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Blood Gas and pH Analysis and Related Measurements; Approved Guideline—Second Edition

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 Clinical and Laboratory Standards Institute consensus process.

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Blood Gas and pH Analysis and Related Measurements; Approved Guideline—Second Edition

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Abstract

This guideline is a consolidation of six CLSI documents and projects. The Area Committee on Clinical Chemistry and Toxicology concluded that CLSI'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 (eg, hemoglobin and hemoglobin fractions, oxygen content, hemoglobin-oxygen saturation, electrolytes, and selected metabolites) as measured in 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 previously published CLSI/NCCLS documents 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 Preanalytical Considerations: Specimen Collection and Controls*; *Approved Guideline;* and C32-P—*Considerations in the Simultaneous Measurement of Blood Gases, Electrolytes, and Related Analytes in Whole Blood; Proposed Guideline;* and unpublished CLSI document C33—*Practical Blood Gas and pH Quality Control*.

Sections of another CLSI/NCCLS document H11 also are included; however, H11 will remain a separate document, because its content is of interest to a broader audience.

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Contents

Contents (Continued)

Foreword

The previous edition of this document, C46-A, was 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 was for this document to serve more effectively the three major constituents (professions, government, and industry) of CLSI.

C46-A consolidated the following documents:

- 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 Preanalytical 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 CLSI/NCCLS document H11[1] were also included; however, H11[1] remained a separate document, because its content includes greater detail and is of interest to a broader audience.

The current revision of the document, C46-A2, includes the following updates:

- Section 5, *Preanalytical Considerations,* was expanded to include a discussion specific to transport of specimens (see Section 5.3). Section 5.4, In Vivo *Effects on Measurements*, replaces the former section, *Patient Condition,* and was expanded.
- Section 6, *Analytical Interferences*, was expanded significantly, including references to recent literature.
- Section 7, *Blood Gas Analyzer Calibration*, was expanded significantly, including current requirements for calibration traceability.
- Section 8, *Blood Gas Quality Control,* includes newer approaches for "alternative" quality control.
- Appendix B, *Recommendations for Measurement and Reporting of Hemoglobin Fractions and Related Quantities*, was added.
- Appendix C, *Measurement Technologies Used in Instruments for Analysis of Blood Gases, pH, and Related Analytes*, was added.

Key Words

Electrolytes, fractional hemoglobins, hemoglobin-oxygen saturation, metabolites, oxygen content, partial pressure of carbon dioxide, partial pressure of oxygen, pH

Blood Gas and pH Analysis and Related Measurements; Approved Guideline—Second Edition

1 Scope

This guideline addresses blood gas, pH, and related measurements (eg, hemoglobin and hemoglobin fractions, oxygen content, hemoglobin-oxygen saturation, electrolytes, hematocrit, glucose, and lactate) as measured in blood. The guideline is limited to devices for measurement of these quantities *in vitro*. Devices for *in vivo* monitoring and patient-attached, *ex vivo* monitors for blood gas, pH, and related measurements, although common in many respects to devices for *in vitro* measurements, are not specifically addressed.

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

This guideline is primarily intended for laboratory technologists, respiratory therapists, 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 Introduction

Several aspects of blood pH and gas analysis 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, 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 QC. 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.

3 Standard Precautions

Because it is often impossible to know what isolates or specimens might be infectious, all patient and laboratory specimens are treated as infectious and handled according to "standard precautions." Standard precautions are guidelines that combine the major features of "universal precautions and body substance isolation" practices. Standard precautions cover the transmission of all infectious agents and thus are more comprehensive than universal precautions, which are intended to apply only to transmission of blood-borne pathogens. Standard and universal precaution guidelines are available from the US Centers for Disease Control and Prevention.[2] For specific precautions for preventing the laboratory transmission of all infectious agents from laboratory instruments and materials and for recommendations for the management of exposure to all infectious disease, refer to CLSI document M29.[3]

4 Terminology

4.1 Concepts and Definitions

This section contains terms and definitions in standard CLSI format 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 were developed with the intent of providing maximum clarity for the typical reader of this document.

The reader is referred to the definitions and explanatory notes found in the CLSI Harmonized Terminology Database, both for related terms and definitions not contained in this document and for a more precise understanding of a term's concept.

4.1.1 pH

pH – the symbol for the negative common logarithm of the relative molal hydrogen ion activity (aH^+), 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."

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

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) 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.[4-6]

4.1.2 Partial Pressure of CO_2 and O_2

partial pressure//tension – *of a gas in a solution,* pressure that would exist in a gas phase, in equilibrium with the solution.[7,8]

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 is used throughout this document. The kilopascal (kPa) is the unit of measure for pressure (partial) in the International System of Units (SI).[9] The relationship between these two units is 1 mmHg = 0.133 kPa. Kilopascal units are reported in the text as (kPa).

4.1.2.1 Symbols

The symbols chosen for use in this document are all compatible with International Federation of Clinical Chemistry and Laboratory Medicine (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 necessary, characterize the type of sample (eg, in blood) and its source (eg, arterial). **NOTE:** 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).

4.1.2.2 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.[10,11]

4.1.3 Apparent pK of CO_2 in Plasma (pK′)

pK′ – the symbol used to represent the negative common 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:

$$pK' = pH + \log cCO_{2,\text{dissolved}} - \log cHCO_3^- \quad (5)$$

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.[12] 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 $mmHg^{-112}$ and the value of pK′ appropriate for the plasma compartment of blood at pH 7.40 and 37 °C is 6.095, when measurements are made in blood. This value was derived from experimental determinations[13] and agrees, within experimental error, with several previous determinations. **NOTE:** The pK value in separated plasma is accepted as 6.105.[13]

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 (eg, in pathological conditions) will bias calculations that include pK′, the magnitude of the bias is rarely, if ever, clinically significant.[14-17] The pK′ may be more intuitively understood as the measured pH when the acid/base pair are in equal concentrations, making the log of base/acid ratio = 0.

4.1.4 Concentration of Total CO_2 in Plasma Compartment of Blood

total CO_2 – the combination of all of the various forms of carbon dioxide in the plasma in equilibrium with 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_2^-, and protein carbamates.

In 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:

$$ctCO_2 = cHCO_3^- + (\alpha'CO_2 \times pCO_2) \quad (7)$$

This equation is appropriate for the plasma compartment of blood at 37 °C.[18]

4.1.5 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:[18]

$$\log cHCO_3^- = pH + \log pCO_2 - 7.608; \quad (8)$$

It is equivalent to the more familiar equation:

$$\log cHCO_3^- = pH + \log (pCO_2 \times 0.0307) - 6.095. \quad (9)$$

4.1.6 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:

$$\beta_{ecf} = \frac{-d\,cHCO_3^-}{d\,pH} \quad (10)$$

where d is the differential.

4.1.6.1 Determination

Nonbicarbonate buffers in extracellular fluid (β_{ecf}) are determined by varying pCO_2 and allowing equilibration with the extracellular fluid (ie, 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.)[19] β_{ecf} was 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.

4.1.7 Base Excess of Extracellular Fluid [$BE_{(ecf)}$]

base excess of extracellular fluid – the {substance} concentration of base determined by titrating a model of extracellular fluid to a pH of 7.40 with a pCO_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 were 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.

4.1.7.1 Calculation of $BE_{(ecf)}$

This quantity may be calculated as:

$$BE_{(ecf)} = cHCO_3^- - cHCO_3^-R + \beta_{ecf}\,(pH - pHR) \quad (11)$$

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:

$$BE_{(ecf)} = cHCO_3^- - 24.8 + 16.2(pH - 7.40) \quad (12)$$

Adopting a constant value for β_{ecf} is an approximation. The value expressed by β_{ecf} is 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.[20,21]

Table 1. Quantities, Units, Symbols, and Constants Used for Calculated Parameters

Quantity		Unit		Constants*
Name	**Symbol**	**Name**	**Symbol**	
pH	pH			7.400
Partial pressure of CO_2	pCO_2	Millimeter of mercury (kilopascal)	mmHg (kPa)	40 mmHg (5.3 kPa)
Partial pressure of O_2	pO_2	Millimeter of mercury (kilopascal)	mmHg (kPa)	95 mmHg (12.6 kPa)
Concentration of hemoglobin	$ctHb$	Grams per deciliter	g x dL^{-1}	15 g x dL^{-1} (9.3 mmol x L^{-1})
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 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}

*Standard values or concentrations applied when the listed quantities are used for calculated parameters.

4.1.8 Base Excess of Blood [BE(B)]

base excess of blood [BE(B)] – 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 4.1.8.1).

4.1.8.1 Calculation of [BE(B)]

Several nomograms and diagrams are currently available that allow this quantity to be estimated from a measured pH, pCO_2, and hemoglobin concentration.[22] Base excess of blood may also be calculated using the following equation[22] based on these nomograms and diagrams.

$$BE(B) = (1 - 0.014\ c\text{tHb})\ [c\text{HCO}_3^- - 24.8 + (1.43\ c\text{tHb} + 7.7)\ (\text{pH} - 7.40)] \quad (13)$$

4.1.8.2 BE(B) vs BE_{ecf}

Care should be taken not to confuse base excess of blood with base excess of extracellular fluid.[18,19] The farther the observed pH is from 7.4, the more difference will be observed between the two quantities.[18,19]

4.1.9 Concentration of Total Hemoglobin (*c*tHb)

total hemoglobin (*c*tHb) – 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,[23] 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.[24] (Refer to CLSI/NCCLS document H15.[25])

cooximeter – term commonly used for a multiwavelength photometer for measurement of hemoglobin concentration and relative amounts of oxy-, deoxy-, carboxy-, and methemoglobin components in blood. The process of measuring these species in blood using a multiwavelength photometer is commonly referred to as "cooximetry." An older term, "hemoximetry," initially referred to the measurement of the oxy- and deoxyhemoglobin species; but it can also include the measurement of carboxy- and methemoglobin, as well.

4.1.10 Hemoglobin "Saturation" and Fractional Derivatives of Hemoglobin

4.1.10.1 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.

4.1.10.2 Oxyhemoglobin Fraction of Total Hemoglobin

oxyhemoglobin – the hemoglobin derivative obtained when hemoglobin (Fe^{++}) binds reversibly with oxygen.

oxyhemoglobin fraction (of total hemoglobin//fractional oxyhemoglobin, ***F*O$_2$Hb) – 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).

$$FO_2Hb = \frac{cO_2Hb}{ctHb} \quad (15)$$

4.1.10.3 Hemoglobin Oxygen Saturation

hemoglobin oxygen saturation (*s*O$_2$) – the amount of oxyhemoglobin in blood expressed as a (percent) fraction of the total amount of hemoglobin able to bind oxygen (ie, 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.[26] They do not account, however, for intracellular erythrocyte diphosphoglycerate (DPG) concentration, which is affected by blood transfusions and several biochemical factors[27,28] 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.

4.1.10.4 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.

$$FHHb = cHHb/ctHb \quad (17)$$

$$FCOHb = cCOHb/ctHb \quad (18)$$

$$FMetHb = cMetHb/ctHb \quad (19)$$

$$FSulfHb = cSulfHb/ctHb \quad (20)$$

Hemoglobin derivatives, which cannot reversibly combine with oxygen, are referred to as "dyshemoglobins" (eg, COHb and MetHb). Elevated levels of dyshemoglobin concentration decrease the oxygen-carrying capacity of blood and are manifested in a decreased fractional oxyhemoglobin (FO_2Hb), but *not* in a decrease in oxygen saturation (% sO_2).

Example: High levels of carboxyhemoglobin (eg, *F*COHb >0.15) will show a decreased FO_2Hb of 0.15 or more (to perhaps 0.81 from 0.96), but % sO_2 will remain normal at 96% to 98%. Spectrophotometric analysis of carboxyhemoglobin (COHb) is generally quite satisfactory to determine levels above the reference range (ie, *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 (eg, 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 (*F*COHb <0.05), gas chromatography appears to be the method of choice.[29,30]

4.1.10.5 Oxygen Saturation From Pulse Oximetry

Typically, claims of accuracy for oxygen saturation measurements by pulse oximetry compared to cooximetry are limited to oxygen saturation values between 70% and 100%. Historically, oxygen saturation obtained from pulse oximetry (spO_2) was not accurate in the presence of elevated concentrations of dyshemoglobins. This is because simple two-wavelength pulse oximeters do not distinguish between normal hemoglobin species and dyshemoglobins, and the dyshemoglobins will be incorrectly considered as species capable of carrying oxygen. Some pulse oximeters that claim to correct for presence of dyshemoglobins assume a fixed value for dyshemoglobins, which may not be correct for a given patient, and can differ among systems from different manufacturers. See CLSI document HS03[31] for more information.

A new generation pulse oximeter is now available that uses multiple wavelengths to measure MetHb and COHb, in addition to the usual measurements of sO_2 and pulse rate. Good correlation to laboratory oximeters was demonstrated for the measurement of MetHb and COHb.[32] Because two-wavelength pulse oximeters will continue to be used in clinical practice for the foreseeable future, sO_2 from pulse oximetry should be interpreted with caution, especially if the presence of dyshemoglobins is suspected.

Laboratory oximeters, using multiple wavelengths that distinguish abnormal derivatives of hemoglobin, provide an accurate measurement of hemoglobin oxygen saturation (see Appendix B).

4.1.11 Oxygen Capacity of Hemoglobin in Blood (BO_2)

oxygen capacity of hemoglobin in blood//hemoglobin-oxygen binding capacity (BO_2) – the maximum amount of oxygen that can be carried by the hemoglobin in a given quantity of blood.

$$BO_2 = [ctHb - (cdysHb)] \times \beta O_2, \quad (21)$$

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:

$$\beta O_2 = (22\,400 \text{ mL/mol } O_2 \times 4 \text{ mol } O_2\text{/mol Hb}) / (64\,458 \text{ g/mol Hb})$$
$$= 1.39 \text{ mL } O_2\text{/g Hb}, \quad (22)$$

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

4.1.12 Oxygen Content (Concentration of Total Oxygen) of Blood

oxygen content (concentration of total oxygen) of blood (ctO_2) – 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[33-36] are of academic interest, but are of little practical value in that they require highly specialized expertise and equipment that is not routinely available in most laboratories. Oxygen content is expressed in mL(STPD)/dL and can best be calculated using the following equation:

$$ctO_2 = (FO_2Hb \times \beta O_2 \times ctHb) + \alpha' O_2 \times pO_2 \quad (23)$$

The concentration solubility coefficient of oxygen in blood plasma (α') expressed in units needed for this equation (mL per dL per mmHg) is 0.00314. βO_2 is the oxygen binding capacity of one gram of hemoglobin (see Section 4.1.11), equivalent to 1.39 mLO_2/g Hb.

The accuracy of oxygen content calculated this way is quite satisfactory for clinical use, provided the three variables (FO_2Hb, $ctHb$, and pO_2) are measured accurately and on the same blood sample. Care should be taken not to substitute FO_2Hb with sO_2 unless it can be demonstrated that they are equivalent. Only in subjects whose blood contains no dyshemoglobins are the values equivalent.

4.1.13 p_{50}

p_{50} (half-saturation oxygen tension) – the symbol used to represent the partial pressure of oxygen in a hemoglobin solution (usually blood) with an oxygen saturation of 50%.[37]

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

4.1.13.1 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-DPG, 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.

4.1.13.2 p_{50} (standard)

p_{50} (standard) – 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.

4.1.13.3 p_{50} (actual)

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

4.2 Abbreviations/Acronyms

ATP	adenosine triphosphate
CV	coefficient of variation
DPG	diphosphoglycerate
FS	functional sensitivity
HEPES	N-2-hydroxyethylpiperazine-N′-2-ethanesulfonic acid
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
IUPAC	International Union of Pure and Applied Chemistry
LoD	limit of detection
LoQ	limit of quantitation
MCHC	mean corpuscular hemoglobin concentration
NIST	National Institute of Standards and Technology
QC	quality control
SI	International System of Units
SRM	Standard Reference Material (NIST)
STPD	Standard Temperature Pressure Dry

5 Preanalytical Considerations

Each laboratory must have policies and written protocols in place to ensure accurate results, and maintain positive patient identification and specimen integrity from the time of collection of the specimen to reporting of the results. (Refer to CLSI document GP02[38] for procedures format.) Each laboratory must develop specific policies and procedures appropriate to its own situation. Information contained in these should be available, understandable, and followed by all personnel associated with collecting and processing blood gas/electrolytes specimens.

The following topics are important to consider when developing policies and procedures for the blood gas laboratory.

5.1 Patient Preparation

5.1.1 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 CLSI document H03.[39]

5.1.2 Patient Assessment

Most specimens for blood gas analysis are collected for emergency, critical care, or diagnostic purposes. While urgent measurements of blood gases require immediate collection of the specimen, in some situations, such as determining the effect of ventilator changes or for pulmonary function tests, it may be desirable to achieve a “steady-state” of ventilation before collecting an arterial blood sample. A stable ventilatory status for 20 to 30 minutes is adequate for most patients following ventilatory changes. Any patient requiring collection of an arterial blood specimen needs evaluation and confirmation of clinical indications, as well as contraindications, regardless of ventilatory status.[40]

5.1.3 Specimen Labeling and Accompanying Information

The specimen must be properly labeled with the patient's full name, a second identifier such as the medical record number, a personal identification number or birth date according to local policies, the date and time of collection, and the identity of the person collecting the specimen. In addition, the following information should be recorded, when available, in the chart or computer system for meaningful clinical interpretation of blood gas results:[41]

- age of patient;
- location of patient;
- body temperature;
- time of sampling;
- FIO_2 or actual flow rate and method of delivery;
- ventilatory status (spontaneous breathing or assisted/controlled ventilation);
- mode of ventilation (ie, pressure support);
- site of the sampling; and
- position and/or activity (ie, rest or exercise).

5.2 Sample Device and Collection Procedures

Collection of blood by arterial puncture is technically more difficult, usually more painful, and potentially more hazardous than venipuncture to the patient. CLSI/NCCLS document H11[1] 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 CLSI/NCCLS document H11,[1] related to preanalytical variables affecting blood gas/electrolytes values, are incorporated in this guideline.

