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GP34-A

Validation and Verification of Tubes for Venous and Capillary Blood Specimen Collection; Approved Guideline

This document provides guidance for conducting validation and verification testing for venous and capillary blood collection tubes.

A guideline for global application developed through the Clinical and Laboratory Standards Institute consensus process.

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Validation and Verification of Tubes for Venous and Capillary Blood Specimen Collection; Approved Guideline

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Abstract

Clinical and Laboratory Standards Institute document GP34-A—*Validation and Verification of Tubes for Venous and Capillary Blood Specimen Collection; Approved Guideline* is a guideline for manufacturers of venous and capillary blood collection tubes and users of blood collection tubes for serum, plasma, and whole blood testing. GP34 provides guidelines for validation and verification of test (examination) performance.

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Contents

Foreword

Currently, no guideline is available for either *in vitro* diagnostic (IVD) manufacturers or clinical laboratories to validate or verify use of the various venous and capillary blood collection tubes within each of the following laboratory medicine disciplines: chemistry, immunochemistry, hematology, and coagulation. However, for microbiology assays or culture methods, several documents address validation and quality control of collection tubes (see CLSI documents M40, M47, and M15).[1-3]

This guideline contains information on tubes for venous and capillary blood collection. It is written for manufacturers of venous and capillary blood collection devices; for assay/instrument manufacturers; and for those who are responsible for acquisition, handling, and use of the equipment described in this document.

Specimen collection devices, especially venous and capillary blood collection tubes, are classified as IVD devices. Because these devices are used to collect patient blood samples that are analyzed on highly sensitive clinical instrumentation, it is extremely critical for accurate and precise test results that these collection devices be verified for use on this instrumentation.

IVD manufacturers are challenged by regulatory agencies to ensure safety and efficacy of their devices as part of the validation process before release of the devices for use in the clinical laboratory. Tube manufacturers can use this guidance document to establish and standardize their validation process for both current and new blood collection tubes. In addition to this document, CLSI standard H01, *Tubes and Additives for Venous Blood Specimen Collection*[4]—a complementary document to this guideline—details the requirements for materials, manufacturing, and labeling of blood collection devices.

Additionally, accrediting organizations challenge clinical laboratories to ensure the acceptability or compatibility of their venous and capillary blood collection devices, with their current instrumentation and patient population.[5] This type of verification will help the clinical laboratories ensure accurate and precise test results for their collection device and test system.

Key Words

Capillary blood collection, instrumentation, validation, venous blood collection tubes, verification

Validation and Verification of Tubes for Venous and Capillary Blood Specimen Collection; Approved Guideline

1 Scope

This document provides step-by-step recommendations for validation and verification of venous and capillary blood collection devices. Capillary blood collection devices addressed in this document include only microcollection devices (see Section 3.2). It also includes guidance for ascertaining the acceptability/compatibility for clinical performance in chemistry, immunochemistry, hematology, and coagulation. This guideline does not address validation and verification for clinical performance in immunohematology, molecular diagnostics, arterial blood gas analysis, proteomics, or genomics.

The focus and procedures of this document are for quantitative measurement only. For qualitative measurement, the study requires a different study design.

This document is written for manufacturers of venous and capillary blood collection devices; assay/instrument manufacturers; all clinical laboratory personnel; and those who are responsible for acquisition, handling, and use of the equipment described in this document.

2 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 known 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.[6] For specific precautions for preventing the laboratory transmission of all known infectious agents from laboratory instruments and materials and for recommendations for the management of exposure to all known infectious disease, refer to CLSI document M29.[7]

3 Terminology

3.1 A Note on Terminology

CLSI, as a global leader in standardization, is firmly committed to achieving global harmonization wherever possible. Harmonization is a process of recognizing, understanding, and explaining differences while taking steps to achieve worldwide uniformity. CLSI recognizes that medical conventions in the global metrological community have evolved differently in the United States, Europe, and elsewhere; that these differences are reflected in CLSI, International Organization for Standardization (ISO), and Comité Européen de Normalisation (European Committee for Standardization; CEN) documents; and that legally required use of terms, regional usage, and different consensus timelines are all important considerations in the harmonization process. In light of this, CLSI's consensus process for development and revision of standards focuses on harmonization of terms to facilitate the global application of standards and guidelines.

