tables. [8, 9]

3.3 Apparent pK of CO_2 in Plasma (pK′)

pK′, *n* - the symbol used to represent the negative decadic logarithm of the apparent dissociation constant quantitatively defined under specified conditions.

The apparent pK of CO_2 in plasma (pK′) is described by the following equation:

$$pK' = pH + \log c_{CO_2,dissolved} - \log c_{HCO_3^-} \quad (5)$$

The concentration of dissolved carbon dioxide is the product of the partial pressure of CO_2 and the concentration solubility coefficient at a given temperature. The solubility coefficient (usually symbolized as α) for CO_2 in plasma at 37 °C is 0.5195 mL of CO_2/mL of plasma.[10] To express the dissolved CO_2 in units of mmol/L per mmHg of pCO_2, the solubility coefficient is α', where

$$CO_2, \text{ dissolved (mmol/L)} = \alpha' CO_2 \times pCO_2 \text{ (mmHg)} \quad (6)$$

The value of α' is 0.0307 mmol x L^{-1} x $mmHg^{-1}$ [10] and the value of pK′ appropriate for the plasma compartment of whole blood at pH 7.40 and 37 °C is 6.095, when measurements are made in whole blood. This value was derived from experimental determinations[11] and agrees, within experimental error, with several previous determinations. (**NOTE**: The pK value in separated plasma is accepted as 6.105.)[11]

pK′ is not a thermodynamic constant; rather, it is a function of several variables including pH, ionic strength, and the solubility coefficient of CO_2. Although variations in these factors (e.g., in pathological conditions) will bias calculations that include pK′ the magnitude of the bias is rarely, if ever, clinically significant. [12-15]

3.4 Concentration of Total CO_2 in Plasma Compartment of Whole Blood

Total CO_2, *n* - the combination of all of the various forms of carbon dioxide in the plasma in equilibrium with whole blood.

The concentration of total CO_2 is expressed in millimoles per liter (mmol/L). Carbon dioxide participates in several chemical equilibria in plasma and exists as several species, including dissolved CO_2, HCO_3^-, H_2CO_3, $CO_3^=$, and protein carbamates.

In blood plasma, only two of these species are quantitatively significant: dissolved CO_2 and HCO_3^-. Dissolved CO_2 may be calculated from pCO_2 using the concentration solubility coefficient, $\alpha' CO_2$. Therefore, a useful approximation is:

$$ctCO_2 = c_{HCO_3^-} + (\alpha' CO_2 \times pCO_2) \quad (7)$$

This equation is appropriate for the plasma compartment of whole blood at 37 °C.[16]

3.5 Bicarbonate Concentration

Bicarbonate concentration is the quantity of bicarbonate ion in a unit volume of plasma.

The direct measurement of bicarbonate in blood or plasma is not usually done. Bicarbonate concentration can be accurately estimated however, and this is usually done from the pCO_2 and either the pH or the total CO_2. The following equation is appropriate for blood at 37 °C:[16]

$$\log c\mathrm{HCO_3^-} = \mathrm{pH} + \log p\mathrm{CO_2} - 7.608; \quad (8)$$

It is equivalent to the more familiar equation:

$$\log c\mathrm{HCO_3^-} = \mathrm{pH} + \log (p\mathrm{CO_2} \times 0.0307) - 6.095. \quad (9)$$

3.6 Apparent Buffer Value of Nonbicarbonate Buffers in Extracellular Fluid (β_{ecf})

The apparent buffer value of nonbicarbonate buffers in extracellular fluid (β_{ecf}) is described by the following equation:

$$\beta\mathrm{ecf} = \frac{-\mathrm{d}\, c\mathrm{HCO_3^-}}{\mathrm{d\ pH}} \quad (10)$$

where d is the derivative.

3.6.1 Determination

Nonbicarbonate buffers in extracellular fluid (β_{ecf}) are determined by varying $p\mathrm{CO_2}$ and allowing equilibration with the extracellular fluid (i.e., blood and interstitial fluid) and then measuring plasma pH and bicarbonate. (Extracellular fluid, as used here, includes the fluid in red cells and other formed elements of the blood.) [17] β_{ecf} has been estimated experimentally by several groups. The value of 16.2 mmol x L^{-1} determined by Siggaard-Andersen is close to a median value at pH 7.40, and it is used in the operational definition of base excess of extracellular fluid.

3.7 Base Excess of Extracellular Fluid [BE($_{ecf}$)]

Base excess of extracellular fluid, *n* - the {substance} concentration of base determined by titrating a model of extracellular fluid to a pH of 7.40 with a $p\mathrm{CO_2}$ of 40 mmHg (5.3 kPa) at 37 °C.

The model is equivalent to one volume of blood diluted with two volumes of its own plasma. Base excess of extracellular fluid is a quantity that reflects only the nonrespiratory component of blood pH disturbances. Of the several quantities that have been proposed for this purpose, base excess of extracellular fluid (also called "*in vivo* base excess") appears to have the best combination of general acceptance and theoretical and experimental validity.

3.7.1 Calculation

This quantity may be calculated as:

$$\mathrm{BE(ecf)} = c\mathrm{HCO_3^-} - c\mathrm{HCO_3^-R} + \beta_{ecf}\,(\mathrm{pH} - \mathrm{pHR}) \quad (11)$$

where R refers to the reference points for bicarbonate concentration, given in Table 1, and pH is measured at 37 °C. If reference values from Table 1 are substituted, the equation becomes:

$$\mathrm{BE(ecf)} = c\mathrm{HCO_3^-} - 24.8 + 16.2(\mathrm{pH}-7.40) \quad (12)$$

Adopting a constant value for β_{ecf} is an approximation. The value expressed by β_{ecf} is actually a function of plasma protein, phosphate, and, most importantly, mean extracellular fluid hemoglobin concentration, which in turn depends on blood hemoglobin concentration, blood volume, and interstitial fluid volume.[18,19]

Table 1. Quantities, Units, Symbols, and Reference Constants Used for Calculations in Text Examples

Quantity Name	Quantity Symbol	Unit Name	Unit Symbol	Reference Constants*
PH	pH			7.400
Partial pressure of CO_2	pCO_2	Millimeter of mercury	mmHg (kPa)	40 mmHg (5.3 kPa)
Partial pressure of O_2	pO_2	Millimeter of mercury	mmHg (kPa)	95 mmHg (12.6 kPa)
Concentration of hemoglobin	cHb	Grams per deciliter	g x dL^{-1}	15 g x dL^{-1} (9.3 mmol x L)
Concentration of bicarbonate	$cHCO_3^-$	Millimole per liter	mmol x L^{-1}	24.8 mmol x L^{-1}
Concentration of total CO_2	$ctCO_2$	Millimole per liter	mmol x L^{-1}	26.0 mmol x L^{-1}
Apparent pK of CO_2 (the pK of whole blood)	pK′			6.095
Concentration solubility coefficient of CO_2	$\alpha' CO_2$	Millimole per liter per millimeter of mercury	mmol x L^{-1} x $mmHg^{-1}$ (kPa)	0.0307 mmol x L^{-1} x $mmHg^{-1}$ (0.230 mmol x L^{-1} x kPa^{-1})
Apparent buffer value of nonbicarbonate buffers in extracellular fluid	β_{ecf}	Millimole per liter	mmol x L^{-1}	16.2 mmol x L^{-1}

*Not necessarily a normal value but a value chosen to use in the examples as a reference.

3.8 Base Excess of Blood [BE(B)]

Base excess of blood, BE(B), *n* - the substance concentration of base determined by titration of blood with a strong acid or base to a pH of 7.40 with pCO_2 of 40 mmHg (5.3 kPa) at 37 °C.

This quantity, frequently called "*in vitro* base excess," was originally determined according to the definition above, but now is almost exclusively determined by calculation (see Section 3.8.1).