5.2.1 Sample Device

In most instances, the ideal collection device for arterial blood sampling is a 1- to 3-mL self-filling, plastic, disposable syringe, containing a small amount of an appropriate anticoagulant, such as lyophilized heparin. The choice of the type of heparin depends on the specific analytes to be determined and the method of analysis. Because ordinary heparin can bind to ionized calcium and other electrolytes that are often analyzed with blood gases and pH, special preparations of heparin are available, which virtually eliminate the interference from heparin binding of these electrolytes.

Leukocytes in stored blood continue to consume oxygen at a rate depending on storage temperature, storage time, and initial level of oxygen in the blood sample.[42,43] 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 glass, polypropylene and other polymer materials of which plastic syringes are made are somewhat permeable to gases.[44] While earlier studies found clinically significant errors in oxygen values when plastic syringes were used,[45,46] later studies identified certain conditions that exacerbate or attenuate change: 1) the initial pO_2 value; 2) the amount of total hemoglobin; 3) time and temperature during storage; and 4) the degree of oxygen-hemoglobin binding, eg, shifts of the position of the oxygen-hemoglobin dissociation curve (p_{50}).[47-51]

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 cool room temperatures for 20 to 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 delay of more than 30 minutes is anticipated before analysis, storage in ice water should be considered. If samples are stored in ice water, the electrolytes, particularly potassium, will undergo transport between cells and plasma that may cause erroneous K^+ values to be measured.

5.2.2 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 is the respiratory component of the acid-base status in a patient, 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 to dissolve the heparin anticoagulant, and promptly analyzed.

For radial artery collections, the Allen test may be used to determine if there is adequate blood circulation to the hand (see CLSI/NCCLS document H11).[1] Arterial line collection requires that an appropriate volume be withdrawn initially to ensure the line contains only uncontaminated arterial blood before the actual sample is collected. This procedure minimizes the chance of specimen contamination with intravenous solutions, ie, liquid heparin, medication, or electrolyte fluids that may be in the line. Consult CLSI/NCCLS document H11[1] for specifics.

5.2.2.1 Use of Local Anesthetics

Although rarely done, the injection of a local anesthetic, such as xylocaine, can minimize the pain of the arterial puncture. However, while this practice may make the arterial puncture less painful and stabilize ventilation in a noncomatose patient, this extra needlestick is also painful and may cause an apprehensive hyperventilation that alters the blood gas result.

The decision of whether or not to inject a local anesthetic before the arterial puncture should be left to the professional judgment of the attending physician or caregiver, according to the policies established at that institution.

5.2.3 "Arterialized" Capillary Specimen

If arterial blood cannot be collected directly, peripheral capillary blood may be collected using an arterialization technique, which will give blood gas results in capillary blood that approximate those in arterial blood. Although "arterialized" capillary blood may be the only practical alternative to arterial blood, adequate sample volume is difficult to obtain and the blood gas results may differ, especially those for pO_2, sO_2, FO_2Hb, and ctO_2.[52-55] As with all blood gas specimens, 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 CLSI document H04.[56]) 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 other electrolytes and for total hemoglobin/hematocrit, oxygen content and oxygen capacity.

5.2.4 Venous Specimen

Venous blood is *not* a satisfactory substitute for arterial blood for routine blood gas analysis. When properly drawn (see CLSI document H03[39]), 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, oxygen content, or oxygen saturation/fractional hemoglobin. Indeed, "evacuated" collection tubes contain a significant amount of oxygen that can markedly alter the pO_2.[57] A significant change (up to 3 mmol/L) in potassium values may occur when venous stasis is combined with forearm exercise (fist clenching).[58] When collecting venous blood, the tourniquet should be left on until the blood is withdrawn and should be released just before removing the needle.[59]

5.2.4.1 "Mixed Venous Blood"

"Mixed" venous blood and arterial blood are essential specimens to evaluate oxygen uptake and cardiac output, and can be used to assess the degree of intrapulmonary shunting. True mixed venous blood is obtained from the pulmonary artery by means of a pulmonary artery catheter. When mixed 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. The blood specimen should be slowly withdrawn from the catheter to avoid obtaining retrograde blood that may be partly arterialized. A 1-mL/5 second withdrawal rate is recommended.

5.2.5 Anticoagulants

When electrolytes and blood gases are measured on a single blood specimen, the type of anticoagulant used must have little or no effect on all the analytes measured. While some preparations of heparin can affect the analytes discussed in this document, special preparations of heparin are now available to minimize potential interferences.

Heparin can influence the results obtained due to: 1) dilution, if liquid heparin is used; 2) the type of heparin salt (eg, Na heparin can increase Na levels by 1 mmol/L to 3 mmol/L even when the collection device is filled with blood); and 3) binding of ionized calcium by heparin. The use of dried, "lyophilized" anticoagulants eliminates the dilution problem associated with heparin dissolved in an aqueous medium. However, if the dried heparin does not dissolve adequately or quickly, clot formation may start within the collection device. Commercial preparations of heparin include calcium-titrated and electrolyte-balanced heparin, and minimal heparin dispersed in a polysaccharide "web" that dissolves rapidly to disperse the heparin in blood at a final heparin level of less than 3 IU/mL.[60] Because these calcium-titrated, electrolyte-balanced, and low-heparin preparations minimize the effect of calcium binding, final heparin concentrations of up to 40 IU/mL have little effect on these electrolyte measurements. If standard lithium or sodium heparins are used, a final heparin concentration of 10 to 20 IU/mL should lower ionized calcium by about 0.02 mmol/L to 0.04 mmol/L. Therefore, the final heparin concentration should be no more than about 20 IU/mL[60,61] (see notes below).

Because of variability among these products, the specific effect on the analysis should be determined either by direct testing or by consulting the manufacturer for any specific recommendations.

The effects of heparin on ionized magnesium measurements are similar but slightly less than those to ionized calcium.[62]

NOTE 1: Heparin acts as an anticoagulant by catalyzing the activation of antithrombin III. Since heparin is a catalyst, very little is needed, but it must be rapidly dissolved in blood to inhibit coagulation. Once coagulation begins, heparin cannot reverse the process.

NOTE 2: Lithium heparin is frequently used as the anticoagulant when electrolytes and blood gases are measured, although lithium heparin cannot be used in samples for lithium measurements. Likewise, sodium heparin cannot be used as the anticoagulant if a sodium measurement is to be made. For analyzing only blood gases, the heparin content of syringes may be high. However, for combined blood gas/electrolyte analysis, syringes should provide a final heparin concentration of no more than about 20 IU/mL blood. Although a low concentration of ordinary heparin will reduce the error, it will not eliminate it, and the special heparin preparations discussed above (balanced or dispersed) are preferable.

NOTE 3: Therapeutic heparin used for systemic anticoagulation should not be used as an anticoagulant for blood gas specimens because it has a very high concentration (10 000 units/mL) that may alter both ionized calcium and pH in the sample.

5.2.6 Syringe Additives

Lubricants and vent-seal additives used to facilitate blood drawing with a syringe may affect multiwavelength hemoglobin photometry (cooximetry) measurements. Syringe design, specific additives, and multiwavelength hemoglobin photometer specimen handling characteristics can influence this effect. Both syringe and instrument manufacturers should be consulted for details. Certain additives may also influence the results obtained with ion-selective magnesium electrodes.[63] Care should be taken and the instrument manufacturers should be consulted in case of questions.

5.3 Transport of Specimens

5.3.1 Hand Carrying of Specimens

Hand carrying of a blood gas sample appears to have minimal effect on the blood gas and pH results, even if some air bubbles are present.[64] Whenever possible, hand carrying of blood gas specimens without any vigorous movement is preferred.

5.3.2 Exposure to Air

Any exposure to the atmosphere can markedly affect the pH, pCO_2, and pO_2. Exposure of blood to the atmosphere generally increases the pO_2 towards ~150 mmHg, unless the patient is on supplemental oxygen where the blood pO_2 may decrease. For example, if a patient on supplemental oxygen has a blood pO_2 of 400 mmHg, the pO_2 in a blood sample from this patient would decrease upon exposure to the atmosphere. Because atmospheric pCO_2 is very low, exposure of blood to air will lower the pCO_2 of blood and increase the pH.

Ionized calcium is also affected by exposure to air and the consequent pH change in the sample. Loss of CO_2 increases the pH, which will lower the ionized calcium due to increased protein binding of Ca ions. On average, ionized calcium decreases by about 0.036 mmol/L for each 0.1 increase in pH.[65]

While pH alterations also affect ionized magnesium concentrations, the effect is about one-third that of ionized calcium. On average, each 0.1 change in pH changes ionized magnesium by about 0.012 mmol/L.[65]

5.3.3 Pneumatic Transport

During pneumatic transport, the blood sample is very rapidly accelerated and decelerated, which can vigorously agitate the blood in a syringe. While this has little effect on the pH and pCO_2 and most clinical chemistry tests, it can have a noticeable effect on the pO_2.[64] If even small air bubbles are present in the blood specimen, pneumatic transport can equilibrate these air bubbles with the blood and have a noticeable effect on the pO_2.[64] Consequently, it is very important to continually emphasize to those

collecting the specimen the importance of removing all air bubbles from a blood gas syringe prior to pneumatic transport.

5.3.4 Specimen 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 to achieve a uniform distribution of red blood cells and plasma prior to specimen insertion into the analyzer. Improperly mixed blood may also produce variable results for other analytes, depending on the measurement technology used. Because anaerobic blood specimens should contain no air bubbles to facilitate mixing, special care must be taken to thoroughly mix the specimen. The specimen should be gently rotated for a minimum of one minute immediately prior to analysis, either manually or using a mechanical device that rotates the specimen through two axes. Shorter mixing intervals may be acceptable, if only one to two minutes (or less) have elapsed since collection. Longer mixing intervals may be required when specimens sit for longer periods. If specimens in capillary tubes contain a metal "flea," they can be mixed by applying an external magnet and moving the flea from end to end for at least five seconds. If no flea is available, extra care must be used to mix blood in capillary tubes. Each laboratory must establish the appropriate specimen mixing procedures for each specimen container.

5.3.5 *In Vitro* Hemolysis

Because the intracellular potassium concentration is about 20 times greater than that of plasma, hemolysis has a significant effect on potassium results.[66]

The transfer of intracellular potassium from the cells into the plasma due to hemolysis is a cause of preanalytical variation with potassium measurements and is exacerbated by exposing the blood sample to trauma during transport (vigorous shaking or by pneumatic tube transport). CLSI/NCCLS documents C29[67] and H18[68] discuss this and other issues, and provide guidelines and recommendations to help minimize these effects.

Because the intracellular content of sodium and ionized calcium in erythrocytes is relatively small compared to plasma, hemolysis can lower the concentrations of these cations in plasma. However, in practice, hemolysis has only small effects on these analytes.[69,70]

5.4 *In Vivo* Effects on Measurements

5.4.1 Obtaining Blood Gas Specimens During Stable Ventilation

If a patient is undergoing changes in his/her delivery of oxygen or ventilatory support, the values of pH, pCO_2, and pO_2 measurements will likely also change. Depending on the rate and magnitude of these changes, the blood gas measurements may take varying times to stabilize, and the results obtained may not represent a stable condition of the patient. The specific clinical situation for each patient determines if a stabilized blood gas measurement is clinically necessary.

Note again the necessity to record the time, ventilatory settings, FIO_2, oxygen flow rates, delivery device, and the patient's temperature when the specimen is collected.

5.4.2 Temperature Correction of pH(T), pCO_2(T), and pO_2(T)

Because pH, pCO_2, and pO_2 are temperature-dependent quantities and are measured at 37 °C, these quantities may have different values in patients whose temperature is different from the analysis temperature of 37 °C. The clinical application of correcting pH, pCO_2, and pO_2 results to the actual temperature of the patient is controversial. Two different strategies for managing this have been adopted.

One is the pH-stat method by which the blood gas values are temperature corrected to the actual patient temperature, assuming a constant pH = 7.40. Another strategy is the α-stat method, according to which blood gas values are used at 37 °C without temperature corrections.

Acid-base status of blood *in vitro* varies with temperature due to the change in the dissociation of weak acids, particularly carbonic acid and proteins, as well as the change in solubility of carbon dioxide and oxygen in blood. Temperature correction algorithms for pH and pCO_2 are implemented in most commercially available blood gas analyzers.

pH*(T)* Correction

The temperature coefficient for plasma pH in blood was experimentally determined by Rosenthal to be:[71]

$$\frac{\mathrm{pH}(T) - \mathrm{pH}\ (37\ ^{\circ}\mathrm{C})}{T - 37\ ^{\circ}\mathrm{C}} = -0.0147 \qquad (24)$$

where pH (37 °C) is measured pH at 37 °C, and *T* is patient temperature.[71]

Adamsons et al showed this temperature coefficient decreases as pH falls and base rises.[72] On the basis of Adamsons' findings, Severinghaus transformed the Rosenthal pH temperature coefficient to the following pH correction algorithm[73]:

$$\mathrm{pH}(T) = \mathrm{pH}(37\ ^{\circ}\mathrm{C}) - \left[0.0147 + 0.0065 \times (\mathrm{pH}(37\ ^{\circ}\mathrm{C}) - 7.40)\right] \times \left[T - 37\ ^{\circ}\mathrm{C}\right] \qquad (25)$$

pCO_2(T) Correction

Nunn et al found the change in pCO_2 with temperature can be calculated on the basis of the pH temperature coefficient, provided the assumption is made that the base excess concentration of plasma is constant.[74]

$$pCO_2(T) = pCO_2(37\ ^{\circ}\mathrm{C}) \times 10^{\left[0.019 \times \left(T - 37\ ^{\circ}\mathrm{C}\right)\right]} \qquad (26)$$

***pO_2(T)* Correction Based on an Empirical Algorithm**

The temperature correction of pO_2 represents a complex problem because: 1) the solubility coefficient of oxygen varies with temperature; and 2) the hemoglobin-oxygen affinity varies with temperature. A theoretical treatment of these effects on pO_2 is beyond the scope of this document, but is presented in detail in the literature.[75,76,77] In some commercially available blood gas analyzers, the change in pO_2 with temperature is calculated using an empirical algorithm where the pO_2 temperature coefficients, as a function of pO_2, agree very closely with those determined by Severinghaus:[78]

$$pO_2(T) = pO_2(37\ ^{\circ}\mathrm{C}) \times 10^{\left(\frac{5.49 \times 10^{-11} \times pO_2^{3.88} + 0.071}{9.72 \times 10^{-9} \times pO_2^{3.88} + 2.30}\right) \times \left(T - 37\ ^{\circ}\mathrm{C}\right)} \qquad (27)$$

5.4.3 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, although potassium values may increase moderately after strenuous exercise.[79] 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.[80]

5.4.4 Ionized Calcium

Ionized calcium is widely recognized as a better indicator than total calcium of physiological calcium status in blood. Generally, the reasons for measuring ionized calcium are for monitoring during acute or critical care and for routine screening or diagnosis of a calcium disorder. In acute settings, ionized calcium is mainly used to monitor trends.

Although physical activity, posture, meals, ventilatory rate, and circadian variation can significantly alter ionized calcium concentration under extreme conditions, these usually have a minor effect when monitoring critically ill patients.

For more detailed information about preanalytical variables affecting ionized calcium determinations, refer to CLSI/NCCLS document C31[81] and a related IFCC publication.[82]

5.4.5 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 slightly higher concentrations of glucose than venous specimens.[80] Diet and drugs can markedly affect glucose concentration. The person collecting the specimen should note if intravenous fluid was given at the time of collection. Some glucose analyzers may report blood values and others may report values corrected to reflect serum/plasma concentrations. The manufacturer's literature should be consulted to ensure the reference range and comparability to main laboratory values are clear to clinical users of the data.

5.4.6 Lactate

Decreased oxygen delivery to tissue results in increases in both lactate (from pyruvate) and acid (by increased degradation of adenosine triphosphate [ATP]), which can increase blood lactate concentrations and decrease blood pH. If a venous specimen for lactate determination is collected, the subject should avoid any forearm exercise, and the blood should be obtained either without using a tourniquet or immediately after the tourniquet is applied. After collection, lactate in blood increases rapidly because of glycolysis. Blood lactate increases by 0.01 to 0.02 mmol/L/minute at room temperature in the absence of antiglycolytic agents. It is recommended that analysis of whole blood lactate without preservatives stored at room temperature should be done within 15 minutes of collection.[83,84]

5.5 Specimen Handling

5.5.1 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 leaks in a malfunctioning sample 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 (eg, 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 (eg, 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 quickly reanalyze specimens with questionable results, because the quality of the specimens deteriorates rapidly.

5.5.2 Reporting

In addition to the blood gas values, a complete report should note the collection time; the source of the sample (arterial, mixed venous, venous, or capillary); the FIO_2 level; any ventilator settings; the type and location of any fluid infusions; the collection site; and patient posture. This information should be recorded in the laboratory report or be available on the patient's record.

Comments regarding quality of the specimen received, transportation delays, and improper storage should also be documented. This information aids both the operator of the analyzer in judging the analytical quality of the results and the clinician in evaluating the relevance to the patient.

While often available in the same test panel, it is not essential to report the pH with the ionized calcium result.[85] It is recommended that the calcium ion concentration adjusted to pH 7.40 be used only either when the specimen is exposed to air for more than a few minutes, or when a delay in analysis alters the pH.

6 Analytical Interferences

6.1 Interferences With Measurement of pH and Blood Gases

pO_2

Interference of anesthetic gases such as nitrous oxide, halothane, and isoflurane with pO_2 sensors has been reported.[86] These substances are electrochemically active and are capable of diffusing across the gas permeable membrane of the pO_2 sensor. Depending on the polarizing voltage applied to the cathode of the sensor, these gases may be reduced along with oxygen, resulting in erroneously high pO_2 readings. The use of newer polymeric materials as gas permeable membranes and appropriate control of the applied potential to the cathode of the sensor largely eliminated this problem in the latest generation of blood gas electrodes.

pCO_2

The Severinghaus-style electrode for pCO_2 is based on potentiometry, and the gas permeable membrane eliminates water-soluble interfering substances from contacting the internal pH sensitive element. There are no reports of specific interfering substances with this style of pCO_2 sensor in clinical applications.

pH

The glass pH sensor is the most rugged of all sensors used for measurement of pH, blood gases, and related analytes. There are no reports of specific interfering substances with this style sensor. Polymeric pH sensors, used in some cartridge-based analyzers, are subject to general interferences with polymer membrane type sensors (see Section 6.6.2).