In order to align the use of terminology in this document with that of ISO, the terms *preexamination*, *examination,* and *postexamination* were adopted. For the sake of introduction and to avoid confusion, the subcommittee chose to include the ISO terms parenthetically where the US terms appear. In addition, the term *sample* replaces the term *specimen* where appropriate, and *measurand* replaces *analyte.* The users of

GP34-A should understand that the fundamental meanings of the terms are identical in many cases, and are defined in the guideline's Definitions section (see Section 3.2). The terms in this document are consistent with those defined in the ISO 15189, ISO 17025, and ISO 9000 series of standards.

3.2 Definitions

accuracy (measurement) – closeness of agreement between a measured quantity value and a true quantity value of a measurand (ISO/IEC Guide 99).[8]

additive – in a specimen collection tube, any ingredient that is placed in a collection container to facilitate an intended function (eg, to prevent the blood from clotting or to prevent glycolysis); **NOTE:** Although the container closure is not considered an additive, it may contain or be coated with additives, which, if they come into contact with the specimen, may be considered additives.

analyte – component represented in the name of a measurable quantity (ISO 17511)[9]; **NOTE 1:** In the type of quantity "mass of protein in 24-hour urine," "protein" is the analyte. In "amount of substance of glucose in plasma," "glucose" is the analyte. In both cases, the long phrase represents the **measurand** (ISO 17511)[9]; **NOTE 2:** In the type of quantity "catalytic concentration of lactate dehydrogenase isoenzyme 1 in plasma," "lactate dehydrogenase isoenzyme 1" is the analyte (ISO 18153).[10]

anticoagulant – an agent that prevents coagulation of blood or blood products.

bias – the difference between the expectation of the test results and an accepted reference value (ISO 3534-1)[11]; **NOTE:** If the comparison method is a reference method, then the difference between the two methods measures the trueness of the new method, measured as bias. If the comparison method is not a reference method, then the trueness of the new method cannot be determined. In this case, one refers to the difference simply as a difference, and not bias.

capillary blood – blood obtained by skin puncture or incision that contains a mixture of undetermined proportions of blood from arterioles, venules, and interstitial and intracellular fluids.

clot activator – material used to initiate the clotting mechanism.

comparative tube – blood collection tube currently used by the clinical laboratory.

control tube – any reference tube used as a comparative tube when evaluating a new or substantially modified tube; **NOTE:** In the United States, these tubes must be US Food and Drug Administration (FDA) cleared.

draw – quantity of blood drawn into the venous blood collection tube from a venipuncture; **NOTE:** For testing purposes, the conditions are defined as follows: 101 kPa (760 mm Hg) pressure and 20 °C ambient temperature. The temperature of the blood collected is assumed to be 37 °C.

error (measurement) – measured quantity value minus a reference quantity value (ISO/IEC Guide 99).[8]

expiration date – date after which the product, when stored under recommended conditions, should no longer be used.

glycolytic inhibitor//antiglycolytic agent – agent that inhibits the use of glucose by blood cells.

imprecision – dispersion of independent results of measurements obtained under specified conditions; **NOTE:** It is expressed numerically as standard deviation (SD) or coefficient of variation (CV).

matrix effect – influence of a property of the sample, other than the measurand, on the measurement of the measurand according to a specified measurement procedure and thereby on its measured value (ISO 17511).[9]

measurand – quantity intended to be measured (ISO/IEC Guide 99).[8]

microcollection devices – proprietary systems or kits with matched components that are used to simplify the processes of collection, storage, centrifugation, and separation of the blood constituents less than 1 mL in volume.

order of draw – standardized sequence used during the blood collection process for the filling of the blood collection tubes to minimize carryover of tube additives from tube to tube.

package insert – instructions for use and other information supplied with the material that is not attached to any part of the package (modified from ISO 15197).[12]

precision (of measurement) – the closeness of agreement between independent test results obtained under stipulated conditions (ISO 3534-1)[11]; **NOTE:** Precision is not typically represented as a numerical value but is expressed quantitatively in terms of imprecision—the standard deviation (SD) or the coefficient of variation (CV) of the results in a set of replicate measurements.