3.8.1 Calculation

Several nomograms and diagrams are currently available that allow this quantity to be estimated from a measured pH, pCO_2, and hemoglobin concentration.[20(p51)] Base excess of blood may also be calculated using the following equation[20 (p51)] based on these nomograms and diagrams.

$$BE(B) = (1 - 0.014\ c\text{Hb})\ [cHCO_3^- - 24.8 + (1.43\ c\text{Hb} + 7.7)\ (pH - 7.40)] \quad (13)$$

3.8.2 BE(B) vs. BE_{ecf}

Care should be taken not to confuse base excess of blood with base excess of extracellular fluid.[16,17] The farther the observed pH is from 7.4, the more difference will be observed between the two quantities.[16,17]

3.9 Concentration of Total Hemoglobin (*c*tHb)

Total hemoglobin, tHb, *n* - the total of all active and inactive (with respect to oxygen binding capability) forms of hemoglobin.

Active components are oxyhemoglobin (O_2Hb) and deoxyhemoglobin (HHb). Inactive components (dyshemoglobins) include carboxyhemoglobin (COHb), methemoglobin (MetHb), and sulfhemoglobin (SulfHb). A minor fraction of as-yet-unidentified components has also been reported,[21] but the concentration of these components is ignored in practice. Thus,

$$c\text{tHb} = c\text{O}_2\text{Hb} + c\text{HHb} + c\text{COHb} + c\text{MetHb} + c\text{SulfHb} \quad (14)$$

The reference method for total hemoglobin is the cyanmethemoglobin method.[22] (Refer to NCCLS document H15—*Reference and Selected Procedures for the Quantitative Determination of Hemoglobin in Blood*.)

3.10 Hemoglobin "Saturation" and Fractional Derivatives of Hemoglobin

3.10.1 Terminology

The term "oxygen saturation" is often used to refer to the two distinctly different quantities described below, hemoglobin oxygen saturation and fractional oxyhemoglobin. This ambiguous use is sometimes unnoticed due to the closeness of the numeric values obtained in most clinical conditions. However, some clinical conditions can result in significantly different values for the two quantities. The unambiguous terminology and/or symbols are described below in order to prevent errors in clinical management when reporting or discussing saturation.

NOTE: Fractions and saturations as defined here may be expressed either as a decimal fraction, or if multiplied by 100, as a percentage.

3.10.2 Oxyhemoglobin Fraction of Total Hemoglobin

Oxyhemoglobin, *n* - the hemoglobin derivative obtained when hemoglobin (Fe^{++}) binds reversibly with oxygen.

Oxyhemoglobin fraction (of total hemoglobin//fractional oxyhemoglobin, ***F*O$_2$Hb**, *n* **- 1)** the amount of oxyhemoglobin expressed as a fraction of the amount of total hemoglobin present; **2)** the oxyhemoglobin substance fraction of the total hemoglobin.

This is more conveniently stated as "fractional oxyhemoglobin," (or percent oxyhemoglobin, if multiplied by 100).

$$F\text{O}_2\text{Hb} = \frac{c\text{O}_2\text{Hb}}{c\text{tHb}} \quad (15)$$

3.10.3 Hemoglobin Oxygen Saturation

Hemoglobin oxygen saturation, *s*O$_2$, *n* - the amount of oxyhemoglobin in blood expressed as a (percent)

fraction of the total amount of hemoglobin able to bind oxygen (i.e., oxyhemoglobin plus deoxyhemoglobin).

This is most often expressed as a percentage

$$sO_2\% = \frac{cO_2Hb}{cO_2Hb + cHHb} \times 100 \quad (16)$$

This quantity may also be referred to as “oxygen saturation,” but the expressions "functional" oxygen saturation or oxygen saturation of "available" or "active" hemoglobin are discouraged.

The quantity oxygen saturation is sometimes estimated from a measured pO_2 and an empirical equation for the oxyhemoglobin dissociation curve. Such calculations, performed manually using a nomogram or automatically using instrument-resident software, typically include "correction" for temperature, pH, and pCO_2.[23] They do not account, however, for intracellular erythrocyte diphosphoglycerate (DPG) concentration, which is affected by blood transfusions and several biochemical factors[24,25] and alter the oxygen-hemoglobin equilibrium, thus invalidating the assumptions of the nomogram or algorithm. Additionally, the relationship usually does not take into account the effects of the dyshemoglobins or fetal hemoglobin. Clinically significant errors can result from incorporation of such an estimated value for oxygen saturation in further calculations, such as shunt fraction, or by assuming that the value obtained is equivalent to fractional oxyhemoglobin.

3.10.4 Other Fractional Derivatives of Hemoglobin

An analogous definition for other fractional derivatives can be written. Equations 17 through 20 are the definitions for fractional deoxyhemoglobin, carboxyhemoglobin, methemoglobin, and sulfhemoglobin, respectively.

$$F_{HHb} = c_{HHb}/c_{tHb} \quad (17)$$

$$F_{COHb} = c_{COHb}/c_{tHb} \quad (18)$$

$$F_{MetHb} = c_{MetHb}/c_{tHb} \quad (19)$$

$$F_{SulfHb} = c_{SulfHb}/c_{tHb} \quad (20)$$

Hemoglobin derivatives, which cannot reversibly combine with oxygen, are referred to as “dyshemoglobins” (e.g., COHb and MetHb). Elevated levels of dyshemoglobin concentration will decrease the oxygen-carrying capacity of blood and is manifested in a decreased fractional oxyhemoglobin (F_{O_2Hb}) but not in a decrease in oxygen saturation (% s_{O_2}).

Example: High levels of carboxyhemoglobin due to heavy smoking (e.g., F_{COHb} >0.15) will show a decreased F_{O_2Hb} of 0.15 or more (to perhaps 0.81 from 0.96), but % s_{O_2} will remain normal at 96 to 98%. Spectrophotometric analysis of carboxyhemoglobin (COHb) is generally quite satisfactory to determine levels above the reference range, i.e., $F_{COHb} > 0.05$, but this method differentiates poorly between F_{COHb} values that fall within the reference range. The limitations of this method need to be recognized, particularly when accuracy and precision are needed in the low-COHb range such as in premature infants with endogenously generated carboxyhemoglobin due to hemolytic anemia or mildly increased levels of carboxyhemoglobin in industrial settings (e.g., a 50% increase in F_{COHb} from 0.02 to 0.03 as measured by spectrophotometry is not necessarily meaningful or significant).

For more precise carboxyhemoglobin measurements in the normal range (FCOHb < 0.05), gas chromatography appears to be the method of choice.[26,27]

3.11 Oxygen Capacity of Hemoglobin in Blood (BO$_2$)

Oxygen capacity of hemoglobin in blood∗hemoglobin-oxygen binding capacity (BO$_2$), *n* — the maximum amount of oxygen that can be carried by the hemoglobin in a given quantity of whole blood.

$$B\mathrm{O}_2 = [c\mathrm{tHb} - (c\mathrm{dysHb})] \times \beta\mathrm{O}_2 \quad (21)$$

where βO$_2$ is the oxygen binding capacity of one gram of hemoglobin. When hemoglobin concentration is in g/dL and hemoglobin oxygen capacity is in mL(STPD)/dL, βO$_2$ is expressed in mL(STPD)/g. STPD refers to Standard Temperature Pressure Dry.

Since the hemoglobin tetramer has a molecular mass of 64 458 g/mole and four O_2 binding sites per molecule, the value for βO$_2$ for human hemoglobin follows from the equation:

$$\begin{aligned}\beta\mathrm{O}_2 &= (22\,400 \text{ mL/mol } O_2 \times 4 \text{ mol } O_2\text{/mol Hb}) / (64\,458 \text{ g/mol Hb}) \\ &= 1.39 \text{ mL } O_2\text{/g Hb,} \quad (22)\end{aligned}$$

where 22 400 is the volume of one mole of gas (oxygen) at STPD.