6.2 Interferences With Measurement of Electrolytes (Na^+, K^+, Ca^{++}, Mg^{++}, and Cl^-)

Na^+, K^+, Ca^{++}

Cationic surfactants—especially benzalkonium compounds, which are used topically as a collection site antiseptic or as an agent in arterial catheters—may interfere with sodium, potassium, and ionized calcium measurements, depending on measuring technology. Increases in sodium can be as much as 50 mmol/L.[87,88]

Mg^{++}

Most commercially available sensors for Mg^{++} suffer interference from Ca^{++} or Na^+, requiring simultaneous determination and correction for the presence of significant levels of these interfering ions.[89] Serum thiocyanate concentrations commonly found in smokers cause a significant decrease in Mg^{++} concentrations measured with an ion-selective electrode.[63]

Cl^-

Most commercially available sensors for Cl^- are based on anion exchange membranes. Anions in the sample that are more lipophilic than Cl^- interfere with analysis of Cl^- using this type of sensor, producing falsely elevated results.[90] Blood samples containing salicylate or thiocyanate, for example, produce positive interference for the measurement of Cl^-.[91] Halides such as bromide and iodide are also included in this category. Repeated exposure of the electrode to the anticoagulant heparin leads to loss of electrode sensitivity toward Cl^- because of extraction of the negatively charged heparin into the membrane.[92]

6.3 Interference With Measurement of Glucose and Lactate

Sensors for glucose and lactate in most critical care analyzers are biosensors based on the electrochemical principle of amperometry, and are therefore subject to interference from oxidizable substances in blood.[93] Included are endogenous substances such as uric acid and ascorbic acid and drugs such as acetaminophen and dopamine.[83,94] A number of approaches are successfully employed to eliminate these interferences for practical application. Because many commercial biosensors for glucose and lactate employ oxidase enzymes (glucose oxidase, lactate oxidase), substances that inhibit enzyme activity produce negative interference with the measurement. For example, fluoride and oxalate, used as preservatives in blood collection, show a negative interference on glucose biosensors.

6.4 Interference With Measurement of Hematocrit

Current methods used to measure hematocrit on multianalyte blood gas analyzers involve either calculation of hematocrit from measured total hemoglobin or the estimation of hematocrit 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 by conductivity may perform the appropriate correction.[95,96] Refer to the manufacturer's literature to determine if this correction is applied for a particular model of analyzer. Conductivity-based hematocrit measurements have other limitations.[97] Abnormal protein levels change plasma conductivity and interfere with the measurement. Low protein concentrations resulting from dilution of blood with protein-free electrolyte

solutions during cardiopulmonary bypass surgery result in erroneously low hematocrit values by conductivity. Preanalytical variables, such as insufficient mixing of the sample, also lead to error.[98]

Estimation of hematocrit from measured total hemoglobin is based on the mean corpuscular hemoglobin concentration (MCHC).

$$MCHC = Hb\ (g/dL) \times 100 / Hct\ (\%) \quad (28)$$

Normal values of MCHC, typically 34%, are assumed when this relationship is used to estimate hematocrit in multianalyte blood gas analyzers. However, certain medical conditions that result in abnormal MCHC affect the accuracy of this estimate.[99]

6.5 Interference With Cooximetry Measurements

Sulfhemoglobin

The rare occurrence of sulfhemoglobin has been reported to produce interference with measurement of oxyhemoglobin using multiwavelength cooximetry.[100]

Hydroxocobalamin and Methylene Blue

When given therapeutically, hydroxocobalamin and methylene blue have been reported to produce interference with measurement of hemoglobin fractions.[101-103] Some analyzers detect and correct for the presence of these substances.

Fetal Hemoglobin

The absorption spectrum of fetal hemoglobin differs slightly from that of adult hemoglobin, and errors may occur if this is not taken into account.[104] The most common error is the false elevation of COHb, but MetHb levels may also be affected.[105] Some analyzers measure and correct for the presence of fetal hemoglobin.[106] Refer to the manufacturer's literature.

Turbidity

Sample turbidity, produced by hyperlipemia or from administration of a lipid emulsion, has been reported to produce interference with measurement of total hemoglobin and hemoglobin fractions.[107,108]

6.6 Other Interferences

6.6.1 Synthetic Oxygen Carriers

Synthetic oxygen carriers (blood substitutes) may interfere with analysis of pH, blood gases, and related quantities. Not enough is known at this time to quantify the effects. A preliminary report suggests accuracy of cooximetry measurements may be affected, but results are still clinically useful.[109] Many of these substances are macromolecules (eg, cross-linked hemoglobin) and would be expected to produce interference with measurement of hematocrit by conductivity.

6.6.2 Additives to External Quality Control Materials

Compounds with lipophilic character may leach into polymeric membranes used in sensors for pH, blood gases, and related substances, producing shifts in the stability of the sensor signal and erroneous reporting of results. These include emulsion-based QC materials containing perfluorocarbon (see Section 8.1.1.2.3),

and some surfactants. Consult the manufacturer of the control material and the device manufacturer for specific information.

6.6.3 Errors in Thermal Control

Because of the large effects of temperature variability on measurement of pH and blood gases, it is important that the analyzer performs the measurements at 37 °C, regardless of the initial temperature of the sample. Excellent reproducibility of sample temperature control during the measurement is required. For example, in order to meet clinically required precision goals for measurement of pO_2, sample temperature must be controlled to 37 ± 0.1 °C during the measurement. The manufacturer's literature should be consulted for claims of temperature control, and limitations on the initial temperature of the sample.

7 Blood Gas Analyzer Calibration

7.1 Principles of Calibration

IUPAC states, "In general, calibration is an operation that relates an output quantity to an input quantity for a measuring system under given conditions."[110]

In clinical chemistry, routine system calibration is carried out by measurement of a set of working calibrators, containing the analyte under investigation in known, suitably graduated concentrations. Manufacturers use materials whose concentrations are known with maximum reliability (ie, with both high precision and trueness). In analytical practice, certified and traceable materials are used to prepare working calibrators. See Section 7.3 for the definition of traceable materials.

7.2 Blood Gas Analyzer Calibration

There are many different designs, protocols, and recommendations from manufacturers regarding calibration. Each analyzer has recommended procedures that include specific calibration materials and frequency depending on the stability and quality of the sensor technology in question, and operators must adhere to these. Manufacturers' calibration materials should be traceable to certified reference materials issued by national or international metrology institutes (eg, the US National Institute of Standards and Technology [NIST]), or natural occurring standards. Manufacturers typically develop primary standards, with the same requirements for traceability, used for routine assignment of concentrations to secondary working calibrators.

User requirements and needs to judge uncertainty of the calibration function in relation to practical analytical and clinically acceptable performance goals should be established by the manufacturer.

7.3 Calibration Traceability

The concept of measurement traceability that has been established in general chemical metrology is now also being introduced to the field of clinical chemical analysis. According to the Vocabulary in Metrology and the Guide to the Expression of Uncertainty in Measurement, measurement traceability is the "property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty."[111-113]

7.3.1 General Requirements for Traceability

ISO 17025, 5.6.3.2 states, "Reference materials shall, where possible, be traceable to SI units of measurement, or to certified reference materials."[114] Strictly speaking, only the value or measurement of the standard or reference material, not the material itself, can be traceable, but it is common usage to speak of a standard as being traceable.

Traceability shall be documented for all materials used to perform internal or external calibrations on testing equipment for pH, blood gases, and related analytes. Documentation should include a statement by the manufacturer regarding traceability, and a certificate of analysis, containing, at a minimum:

- name and address of the manufacturer;
- manufacturer's accreditation number (if applicable);
- how the traceability was achieved; and
- traceable values and their associated uncertainties.

If traceable standards do not exist for a particular analyte, then traceability requirements may be met by one of the following:

a) Use of certified materials of known purity provided by a competent supplier with reliable physical or chemical characterization.

b) Use of specified methods and/or consensus standards that are clearly described and agreed to by all parties concerned.

c) Participation in a suitable program of interlaboratory comparisons.

Traceability of calibration materials without specific knowledge of uncertainty of the calibration does not in itself ensure acceptable analytical calibration of any measurement device in the clinical setting. Therefore, proper QC materials that are traceable and a proper quality assurance program are also required to meet acceptable analytical performance for clinical application. See Section 8.

7.3.2 Natural Standards

Natural standards are pure, nonsynthetic materials with known properties, used to standardize analytical instrumentation. An example is the triple point of water, an acknowledged standard for thermometer calibration or verification. Natural standards may be used with the same confidence as traceable standards.

The simplest and best known natural standard with applicability to blood gas analysis is atmospheric air (O_2 content 20.946 ± 0.002%). Atmospheric air may be used for calibration of pO_2 sensors in blood gas analyzers with the same confidence as other traceable standards. Commercially available precision gas mixtures of O_2 in N_2 have a typical uncertainty of 0.1% (±0.02% at 20% oxygen).

An example of a possible error in using atmospheric air for pO_2 sensor standardization would be caused by variability in ambient temperature. For example, in an air-conditioned intensive care unit, variability in oxygen calibration may be considered to be 1% or less, and of little clinical consequence.

7.3.3 Examples of Certified Reference Materials for pH, Blood Gas, and Related Measurements

pH

Primary pH standards should be traceable to the reference method for pH, calibrated with phosphate buffers from NIST (Standard Reference Material [SRM] 186I and 186II).[115]

pCO_2 and pO_2

Blood tonometry is the reference method for establishing accuracy for pO_2 and pCO_2, provided gases used for tonometry have a composition with certified accuracy < ±0.3% of the stated concentration.[116] Manufacturers should use blood tonometry with certified gases as a reference method for establishing

accuracy for pO_2 and pCO_2 measuring devices. The certified gases should be traceable to SRM such as a series of pO_2 and pCO_2 gas mixtures available from NIST.

Cooximetry

The fractional value for each hemoglobin derivative (FO_2Hb, *F*HHb, *F*COHb, *F*MetHb, *F*SulfHb) is based on ratios of absorbencies, and thus requires no separate calibration as long as the measuring wavelengths remain the same.

***c*K$^+$ and *c*Na$^+$**

The primary standards are gravimetric solutions produced from KCl and NaCl salts of high purity. These primary working standards may be traceable to SRM 918 and 919 produced by NIST.

***c*Ca^{2+}**

The primary standards used are the so-called Ca^{2+} transfer standards, produced from $CaCO_3$ buffered to pH = 7.4, with 1 mmol/L N-2-hydroxyethylpiperazine-N′-2-ethanesulfonic acid (HEPES) and an ionic strength of 160 mmol per kg.[117] Traceability of the Ca^{2+} transfer standards is done using similar standards produced from NIST SRM 915.

***c*Cl$^-$**

The primary standards are gravimetric standards, prepared from KCl salt of high purity. The primary standards are validated by titration using similar standards prepared from NIST SRM 999 (KCl). The titrations are done using $AgNO_3$ as the titrant, and potentiometric titration equipment.

***c*Glucose**

The primary standards are prepared from NIST SRM 917a (D-glucose). These primary standards are used to determine the glucose concentration of working calibrators. The concentrations of the primary standards are assigned using the glucose reference method.[118]

***c*Lactate**

No certified SRM for lactate is available at present. Primary standards may be prepared from a pure commercially available material, for example, the lithium salt of L (+) lactic acid (> 99% purity).

7.4 Internal Electronic Barometer

Traditional systems for measurement of blood gases are calibrated with humidified gas mixtures and require correction for ambient barometric pressure to derive the partial pressure of pO_2 and pCO_2 in the mixtures, according to the following relationship governed by Dalton's Law:

$$pX = (BP - 47)\ (\text{mole\% of a component gas in the mixture}) \quad (29)$$

where:
*p*X = partial pressure of the component gas
BP = barometric pressure in mmHg
47 = partial pressure of water vapor in a humidified gas at 37°C in mmHg

Partial pressure of the component gas is directly related to ambient barometric pressure. Traditional systems include an internal electronic barometer to measure and correct for ambient barometric pressure,

which is critical to their accurate calibration. The function of the internal barometer should be checked regularly by comparing its reading 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 adjusted to sea-level readings.

NOTE: Some instruments are designed to eliminate the need for a barometer, such as systems using single phase calibrators (see Section 7.5). Consult the manufacturer for details.

7.5 Calibration of pO_2 and pCO_2 in Systems for Point-of-Care Testing

Newer systems designed for point-of-care testing of blood gases and related analytes have general requirements of portability, low maintenance, and ease of use. In traditional systems, routine calibration of pO_2 and pCO_2 sensors is carried out with gas mixtures with known accuracy and traceability, and requires connection of gas tanks to the instrument. In newer systems for point-of-care testing, gas tanks have been replaced with single phase, liquid calibrators, preequilibrated to specific gas tensions, and sealed in gas impermeable bags with zero headspace. The requirements for traceability and accuracy of working calibrators for pO_2 and pCO_2 sensors given in this section also apply to single phase calibrators. Since, in theory, single phase calibrators are isolated from ambient conditions, correction of gas tensions for barometric pressure is not performed and an internal barometer is not included in most systems. However, little data are available to prove that variations in barometric pressure do not affect the accuracy of blood gas measurements. Consult the manufacturer for details.

8 Blood Gas Quality Control

A systems approach for the assurance of quality blood gas testing is necessary. QC is just one component of a quality management system. The general goal of a QC program is to determine whether an analyzer works properly before patient samples are measured or after suspicious results are obtained. The specific goal is to evaluate the instrument's performance in terms of both inaccuracy and imprecision. See CLSI document C24[119] for detailed information on day-to-day processes and procedures for QC.

8.1 Types of Quality Control

8.1.1 Surrogate Sample Controls

Surrogate sample QC material is a stable liquid sample designed to simulate a patient sample and is analyzed the same as patient samples. Some manufacturers have integrated surrogate samples into their analytical system; however, this has eliminated the ability of this type of QC to assess all sample handling techniques, and may or may not validate the entire sample pathway.

8.1.1.1 Tonometry

Tonometry is the process of equilibrating a fluid under controlled conditions (ie, temperature, barometric pressure, humidification) with a known mixture of gases. It is rarely used in clinical laboratories.

8.1.1.1.1 Blood Tonometry

When NIST-traceable gas mixtures are used, fresh blood tonometry is considered the reference procedure to establish the accuracy for blood pO_2 and pCO_2. Tonometered 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 QC. On the other hand, absolute accuracy of pO_2 and pCO_2 cannot be assessed without blood tonometry.

8.1.1.1.2 Nonblood Tonometry

Tonometry of specially prepared aqueous solutions, which do not contain hemoglobin, is possible.[120,121] This approach is useful for pH and pCO_2 assessment, and of more limited value for pO_2, since there is no hemoglobin to buffer pO_2.

Aqueous hemoglobin solutions, which have an oxygen buffering capacity similar to that of fresh, human blood (ie, 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 QC for pH.[122,123] Another advantage of using these materials is they do not pose a biohazard.

8.1.1.2 Commercial Controls

At present, different types of commercial controls are available (eg, buffered aqueous solutions, buffered blood-based solutions containing free hemoglobin, and buffered perfluorocarbon emulsions). They may be external to the analytical system and introduced by the operator, or integrated into the analytical system and assayed automatically.

8.1.1.2.1 Aqueous Control Solutions

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 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.

8.1.1.2.2 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.

8.1.1.2.3 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). While these controls are better than aqueous control solutions in resisting oxygen changes, the surface tension and density of these controls are not identical to that of blood. These controls may interfere with the functionality of certain types of pH, blood gas, and electrolyte sensors, leading to erroneous results. Contact the manufacturer for more information.

8.1.1.2.4 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.[124] Most blood gas analyzers allow the user to enter the ambient temperature when controls are run; this may be important if the ambient temperature is significantly different from 25 ºC, particularly for pO_2.

8.1.1.2.5 Oximetry Controls

Typically, QC 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 dye solutions are stable. The actual hemoglobin species are not stable enough in solution to be used as control materials.

8.1.2 Nonsurrogate (Alternative) Quality Control

Nonsurrogate quality controls include all forms of QC other than the measurement of a surrogate sample. This includes QC mechanisms that are integrated into the design of the device, such as electronic QC, which monitors instrument circuitry and signal processing; automated procedural controls, which ensure that certain steps of the sample measurement procedure occur appropriately; and automated internal checks, which may, for example, ensure the quality of a raw sensor signal during analysis of an on-board reagent or patient sample. Such controls may check all or a portion of the test system's analytical components each time an on-board reagent or patient sample is analyzed, and may be used in combination with or in place of testing traditional external control materials.[125,126] Parameters such as temperature, incubation time, correct transfer of volume of reagent or sample, integrity of the sample (eg, presence of an interfering substance or blood clot), etc. are often monitored, and any failures to operate within acceptable limits reported to the operator. If a situation outside acceptable limits is detected, the system may automatically initiate and document corrective actions. An affected sensor may be disabled or instrument operation halted if a corrective action is not effective. These integrated and automated functions have the advantages of being consistent and ongoing with little or no operator intervention. However, if these integrated QC functions only monitor a portion of the test system's analytical components, additional surrogate QC material should be tested at periodic intervals, the frequency of which is determined by the laboratory director.

8.1.2.1 Electronic Quality Control

This approach uses a simulation to test the electronic components of the analytical system. This sample simulation may be built into the analytical system or it may be a separate device used in place of a test module to evaluate system function. This has the advantage that it is simple, inexpensive, quick, and takes little training time with little dependence on operator skill. However, electronic QC may only monitor a portion of the device's analytical components. Typically, electronic QC cannot verify the performance of any portion of the analytical process that involves actual chemical reactions or sampling related functions.