3.12 Oxygen Content//(Concentration of Total Oxygen) of Blood

Oxygen content//(concentration of total oxygen) of blood, (ctO$_2$), *n* - the sum of the substance concentrations of the oxygen bound to hemoglobin as O_2Hb plus the amount dissolved in blood (intra- and extracellular).

The more commonly used term to represent this quantity is "oxygen content." "Definitive" and/or "reference" methods for the measurement of oxygen content are currently not available. Elaborate, chemical methods that approximate "definitive" or "reference" methods [28-31] are of academic interest but are of little practical value in that they require highly specialized expertise and equipment which is difficult to come by. Oxygen content is expressed in mL(STPD)/dL and can best be calculated using the following equation:

$$c\mathrm{tO}_2 = (F\mathrm{O}_2\mathrm{Hb} \times \beta\mathrm{O}_2 \times c\mathrm{tHb}) + \alpha'\mathrm{O}_2 \times p\mathrm{O}_2 \quad (23)$$

The solubility coefficient of oxygen in blood plasma (α') expressed in units needed for this equation (mL per dL per mmHg) is 0.00314.

The accuracy of oxygen content calculated this way is quite satisfactory for clinical use, provided the three variables (FO$_2$Hb, ctHb, and pO$_2$) are measured accurately and on the same blood sample. Care should be taken not to substitute FO$_2$Hb with SO$_2$ unless it can be demonstrated that they are equivalent.

3.13 p_{50}

p_{50} (half-saturation oxygen tension), *n* - the symbol used to represent the partial pressure of oxygen in a hemoglobin solution (usually whole blood) with an oxygen saturation of 50%.[32]

Like pH, p_{50} is used both for the symbol of the quantity and the name of the quantity.

3.13.1 p_{50} and the Oxygen-Hemoglobin Equilibration Curve

p_{50} is a function of the oxygen-binding characteristics of a hemoglobin solution and, for practical purposes, identifies the position of the oxygen-hemoglobin equilibration curve. p_{50} is a function of several variables, including pH, temperature, pCO_2, 2,3-diphosphoglycerate, carboxyhemoglobin, methemoglobin, and the concentrations of any hemoglobin variants that may be present. A low p_{50} indicates increased O_2 affinity, and a high p_{50} indicates decreased O_2 affinity.

3.13.2 p_{50} (standard)

p_{50} (standard), *n* - the partial pressure of oxygen in blood with an oxygen saturation of 50% with the "standard" conditions of pH = 7.40, pCO_2 = 40 mmHg (5.3 kPa), and temperature = 37 °C.

3.13.3 p_{50} (actual)

p_{50} (actual), *n* - the partial pressure of oxygen in blood with an oxygen saturation of 50% at actual values of pH, pCO_2, and temperature.

4 Preanalytical Considerations

Good laboratory management requires each laboratory to have policies and written protocols in place to ensure accurate results while maintaining positive patient identification and specimen integrity from the time of collection of the specimen to reporting of the results. (Refer to NCCLS document GP2— *Clinical Laboratory Technical Procedure Manuals* for procedures format.) Each laboratory must develop specific policies and procedures appropriate to its own situation. Information contained in these should be available, understood, and followed by all personnel associated with collection and processing of blood gas/electrolytes specimens.

The following topics must be considered when developing policies and procedures specifically for the blood gas laboratory.

4.1 Patient Preparation

4.1.1 Patient Identification

Patient identification is absolutely essential before a blood specimen is collected. The method for identifying patients when collecting blood specimens, under a variety of circumstances is obtained in NCCLS document H3—*Procedures for the Collection of Diagnostic Blood Specimens by Venipuncture.*

4.1.2 Patient Assessment

It is important to ascertain a "steady-state" of ventilation before obtaining arterial blood samples. A stable ventilatory status for 20 to 30 minutes is desirable for spontaneously breathing patients; other patients may require 30 minutes or more to equilibrate following ventilatory changes.[33] However less time may elapse for specific applications, such as seeking confirmation that a change in ventilator settings is having a desired effect without waiting for complete equilibration.

4.1.3 Specimen Labeling and Accompanying Information

The specimen should be properly labeled and accompanied by information completed at the time the specimen is obtained. In addition to the usual information (i.e., patient's full name, location, date, I.D. number, and the identity of the person collecting the specimen), for meaningful clinical interpretations of

blood gas results, the following information should be recorded (realizing that in some situations not all of these data will be available) and be available in the chart or computer system: [34]

- body temperature;
- time of sampling;
- FIO_2 or prescribed flow rates;
- ventilatory status (spontaneous breathing or assisted/controlled ventilation);
- mode of ventilation (i.e., pressure support);
- site of the sampling;
- position and/or activity (i.e., rest or exercise); and
- date of birth.

4.2 Sample Device and Collection Procedures

Collection of blood by arterial puncture is technically more difficult than venipuncture and can be hazardous to the patient. NCCLS document H11—*Procedures for the Collection of Arterial Blood Specimens,* contains step-by-step procedures for performing needle punctures and obtaining samples from in-dwelling cannulae and catheters. It includes recommendations on dead-space flush withdrawal to avoid sample contamination and safe use of high-pressure flush devices to avoid flush solutions embolus. Key sections of H11, related to preanalytical variables affecting blood gas/electrolytes values, are incorporated in this guideline.

4.2.1 Sample Device

In most instances, the ideal collection device for arterial blood sampling is a 1-, 3-, or 5-mL self-filling, plastic, disposable syringe, prefilled with a small amount of an appropriate type of lyophilized heparin salt or other suitable anticoagulant. The choice of the type of heparin depends on the specific analytes to be determined and the method of analysis.

Leukocytes in shed blood continue to consume oxygen at a rate depending on storage temperature, storage time, and initial level of oxygen partial pressure in the blood sample.[35,36] Before the era of plastic syringes it was customary to collect blood gas specimens in glass syringes and ice these samples immediately to slow down the metabolic rate of the leukocytes and minimize the reduction in oxygen levels. Unlike polypropylene and other polymer material of which plastic syringes are made, glass is impermeable to gases.[37] Earlier studies suggested clinically significant errors in oxygen values when plastic syringes were used.[38,39] Later studies found similar changes in oxygen values and identified certain conditions that exacerbate or attenuate change: 1) the degree of oxygen-hemoglobin binding, e.g., shifts of the position of the oxygen-hemoglobin dissociation curve (p_{50}); 2) the initial pO_2 values; 3) the amount of total hemoglobin; and 4) time and, especially, the temperature during storage.[40-44]

Based on these findings, it is recommended that plastic syringes should not be iced, but kept at room temperature as long as the blood is analyzed within 30 minutes of collection. Oxygen and carbon dioxide levels in blood kept at room temperature for 30 minutes or less are minimally affected except in the presence of an elevated leukocyte or platelet count. Blood collected for special studies (A-a O_2 gradients, or "shunt" studies) should be analyzed within five minutes of collection. If a prolonged time delay before analysis is anticipated (more than 30 minutes), the use of glass syringes and storage in ice water are recommended.

4.2.2 Arterial Specimens

Blood gas measurements for the purpose of evaluating the gas exchange function of the lungs (pO_2 and pCO_2) should be performed on arterial blood only. Because pCO_2 in arterial blood reflects the respiratory

component of an acid-base status in a patient, the use of arterial blood is also essential to determine the presence of a "respiratory" acidosis/alkalosis. Arterial blood may also be used for assessment of "metabolic" acid-base disorders and electrolytes. The blood should be collected under anaerobic conditions, mixed immediately with the heparin anticoagulant, and promptly analyzed. Arterial line collection requires that an appropriate volume be withdrawn initially to assure that the line contains only uncontaminated arterial blood before the actual sample is collected. This procedure minimizes the chance of specimen contamination with intravenous solutions, i.e., liquid heparin, medication, or other fluids that may be in the line. Consult NCCLS document H11— *Procedures for the Collection of Arterial Blood Specimens,* for specifics.

4.2.2.1 Local Anesthetics

The use of local anesthesia before an arterial puncture is somewhat controversial. Local anesthesia eliminates or reduces arterial spasm, which sometimes accompanies an arterial puncture attempt, to make the arterial puncture easier to accomplish. While local anesthesia minimizes pain and discomfort and therefore stabilizes ventilation in the noncomatose patient, the process of anesthetization itself may be initially uncomfortable, leading to apprehensive hyperventilation and altering of blood gas results.

Determination of whether or not to use local anesthetic is best left to the professional judgment of the attending physician, in the context of the patient's condition and institutional policy/procedures.

4.2.3 "Arterialized" Capillary Specimen

If circumstances contraindicate direct collection of arterial blood, peripheral capillary blood may be obtained using an arterialization technique. Although "arterialized" capillary blood may be the only practical alternative to arterial blood, the blood gas results must be interpreted cautiously. In addition to sample inadequacies, the process of capillary collection may change pO_2, pCO_2, sO_2, FO_2Hb, and ctO_2 levels significantly.[45-47] The presence of air bubbles in the specimen must be avoided because of their effects on those quantities.

Arterialization is accomplished by warming the skin to about 42 °C. (For specifics see NCCLS document H4—*Procedures and Devices for the Collection of Diagnostic Blood Specimens by Skin Puncture.*) After making a single, deep puncture, allow a droplet to form before collecting blood from the *center* of the droplet of blood. Capillary tube collection is facilitated by the use of narrow-bore tubes.

When collecting capillary blood samples, strong repetitive pressure (milking) should not be applied, since this may cause hemolysis and/or contamination of the specimen with tissue fluid. Tissue fluid in the sample elevates the potassium level and dilutes the blood, causing lower values for total hemoglobin/hematocrit, oxygen content, and capacity.

4.2.4 Venous Specimen

Venous blood is *not* a satisfactory substitute for arterial blood for routine blood gas analysis. When properly drawn (see NCCLS document H3—*Procedures for the Collection of Diagnostic Blood Specimens by Venipuncture*), venous blood is suitable for pH and pCO_2, electrolytes, and for the assessment of the levels of dyshemoglobins such as COHb and MetHb. Venous samples collected in heparinized vacuum tubes are not suitable for the analysis of pO_2, pCO_2, oxygen content, or oxygen saturation/fractional hemoglobin. A significant change (up to 3 mmol/L) in potassium values may occur when venous stasis is combined with forearm exercise (fist clenching).[48] When collecting venous blood, the tourniquet should be left on until the blood has been withdrawn and should be released just before removing the needle.[49]

4.2.4.1 "Mixed Venous Blood"

"Mixed" venous blood, also referred to as "central" venous blood, in conjunction with arterial blood, is an essential specimen in the evaluation of oxygen uptake and cardiac output and is useful in assessing intrapulmonary shunts. Central venous blood is obtained from a pulmonary artery catheter or a central venous line. When central venous blood is withdrawn from a pulmonary artery catheter, the tip of the catheter should be located in the pulmonary artery tree in such way that the catheter tip is not wedged or nearly wedged. The blood specimen should be slowly withdrawn from the catheter to avoid obtaining retrograde blood that may be partly arterialized. A 1.0-mL/5 seconds withdrawal rate is recommended.

4.2.5 Anticoagulants

When electrolytes and blood gases are measured on a single whole-blood specimen, the type of anticoagulant used must have little or no effect on the analytes to be measured. Thus, heparin is the anticoagulant of choice for the measurement of analytes discussed in this document.

The heparin chosen can influence the results obtained as a result of 1) dilution (if liquid heparin is used); 2) the type of heparin salt (e.g., Na heparin will increase Na levels measured by approximately 3 mmol/L even when there is a correct proportion of heparin and blood); and 3) the direct binding of ionized calcium by the heparin. Heparin can be prepared with a number of cations. Commercial products include sodium, lithium, calcium-titrated, and electrolyte-balanced heparin. Using calcium-titrated or electrolyte-balanced heparin minimizes the effect of calcium binding. If other heparin products are used, the final heparin concentration should be less than 10 IU/mL to minimize the calcium binding. Because there is a great deal of variability in the preparation of these products, the manufacturer of the analyzer should be consulted for specific unit recommendations. Use of heparin anticoagulants may induce alterations in calcium by dilution, by chelation, and, for titrated products, by addition of calcium to the specimen. (Refer to NCCLS document C31—*Ionized Calcium Determinations: Precollection Variables, Specimen Choice, Collection, and Handling*.)

The use of dried, "lyophilized" anticoagulants eliminates the dilution problem associated with heparin dissolved in an aqueous medium. However, the dried heparin may not dissolve adequately or quickly, which may result in clot formation within the collection device.

Generally, lithium heparin is the anticoagulant of choice when electrolytes are measured, and it is the standard anticoagulant for blood gases. Lithium heparin may invalidate the sample for lithium measurements. When sodium heparin is used and sodium is to be measured, particular attention must be paid to minimize interferences from the amount of sodium contributed by the heparin. "Low-concentration" sodium heparin blood gas kits are available that provide a final heparin concentration of <20 IU/mL blood. This concentration may be about one-tenth the amount of sodium heparin found in some kits produced for blood gases alone. Although these low-heparin kits reduce the error, they do not eliminate it. To minimize such interferences, minimum blood volume requirements should be established and followed, and again the recommendations of the analyzer's manufacturer should be observed.

Therapeutic heparin used for systemic anticoagulation should not be used as an anticlotting agent for blood gas specimens. Its high concentration (10 000 units/mL) may alter the pH and the ionized calcium values of the sample.

4.2.6 Syringe Additives

Lubricants and vent-seal additives used to facilitate blood drawing with a syringe may affect multi-wavelength hemoglobin photometry performance. Syringe design, specific additives, and multi-wavelength hemoglobin photometer specimen handling characteristics can influence the extent of such a situation. Both syringe and instrument manufacturers should be consulted for details. Certain additives

may also influence the results obtained with ion-selective magnesium electrodes.[50] These additives may change without notice to the user. Care should be taken and the instrument manufacturers should be consulted in case of questions.

4.2.7 Preparation Prior to Analysis

Blood used for the analysis of total hemoglobin concentration, hemoglobin derivatives and/or oxygen content must be thoroughly mixed immediately prior to analysis. A uniform distribution of red blood cells and plasma prior to specimen insertion into the analyzer is an absolute requirement for reliable results. With an anaerobic blood specimen care must be taken to mix the specimen effectively. It is recommended that the specimen be gently rotated for a minimum of two minutes immediately prior to analysis, either manually or using a mechanical device in a manner that produces a motion that rotates the specimen through two axes. Shorter mixing intervals may be acceptable, if only seconds or a "few" minutes have elapsed since collection. Longer intervals may be required in other circumstances (e.g., specimens that have been in ice water for 30 minutes or more). Remix specimens in capillary tubes by applying an external magnet and moving the metal "flea" from end to end for at least five seconds. Each laboratory must establish the appropriate specimen management procedures.

4.2.8 *In Vitro* Hemolysis

Because the sodium concentration in erythrocytes is 10% of that in plasma, hemolysis has only a small effect on the sodium concentration. In contrast, intracellular potassium is about 23 times greater than that of plasma and the same percentage hemolysis has a more significant effect.[51]

The transfer of intracellular potassium from the cells into the plasma is the predominant cause of many preanalytical variations experienced with potassium measurements and is exacerbated by exposing the whole blood sample to trauma during transport (pneumatic tube systems) and cooling during storage.[52] NCCLS documents C29—*Standardization of Sodium and Potassium Ion-Selective Electrode Systems to the Flame Photometric Reference Method,* and H18—*Procedures for the Handling and Processing of Blood Specimens,* discuss these and other issues and provide guidelines and recommendations to help minimize this effect.