8.1.3 Calibration Check or Verification

Calibration checks involve either a comparison of the calibrator(s) raw data output (eg, absorbance or response) to previous calibrator output or an evaluation of the shape of the calibration curve. Many analytical systems have a calibration check built into the device design, which is automatically performed when the device is calibrated. This process can proactively detect errors before running QC and patient samples, thereby saving resources and preventing the reporting of erroneous patient results. One weakness of this concept is that, due to matrix effects, recovery of expected calibrator values may not

always accurately reflect performance with patient samples. A calibration check must be performed according to the measurement procedure or device manufacturer's instructions

8.1.4 Duplicate Assay

A laboratory may choose to augment QC by using two or more instruments for simultaneous analysis of a sample.[121,127-130] 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.

References

1 CLSI/NCCLS. *Procedures for the Collection of Arterial Blood Specimens; Approved Standard—Fourth Edition.* CLSI/NCCLS document H11-A4. Wayne, PA: NCCLS; 2004.

2 Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings 2007. http://www.cdc.gov/ncidod/dhqp/gl_isolation.html. Accessed 19 March 2008.

3 CLSI. *Protection of Laboratory Workers From Occupationally Acquired Infections; Approved Guideline—Third Edition.* CLSI document M29-A3. Wayne, PA: Clinical and Laboratory Standards Institute; 2005.

4 Covington AK, Bates RG, Durst RA. Definition of pH scales, standard reference values, measurement of pH, and related terminology. *Pure Appl Chem*. 1985;57:531-542.

5 Bates RG. *Determination of pH, Theory, and Practice*. 2nd ed. New York, NY: John Wiley and Sons; 1973.

6 Wu YC, Koch WF, Durst RA. *Standard Reference Materials: Standardization of pH Measurements*. National Bureau of Standards Special Publication 260-53. Washington, DC: US Government Printing Office; 1988.

7 Siggaard-Andersen O, Durst RA, Maas AHJ. Approved IUPAC/IFCC recommendations (1984) on physico-chemical quantities and units in clinical chemistry with special emphasis on activity and activity coefficients. *J Clin Chem Clin Biochem*. 1987;45:89-109.

8 Burnett RW, Covington AK, Fogh-Andersen N, et al. Approved IFCC recommendation on definitions of quantities and conventions related to blood gases and pH. *Eur J Clin Chem Clin Biochem.* 1995;33:399-404.

9 Taylor BN. Guide for the Use of the International System of Units (SI). NIST Special Publication 811. Washington, DC: National Institute of Standards and Technology; 1995.

10 Smithsonian Institute. *Smithsonian Metrological Tables*. 6th ed. Washington, DC: Smithsonian Institute; 1986.

11 Ciba-Geigy Corp. *The Geigy Scientific Tables*. Vol. 3. West Caldwell, NJ: Ciba-Geigy Corp.; 1984:32.

12 Austin WH, Lacombe E, Rand PW, Chatterjee M. Solubility of carbon dioxide in serum from 15 to 38 C. *J Appl Physiol*. 1963;18:301.

13 Maas AHJ, Rispens P, Siggaard-Andersen O, Zijlstra WG. On the reliability of the Henderson-Hasselbalch equation in routine clinical acid-base chemistry. *Ann Clin Biochem.* 1984;21:26-39.

14 Trenchard D, Noble MIM, Guz A. Serum carbonic acid pK abnormalities in patients with acid-base disturbances. *Clin Sci.* 1967;32:189.

15 Austin WH, Ferrante V, Anderson C. Evaluation of whole blood pK in the acutely ill patient. *J Lab Clin Med.* 1968;72:129.

16 Austin WH, Ferrante V, Ritchie RF. Effect of abnormal plasma constituents on the pK of whole blood. *Am J Clin Pathol.* 1969;15:799.

17 Natelson S, Nobel D. Effect of the variation of the pK of the Henderson-Hasselbalch equation on values obtained for total CO_2 calculated from pCO_2 and pH values. *Clin Chem.* 1977;23:767.

18 Burnett RW, Noonan DC. Calculations and correction factors used in determination of blood pH and blood gases. *Clin Chem.* 1974;20:1499.

19 Collier CR, Hackney JD, Mohler JG. Use of extracellular base excess in diagnosis of acid-base disorders: a conceptual approach. *Chest.* 1972(suppl);61:6S-12S.

20 Dell RB, Winters RW. A model for the *in vivo* CO_2 equilibration curve. *Am J Physiol.* 1970;219:37-44.

21 Dell RB, Lee CE, Winters RW. Influence of body composition on the *in vivo* response to acute hypercapnia. *Pediatr Res.* 1971;5:523-538.

22 Siggaard-Andersen O. *The Acid-Base Status of the Blood*. 4th ed. Baltimore, MD: Williams and Wilkins; 1974:51,116.

23 Dijkhuizen P, Buursma A, Fongers TME, Gerding AM, Oeseburg B, Zijlstra WG. The oxygen binding capacity of human haemoglobin, Huefner's factor redetermined. *Pfluegers Arch.* 1977;369:223-231.

24 International Council for Standardization in Haematology. Recommendations for reference method for haemoglobinometry in human blood (ICSH Standard 1995) and specifications for international haemiglobincyanide reference preparation. 4th ed. *J Clin Pathol.* 1996;49:271-274.

25 CLSI/NCCLS. *Reference and Selected Procedures for the Quantitative Determination of Hemoglobin in Blood; Approved Standard—Third Edition*. CLSI/NCCLS document H15-A3. Wayne, PA: NCCLS; 2000.

26 Bromberg PA. The blood oxygen dissociation curve. *Am J Med Sci*. 1970;260:261.

27 Bunn HF, Forget BG. *Hemoglobin: Molecular, Genetic and Clinical Aspects*. Philadelphia, PA: WB Saunders; 1986.

28 Shappell SD. Hemoglobin affinity for oxygen, 2,3-DPG, and cardiovascular disease. *Cardiology Digest*. 1972;9-15.

[29] Vreman HJ, Kwong LK, Stevenson DK. Carbon monoxide in blood: an improved micro-liter blood-sample collection system, with rapid analysis by gas chromatography. *Clin Chem.* 1984;30:1382-1386.

[30] Vreman HJ, Zwart A, Stevenson DK. Comparison of carboxyhemoglobin analysis by gas chromatography and multicomponent spectrophotometry. *Clin Chem.* 1987:33:694-697.

[31] CLSI. *Pulse Oximetry; Approved Guideline*. CLSI document HS03-A. Wayne, PA: Clinical and Laboratory Standards Institute; 2005.

[32] Barker SJ, Redford D, Morgan S. Measurement of carboxyhemoglobin and methemoglobin by pulse oximetry: a human volunteer study. *Anesthesiology.* 2006;105:892-897.

[33] Van Slyke DD, Neill JN. The determination of gases in blood and other solutions by vacuum extraction and manometric measurement. *J Biol Chem*. 1924;61:523-573.

[34] Dijkhuizen P, Kwant G, Zijlstra WG. A new reference method for the determination of the oxygen content of blood. *Clin Chim Acta*. 1976;8:79-85.

[35] Natelson S, Menning C. Improved methods of analysis for oxygen, carbon monoxide and iron on fingertip blood. *Clin Chem*. 1955;1:165.

[36] Natelson S. Route use of ultramicro methods in the clinical lab. *J Clin Path*. 1951;21:1153-1172.

[37] Wimerley PD, Burnett RW, Covington AK, et al. Guidelines for routine measurement of blood hemoglobin oxygen affinity. *Scand J Clin Lab Invest*. 1990;50(Suppl. 203):227-234.

[38] CLSI. *Laboratory Documents: Development and Control; Approved Guideline—Fifth Edition*. CLSI document GP02-A5. Wayne, PA: Clinical and Laboratory Standards Institute; 2006.

[39] CLSI. *Procedures for the Collection of Diagnostic Blood Specimens by Venipuncture; Approved Standard—Sixth Edition*. CLSI document H03-A6. Wayne, PA: Clinical and Laboratory Standards Institute; 2007.

[40] Shrake K, Blonshine S, Brown R, Ruppel G, Wanger J, Kochansky M. AARC clinical practice guideline: sampling for arterial blood gas analysis. *Respir Care.* 1992;37:913-914.

[41] AARC Clinical Practice Guideline: Sampling for arterial blood gas analysis. *Respir Care*. 1992;37:913-917.

[42] Eldridge F, Fretwell LK. Change in oxygen tension of shed blood at various temperatures. *J Appl Physiol*. 1965;20:790.

[43] Hess CE, Nichols AB, Hunt WB, Suratt PM. Pseudohypoxemia secondary to leukemia and thrombocytosis. *New Engl J Med*. 1979;301:361.

[44] Aminabhavi TM, Aithal US. Molecular transport of oxygen and nitrogen through polymer films. *JMS-Rev MacroMolecular Chem and Physics.* 1991;C31:117.

[45] Harsten A, Berg IS, Muth L. Importance of correct handling of samples for the result of blood gas analysis. *Acta Anaesthesiol Scand*. 1988;32:365.

[46] Scott PV, Horton JN, Mapleson WW. Leakage of oxygen from blood and water samples stored in plastic and glass syringes. *BMJ.* 1971;3:512.

[47] Muller-Plathe O, Heyduck S. Stability of blood gases, electrolytes, and hemoglobin in heparinized whole blood samples: Influence of the type of syringe. *Euro J Clin Chem Clin Biochem*. 1992;30:349-355.

[48] Wu EY, Barazanji KW, Johnson RL. Source of error on A-aDO2 calculated from blood stored in plastic and glass syringes. *J Appl Physiol*. 1997;82:196-202.

[49] Mahoney JJ, Harvey JA, Wong RJ, Van Kessel AL. Changes in oxygen measurement when whole blood is stored in iced plastic or glass syringes. *Clin Chem.* 1991;37:1244-1248.

[50] Smeenk FW, Janssen JD, Arends BJ, et al. Effects of four different methods of sampling arterial blood and storage time on gas tensions and shunt calculations in the 100% oxygen test. *Euro Respir J*. 1997;10:910-913.

[51] Mahoney JJ, Hodgkin JE, Van Kessel AL. Arterial blood gas analysis. In: Burton GG, Hodgkin JE, Ward JJ, eds. *Respiratory Care.* 4th ed. Philadelphia, PA: Lippincott; 1997.

[52] Graham G, Kenny MA. Changes in transcutaneous oxygen tensions during capillary blood-gas sampling. *Clin Chem*. 1980;26:1860-1863.

[53] Kost GJ, Chow JL, Kenny M. Unpredictable fluctuations in transcutaneous pCO_2 from capillary blood gas determinations. *Clin Chem*. 1982;28:1514-1516.

[54] Van Kessel AL, Ariagno RL, Robin ED. Clinical application of capillary and transcutaneous gas measurements in prematurely born infants. *Physiology and Methodology of Blood Gases and pH.* Vol. 6. IFCC Workshop Helsinki; 1985.

[55] McLain BI, Evans J, Dear PRF. Comparison of capillary and arterial blood gas measurements in neonates. *Arch Dis Childhood.* 1988; 63:743-747.

[56] CLSI. *Procedures and Devices for the Collection of Diagnostic Capillary Blood Specimens; Approved Standard—Sixth Edition*. CLSI document H04-A6. Wayne, PA: Clinical and Laboratory Standards Institute; 2008.

[57] Lang GE, Mueller RG, Hunt PK. Possible error resulting from use of "nitrogen-filled" vacutainers for blood gas determinations. *Clin Chem.*1973;19:559-563.

[58] Don BR, Sebastain A, Cheitlin M, Christiansen M, Schambelan M. Pseudohyperkalemia caused by fist clenching during phlebotomy. *N Engl J Med.* 1990;322:1290-1292.

[59] Koepke J, McFarland E, Mein M, Winkler B, Slockbower JM. Venipuncture procedures. In: Slockbower JM, Blumenfeld TA, eds. *Collection and Handling of Laboratory Specimens: A Practical Guide*. Philadelphia, PA: JB Lippincott; 1983:3-45.

[60] Toffaletti J. Use of novel preparations of heparin to eliminate interference ionized calcium measurements: Have all the problems been solved? *Clin Chem.* 1994;40:508-509.

[61] Toffaletti J, Ernst P, Hunt P, Abrams B. Dry electrolyte balanced heparinized syringes evaluated for determining ionized calcium and other electrolytes in whole blood. *Clin Chem.* 1991;37:1730-1173.

[62] Toffaletti JG, Wildermann RF. The effects of heparin anticoagulants and fill volume in blood gas syringes on ionized calcium and magnesium measurements. *Clin Chim Acta.* 2001;304:147-151.

[63] Rehak NN, Cecco SA, Niemela JE, Elin RJ. Thiocyanate in smokers interferes with the Nova magnesium ion-selective electrode. *Clin Chem.* 1997;43:1595-1600.

[64] Astles JR, Lubarsky D, Loun B, Sedor FA, Toffaletti JG. Pneumatic transport exacerbates interferences of room air contamination in blood gas samples. *Arch Pathol Lab Med.* 1996;120:642-647.

[65] Wang S, McDonnell EH, Sedor FA, Toffaletti JG. pH effects on measurement of ionized calcium and ionized magnesium in blood. *Arch Pathol Lab Med.* 2002;126:947-950.

[66] Zhang DJ, Elswick RK, Miller WG, Bailey JL. Effect of serum-clot contact time on clinical chemistry laboratory results. *Clin Chem.* 1998;44:1325-1333.

[67] CLSI/NCCLS. *Standardization of Sodium and Potassium Ion-Selective Electrode Systems to the Flame Photometric Reference Method; Approved Standard—Second Edition*. CLSI/NCCLS document C29-A2. Wayne, PA: NCCLS; 2000.

[68] CLSI/NCCLS. *Procedures for the Handling and Processing of Blood Specimens; Approved Guideline—Third Edition*. CLSI/NCCLS document H18-A3. Wayne, PA: NCCLS; 2004.

[69] Graham G, Schoen I, Johnson L. The effect of specimen choice, collection, processing, and storage on ionized calcium determinations. In: Moran RF, ed. *Ionized Calcium: Its Determination and Clinical Usefulness*. Galveston, TX: University of Texas Printing; 1986:88-92.

[70] Buckley BM, Rawson KM, Russell LJ. The effect of hemolysis on ionized calcium measurement. In: Burritt MF, Cormier AD, Maas AHJ, Moran RF, O'Connell KM, eds. *Methodology and Clinical Applications of Ion-Selective Electrodes.* Vol. 9. Rochester, MN: International Federation of Clinical Chemistry; 1988:141-145.

[71] Rosenthal TB. The effect of temperature on the pH of blood and plasma in vitro. *J Biol Chem*. 1948:173:25-30.

[72] Adamsons K, Daniel SS, Gandy G, James LS. Influence of temperature on blood pH of the human adult and newborn. *J Appl Physiol.* 1964;19:897-900.

[73] Severinghaus JW. Blood gas calculator. *J Appl Physiol.* 1966;21:1108-1116.

[74] Nunn JF, Bergman A, Bunatyan A, Coleman AJ. Temperature coefficient for pCO2 and pO2 of blood in vitro. *J Appl Physiol.* 1965;20:23-26.

[75] Siggaard Andersen O, Wimberley PD, Gøthgen IH, Siggaard Andersen M. A mathematical model of the hemoglobin oxygen dissociation curve of human blood and of the oxygen partial pressure as a function of temperature. *Clin Chem.* 1984;30:1646-1651.

[76] Siggaard Andersen O, Siggaard Andersen M. The oxygen status algorithm: a computer program for calculating and displaying pH and blood gas data. *Scand J Clin Lab Invest.* 1990;50 (Suppl) 203:29-45.

[77] Siggaard Andersen M, Siggaard Andersen O. Oxygen status algorithm, version 3, with some applications. *Acta Anaesth Scand.* 1995;39:Suppl. 107:13-20.

[78] Severinghaus JW. Simple, accurate equations for human blood O_2 dissociation computations. *J Appl Physiol.* 1979;46:599-602.

[79] Hutchinson RG, Barksdale B, Watson RL. The effects of exercise on serum potassium levels. *Chest.* 1992;101:398-400.

[80] Ladenson JH. Nonanalytical sources of variation in clinical chemistry results. In: Sonnenwirth AC, Jarett L, eds. *Gradwhol's Clinical Laboratory Methods and Diagnosis*. Vol 1. St. Louis, MO: CV Mosby; 1980;150-165, 174-175.

[81] CLSI/NCCLS. *Ionized Calcium Determinations: Precollection Variables, Specimen Choice, Collection, and Handling; Approved Guideline—Second Edition.* CLSI/NCCLS document C31-A2. Wayne, PA: NCCLS; 2001.

[82] Boink ABJJ, Buckley BM, Christiansen TF, et al. IFCC document – Recommendation on sampling, transport and storage for the determination of the concentration of ionized calcium in whole blood, plasma and serum. *Clin Chim Acta.* 1991;202:S13-S22.

[83] Kost GJ, Nguyen TH, Tang Z. Whole blood glucose and lactate: trilayer biosensors, drug interference, metabolism and practical guidelines. *Arch Pathol Lab Med.* 2000;124:1128-1134.

[84] Toffaletti J, Hammes ME, Gray R, Lineberry B, Abrams B. Lactate measured in diluted and undiluted whole blood and plasma: Comparison of methods and effect of hematocrit. *Clin Chem.* 1992;38:2430-2434.

[85] Fogh-Andersen N, Christiansen TF, Komarmy L, Siggaard-Andersen O. Measurement of free calcium ion in capillary blood and serum. *Clin Chem.* 1978;24:1545-1552.

[86] Eberhard P, Mindt W. Interference of anesthetic gases at oxygen sensors. *Birth Defects: Original Article Series.* 1979;15:65-74.

[87] Koch TR, Cook JD. Benzalkonium interference with test methods for potassium and sodium. *Clin Chem.* 1990;36:807.

[88] Cook JD, Koch TR, Knoblock EC. Erroneous electrolyte results caused by catheters (Letter). *Clin Chem*. 1988;34:211.