Ionized calcium is reduced in the presence of *in vitro* hemolysis.[53,54] This is the result of the significant difference in concentration between the blood and intracellular water (intracellular ionized calcium is about one one-thousandth of blood ionized calcium). As more intracellular fluid is released, the ionized calcium in the specimen is increasingly diluted. Gross hemolysis can result in significant changes in ionized calcium.

4.3 Patient Condition

4.3.1 Blood Gases

Changes in the delivery of oxygen or ventilatory support can change the values of pH, pO_2, and pCO_2 measurements. Depending on the underlying condition, the effects of these changes take varying times to stabilize. If the patient has not been subject to a new set of conditions for an adequate amount of time, the results obtained may not represent the final, stable patient condition.

The ventilatory settings, FIO_2, the time of collection, oxygen flow rates, and the patient's condition must be checked and recorded.

4.3.2 Temperature "Correction" Algorithms

Because pH, pCO_2, and pO_2 are all temperature-dependent quantities and are measured at 37 °C, they can be modified based on the body temperature of the individual to reflect the *in vitro* changes that take place in the blood sample when it is drawn from a patient at one temperature and then analyzed at 37 °C. The clinical application of adjusted or "corrected" values of pH, pO_2, and pCO_2 to the patient's actual temperature is controversial. It is beyond the scope of this document to address the clinical controversy; however, some analytical and reporting aspects are noted below:

- Temperature-adjusted or "corrected" values for pH, pO_2, and pCO_2, if reported, must be corrected using the established Equations 24 through 26.[20 (p116), 55-59]

- If temperature-adjusted values are reported, the measured 37 °C values must also be reported to allow the physician to make an informed clinical judgment.

- If temperature-adjusted values are reported, they must be clearly labeled as such in any report.

$$\Delta \text{ pH}/\Delta \text{ T} = -0.0147 + 0.0065\ (7.4 - \text{pH}) \qquad (24)$$

where pH is that measured at 37 °C.

$$\frac{\Delta \log pCO_2}{\Delta \text{ T}} = 0.019 \qquad (25)$$

$$\frac{\Delta \log pO_2}{\Delta \text{ T}} = \frac{5.49 \times 10^{-11} \times pO_2^{3.88} + 0.071}{9.72 \times 10^{-9} \times pO_2^{3.88} + 2.30} \qquad (26)$$

(For equations 24, 25 and 26, T = temperature in degrees Celsius)

NOTE: Values for the "gas exchange indices" (e.g., alveolar-arterial oxygen gradients) must be determined using temperature-adjusted values for blood pO_2 and pCO_2. This determination is based on alveolar-inspired/expired gases, which are in a dynamic equilibrium with blood gases and have temperatures equivalent to the patient's temperature. The gas laws require that such determinations be made at the same temperature.

Other quantities, such as bicarbonate and base excess, are defined at 37 °C and based solely on 37 °C values for input/measured variables.

4.3.3 Sodium and Potassium

Specimens collected for the measurement of sodium are relatively free of physiologic effects such as changes in posture, prolonged bed rest, ingestion of food, timing of sampling, and exercise. Potassium values may increase moderately after exercise.[61] Smaller changes in potassium are observed as a result of circadian variation, with noon and early evening values being slightly higher than night and morning values.[62(pp 174-175)] Cationic surfactants—especially benzalkonium compounds, which may be used topically as a collection site antiseptic or as an agent in arterial catheters—may interfere with sodium and potassium measurements depending on measuring technology. Increases in sodium can be as much as 50 mmol/L.[63-65]

4.3.4 Ionized Calcium

Ionized calcium is widely recognized as being a better indicator than total calcium of physiological calcium status in blood. Generally, the reasons for measuring ionized calcium can be divided into three categories: acute or critical care, routine diagnostic care (e.g., to diagnose a calcium disorder), and research. In acute settings, where ionized calcium is mainly used to monitor trends, some loss of accuracy caused by preanalytical variables is not as crucial as for diagnostic purposes or research.

Ionized calcium may be affected by pH changes of the sample, calcium binding by heparin, and dilution of the sample with anticoagulant solution. To minimize pH changes, the blood should be handled anaerobically, as for blood gas determinations. To avoid calcium binding by heparin, the use of calcium-titrated heparin is recommended. Dilution effects can be managed by using lyophilized instead of liquid heparin.

Influences of physical activity, posture, meals, ventilatory rate, and circadian variation can significantly alter ionized calcium concentration under extreme conditions, but have a modest effect when monitoring critically ill patients.

For more detailed information about preanalytical variables affecting ionized calcium determinations, the reader is referred to the most current edition of NCCLS document C31—*Ionized Calcium Determinations: Precollection Variables, Specimen Choice, Collection, and Handling,* and IFCC document—Recommendation on sampling, transport and storage for the determination of the concentration of ionized calcium in whole blood, plasma and serum*,* in *Clinica Chimica Acta, 202 (1991) S13-S22.*

4.3.5 Glucose

Under fasting conditions, the glucose concentration throughout the circulatory system is quite uniform. Because glucose normally is catabolized in the tissues, arterial and capillary specimens may contain higher concentrations of glucose than venous [62(pp 150-165)] specimens. Diet and drugs will markedly affect glucose concentration. The person collecting the specimen should note if intravenous fluid was being given at the time of collection. Some glucose analyzers may report whole blood values and others may report values corrected to reflect serum/plasma concentrations. The manufacturer's literature should be consulted to ensure that the reference range and comparability to main laboratory values is clear to clinical users of the data.

4.3.6 Lactate

Decreased oxygen delivery to tissue results in an increase in lactic acid production, which is reflected in decreased blood pH and increased blood lactate concentration. If a venous specimen for lactate determination is desired, it should be obtained without using a tourniquet, or immediately after the tourniquet is applied. Lactate increases in whole blood after collection because of glycolysis, so the same time constraints that were discussed in Section 4.2.1 for pH and pO_2 also apply to lactate determinations.

4.4 Specimen Handling

4.4.1 Analysis

The manufacturer's instructions should be followed carefully when introducing samples into blood gas/pH instruments. Incorrect introduction of samples can cause erroneous results, especially by contamination from air bubbles, clots or the leaking of sample due to compromise of the measuring chamber, electrode membranes, or fluid path by too rapid or too vigorous injection.

When blood samples are introduced into the analyzer by aspiration, an air bubble may form in the remainder of the blood sample. This should be removed immediately in case the measurement needs to be repeated.

An analysis should be repeated immediately (preferably on another instrument) if the results fall into any of the following categories:

- Inconsistent with the patient's past results and/or condition;
- Internally inconsistent [e.g., pH 7.40, pCO_2 25 mmHg (3.3 kPa), and a reported bicarbonate of 24 mmol/L or the sum of pO_2+ pCO_2 >150 mmHg (20.0 kPa) for patients breathing room air]; or
- At the extremes of the range of expected values [e.g., pH below 7.20 or above 7.60; pCO_2 below 30 (4.0 kPa) or above 48 mmHg (6.4 kPa); pO_2 below 50 (6.6 kPa) or above 300 mmHg (40.0 kPa)].

It is important to reanalyze specimens with aberrant results quickly, because accurate results in these ranges should be reported to the physician as soon as possible, and the quality of the specimens deteriorates rapidly.

4.4.2 Reporting

Ideally, a complete report should note the exact conditions of collection, including collection time; source (arterial, mixed venous, venous, or capillary); FIO_2 level; ventilatory settings; fluid infusions and location; specific collection site; and patient posture, along with the values obtained by the analyzer itself. This information should be recorded in the laboratory report or be available on the chart or computer system.