[89] Rehak N, Cecco SA, Niemela JE, et al. Linearity and stability of the AVL and Nova magnesium and calcium ion selective electrodes. *Clin Chem.* 1996;42:880-887.

[90] D'Orazio P, Meyerhoff ME. Electrochemistry and chemical sensors. In: Burtis CA, Ashwood ER, Bruns DE, eds. *Clinical Chemistry and Molecular Diagnostics.* 4th ed. St. Louis, MO: Elsevier Saunders; 2006;97.

[91] Lewandowski R, Sokalski T, Hulanicki A. Influence of aspirin on in vitro direct potentiometry of chloride in serum. *Clin Chem.* 1989;35:2146.

[92] Ma SC, Meyerhoff ME, Yang V. Heparin-responsive electrochemical sensor: a preliminary report. *Anal Chem.* 1992;64:694-697.

[93] D'Orazio P. Biosensors in clinical chemistry. *Clin Chim Acta.* 2003;334:41-69.

[94] D'Orazio P, Parker B. Interference by the oxidizable pharmaceuticals acetaminophen and dopamine at electrochemical biosensors for blood glucose. *Clin Chem.* 1995;41:5156.

[95] McMahon DJ, Carpenter RL. A comparison of conductivity-based hematocrit determinations with conventional laboratory methods in autologous blood transfusions. *Anesth Analg.* 1990;71:1541-1544.

[96] Stott RAW, Horton GL, Wilhite TR, et al. Analytical artifacts in hematocrit measurements by whole blood chemistry analyzers. *Clin Chem.* 1995;41:306-311.

[97] Hopfer SM, Nadeau FL, Sundra M, et al. Effect of protein on hemoglobin and hematocrit assays with a conductivity-based point-of-care testing device: Comparison to optical methods. *Ann Clin Lab Sci.* 2004;34:75-82.

[98] Zaloga GP, Hill TR, Strickland RA, et al. Bedside blood gas and electrolyte monitoring in critically ill patients. *Crit Care Med.* 1989;17:920-925.

[99] Bauer JD. Numerical evaluation of formed elements in blood. In: Sonnenwirth A, Jarett LD, eds. *Gradwohl's Clinical Laboratory Methods and Diagnosis*. St. Louis, MO: CV Mosby; 1980:802-803.

[100] Wu C, Kenny MA. A case of sulfhemoglobinemia and emergency measurement of sulfhemoglobin with an OSM3 CO-Oximeter. *Clin Chem.* 1997;43:162-166.

[101] Lee J, Mukai D, Kreuter K, et al. Potential interference by hydroxocobalamin on CO-Oximetry hemoglobin measurements during cyanide and smoke inhalation treatments. *Ann Emerg Med.* 2007;49:802-805.

[102] Gourlain H, Buneaux F, Borron SW, et al. Interference of methylene blue with CO-Oximetry of hemoglobin derivatives. *Clin Chem.* 1997;43:1078-1080.

[103] Baraka AS, Ayoub CM, Yazbeck-Karam V, et al. Prophylactic methylene blue in a patient with congenital methemoglobinemia. *Can J Anesth.* 2005;52:258-261.

[104] Zijilstra WG, Buursma A, Meuwsen-vanderRoest WP. Absorption spectra of human fetal and adult oxyhemoglobin, deoxyhemoglobin, carboxyhemoglobin and methemoglobin. *Clin Chem.* 1991;37:1633-1638.

[105] Zwart A, Buursma A, Oeseburg B, et al. Determination of hemoglobin derivatives with the IL 282 multiwavelength hemoglobin photometer as compared with a manual spectrophotometric five-wavelength method. *Clin Chem.* 1981;27:1903-1907.

[106] Egberts J, Van Pelt J. Evaluation of the blood analyzer ABL 735 Radiometer for determination of the percentage of fetal hemoglobin in fetal and neonatal blood. *Scand J Clin Lab Invest.* 2004;64:128-131.

[107] Spurzem JR, Bonekat HW, Shigeoka JW. Factitious methemoglobinemia caused by hyperlipemia. *Chest.* 1984;1:84-86.

[108] Sehgal LR, Sehgal HL, Rosen AL, et al. Effect of Intralipid on measurements of total hemoglobin and oxyhemoglobin in whole blood. *Crit Care Med.* 1984;12:907-909.

[109] Ali AA, Ali GS, Steinke JM, et al. CO-Oximetry interference by hemoglobin-based blood substitutes. *Anesth Analg.* 2001;92:863-869.

[110] Klaus D, Lloyd AC. Guidelines for calibration in Analytical Chemistry. *Pure Appl Chem.* 1998;70:993-1014.

[111] ISO. *International vocabulary of metrology — Basic and general concepts and associated terms (VIM).* ISO/IEC Guide 99. Geneva: International Organization for Standardization; 2007.

[112] ISO/IEC. *Guide to the Expression of Uncertainty in Measurement (GUM).* ISO/IEC Guide 98. Geneva: International Organization for Standardization; 1995.

[113] ISO. In vitro *diagnostic medical devices – Measurement of quantities in samples of biological origin – Metrological traceability of values assigned to calibrators and control materials*. prEN ISO 17511. Geneva: International Organization for Standardization; 1999.

[114] ISO. *General requirements for the competence of testing and calibration laboratories.* ISO 17025. Geneva: International Organization for Standardization; 2005.

[115] Maas AHJ, Weisberg FH, Burnett RW, et al. Reference method for pH measurement in blood. *J Clin Chem Clin Biochem.* 1987;25:281-289.

[116] Burnett RW, Covington AK, Maas AHJ, et al. IFCC method for tonometry of blood; reference materials for pCO_2 and pO_2. *J Biomed Lab Sci*. 1989;2:185-192. (An approved IFCC recommendation.)

[117] Burnett RW, Christiansen TF, Covington AK. IFCC recommended reference method for the determination of the substance concentration of ionized calcium in undiluted serum, plasma or whole blood. *Clin Chem Lab Med.* 2000;38:1301-1314.

[118] Neese JW, Duncan P, Bayse D, et al. Development and evaluation of a hexokinase/glucose-6-phosphate dehydrogenase procedure for use as a national glucose reference method. Atlanta, GA: US Department of Health Education and Welfare, Public Health Service, Centers for Disease Control and Prevention; 1976. Publication number (CDC) 77-8330.

[119] CLSI. *Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions; Approved Guideline—Third Edition.* CLSI document C24-A3. Wayne, PA: Clinical and Laboratory Standards Institute; 2006.

[120] Burnett RW, Maas AH, Moran RF. Quality control in blood pH and gas analysis by use of a tonometered bicarbonate solution and duplicate blood analysis. *Clin Chem.* 1981;27:1761-1766.

[121] Noonan DC, Burnett RW. Quality control system for blood pH and gas measurements with use of tonometered bicarbonate-chloride solution and duplicate samples of whole blood. *Clin Chem.* 1974;20:660-665.

[122] Mahoney JJ, Wong RJ, Van Kessel AL. Reduced bovine hemoglobin solution evaluated for use as a blood gas quality-control material. *Clin Chem.* 1993;39:874-879.

[123] Liffmann SM, Holland J, MacDonald M, et al. Multisite evaluation of a hemoglobin-based control for pH and blood gas, electrolyte, and CO-oximetry instruments. *Respir Care.* 1992;40:820-831.

[124] Ong ST, David D, Snow M, Hansen JE. Effect of variations in room temperature on measured values of blood gas quality control materials. *Clin Chem*. 1983;29:502-505.

[125] Toffaletti JG, McDonnell EH, Ramanathan LV, et al. Validation of a quality assessment system for blood gas and electrolyte testing. *Clin Chim Acta.* 2007;382:65-70.

[126] Nichols JH, Karim S, Arabadjief M. Evaluation of QC3: The automated quality control system on the ABL 80 FLEX. *Point of Care*. 2008;7:54-59.

[127] Elser RC, Sitler J, Garver C. A flexible and versatile program for blood gas quality control. *Am J Clin Pathol.* 1982;78:471-478.

[128] Metzger LF, Stauffer WB, Krupinski AV, Millman RP, Cembrowski GS, Pack AI. Detecting errors in blood gas measurements by analysis with two instruments. *Clin Chem.* 1987;33:512-517.

[129] Elser R, Hess D, Moran RF. Assessment of the agreement between duplicate whole blood measurements of blood gases and pH on independently calibrated analyzers. In: *Methodology and Clinical Applications of Electrochemical and Fiber Optic Sensors.* Vol. 11. Rochester, MN: AACC, Electrolytes Blood Gas Division; 1990.

[130] Elser R, Hess D, Moran RF. Multilevel multishift QC necessary for blood gas analyzers. In: *Measurement and Clinical Applications of Blood Gases, pH, Electrolytes and Sensor Technology.* Vol. 12. Monterey, CA: IFCC/WGSE; 1990.

Appendix A. Instrument 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 vs Reportable Range

The measurement range is the range of analyte concentrations over which meaningful results can be acquired.

The reportable range is the range of analyte concentrations over which the acceptability criteria for the method are met; that is, where errors due to nonlinearity, imprecision, or other sources are within defined limits.

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

NOTE: The measurement range will be equal to or wider than the reportable range.

A4. Detection Limit

Detection limit, as defined in CLSI/NCCLS document EP17,[1] may be expressed as the limit of detection (LoD) and limit of quantitation (LoQ). Another practical alternative to determine LoQ, functional sensitivity (FS), is also presented.

A4.1 Limit of Detection

LoD is defined as the lowest concentration of analyte in a sample that can be detected with stated probability, although perhaps not quantified as an exact value. LoD relates to the lower limit of the measurement range (see Section A3).

A4.2 Limit of Quantitation

LoQ is defined as the lowest concentration of analyte in a sample that can be quantitatively determined with stated acceptable precision and trueness, under stated experimental conditions. LoQ relates to the lower limit of the reportable range (see Section A3).

A4.3 Functional Sensitivity

FS is estimated as the mean concentration for a spiked sample whose coefficient of variation (CV) is 20%.[2,3] To estimate FS, several spiked concentrations must be assayed to determine the precision profile at the low concentration range, and to select the concentration at which a 20% CV is obtained.

Appendix A. (Continued)

A5. Recalibration Interval

A5.1 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 (ie, 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)

A5.2 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 the claimed inaccuracy and imprecision values are valid.

Example: 45 samples

A6. 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

A7. Sample Temperature

A7.1 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: $4 \leq T \leq 42$ °C

A7.2 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: $36.8 \leq T \leq 37.2$ °C

A8. 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

Appendix A. (Continued)

for the instrument output to stabilize within the limits of the claimed inaccuracy and imprecision.) Sample analysis time may be specified: (a) for samples with specific analytes within specific concentration ranges; and (b) for samples with specific analyte concentrations over the remainder of the reportable range.

Example:	Less than two minutes	30 mmHg (4.0 kPa) ≤ pCO_2 ≤ 50 mmHg (6.6 kPa)
	Less than two minutes	80 mmHg (10.6 kPa) ≤ pO_2 ≤100 mmHg (13.3 kPa)
	Less than three minutes	(total measurement range)

A9. 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 may specify the rate that can be expected with specific analytes within specific concentration ranges. In addition, the throughput rate that can be expected over the remainder of the claimed reportable range should be specified.

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

A10. Inaccuracy and Imprecision

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

References for Appendix A

[1] CLSI/NCCLS. *Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline*. CLSI/NCCLS document EP17-A. Wayne, PA: NCCLS; 2004.

[2] Westgard JO. Method validation – the detection limit experiment. http://www.westgard.com/lesson29.htm. Accessed 20 March 2008.

[3] Klee GG, Dodge LA, Zincke H, et al. Measurement of serum prostate specific antigen using Imx prostate specific antigen assay. *J Urol.* 1994;151:94-98.

Appendix B. Recommendations for Measurement and Reporting of Hemoglobin Fractions and Related Quantities

B1. Instrument Requirements

B1.1 Wavelength Requirements

Oxygen saturation, plus fractional oxyhemoglobin, carboxyhemoglobin, and methemoglobin in blood, when needed for clinical, diagnostic, and therapeutic purposes, should be quantified using either a multiwavelength spectrophotometer or a photometer designed specifically for the measurement of hemoglobin and its derivatives (commonly called multiwavelength hemoglobin photometers or cooximeters). Minimum capabilities of the analytical system shall include the ability to discriminate between and quantify *c*tHb, FO_2Hb, *F*COHb, *F*HHb, and *F*MetHb. Total hemoglobin concentration, when required for quantification of oxygen content and quantities derived from it such as physiological shunt (Qsp/Qt), should be measured on the same specimen as the hemoglobin fractions.

The characteristics of multicomponent photometric analysis of hemoglobin derivatives, as well as subject-to-subject variability in hemoglobin's optical characteristics, limit its usefulness in discriminating low fractional values (eg, <0.025 or 2.5%). Attempts to characterize/discriminate for either clinical or research purposes at such low levels of COHb and MetHb should utilize methodology other than that discussed in this document.

Simple two-wavelength oximeters, including most pulse and indwelling oximeters, cannot specifically measure dyshemoglobins, and may give misleading estimates of the oxygen content of blood in the presence of elevated levels of COHb or MetHb (see Section 4.1.12). This is not necessarily an error in the measurement by the simple oximeter, but is more likely a mistake in the interpretation of the difference between oxygen saturation and fractional oxyhemoglobin (see Section 4.1.10). Section 4.1.10.5 provides information regarding a new generation, multiwavelength pulse oximeter capable of measuring COHb and MetHb with reported good correlation to multiwavelength laboratory oximeters.

Some special purpose, multiwavelength oximeters (eg, those applied to continuous, *in vivo,* or skin surface monitoring), may also be limited in their ability to detect dyshemoglobins depending on the specific wavelengths of light used in the instrument's sensor system.

B1.2 Instrument Calibration

The *c*tHb (equivalent) value of the calibrators used (dye or hemoglobin solution) on an *in vitro* analyzer must be referenced to and correspond to the reference method (see CLSI/NCCLS document H15).[1]

Simple oximeters that have the capability should be calibrated to correspond to an *in vitro* oxygen saturation (sO_2) measurement. **NOTE:** Values for saturation obtained from instruments designed for "trending" or other simple oximeters must not be used for further calculations such as shunt fraction or oxygen content, since clinically significant errors can result.

B2. Reporting Results

B2.1 Oxygen Saturation, Fractional Oxyhemoglobin, Total Hemoglobin Concentration, and Oxygen Content

The analyzer must clearly distinguish between oxygen saturation (sO_2) and fractional oxyhemoglobin (FO_2Hb) in its reporting format if both entities are reported from the same analyzer for the same

Appendix B. (Continued)

specimen. sO_2 should be reported as a percentage (%), while *F*O2Hb may be reported as a fraction (ie, 0.9) or as a percentage (ie, 90%).

NOTE: Measurements of arterial blood oxygen saturation, sO_2 (a), can be used instead of measurements of pO_2 (a) for assessing the adequacy of the transfer of oxygen to arterial blood by the lungs. Because of the sigmoid shape of the oxyhemoglobin dissociation curve (the plot of sO_2 vs pO_2), and because of the dependence of sO_2 on pH, levels of 2,3-DPG, and other factors, measurements of sO_2 (a) at values above 80% are much less sensitive indicators of the effectiveness of the transfer of oxygen to arterial blood than are measurements of pO_2.

NOTE: Estimates of sO_2 (a) by pulse oximeters are widely used clinically for rapidly detecting marked worsening of lung function and resultant hypoxemia, as may occur during surgery or in critically ill patients in intensive care units. However, such estimates of sO_2 (a) are not appropriate for the detection of early lung disease that may result in small decreases in sO_2 (a) (eg, 96% to 94%) but moderate and readily recognizable decreases in pO_2 (a) (eg, 85 mmHg to 69 mmHg).

The concentration of total hemoglobin, *c*tHb, and oxygen content, ctO_2, are to be reported simultaneously, on the same specimen. Units for reporting *c*tHb are g/dL (preferred), g/L, or mmol/L. Units for reporting ctO_2 are mL(STPD)/dL (preferred), mL(STPD)/L, or mmol/L. The value for ctO_2 reported must be based on direct measurement or derivation from measured values for pO_2, FO_2Hb, and *c*tHb and application of equation 23 in Section 4.1.12.

NOTE: Measurements of sO_2 are useful for quantifying the oxygen content of blood only if combined with knowledge of the concentrations/fractions of nonoxygen-carrying hemoglobin derivatives such as carboxyhemoglobin, as well as the total hemoglobin concentration. This is especially important, since further calculation of clinically important quantities such as shunt fraction (Qsp/Qt) and arteriovenous oxygen content differences depend on valid oxygen content values. Thus, in order to avoid any ambiguity in these applications, expressing oxyhemoglobin as both FO_2Hb and sO_2 is necessary on each specimen measured for oxygenation assessment.

B2.2 Fractional COHb, MetHb, and HHb

Other fractional derivatives of hemoglobin are reported either as a decimal fraction (ie, 0.01) or as a percentage (ie, 1%).

B2.3 Oximeter Readings

Oxygen saturation measured by simple oximeters is reported only after evaluating the potential presence of dyshemoglobins (see Sections B1.1 and 4.1.10.5).

B2.4 Reported Quantities

All quantities reported are identified by a specific abbreviation that describes the sampling site unless, in the context of the report, the site is unambiguous. For example, oxygen saturation in arterial blood is formally represented by sO_2 (aB). The symbol B for blood, however, may usually be omitted; in most reporting situations, it is redundant. An alternate, acceptable format, using the same example, is sO_2(a).

Reference for Appendix B

[1] CLSI/NCCLS. *Reference and Selected Procedures for the Quantitative Determination of Hemoglobin in Blood; Approved Standard—Third Edition.* CLSI/NCCLS document H15-A3. Wayne, PA: NCCLS; 2000.

Appendix C. Measurement Technologies Used in Instruments for Analysis of Blood Gases, pH, and Related Analytes

Measurement technologies used in instruments for blood gases, pH, and related analytes fall into two major categories: electrochemical and optical. Application of these two general technologies to specific analytes is shown in Table C1.

Table C1. Measurement Technologies Used in Instruments for Blood Gases, pH, and Related Analytes

	Electrochemical			Optical
	Potentiometry	**Amperometry**	**Conductometry**	**Absorption Spectrometry**
pH and Gases	pH, pCO_2	pO_2		
Electrolytes	Na^+, K^+, Cl^-, Ca^{++}, Mg^{++}			
Metabolites		glucose, lactate		
Hematocrit, Hemoglobin, Hemoglobin Fractions			hematocrit	hemoglobin hemoglobin fractions

C1. Electrochemical Measurements

Electrochemical sensors are well suited to blood analysis for the following reasons:

- The sensors are direct reading and may be used in a turbid matrix without sample dilution or pretreatment.
- The measurement is nondestructive, allowing simultaneous measurement of multiple parameters from a single sample.
- Other critical care analytes, beyond pH and blood gases, may be measured using a common measurement technology, simplifying instrument design.

Subcategories of electrochemistry are presented below, and the reader is referred to technology reviews for details of specific applications. [1]

C1.1 Potentiometry

A cell potential (voltage developed between two electrodes) is proportional to the concentration of a specific analyte, with zero current flow between the electrodes. The two electrodes are called the indicator and reference electrodes. Applications include ion-selective electrodes for pH, Na^+, K^+, Ca^{++}, Mg^{++}, Cl^-, and the internal pH electrode for the Stow-Severinghaus pCO_2 sensor.

C1.2 Amperometry

A constant potential applied between two electrodes (anode and cathode) is used to drive a chemical reaction, resulting in a current flow between the electrodes. Applications include the Clark pO_2 sensor and the H_2O_2 electrode used as the internal transducer for most glucose and lactate and biosensors. Glucose and lactate biosensors are also amperometric sensors, but include in addition an enzyme as a recognition element for the analyte of interest.

Appendix C. (Continued)

C1.3 Conductometry

The passage of current between two electrodes (conductance) by ion migration under a potential gradient is proportional to the concentration of an analyte. Applications include measurement of erythrocyte volume fraction (hematocrit), since red blood cells are electrical insulators.

C2. Optical Measurements

Absorption spectrometry is used for the measurement of hemoglobin and fractional components of hemoglobin by taking advantage of the differences in the absorption spectra of the fractional components in the visible region (see Figure C1). This technology is commonly referred to as cooximetry. Measurements are made at several wavelengths in order to differentiate the fractions, and total hemoglobin is the sum of all the fractions.

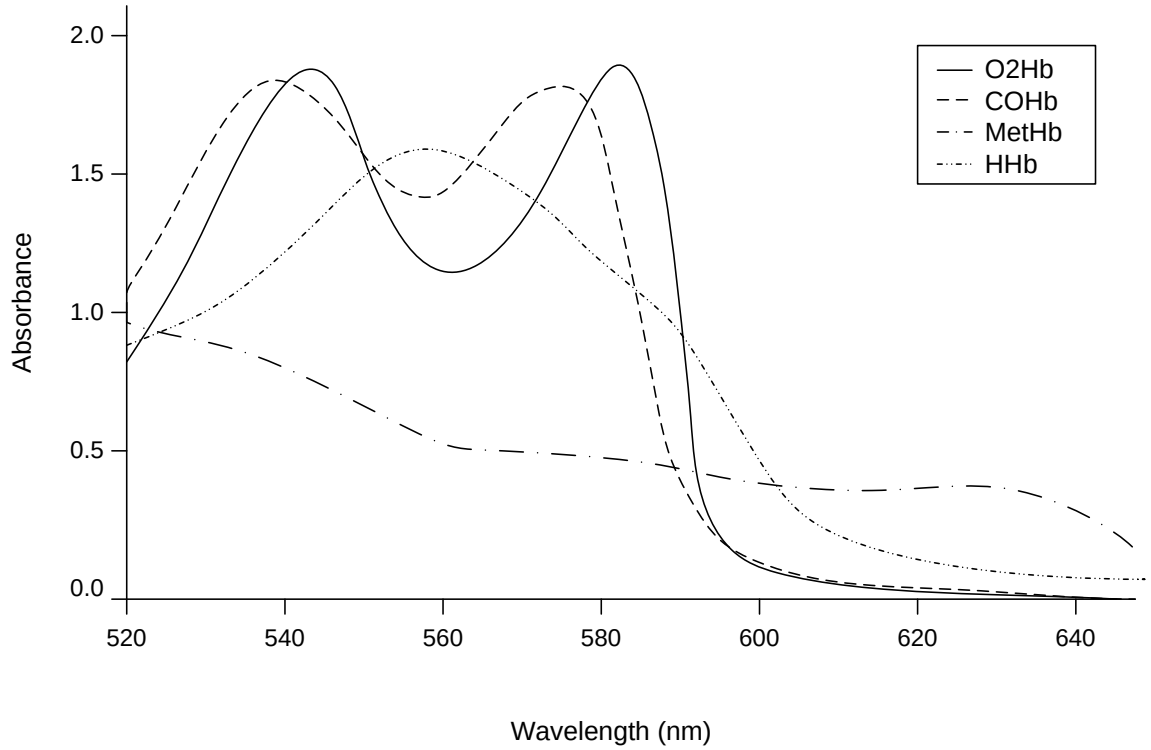

Figure C1. Absorption Spectra of the Fractional Components of Hemoglobin

C2.1 Cooximetry Using Lysed and Unlysed Blood

Traditionally, blood for cooximetry measurements has red blood cells lysed, either chemically or mechanically, to eliminate scattering during the optical measurement. More recently, some analyzers use unlysed whole blood for cooximetry measurements, with mathematical correction for scattering produced by red blood cells.

C3. Technologies Used in Systems for Point-of-Care Testing

Many hand-held and portable systems for point-of-care testing use sensors and reagents contained within disposable measurement cartridges. These cartridges are used to assay a fixed number of samples, ranging

Appendix C. (Continued)

from one (single-use cartridge) to several hundred over several weeks. The sensors may be assembled in planar formats on plastic or other inexpensive substrates, which are disposed of when the measurement cartridge reaches its sample capacity. Sensor technologies are the same as the larger, traditional laboratory-based systems with a few exceptions. Some systems designed for point-of-care testing use optical-based sensors for measurement of blood gases, pH, and electrolytes; however, these sensors are limited to systems for unit-use testing, because of the nonreversibility of the sensing reactions.[1]

Sensors for pH, Na^+, and the internal pH sensor used in traditional, laboratory-based systems are assembled from ion-selective glasses. Because glass sensors cannot be fabricated on plastic substrates, newer systems designed for point-of-care testing use polymer-based sensors for these applications. While not as robust as glass sensors, polymer-based pH and Na^+ sensors are acceptable for analysis of a limited number of samples, and are acceptable for cartridge-based systems for point-of-care application.

Reference for Appendix C

[1] D'Orazio P, Meyerhoff ME. Electrochemistry and chemical sensors. In: *Tietz Handbook of Clinical Chemistry and Molecular Diagnostics.* 4th ed. St. Louis, MO: Elsevier Saunders; 2006:93-119.

Clinical and Laboratory Standards Institute consensus procedures include an appeals process that is described in detail in Section 8 of the Administrative Procedures. For further information, contact CLSI or visit our website at www.clsi.org.

Summary of Consensus Comments and Working Group Responses

C46-A: *Blood Gas and pH Analysis and Related Measurements; Approved Guideline*

General

1. I learned that CLSI/NCCLS document C25-A was discontinued in 2000 and that it was replaced by C46-A. However, I bought a copy of C46-A, and was surprised to see that CLSI's wisdom and "essential recommendations" regarding oximetry and cooximetry were not included in the new document. Just to cite a few examples from CLSI/NCCLS document C25-A, CLSI: 1) designated multiwavelength spectrophotometry as the method of choice for measuring the oxyhemoglobin fraction in blood samples; 2) discouraged the use of "saturation" values estimated from oxygen tension measurements; 3) warned of "clinically significant errors" that result from using an "estimated value for sO2"; and 4) recommended that simple two-wavelength oximeters not be used clinically until the presence of dyshemoglobins was ruled out. Surprisingly, none of this important advice appears in C46-A, yet there is a continuing and urgent need for it.

- **The cooximetry essential recommendations were added to the document as Appendix B.**

2. The long-time supervisor of our blood gas laboratory reviewed the document and the comments. He felt the document was current and acceptable, but agreed with the comments that the oximetry and cooximetry "essential recommendations" should be added back into the document.

- **The cooximetry essential recommendations were added to the document as Appendix B.**

3. C46-A, which consolidates several older CLSI documents, remains a very useful document. The fundamentals of pH, blood gas, cooximetry measurements, and derived parameters, discussed in Section 3, are sound. The only update to this section might be to review the older CLSI/NCCLS document C25-A to see if the cooximetry "essential recommendations" need to be included in C46-A, as a comment on this point was received from a reviewer.

- **The cooximetry essential recommendations were added to the document as Appendix B.**

Section 1, Scope (formerly Section 2)

4. The stated Scope, "This guideline addresses blood gas, pH, and related measurements (eg, fractional oxyhemoglobin, oxygen content, hemoglobin-saturation, and selected electrolytes as measured in whole blood)" is grammatically incorrect. It should be, "This guideline addresses blood gas, pH, and related measurements (eg, fractional oxyhemoglobin, oxygen content, hemoglobin-saturation, and selected electrolytes) as measured in blood." Note the change in parenthesis closure.

- **The first sentence in the Scope was revised.**

5. For consideration of the relevance of the Scope and content of C46, I wonder about the apparent exclusion of *in vivo* devices that measure pH, electrolytes, glucose, and so on. I didn't see mention of those "whole blood" measurements, as can be done during surgery using the various indwelling analyzers that are currently commercially available and in use. These approaches have special considerations, including calibration, agreement with the clinical laboratory's results, quality control, etc. Perhaps, the Scope should state if these are not to be covered.

- **It is now stated in the Scope that devices for *in vivo* monitoring and patient-attached, *ex vivo* monitors for blood gas, pH, and related measurements are not specifically addressed in the document.**

Section 5, Preanalytical Considerations (formerly Section 4)

6. Review to determine if references to other CLSI documents are current, especially with respect to sample collection devices and procedures.

- **Agreement with existing CLSI documents was checked.**

Section 5.2.4.1, "Mixed Venous Blood" (formerly Section 4.2.4.1)

7. Define "mixed venous" as drawn from the pulmonary artery by means of a PA catheter.

- **The recommended change was made to Section 5.2.4.1.**

8. Don't use the term "central" and don't say mixed venous blood can be drawn from a CVP or a PA catheter.

- **The recommended change was made to Section 5.2.4.1.**

9. It might be preferable to drop the term "central" altogether.

- **The recommended change was made to Section 5.2.4.1.**

Section 5.3.4, Preparation Prior to Analysis (formerly Section 4.2.7)

10. Mixing (or failing to mix completely) may also affect pH and pCO_2 measurement in analyzers that use dry, optical technology. These analyzers use spectrophotometric measurements for pH and pCO_2, and my experience has been that poorly mixed samples tend to be variable.

- **The text in Section 5.3.4 was revised to address improperly mixed blood specimens.**

Section 6, Analytical Interferences (formerly Section 5, General Analytical Interferences)

11. This section requires more extensive revision. It is not complete and should be revised to address several other potential interfering substances for blood gas, pH, and cooximetry measurements. These include effects of anesthetic agents, bilirubin, dyes used in certain medical procedures, and possibly other substances. Also, more is known today about the interference of blood substitutes with the measurements.

- **The section dealing with interfering substances was extensively revised to include other interfering substances.**

Section 7.5, Calibration of pO_2 and pCO_2 in Systems for Point-of-Care Testing (formerly Section 6, Blood Gas Analyzer Calibration)

12. This should include a discussion of single phase calibrators used in newer blood gas analyzers, how these calibrators meet the traceability requirements in Section 6.1, and how they are validated for use in routine analyzers.

- **Section 7.5 was added to address single phase calibrators.**

Section 8.1.1.2.4, Temperature Equilibration of Commercial Controls (formerly Section 7.1.2.4)

13. The document suggests that commercial controls need to equilibrate at room temperature. Most analyzers allow the user to enter the ambient temperature when controls are run; this may be important if the ambient temperature is significantly different from 25 ºC, particularly for pO_2.

- **The recommended change was made to Section 8.1.1.2.4.**

Section 8.1.2, Nonsurrogate (Alternative) Quality Control (formerly Section 7, Blood Gas Quality Control)

14. This deals almost exclusively with assaying external, "blood-like" quality control materials to determine if an analyzer is performing properly. Electronic quality control is briefly discussed and dismissed, because it does not monitor the complete analytical process. However, since C46-A was approved, other integrated quality control approaches were recommended and implemented by instrument manufacturers. These include on-board process control solutions and various system checks beyond just electronics, including system fluidic checks, sensor function checks, and sample integrity checks. There are some CLSI documents in draft form under the Evaluation Protocols area committee that address manufacturer-recommended quality control. While these documents are not yet approved, devices including this type of quality control are already on the market. Therefore, I believe mention of this should be included in a revision of C46.

- **Section 8.1.2 was added to address "nonsurrogate (alternative) quality control."**

Summary of Delegate Comments and Working Group Responses

C46-A2: *Blood Gas and pH Analysis and Related Measurements; Approved Guideline—Second Edition*

General

1. General style: I do not use the word "actually," because nothing is "virtually" done when making blood gas measurements. Delete "actually" from the sentences.

- **The word "actually" was deleted from the document.**

2. I recommend adding to the document a section on the effect of ambient barometric pressure on the accuracy of the measurement for blood gases.

- **Instead of creating a new section, information about the effect of ambient barometric pressure on accuracy of blood gas measurements was added to Section 7.4.**

3. The electronic quality control (QC) cannot monitor all parts of the analytical process. Perhaps the use of other QC material periodically may be helpful.

- **The working group agrees with this comment. The need to periodically assay QC materials if an automated QC system only monitors a portion of the analytical process is stated in the last sentence of Section 8.1.2.**

4. The lowercase "p" for gas tension is troublesome for me. The style of *Scientific Style and Format. The CBE Manual for Authors, Editors, and Publishers* uses an italicized uppercase *"P"* with small caps and subscript for the gas, as in "PCO_2."

- **According to the CLSI Style Guide for Authors, subcommittees/working groups that draft standards and guidelines are required to use the International Union of Pure and Applied Chemistry/International Federation of Clinical Chemistry and Laboratory Medicine (IUPAC/IFCC)-recommended units and symbols whenever feasible. The IUPAC symbol for partial pressure is "*p*" and the partial pressure of a gas is written as "p_{CO2}." However, for better readability, the working group chose to use the alternative representation "pCO_2" as presented in the Tietz Textbook of Clinical Chemistry and Molecular Diagnostics, Fourth Edition, 2006.**

Foreword

5. The Foreword really applies only to the first edition of C46, which was a consolidation of the documents mentioned. It may be useful to retain this history, but it would be more appropriate to revise the Foreword to explain the evolution from C46-A to C46-A2 and any important issues that were addressed in the latest edition. As written, it seems that C46-A2 is a consolidation of the earlier documents.

- **The working group agrees with this comment. The Foreword was rewritten to specifically point out the changes that were made at each stage of revision.**

Section 4.1.3, Apparent pK of CO_2 in Plasma(pK')

6. The "concentration solubility coefficient, α"' is not stated until Section 4.1.12 as "The solubility coefficient of oxygen in blood plasma (α')." Use the same terminology in both sections, and refer to Section 4.1.12 at first use in Section 4.1.3; or just give the value in Section 4.1.3 and refer back in Section 4.1.12.

- **The concentration solubility coefficient for CO_2 in plasma (α´) is first introduced and defined in Section 4.1.3, which precedes the discussion in Section 4.1.12.**

Section 4.1.7.1, Calculation of $BE_{(ecf)}$

7. Second paragraph – "Adopting a constant… The value expressed by ßecf is *actually* a function…"

- **The word "actually" was deleted from the document.**

Section 5.1.3, Specimen Labeling and Accompanying Information

8. First paragraph: Revise to clearly indicate that this additional information is not needed on the specimen label. I suggest: "The specimen must be properly labeled with the patient's full name, a second identifier such as the medical record number, a personal identification number or birth date according to local policies, the date and time of collection, and the identity of the person collecting the specimen. In addition, the following information should be recorded, when available, in the chart or computer system for meaningful clinical interpretation of blood gas results." Add the age and location to the list of bulleted items that follows.

- **The text was revised as suggested.**

Section 5.2.1, Sample Device

9. This section should have a sentence added to the last paragraph: "If samples are stored in ice water, the electrolytes, particularly potassium, will undergo transport between cells and plasma that may cause erroneous K^+ values to be measured."

- **The proposed sentence was added to the end of Section 5.2.1.**

Section 5.2.4.1, "Mixed Venous Blood"

10. As a minor suggestion, in the first sentence of this paragraph, the subject and verb do not agree and I believe the word "for" is left out. I believe the sentence should be: "The collection of both "mixed" venous blood and arterial blood ~~are~~ is essential for specimens to evaluate oxygen uptake…"

- **Omitting "The collection of both" from the beginning of the sentence clarifies the meaning of the sentence and addresses the points raised by this comment.**

Section 5.2.5, Anticoagulants

11. Note 1. Heparin acts… very little is *actually* needed.

- **The word "actually" was deleted from the document.**

12. Technical: Note 2. Lithium heparin…, although lithium heparin *should not* be used… Lithium heparin *cannot* be used if a lithium level is going to be determined. The same is true for sodium heparin when a sodium measurement is made.

- **"Should not" was replaced by "cannot" in the first sentence. The second sentence was revised to not allow sodium heparin to be used as an anticoagulant when sodium is measured.**

Section 5.3.4, Specimen Preparation Prior to Analysis

13. Fifth sentence: Remove the parentheses with "(eg, specimens that have been in ice water for 30 minutes or more)" from the sentence "Longer mixing intervals may be required when specimens have sat for longer periods (eg, specimens that have been in ice water for 30 minutes or more)." It is not recommended to use iced samples and this example is inappropriate. The correct information is given without the text in parentheses.