Comments, such as the quality of the specimen as received, transportation delays, and improper storage, should be documented. This information will aid both the operator of the analyzer in judging the analytical quality of the results and the clinician in evaluating the patient.

Ionized calcium results should be reported with a simultaneously measured pH.[66] It is recommended that the calcium ion concentration adjusted to pH 7.40 be used cautiously. (See NCCLS document C31—*Ionized Calcium Determinations: Precollection Variables, Specimen Choice, Collection, and Handling*, for more information.)

5 General Analytical Interferences

5.1 Hematocrit

Current methods used to measure hematocrit on multianalyte blood gas analyzers involve either the calculation of hematocrit from a measured total hemoglobin or the estimation from a conductivity measurement. Because the conductivity measurement is dependent upon electrolyte concentrations, variation in the electrolyte concentration may affect the hematocrit value if not taken into consideration. Analyzers that simultaneously measure sodium along with hematocrit (conductivity) may perform the appropriate correction.[67-69] Check the manufacturer's literature.

5.2 Errors in Thermal Control

It is often difficult to check the inaccuracy of the thermal control of the sample cuvette. Because of the large thermal coefficients of the pH and blood gas, it is important that the analyzer measures[a] all values at 37 °C regardless of the sample's initial temperature. The manufacturer's literature should be consulted for limitations on the initial temperature of the sample.

5.3 Hemoglobin F (Fetal Hemoglobin)

The absorption spectra of HbF derivatives differ slightly from those of adult hemoglobins, and errors may occur if this is not taken into account.[70] The most common error is the false elevation of F_{COHb},[71] but MetHb levels may also be affected. See the manufacturer's literature.

5.4 Blood Substitutes

Blood substitutes may interfere with analysis of pH, blood gases and related quantities. Not enough is known at this time to quantify the effects.

5.5 Abnormal Hemoglobins

Non-HbA species (e.g., hemoglobin Kansas, hemoglobin Yakima) may have different spectral characteristics and, therefore, may yield erroneous results when using a conventional oximeter.

6 Blood Gas Analyzer Calibration

6.1 Calibration

Because of the many designs, protocols, and recommendations from manufacturers, it is not possible to give specific guidelines for blood gas analyzer calibration. Each analyzer has recommended procedures that include specific calibration material and frequency. Operators must adhere to these. Manufacturers' calibration materials should be traceable to certified reference materials (e.g., the U.S. National Institute of Standards and Technology [NIST], etc.).

Whole blood tonometry is the reference method for establishing accuracy for p_{O_2} and p_{CO_2}, provided that gases used for tonometry have a composition traceable to certified reference materials. Manufacturers should use whole blood tonometry using certified gases as a reference method for establishing accuracy for p_{O_2} and p_{CO_2} measuring devices.

The fractional value for each hemoglobin derivative (F_{O_2Hb}, F_{HHb}, F_{COHb}, F_{MetHb}, F_{SulfHb}) is based on ratios of absorbencies and thus needs no separate calibration as long as the measuring wavelengths remain the same.

6.2 Internal Electronic Barometer

The internal electronic barometer found in some automated analyzers is critical to their accurate calibration. Its function should be checked by comparing its value to a reliable independent measurement. Using an aneroid barometer that is set to nonlocal, weather bureau, sea-level-adjusted, barometric pressure is a potential source of error. The instrument manufacturer's recommendations regarding barometric checks should be followed. Barometric readings should read local conditions and not be

[a] Certain approaches to sensing temperature and to reporting a "37 °C" value may avoid actually measuring the chamber temperature at 37 °C. Whatever approach is chosen by the manufacturer, the system performance shall be equivalent to the traditional 37 °C +/- 0.1.

adjusted to sea-level readings. (**NOTE**: Some instruments are designed to eliminate the need for a barometer. Consult the manufacturer for details.)

7 Blood Gas Quality Control

The general goal of a QC program is to determine whether an analyzer works properly before patient samples are measured or after suspicious results have been obtained. The specific goal is to evaluate the instrument's performance in terms of both inaccuracy and imprecision. See NCCLS document C24—*Statistical Quality Control for Quantitative Measurements: Principles and Definitions*, for detailed information on day-to-day processes and procedures for quality control.

7.1 Materials Used for Quality Control

7.1.1 Tonometry

Tonometry is the process of equilibrating a fluid under controlled conditions (i.e., temperature, barometric pressure, humidification, etc.) with a known mixture of gases.

7.1.1.1 Whole-Blood Tonometry

When NIST-certified Standard Reference Material (SRM) gases are used, fresh whole-blood tonometry is considered the reference procedure to establish the accuracy for blood pO_2 and pCO_2.[1] Tonometered whole blood is not useful for assessing pH.

For various reasons it may not be practical for all blood gas laboratories to have a tonometer readily available for routine quality control. On the other hand, absolute accuracy of pO_2 and pCO_2 cannot be assessed without whole-blood tonometry.

If tonometry is not directly available in a laboratory, it should be made available through some arrangement with other nearby laboratories or the manufacturer so that when issues of true accuracy arise, the assessment can be made, based on a reference method rather than artificial materials.

7.1.1.2 Non-Whole-Blood Tonometry

Tonometry of specially prepared aqueous solutions, which do not contain hemoglobin, has been reported.[72, 73] This approach is useful for pH assessment and pCO_2, and of more limited value for pO_2.

Aqueous hemoglobin solutions, which have an oxygen buffering capacity similar to that of fresh, human whole blood (i.e., a p_{50} of approximately 26 mmHg (3.5 kPa)), can be used as satisfactory tonometry media for the purpose of assessing the accuracy of blood gas electrodes as well as quality control for pH.[74,75] Another advantage of using these materials is that they do not pose a biohazard.

7.1.2 Commercial Controls

At present, different types of commercial controls are available (e.g., buffered aqueous solutions [in some cases containing various additives for enhancement]; buffered blood-based solutions containing free hemoglobin; and buffered perfluorocarbon emulsions.)

7.1.2.1 Aqueous Control Solutions

These bicarbonate buffered solutions are equilibrated with gas mixtures and sealed in ampules with a small headspace containing the gas mixture. The type and concentration of the buffer and the pH of the solution determine the buffering capacity. These solutions typically behave like blood with respect to pH

and pCO_2 buffering. However, they have very low oxygen buffering capacity and, therefore, resist changes in pO_2 poorly. They are especially subject to variability based on storage temperature or handling temperature.

Because viscosity, surface tension, and electrical conductivity do not usually match those of whole blood, aqueous controls do not detect certain problems that can occur with an analyzer. For example, the thermal coefficients of these solutions are low in some cases and may not detect cuvette temperature problems.

7.1.2.2 Hemoglobin-Containing Control Solutions

Hemoglobin-containing controls consist of red blood cells or hemolysate, treated with various stabilizing agents, added to an aqueous buffered salt solution. The presence of hemoglobin enhances the pO_2 buffering, assuming the p_{50} of the solution is approximately normal.

These controls are normally stored at refrigerator temperatures. They need to be equilibrated to the temperature recommended by the manufacturer before opening.

7.1.2.3 Emulsion Control Solutions

Emulsion controls consist of oils, typically perfluorocarbon in buffered aqueous salt solutions. The solubility of oxygen in these controls is four to five times greater than in aqueous solutions, but is far less than the solubility of oxygen in blood at pO_2 levels below 100 mmHg (13.3 kPa). These controls are better than aqueous control solutions in resisting oxygen changes. Also, the surface tension and density of these controls are not identical to that of blood.