- **This suggested change was made.**

Section 5.3.5, *In Vitro* Hemolysis

14. Second paragraph: The phrase "(b) icing the blood during storage" should be removed. I do not think icing causes hemolysis; rather, it affects the Na/K membrane pump and causes potassium exchange across the membrane.

- **The commenter is correct. The effect of icing was removed from this section, and was added to Section 5.2.1 as recommended in comment 9.**

Section 5.4.5, Glucose

15. Fourth sentence: This may not be current. I believe the current recommendation from the American Diabetes Association and other professional organizations is to report whole blood glucose in plasma equivalent values. This point should be clarified and a recommendation made that is consistent with current professional guidelines.

- **The commenter correctly states the current guideline to report whole blood glucose results as plasma equivalent concentrations. However, at present, not all analyzers found in the field follow the recommendation. The working group believes the precaution stated in this section relative to blood vs serum/plasma glucose results should remain.**

Section 6.2, Interferences With Measurement of Electrolytes (Na^+, K^+, Ca^{++}, Mg^{++}, and Cl^-)

16. The document refers to the interference by silicon for a magnesium ion selective electrode (ISE). This is correct but no longer applicable. The silicon additive interfered with one manufacturer's electrode. That manufacturer was bought out by another company that phased out this electrode. Thus, there are only a very small number of laboratories in the United States that still use the magnesium ISE. The only electrode for ionized magnesium in the United States has an interference from thiocyanate (*Clin Chem.* 1997;43:1595-1600). People who smoke have an increased thiocyanate concentration in their blood. Even though the manufacturer has attempted to correct this interference, there is still significant negative interference by thiocyanate on the ISE for magnesium.

    I recommend making this section current by replacing the information on silicon with the information on thiocyanate.

- **This suggested change was made.**

Section 6.6.2, Additives to External Quality Control Materials

17. The last sentence should be modified to also contact the device manufacturer in addition to the QC product manufacturer.

- **This suggested change was made.**

Section 7.3, Calibration Traceability

18. Reference 111 needs to be updated to the 2007 VIM and the text in the section updated accordingly.

- **The correction was made.**

Section 8.1.1.1.1, Blood Tonometry

19. Third paragraph: This is an ideal situation that is not practical for most laboratories as already stated in the preceding paragraph. This sentence should be deleted and the section should end with the preceding paragraph.

- **The paragraph was deleted as suggested.**

Other

20. Overall, the guideline is a review article. This is evidenced by the dates of the cited literature. There are very few references less than 10 years old. The blood gas instruments now available are provided with all the information needed to make a reliable measurement.

- **The foundations of blood gas analysis, as published in the early work by Severinghaus, Siggaard-Andersen, and others, are important references to retain in this document. It is true that modern blood gas analyzers are highly sophisticated and contain all the information needed to make reliable measurements. However, to avoid treating these systems as "black boxes," the working group believes it is important to retain reference in C46-A2 to the early work. The same is true of Section 5, because the preanalytical requirements for quality blood gas measurements have not changed much over the years, with the exception of introduction of some new sample collection devices.**

  The major changes in C46-A2 were made in Sections 6, 7, and 8, where new information was added, particularly for requirements of calibration traceability and new approaches to quality control (Sections 7 and 8), and to fill in gaps that existed in C46-A with respect to interfering substances (Section 6).

  The working group apologizes if the style of the document resembles a review article, but C46-A2 is a revision of an earlier document, not a newly created document, and there was no intention to change the style or omit important content of what was already a very successful document.

21. Emphasis should be placed on specimen handling, which can be done in a few paragraphs.

- **Sample handling in Section 5.5 is limited to introduction of the specimen into the analyzer. Sample collection and transport are described in Sections 5.2 and 5.3, respectively.**

The Quality Management System Approach

Clinical and Laboratory Standards Institute (CLSI) subscribes to a quality management system approach in the development of standards and guidelines, which facilitates project management; defines a document structure via a template; and provides a process to identify needed documents. The approach is based on the model presented in the most current edition of CLSI/NCCLS document HS01—*A Quality Management System Model for Health Care.* The quality management system approach applies a core set of "quality system essentials" (QSEs), basic to any organization, to all operations in any health care service's path of workflow (ie, operational aspects that define how a particular product or service is provided). The QSEs provide the framework for delivery of any type of product or service, serving as a manager's guide. The QSEs are:

Documents & Records	Equipment	Information Management	Process Improvement
Organization	Purchasing & Inventory	Occurrence Management	Customer Service
Personnel	Process Control	Assessments—External & Internal	Facilities & Safety

C46-A2 addresses the QSEs indicated by an "X." For a description of the other documents listed in the grid, please refer to the Related CLSI Reference Materials section on the following page.

Documents & Records	Organization	Personnel	Equipment	Purchasing & Inventory	Process Control	Information Management	Occurrence Management	Assessments—External & Internal	Process Improvement	Customer Service	Facilities & Safety
GP02 H11		H11	H11	H03	X C24 C29 EP17 H03 H04 H11 H18 HS03 M29	GP02			H11		H03 H11 M29

Adapted from CLSI/NCCLS document HS01—*A Quality Management System Model for Health Care*.

Path of Workflow

A path of workflow is the description of the necessary steps to deliver the particular product or service that the organization or entity provides. For example, CLSI/NCCLS document GP26—*Application of a Quality Management System Model for Laboratory Services* defines a clinical laboratory path of workflow, which consists of three sequential processes: preexamination, examination, and postexamination. All clinical laboratories follow these processes to deliver the laboratory's services, namely quality laboratory information.

C46-A2 addresses the clinical laboratory path of workflow steps indicated by an "X." For a description of the other documents listed in the grid, please refer to the Related CLSI Reference Materials section on the following page.

Preexamination				**Examination**			**Postexamination**	
Examination ordering	Sample collection	Sample transport	Sample receipt/processing	Examination	Results review and follow-up	Interpretation	Results reporting and archiving	Sample management
X H03 H11	X C31 H03 H04 H11 H15	X C31 H03 H11 H18	X C31 H03 H11 H15 H18	X H03 H15 H18	X H03 H15	X	X	

Adapted from CLSI/NCCLS document HS01—*A Quality Management System Model for Health Care*.

Related CLSI Reference Materials*

C24-A3 **Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions; Approved Guideline—Third Edition (2006).** This guideline provides definitions of analytical intervals; planning of 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 on the expression of the results of ion-selective electrode measurement of sodium and potassium ion activities in undiluted serum, plasma, or whole-blood in clinical practice.

C31-A2 **Ionized Calcium Determinations: Precollection Variables, Specimen Choice, Collection, and Handling; Approved Guideline—Second Edition (2001).** This document addresses preanalytical considerations, such as patient condition, specimen choice, collection, and handling—that can influence the accuracy and clinical utility of ionized calcium measurements.

EP17-A **Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline (2004).** This document provides guidance for determining the lower limit of detection of clinical laboratory methods, for verifying claimed limits, and for the proper use and interpretation of the limits.

GP02-A5 **Laboratory Documents: Development and Control; Approved Guideline—Fifth Edition (2006).** This document provides guidance on development, review, approval, management, and use of policy, process, and procedure documents in the medical laboratory community.

H03-A6 **Procedures for the Collection of Diagnostic Blood Specimens by Venipuncture; Approved Standard—Sixth Edition (2007).** This document provides procedures for the collection of diagnostic specimens by venipuncture, including line draws, blood culture collection, and venipuncture in children.

H04-A6 **Procedures and Devices for the Collection of Diagnostic Capillary Blood Specimens; Approved Standard—Sixth Edition (2008).** This document provides a technique for the collection of diagnostic capillary blood specimens, including recommendations for collection sites and specimen handling and identification. Specifications for disposable devices used to collect, process, and transfer diagnostic capillary blood specimens are also included.

H11-A4 **Procedures for the Collection of Arterial Blood Specimens; Approved Standard—Fourth Edition (2004).** This document provides principles for collecting, handling, and transporting arterial blood specimens to assist with 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 document describes the principle, materials, and procedure for reference and standardized hemoglobin determinations. It includes specifications for secondary hemiglobincyanide (HiCN) standards.

H18-A3 **Procedures for the Handling and Processing of Blood Specimens; Approved Guideline—Third Edition (2004).** This document includes criteria for preparing an optimal serum or plasma sample and for the devices used to process blood specimens.

HS03-A **Pulse Oximetry; Approved Guideline (2005).** Pulse oximetry is a widely used device for the clinical assessment of arterial oxygenation and pulse rate. The clinical applications, quality assessment, and limitations are discussed in this guideline.

M29-A3 **Protection of Laboratory Workers From Occupationally Acquired Infections; Approved Guideline—Third Edition (2005).** Based on US regulations, this document provides guidance on the risk of transmission of infectious agents by aerosols, droplets, blood, and body substances in a laboratory setting; specific precautions for preventing the laboratory transmission of microbial infection from laboratory instruments and materials; and recommendations for the management of exposure to infectious agents.

* Proposed-level documents are being advanced through the Clinical and Laboratory Standards Institute consensus process; therefore, readers should refer to the most current editions.

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Vital Diagnostics S.r.l.
Watin-Biolife Diagnostics and Medicals
Watson Pharmaceuticals
Wellstat Diagnostics, LLC
Wyeth Research
XDX, Inc.
YD Consultant

Associate Active Members

3rd Medical Group
48th Medical Group/MDSS RAF Lakenheath (APO)
5th Medical Group/SGSL (ND)
55th Medical Group/SGSAL (NE)
59th MDW/859th MDTS/MTL Wilford Hall Medical Center (TX)
81st MDSS/SGSAL (MS)
Academisch Ziekenhuis-VUB (Belgium)
ACL Laboratories (IL)
ACL Laboratories (WI)
Adams County Hospital (OH)
Adena Regional Medical Center Hospital (OH)
The AGA Khan University Hospital (Pakistan)
Akron's Children's Hospital (OH)
Al Hada Armed Forces Hospital/TAIF/KSA (Saudi Arabia)
Alameda County Medical Center (CA)
Albany Medical Center Hospital (NY)
Albemarle Hospital (NC)
All Children's Hospital (FL)
Allegheny General Hospital (PA)
Allegiance Health (MI)
Alpena General Hospital (MI)
Alta Bates Summit Medical Center (CA)
American University of Beirut Medical Center (NJ)
Antelope Valley Hospital District (CA)
Arkansas Children's Hospital (AR)
Arkansas Dept of Health Public Health Laboratory (AR)
Arkansas Methodist Medical Center (AR)
Asan Medical Center (Korea)
Asante Health System (OR)
Asiri Group of Hospitals Ltd. (Sri Lanka)
Aspirus Wausau Hospital (WI)
Atlantic City Medical Center (NJ)
Auburn Regional Medical Center (WA)
Aultman Hospital (OH)
Avera McKennan (SD)
Az Sint-Jan (Belgium)
Azienda Ospedale Di Lecco (Italy)
Baffin Regional Hospital (Canada)
Baptist Hospital for Women (TN)
Baptist Hospital of Miami (FL)
Baton Rouge General (LA)
Baxter Regional Medical Center (AR)
Bay Regional Medical Center (MI)
BayCare Health System (FL)
Baylor Health Care System (TX)
Bayou Pathology, APMC (LA)
Baystate Medical Center (MA)
B.B.A.G. Ve U. AS., Duzen Laboratories (Turkey)
Beebe Medical Center (DE)
Belfast HSS Trust Royal Victoria Hospital (Ireland)
Beloit Memorial Hospital (WI)
Ben Taub General Hospital (TX)
The Bermuda Hospitals Board (Bermuda)
Beth Israel Medical Center (NY)
Bonnyville Health Center (Canada)
Boston Medical Center (MA)
Boulder Community Hospital (CO)
Brantford General Hospital (Canada)
Bridgeport Hospital (CT)
Broward General Medical Center (FL)
Cadham Provincial Laboratory-MB Health (Canada)