7.1.2.4 Temperature Equilibration of Commercial Controls

All blood gas control solutions packaged in ampules have a gas phase. Because the partial pressures of the gases in the space change with temperature, care must be taken to equilibrate the control solution to the appropriate temperature before opening.[76]

7.1.2.5 Oximetry Controls

Typically, quality control for oximetry is performed with solutions of dyes chosen to have absorbance readings at wavelengths appropriate to simulate mixtures of deoxy-, oxy-, carboxy- and methemoglobin over the range of concentrations of clinical interest. These solutions are stable. The actual hemoglobin species are not stable enough in solution to be used as control materials.

7.1.3 Duplicate Assay

A laboratory may choose to augment quality control by using two or more instruments for simultaneous analysis of a sample.[73, 77-80] Any two instruments are assumed unlikely to have the same error at the same time. The duplicate assay approach is not to be used as the sole method of QC.

7.1.4 Electronic Quality Control (EQC)

EQC is available for some blood gas devices. EQC devices monitor the instrument only. This approach tests the electronics of the measurement system but does not directly test the electrode performance, reagent stability, or the temperature control. Because some portions of the testing process are not evaluated, additional (nonelectronic) quality control material should be tested at periodic intervals, the frequency of which is to be determined by the laboratory director.

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Appendix. Performance Characteristics to be Specified by the Manufacturer

A1 Measured Quantity

Examples: Measured Quantity: pCO_2 mmHg (kPa)
Measured Quantity: pO_2 mmHg (kPa)

A2 Calculated Quantity

Calculated quantities are those output values calculated from one or more measured quantities. These quantities shall be designated as "calculated."

A3 Measurement Range

The measurement range is the total range of values for a quantity to which the stated inaccuracy and imprecision values apply.

Examples: pCO_2: 5 to 125 mmHg (0.7 to 16.6 kPa)
pO_2: 0 to 600 mmHg (0 to 79.8 kPa)

A4 Recalibration Interval

A4.1 Recalibration Interval in Operational Mode

The recalibration interval in operational mode is considered the maximum length of time after calibration by the manufacturer's specified method during which the stated inaccuracy and imprecision values are valid. The instrument is assumed to be in the operational mode during this time (i.e., while no blood samples are run during the interval, a valid pCO_2 or pO_2 determination could be performed at any time without allowing for any instrument start-up time, warm-up time, or recalibration).

Example: 30 minutes (automatic)

A4.2 Recalibration Interval in Sampling Mode

The recalibration interval in sampling mode is considered the maximum number of blood samples that can be run before recalibration becomes necessary to ensure that the claimed inaccuracy and imprecision values are valid.

Example: 45 samples

A5 Blood Sample Volume

The minimum total blood sample volume in microliters is that which must be introduced into the instrument in order to perform an analysis (within the limits of the claimed inaccuracy and imprecision). This is to be given for both microsample and macrosample modes, if applicable.

Example: Microsample: 150 µL
Macrosample: 500 µL.

A6 Sample Temperature

A6.1 Input Temperature

Within the range of the blood sample temperatures (T) in degrees Celsius, the input temperature is that which can be introduced into the instrument without affecting the claimed inaccuracy, imprecision, sample analysis time, or throughput rate.

Example: $4 \leq T \leq 42\ ^{o}C$

A6.2 Analysis Temperature

Within the temperature range in degrees Celsius, the analysis temperature is the temperature at which the blood sample is maintained during measurement.

Example: $36.8 \leq T \leq 37.2\ ^{o}C$

A7 Sample Analysis Time

The sample analysis time is the elapsed time between the introduction of a sample and the availability of output data. (The number specified for this quantity should represent the greatest length of time necessary for the instrument output to stabilize within the limits of the claimed inaccuracy and imprecision.) Sample analysis time should be specified (a) for samples with pCO_2 within the range of 30 to 50 mmHg (4.0 to 6.6 kPa), or pO_2 within the range of 80 to 100 mmHg (10.6 to 13.3 kPa); and (b) for samples with pCO_2 or pO_2 over the remainder of the entire claimed measurement range.

Example:	Less than 2 minutes	30 mmHg (4.0 kPa) $\leq pCO_2 \leq$ 50 mmHg (6.6 kPa)
	Less than 2 minutes	80 mmHg (10.6 kPa) $\leq pO_2 \leq$ 100 mmHg (13.3 kPa)
	Less than 3 minutes	(total measurement range).

A8 Throughput Rate

The throughput rate is the average number of blood samples that can be completely analyzed (within the limits of the claimed inaccuracy and imprecision) in a typical one-hour period. This time includes washout and calibration procedures, but not service or maintenance. The throughput rate should specify the rate that can be expected when measuring pCO_2 in the range of 30 to 50 mmHg (4.0 to 6.6 kPa) or pO_2 in the range of 80 to 100 mmHg (10.6 to 13.3 kPa). In addition, the throughput rate that can be expected over the remainder of the claimed measurement range shall be specified.

Example:	20 samples/hour	30 mmHg (4.0 kPa) $\leq pCO_2 \leq$ 50 mmHg (6.6 kPa)
	20 samples/hour	80 mmHg (10.6 kPa) $\leq pO_2 \leq$ 100 mmHg (13.3 kPa)
	15 samples/hour	(total measurement range).

A9 Inaccuracy and Imprecision

Performance claims for inaccuracy and imprecision should be made. These claims may be evaluated using NCCLS evaluation protocol documents.

NCCLS consensus procedures include an appeals process that is described in detail in Section 9.0 of the Administrative Procedures. For further information contact the Executive Offices or visit our website at www.nccls.org.

Summary of Comments and Working Group Responses

C46-P: *Blood Gas and pH Analysis and Related Measurements; Proposed Guideline*

General

1. As C46 is advanced to the approved level, reinsertion of operations/procedures that could be helpful to manufacturers should be considered. In some cases, an appropriate option may be to include such information in appendices.

- **The working group reviewed the documents that were merged into C46 and believes that all relevant information has been included in the C46 guideline. For some information that has not been included in the merge, reference has been made in C46, where relevant, to other NCCLS documents, especially evaluation protocol documents.**

Section 3.2

2. Third paragraph: We would recommend that SI units be added throughout the document in parentheses to improve international usefulness.

- **SI units have been included in the text, in accord with NCCLS policy, where appropriate. SI units have not been added to the equations, because the working group felt that the SI units would make the equations confusing.**

Section 3.2.1

3. Third paragraph: We would recommend that "whole blood" be used in place of "blood" throughout the document. "Blood" is sometimes used in a broader way.

- **"Whole" blood was added to the third paragraph of Section 3.2.1. The working group believes that "whole" blood is used appropriately elsewhere in the text. The working group did not incorporate "whole" throughout the document, because it believes some of the text would become awkward, especially in Section 4.2.**

Section 3.13

4. Do we know if anyone is still doing this measurement (P_{50} = half-saturation oxygen tension)? I did it years ago, but have not heard of anyone still doing it. Are enough people using this measurement to include it in this document? I would be inclined to leave it out.

- **Although this measurement is not performed often, the working group decided to maintain this information, because P_{50} is a useful measurement of hemoglobin oxygen affinity and is sometimes used for patient care.**

Section 4.1.3

5. I did not see that the name or initials of the individual obtaining the sample listed with the information needed to accompany the sample for analysis. Was it omitted by design?

- **As suggested, the identity of the person collecting the specimen has been added to Section 4.1.3.**

Section 4.2

6. As the guideline is advanced to the approved level, consider adding more information on how to recognize that a sample drawn from an in-dwelling line may be contaminated.

- **The working group believes there is no certain way to determine that the sample has been contaminated. The working group suggests in C46 to follow the recommendations in NCCLS document H11—*Procedures for the Collection of Arterial Blood Specimen*s, to prevent contamination of the samples.**

Section 4.2.2

7. The sentence, "Arterial line collection requires that an appropriate volume be withdrawn and subsequently discarded..." describes old methodology. Waste-less arterial line collection should be promoted, with the old system listed secondarily.