Calgary Health Region (Canada)
California Pacific Medical Center (CA)
Cambridge Health Alliance (MA)
Camden Clark Memorial Hospital (WV)
Canadian Science Center for Human and Animal Health (Canada)
CANNON AFB (NM)
Cape Breton Healthcare Complex (Canada)
Cape Cod Hospital (MA)
Cape Fear Valley Medical Center Laboratory (NC)
Capital Coast Health (New Zealand)
Capital Health - Regional Laboratory Services (Canada)
Capital Health/QE II Health Sciences Centre (Nova Scotia, Canada)
Capital Health System Mercer Campus (NJ)
Carilion Labs Charlotte (NC)
Carl R. Darnall Army Medical Center (TX)
Carolinas Healthcare System (NC)
Cavan General Hospital (Ireland)
Cedars-Sinai Medical Center (CA)
Central Kansas Medical Center (KS)
Central Texas Veterans Health Care System (TX)
Centralized Laboratory Services (NY)
Centre Hospitalier Anna-Laberge (Canada)
Centre Hospitalier Brome-Missisquoi-Perkins (Canada)
Chaleur Regional Hospital (Canada)
Chang Gung Memorial Hospital (Taiwan)
Changhua Christian Hospital (Taiwan)
Charleston Area Medical Center (WV)
The Charlotte Hungerford Hospital (CT)
Chatham - Kent Health Alliance (Canada)
Chesapeake General Hospital (VA)
Chester County Hospital (PA)
Children's Healthcare of Atlanta (GA)
Children's Hospital and Regional Medical Center (WA)
Children's Hospital Medical Center (OH)
Children's Hospital of Philadelphia (PA)
Children's Hospitals and Clinics (MN)
Children's Medical Center (OH)
Children's Medical Center (TX)
Children's Memorial Hospital (IL)
The Children's Mercy Hospital (MO)
Childrens Hosp. – Kings Daughters (VA)
Childrens Hospital Los Angeles (CA)
Childrens Hospital of Wisconsin (WI)
Chilton Memorial Hospital (NJ)
Christiana Care Health Services (DE)
Christus St. John Hospital (TX)
CHU Sainte-Justine (Quebec, Canada)
City of Hope National Medical Center (CA)
Clarian Health – Clarian Pathology Laboratory (IN)
Clinical Labs of Hawaii (HI)
Clinton Memorial Hospital (OH)
Colchester East Hants Health Authority (Canada)
College of Physicians and Surgeons of Alberta (Canada)
Columbia Regional Hospital (MO)
Commonwealth of Virginia (DCLS) (VA)
The Community Hospital (OH)
Community Hospital of the Monterey Peninsula (CA)
Community Medical Center (NJ)
Community Memorial Hospital (WI)
Consultants Laboratory of WI LLC (WI)
Contra Costa Regional Medical Center (CA)
Cook Children's Medical Center (TX)
Cornwall Community Hospital (Canada)
Covance CLS (IN)
The Credit Valley Hospital (Canada)
Creighton University Medical Center (NE)
Crozer-Chester Medical Center (PA)
Cumberland Medical Center (TN)
Darwin Library NT Territory Health Services (Australia)
David Grant Medical Center (CA)
Daviess Community Hospital (IN)
Deaconess Hospital Laboratory (IN)
Dean Medical Center (WI)
DeWitt Healthcare Network (USA Meddac) (VA)
DHHS NC State Lab of Public Health (NC)
Diagnostic Laboratory Services, Inc. (HI)
Diagnostic Services of Manitoba (Canada)
Diagnósticos da América S/A (Brazil)
Diaz Gill-Medicina Laboratorial S.A. (Paraguay)
Dimensions Healthcare System Prince George's Hospital Center (MD)
DME University Laboratories (MI)
Dr. Erfan & Bagedo General Hospital (Saudi Arabia)
DRAKE Center (OH)
Driscoll Children's Hospital (TX)
DUHS Clinical Laboratories Franklin Site (NC)
Dundy County Hospital (NE)
Dunn Memorial Hospital (IN)
DVA Laboratory Services (FL)
E. A. Conway Medical Center (LA)
East Central Health (Canada)
East Georgia Regional Medical Center (GA)
Eastern Health Pathology (Australia)
Easton Hospital (PA)
Edward Hospital (IL)
Effingham Hospital (GA)
Eliza Coffee Memorial Hospital (AL)
Elmhurst Hospital Center (NY)
Emory University Hospital (GA)
Evangelical Community Hospital (PA)
Evans Army Community Hospital (CO)
Evanston Hospital (IL)
Exeter Hospital (NH)
Federal Medical Center (MN)
Fletcher Allen Health Care (VT)
Fleury S.A. (Brazil)
Florida Hospital (FL)
Florida Hospital Waterman (FL)
Fort St. John General Hospital (Canada)
Forum Health Northside Medical Center (OH)
Fox Chase Cancer Center (PA)
Franciscan Skemp Medical Center (WI)
Frankford Hospital (PA)
Fraser Health Authority Royal Columbian Hospital Site (Canada)
Fresenius Medical Care/Spectra East (NJ)
Fundacio Joan Costa Roma Consorci Sanitari de Terrassa (Spain)
Garden City Hospital (MI)
Garfield Medical Center (CA)
Geisinger Medical Center (Danville, PA)
General Leonard Wood Army Community Hospital (MO)
Genesis Healthcare System (OH)
George Washington University Hospital (DC)
Georgetown University Hospital - Medstar Health (MD)
Ghent University Hospital (Belgium)
Good Samaritan Hospital (OH)
Good Shepherd Medical Center (TX)
Grana S.A. (TX)
Grand Strand Reg. Medical Center (SC)
Gundersen Lutheran Medical Center (WI)
Guthrie Clinic Laboratories (PA)
Haga Teaching Hospital (Netherlands)
Hagerstown Medical Laboratory (MD)
Hamad Medical Corporation (Qatar)
Hamilton Regional Laboratory Medicine Program (Canada)
Hanover General Hospital (PA)
Harford Memorial Hospital (MD)
Harris Methodist Fort Worth (TX)
Hartford Hospital (CT)
Health Network Lab (PA)
Health Partners Laboratories Bon Secours Richmond (VA)
Health Quest (NY)
Health Sciences Research Institute (Japan)
Health Waikato (New Zealand)
Heart of Florida Regional Medical Center (FL)
Heartland Health (MO)
Heidelberg Army Hospital (APO, AE)
Helen Hayes Hospital (NY)
Hema-Quebec (Canada)
Hennepin Faculty Association (MN)
Henry Ford Hospital (MI)
Henry M. Jackson Foundation (MD)
Hi-Desert Medical Center (CA)
Highlands Medical Center (AL)
Hoag Memorial Hospital Presbyterian (CA)
Holy Cross Hospital (MD)
Holy Family Medical Center (WI)
Holy Name Hospital (NJ)
Holy Spirit Hospital (PA)
Hopital Cite de La Sante de Laval (Canada)
Hopital du Haut-Richelieu (Canada)
Hôpital Maisonneuve - Rosemont (Montreal, Canada)
Hôpital Sacré-Coeur de Montreal (Quebec, Canada)
Hopital Santa Cabrini Ospedale (Canada)
Hospital das Clinicas-FMUSP (Brazil)
Hospital Dirino Espirito Santa (Portugal)
The Hospital for Sick Children (Canada)
Hôtel Dieu Grace Hospital Library (Windsor, ON, Canada)
Hotel-Dieu De Levis (Canada)
Imelda Hospital (Belgium)
Indian River Memorial Hospital (FL)
Indiana University - Chlamydia Laboratory (IN)
Inova Fairfax Hospital (VA)
Institut fur Stand. und Dok. im Med. Lab. (Germany)
Institut National de Santé Publique du Quebec Centre de Doc. – INSPQ (Canada)
Institute of Clinical Pathology and Medical Research (Australia)
International Health Management Associates, Inc. (IL)
IWK Health Centre (Canada)
Jackson County Memorial Hospital (OK)
Jackson Health System (FL)
Jackson Purchase Medical Center (KY)
Jacobi Medical Center (NY)
John C. Lincoln Hospital – N.MT. (AZ)
John F. Kennedy Medical Center (NJ)
John H. Stroger, Jr. Hospital of Cook County (IL)
John T. Mather Memorial Hospital (NY)
Johns Hopkins Medical Institutions (MD)
Johns Hopkins University (MD)
Johnson City Medical Center Hospital (TN)
Kadlec Medical Center (WA)
Kaiser Permanente (CA)
Kaiser Permanente (MD)
Kaiser Permanente (OH)
Kaiser Permanente Medical Care (CA)
Kaleida Health Center for Laboratory Medicine (NY)
Kangnam St. Mary's Hospital (Korea)
Kantonsspital Aarau AG (Switzerland)
Kenora-Rainy River Reg. Lab. Program (Canada)
King Abdulaziz University Hospital (Saudi Arabia)
King Fahad Medical City (Saudi Arabia)
King Fahad National Guard Hospital KAMC – NGHA (Saudi Arabia)
King Faisal Specialist Hospital (MD)
King Hussein Cancer Center (Jordan)
Kings County Hospital Center (NY)
Kingston General Hospital (Canada)
Lab Medico Santa Luzia LTDA (Brazil)
Labette Health (KS)
Laboratory Alliance of Central New York (NY)
LabPlus Auckland Healthcare Services Limited (New Zealand)
Labway Clinical Laboratory Ltd (China)
Lafayette General Medical Center (LA)
Lakeland Regional Laboratories (MI)
Lakeland Regional Medical Center (FL)
Lancaster General Hospital (PA)
Landspitali Univ. Hospital (Iceland)
Landstuhl Regional Medical Center (APO, AE)
Langley Air Force Base (VA)
LeBonheur Children's Medical Center (TN)
Legacy Laboratory Services (OR)
Lethbridge Regional Hospital (Canada)
Lewis-Gale Medical Center (VA)
Licking Memorial Hospital (OH)
LifeBridge Health Sinai Hospital (MD)
LifeLabs Medical Laboratory Services (Canada)
Littleton Hospital (NH)
Long Beach Memorial Medical Center (CA)
Los Angeles County Public Health Lab (CA)
Louisiana Office of Public Health Laboratory (LA)
Louisiana State University Medical Ctr. (LA)
Lower Columbia Pathologists, P.S. (WA)
Maccabi Medical Care and Health Fund (Isreal)
Mackay Memorial Hospital (Taiwan)
Madigan Army Medical Center (WA)
Madison Parish Hospital (LA)
Mafraq Hospital (UAE)
Magnolia Regional Health Center (MS)
Main Line Clinical Laboratories, Inc. (PA)
Makerere University Walter Reed Project Makerere University Medical School (Uganda)
Maricopa Integrated Health System (AZ)
Marquette General Hospital (MI)
Marshfield Clinic (WI)
Martha Jefferson Hospital (VA)
Martin Luther King, Jr. Harbor Hospital (CA)
Martin Memorial Health Systems (FL)
Mary Hitchcock Memorial Hospital (NH)
Mary Imogene Bassett Hospital (NY)
Massachusetts General Hospital (MA)
Maxwell Air Force Base (AL)
Mayo Clinic (MN)
Mayo Clinic Florida (FL)
Mayo Clinic Scottsdale (AZ)
Meadows Regional Medical Center (GA)
Medecin Microbiologiste (Canada)
Medical Center Hospital (TX)
Medical Center of Louisiana at NO-Charity (LA)
Medical Center of McKinney (TX)
Medical Centre Ljubljana (Slovenia)
Medical College of Georgia - Biomedical and Radiological Technologies (GA)
Medical College of Virginia Hospital (VA)
Medical Specialists (IN)
Medical Univ. of South Carolina (SC)
MediCorp - Mary Washington Hospital (VA)
Memorial Hermann Healthcare System (TX)
Memorial Hospital at Gulfport (MS)
Memorial Medical Center (IL)
Memorial Medical Center (PA)
Memorial Regional Hospital (FL)
Mercy Franciscan Mt. Airy (OH)
Mercy Hospital (ME)
Methodist Dallas Medical Center (TX)
Methodist Hospital (Houston, TX)
Methodist Hospital (San Antonio, TX)
Methodist Hospital Pathology (NE)
MetroHealth Medical Center (OH)
Metropolitan Medical Laboratory, PLC (IA)
The Michener Inst. for Applied Health Sciences (Canada)
Mid Michigan Medical Center – Midland (MI)
Middelheim General Hospital (Belgium)
Mike O'Callaghan Federal Hospital (NV)
Mississippi Baptist Medical Center (MS)
Mississippi Public Health Lab (MS)
Monongalia General Hospital (WV)
Montreal General Hospital (Quebec, Canada)
Mt. Sinai Hospital - New York (NY)
MuirLab (CA)
Nassau County Medical Center (NY)
National Cancer Center (S. Korea)
National Healthcare Group (Singapore)
National Institutes of Health, Clinical Center (MD)
National Naval Medical Center (MD)
National University Hospital Department of Laboratory Medicine (Singapore)
Nationwide Children's Hospital (OH)
Naval Hospital Great Lakes (IL)
Naval Hospital Oak Harbor (WA)
Naval Medical Center Portsmouth (VA)
NB Department of Health (Canada)
The Nebraska Medical Center (NE)
New England Baptist Hospital (MA)
New England Fertility Institute (CT)
New England Sinai Hospital (MA)
New Lexington Clinic (KY)
New York City Department of Health and Mental Hygiene (NY)
New York Presbyterian Hospital (NY)
New York University Medical Center (NY)
Newark Beth Israel Medical Center (NJ)
Newton Memorial Hospital (NJ)
North Carolina Baptist Hospital (NC)
North Coast Clinical Laboratory, Inc. (OH)
North District Hospital (Hong Kong, China)
North Mississippi Medical Center (MS)
North Shore Hospital Laboratory (New Zealand)
Northridge Hospital Medical Center (CA)
Northside Hospital (GA)
Northwest Texas Hospital (TX)
Northwestern Memorial Hospital (IL)
Norton Healthcare (KY)
Ochsner Clinic Foundation (LA)
Ohio State University Hospitals (OH)
Onze Lieve Vrouw Ziekenhuis (Belgium)
Ordre Professionel des Technologistes Medicaux du Quebec (Quebec, Canada)
Orebro University Hospital (Sweden)
Orlando Regional Healthcare System (FL)
Ospedale Casa Sollievo Della Sofferenza – IRCCS (Italy)
The Ottawa Hospital (Canada)
Our Lady of Lourdes Medical Center (NJ)
Our Lady of Lourdes Reg. Medical Ctr. (LA)
Our Lady's Hospital for Sick Children (Ireland)
Palmetto Health Baptist Laboratory (SC)
Pathlab (IA)
Pathology and Cytology Laboratories, Inc. (KY)
Pathology Associates Medical Laboratories (WA)
Pathology Associates of Boone (NC)
Penn State Hershey Medical Center (PA)
Pennsylvania Hospital (PA)
The Permanente Medical Group (CA)
Peterborough Regional Health Centre (Canada)
PHS Indian Hospital - Pine Ridge (SD)
Piedmont Hospital (GA)
Pitt County Memorial Hospital (NC)

Prairie Lakes Hospital (SD)
Presbyterian Hospital - Laboratory (NC)
Presbyterian Hospital of Dallas (TX)
Presbyterian/St. Luke's Medical Center (CO)
Prince County Hospital (Canada)
Providence Alaska Medical Center (AK)
Providence Health Care (Canada)
Providence Medford Medical Center (OR)
Provincial Health Services Authority (Vancouver, BC, Canada)
Provincial Laboratory for Public Health (Edmonton, AB, Canada)
Queen Elizabeth Hospital (Canada)
Queen Elizabeth Hospital (China)
Queensland Health Pathology Services (Australia)
Quest Diagnostics, Inc
Quest Diagnostics Laboratories (WA)
Quincy Hospital (MA)
Rady Children's Hospital San Diego (CA)
Ramathibodi Hospital (Thailand)
Redington-Fairview General Hospital (ME)
Regional Health Authority Four (RHA4) (Canada)
Regions Hospital (MN)
Reid Hospital & Health Care Services (IN)
Renown Regional Medical Center (NV)
Research Medical Center (MO)
Reston Hospital Center (VA)
Riverside County Regional Medical Center (CA)
Riverside Methodist Hospital (OH)
Riyadh Armed Forces Hospital, Sulaymainia (Saudi Arabia)
Robert Wood Johnson University Hospital (NJ)
Rockford Memorial Hospital (IL)
Roxborough Memorial Hospital (PA)
Royal Victoria Hospital (Canada)
Rush North Shore Medical Center (IL)
SAAD Specialist Hospital (Saudi Arabia)
Sacred Heart Hospital (FL)
Sacred Heart Hospital (WI)
Sahlgrenska Universitetssjukhuset (Sweden)
St. Anthony Hospital (OK)
St. Anthony's Hospital (FL)
St. Barnabas Medical Center (NJ)
St. Elizabeth Community Hospital (CA)
St. Eustache Hospital (Canada)
St. Francis Hospital (SC)
Saint Francis Hospital & Medical Center (CT)
St. John Hospital and Medical Center (MI)
St. John's Hospital (IL)
St. John's Hospital & Health Ctr. (CA)
St. John's Mercy Medical Center (MO)
St. John's Regional Health Center (MO)
St. Joseph Health Center (MO)
St. Joseph Mercy Hospital (MI)
St. Joseph's Medical Center (CA)
St. Joseph's Regional Medical Center (NJ)
St. Jude Children's Research Hospital (TN)
St. Louis University Hospital (MO)
St. Luke's Hospital (IA)
St. Luke's Hospital (PA)
St. Martha's Regional Hospital (Canada)
St. Mary Medical Center (CA)
St. Mary's Hospital (WI)
Saint Mary's Regional Medical Center (NV)
St. Tammany Parish Hospital (LA)
Saints Memorial Medical Center (MA)
Samaritan Health Services (OR)
Sampson Regional Medical Center (NC)
Samsung Medical Center (Korea)
San Francisco General Hospital-University of California San Francisco (CA)
Sanford USD Medical Center (SD)
Santa Clara Valley Medical Center (CA)
Saudi Aramco Medical (Saudi Arabia)
Schneck Medical Center (IN)
Scott & White Memorial Hospital (TX)
Scott Air Force Base (IL)
Seoul National University Hospital (Korea)
Seton Medical Center (CA)
Sheik Kalifa Medical City (UAE)
Shiel Medical Laboratory Inc. (NY)
Shore Memorial Hospital (NJ)
Shriners Hospitals for Children (SC)
Singapore General Hospital (Singapore)
SJRMC Plymouth Laboratory (IN)
South County Hospital (RI)
South Miami Hospital (FL)
Southern Health Care Network (Australia)
Southern Maine Medical Center (ME)
Southwest General Health Center (OH)
Spectrum Health - Blodgett Campus (MI)
Stanford Hospital and Clinics (CA)
Stanton Territorial Health Authority (Canada)
State of Connecticut Department of Public Health (CT)
State of Ohio/Corrections Medical Center (OH)
State of Washington-Public Health Labs (WA)
Stillwater Medical Center (OK)
Stony Brook University Hospital (NY)
Stormont-Vail Regional Medical Ctr. (KS)
Sudbury Regional Hospital (Canada)
Suncoast Medical Clinic (FL)
Sunnybrook Health Science Centre (ON, Canada)
Sunrise Hospital and Medical Center (NV)
Sydney South West Pathology Service Liverpool Hospital (Australia)
T.J. Samson Community Hospital (KY)
Taipei Veterans General Hospital (Taiwan)
Taiwan Society of Laboratory Medicine (Taiwan)
Tallaght Hospital (Ireland)
Tartu University Clinics (Estonia)
Texas Children's Hospital (TX)
Texas Department of State Health Services (TX)
Thomason Hospital (TX)
Timmins and District Hospital (Canada)
Tokyo Metro. Res. Lab of Public Health (Japan)
The Toledo Hospital (OH)
Touro Infirmary (LA)
Tri-Cities Laboratory (WA)
Tri-City Medical Center (CA)
Trident Medical Center (SC)
Trinity Medical Center (AL)
Tripler Army Medical Center (HI)
Tufts Medical Center Hospital (MA)
Tulane Medical Center Hospital & Clinic (LA)
Turku University Central Hospital (Finland)
Twin Lakes Regional Medical Center (KY)
UCI Medical Center (CA)
UCLA Medical Center Clinical Laboratories (CA)
UCSD Medical Center (CA)
UCSF Medical Center China Basin (CA)
UMass Memorial Medical Center (MA)
UMC of Southern Nevada (NV)
UNC Hospitals (NC)
Union Clinical Laboratory (Taiwan)
United Christian Hospital (Hong Kong)
United Clinical Laboratories (IA)
United States Air Force School of Aerospace Medicine/PHE (TX)
Unity HealthCare (IA)
Universita Campus Bio-Medico (Italy)
Universitair Ziekenhuis Antwerpen (Belgium)
University College Hospital (Ireland)
University Hospital Center Sherbrooke (CHUS) (Canada)
University Medical Center at Princeton (NJ)
University of Alabama Hospital Lab (AL)
University of Arkansas for Medical Sci. (AR)
University of Chicago Hospitals (IL)
University of Colorado Health Sciences Center (CO)
University of Colorado Hospital (CO)
University of Illinois Medical Center (IL)
University of Iowa Hospitals and Clinics (IA)
University of Kentucky Med. Ctr. (KY)
University of Maryland Medical System (MD)
University of Miami (FL)
University of Missouri Hospital (MO)
University of MN Medical Center - Fairview (MN)
University of MS Medical Center (MS)
University of Pennsylvania Health System (PA)
University of Pittsburgh Med. Ctr. (PA)
University of So. Alabama Children's and Women's Hospital (AL)
University of Texas Health Center (TX)
The University of Texas Medical Branch (TX)
University of the Ryukyus (Japan)
University of Virginia Medical Center (VA)
University of Washington (WA)
UPMC Bedford Memorial (PA)
U.S. Naval Hospital (FPO AP)
U.S. Naval Hospital Guantanamo Bay
US Naval Hospital Naples (FPO)
U.S.A. Meddac (Pathology Division) (MO)
UW Hospital (WI)
UZ-KUL Medical Center (Belgium)
VA (Asheville) Medical Center (NC)
VA (Bay Pines) Medical Center (FL)
VA (Biloxi) Medical Center (MS)
VA (Chillicothe) Medical Center (OH)
VA (Cincinnati) Medical Center (OH)
VA (Dayton) Medical Center (OH)
VA (Decatur) Medical Center (GA)
VA (Hampton) Medical Center (VA)
VA (Indianapolis) Medical Center (IN)
VA (Long Beach) Medical Center (CA)
VA (Miami) Medical Center (FL)
VA New Jersey Health Care System (NJ)
VA (San Diego) Medical Center (CA)
VA (Seattle) Medical Center (WA)
VA (Sheridan) Medical Center (WY)
Valley Health (VA)
Vancouver Coastal Health Regional Laboratory (BC, Canada)
Vancouver Island Health Authority (SI) (Canada)
Vanderbilt University Medical Center (TN)
Veterans Hospital (FL)
Via Christi Regional Medical Center (KS)
Virga Jessezieukenhuis (Belgium)
Virtua - West Jersey Hospital (NJ)
WakeMed (NC)
Walter Reed Army Medical Center (DC)
Warren Hospital (NJ)
Washington Hospital Center (DC)
Waterbury Hospital (CT)
Waterford Regional Hospital (Ireland)
Wayne Memorial Hospital (NC)
Weirton Medical Center (WV)
West China Second University Hospital, Sichuan University (China)
West Jefferson Medical Center (LA)
West Shore Medical Center (MI)
West Valley Medical Center Laboratory (ID)
Western Baptist Hospital (KY)
Western Healthcare Corporation (Canada)
Western Pennsylvania Hospital (PA)
Wheaton Franciscan & Midwest Clinical Laboratories (WI)
Wheeling Hospital (WV)
William Beaumont Army Medical Center (TX)
William Beaumont Hospital (MI)
William Osler Health Centre (Canada)
Winchester Hospital (MA)
Winn Army Community Hospital (GA)
Wishard Health Sciences (IN)
Womack Army Medical Center (NC)
Woodlawn Hospital (IN)
York Hospital (PA)

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