- **In Section 4.2.2, the fifth sentence has been revised as follows: "Arterial line collection requires that an appropriate volume be withdrawn initially to assure that the line contains only uncontaminated arterial blood before the actual sample is collected."**

Section 4.2.5

8. While 10 IU/mL heparin is clearly advisable to minimize the side effects of heparin, it should be expected that this low concentration might not eliminate the clotting processes within all analyzers. We have noted, with certain blood specimens, that even concentrations as high as 150 IU/mL are insufficient. The last sentence in paragraph 4 further confounds the situation. While the recommendation that minimum blood volume requirements should be established, it must be realized that minimum sample volumes require small sample channels within the instrumentation; a higher ratio of surface area to sample volume and, in turn, a need for higher heparin concentrations to prevent clotting. For these two points, we recommend that the recommendation of the manufacturer be followed for both type and concentration of heparin for best performance with particular analyzers.

- **The fifth sentence of the paragraph in reference, indicates that the manufacturer should be consulted. For clarification, the working group revised the sentence to read, "…the manufacturer *of the analyzer* should…"**

9. Generally, heparin does bind every cation, not just calcium. Calcium is the most significant one. Conversely, heparin may introduce ions to the sample other than as expected. Sodium heparin may contain significant amounts of potassium, thus elevating the potassium result in the sample. The use of lithium heparin is mentioned (3rd sentence), but it should be added that the use of lithium heparin invalidates the sample for measurement of lithium.

- **The first two sentences of the fourth paragraph in Section 4.2.5 have been revised to address the comment.**

Section 4.2.6

10. It should be mentioned that vent-seal additives might influence the measurement of ionized magnesium in the sample.

- **Section 4.2.6 has been revised to address this issue.**

Section 4.3.2

11. Equations 4, 24, 25 and 26 could be improved by providing range limits for valid temperature values.

- **The references listed for Equations 24 through 26 report that these formulas are valid for temperatures over the entire physiological range. Equation 4 is valid for much wider ranges then the physiological range and can be looked up by the user. References 8 and 9.**

Section 4.3.6

12. Adding a section for lactic acid would be appropriate here.

- **As suggested, Section 4.3.6, entitled Lactate, has been added.**

Section 4.4.1

13. The first paragraph should be deleted: Expelling a portion of the sample exposes the operator to additional risk, and if the syringe is held improperly, will only serve in reducing the unclotted portion of the sample, with the clot catching somewhere around the collar of the syringe. The suggested quantity of 0.1 to 0.2 mL is also impractical for neonate samples.

    The fourth paragraph should be removed from the Analysis Section. The listed items are examples of postanalytical assessments for a Quality Management program. They should be presented within that context, which may be beyond the scope of guideline C46.

- **As suggested, the first paragraph of Section 4.4.1 has been deleted. The working group decided to maintain the fourth paragraph of Section 4.4.1, because the information is relevant and important. We did not want the user to have to refer to another document on quality management for the information. The working group revised the fourth paragraph by deleting "Assuming the QC results are acceptable" from the first sentence.**

Section 7

14. We would prefer more detail regarding quality control, as this is not addressed fully in C24-A2, either. Specifically, it would be helpful to address frequency of QC and guidelines for low-volume laboratories (fewer samples than every day).

- **The working group considers NCCLS document C24—*Statistical Quality Control for Quantitative Measurements: Principles and Definitions* to be the best source for details on statistical internal quality control. The working group does not believe there are special requirements for low-volume laboratories.**

Related NCCLS Publications*

C24-A2 **Statistical Quality Control for Quantitative Measurements: Principles and Definitions; Approved Guideline—Second Edition (1998)**. This guideline provides definitions of analytical intervals; plans for quality control procedures; and guidance for quality control applications.

C29-A2 **Standardization of Sodium and Potassium Ion-Selective Electrode Systems to the Flame Photometric Reference Method; Approved Standard—Second Edition (2000).** This standard contains recommendations for the expression of results of ion-selective electrode measurement of sodium and potassium ion activities in undiluted serum, plasma, or whole blood in clinical practice.

C30-A **Ancillary (Bedside) Blood Glucose Testing in Acute and Chronic Care Facilities; Approved Guideline (1994).** This document offers guidelines for performance of bedside blood glucose testing emphasizing quality control, training, and administrative responsibility.

C31-A **Ionized Calcium Determinations: Precollection Variables, Specimen Choice, Collection, and Handling; Approved Guideline (1995).** This document addresses preanalytical considerations – such as patient condition, specimen choice, collection, and handling – that can influence accuracy and clinical utility of ionized calcium measurements.

EP5-A **Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline (1999).** This document provides guidance for designing an experiment to evaluate the precision performance of clinical chemistry devices; recommendations for comparing the resulting precision estimates with manufacturer's precision performance claims and determining when such comparisons are valid; as well as manufacturer's guidelines for establishing claims.

EP7-P **Interference Testing in Clinical Chemistry; Proposed Guideline (1986).** This document provides background information and procedures for characterizing the effects of interfering substances on test results.

GP2-A3 **Clinical Laboratory Technical Procedure Manuals—Third Edition; Approved Guideline (1996).** This document provides guidelines that address the design, preparation, maintenance, and use of technical procedure manuals whether they are in paper or electronic formats, for use by the patient-testing community.

H1-A4 **Evacuated Tubes and Additives for Blood Specimen Collection—Fourth Edition; Approved Standard (1996).** This standard contains requirements for blood collection tubes and additives including heparin, EDTA, and sodium citrate.

* Proposed- and tentative-level documents are being advanced through the NCCLS consensus process; therefore, readers should refer to the most recent editions.

Related NCCLS Publications (Continued)

H3-A4 **Procedures for the Collection of Diagnostic Blood Specimens by Venipuncture; Approved Standard—Fourth Edition (1998).** This document provides procedures for the collection of diagnostic specimens by venipuncture, including line draws, blood culture collection, and venipuncture in children. Includes recommendations on order of draw.

H4-A4 **Procedures and Devices for the Collection of Diagnostic Blood Specimens by Skin Puncture; Approved Standard—Fourth Edition (1999).** This document provides a technique for the collection of diagnostic blood specimens by skin puncture, including recommendations for collection sites and specimen handling and identification. Specifications for disposable devices used to collect, process, and transfer diagnostic blood specimens obtained by skin puncture are also included.

H11-A3 **Procedures for the Collection of Arterial Blood Specimens; Approved Standard—Third Edition (1999).** This standard describes principles for collecting, handling, and transporting arterial blood specimens. The document is aimed at reducing collection hazards and ensuring the integrity of the arterial specimen.

H15-A3 **Reference and Selected Procedures for the Quantitative Determination of Hemoglobin in Blood; Approved Standard—Third Edition (2000).** This standard describes the principle, materials, and procedure for reference and standardized hemoglobin determinations. It includes specifications for secondary hemiglobincyanide (HiCN) standards.

H18-A2 **Procedures for the Handling and Processing of Blood Specimens; Approved Guideline—Second Edition (1999).** This document addresses multiple factors associated with handling and processing specimens, and factors that can introduce imprecision or systematic bias into results.

M29-A **Protection of Laboratory Workers from Instrument Biohazards and Infectious Disease Transmitted by Blood, Body Fluids, and Tissue; Approved Guideline (1997).** A consolidation of M29-T2 and I17-P, this document provides guidance on the risk of transmission of hepatitis viruses and human immunodeficiency viruses in any laboratory setting; specific precautions for preventing the laboratory transmission of blood-borne infection from laboratory instruments and materials; and recommendations for the management of blood-borne exposure.

NRSCL8-A **Terminology and Definitions for Use in NCCLS Documents; Approved Standard (1998).** This document provides standard 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 (NRSCL).

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