repeatability (measurement) – measurement precision under a set of repeatability conditions of measurement (ISO/IEC Guide 99).[8]

repeatability condition (of measurement) – condition of measurement, out of a set of conditions that includes the same measurement procedure, same operators, same measuring system, same operating conditions and same location, and replicate measurements on the same or similar objects over a short period of time (ISO/IEC Guide 99).[8]

reproducibility (measurement) – measurement precision under reproducibility conditions of measurement (ISO/IEC Guide 99).[8]

reproducibility condition (of measurement) – condition of measurement out of a set of conditions that includes different locations, operators, measuring systems, and replicate measurements on the same or similar objects (ISO/IEC Guide 99).[8]

sample – one or more parts taken from a system and intended to provide information on the system, often to serve as a basis for decision on the system or its production (ISO 15189)[13]; **NOTE:** For example, a volume of serum taken from a larger volume of serum (ISO 15189).[13]

specimen (patient) – the discrete portion of a body fluid or tissue taken for examination, study, or analysis of one or more quantities or characteristics to determine the character of the whole.

thixotropic separator gel – inert material that undergoes a temporary change in viscosity during centrifugation; **NOTE:** It has a density intermediate to cells/clot and plasma/serum.

total analytical error – the interval that contains a specified proportion (usually 90%, 95%, or 99%) of the distribution of differences in concentration between the test and reference method; **NOTE 1:** For example, 97.2% of the differences between the test and reference method fell within the limits of ±4 mmol/L; hence, the 95% total analytical error goal was met; **NOTE 2:** Both "total analytical error" and "error of measurement" contain random and systematic effects (EP21).[14]

trueness (measurement) – closeness of agreement between the average of an infinite number of replicate measured quantity values and a reference quantity value (ISO/IEC Guide 99).[8]

uncertainty (of measurement) – non-negative parameter characterizing the dispersion of the quantity values being attributed to a measurand, based on the information used (ISO/IEC Guide 99)[8]; **NOTE 1:** Measurement uncertainty includes components arising from systematic effects, such as components associated with corrections and the assigned quantity values of measurement standards, as well as the definitional uncertainty. Sometimes estimated systematic effects are not corrected for but, instead, associated measurement uncertainty components are incorporated (ISO/IEC Guide 99)[8]; **NOTE 2:** The parameter may be, for example, a standard deviation called standard measurement uncertainty (or a specified multiple of it), or the half-width of an interval, having a stated coverage probability (ISO/IEC Guide 99).[8]

validation – confirmation, through the provision of objective evidence, that requirements for a specific intended use or application have been fulfilled (ISO 9000)[15]; **NOTE 1:** The World Health Organization (WHO) defines validation as "the action (or process) of proving that a procedure, process, system, equipment, or method used works as expected and achieves the intended result" (WHO-BS/95.1793)[16]; **NOTE 2:** In the context of this document, within the clinical laboratory environment, validation is primarily a manufacturer's responsibility to ensure that design goals are met and performance claims are stated.

verification – confirmation, through the provision of objective evidence, that specified requirements have been fulfilled (ISO 9000)[15]; **NOTE 1:** A one-time process completed to determine or confirm test performance characteristics before the test system is used for patient testing; **NOTE 2:** In the context of this document, this is an end-user (clinical laboratory) responsibility to confirm that manufacturer's claims are met on the specific device in its hands, and also that medical needs are met.

3.3 Abbreviations and Acronyms

ACD	acid citrate dextrose
ACTH	adrenocorticotropic hormone
CAL	clinical acceptance limit
CEN	Comité Européen de Normalisation (European Committee for Standardization)
CTAD	citrate theophylline adenosine dipyridamole
CV	coefficient of variation
DRF	data report form
EDTA	ethylenediaminetetraacetic acid
FDA	US Food and Drug Administration
FMEA	failure mode and effects analysis
FRACAS	failure reporting and corrective action systems
ISO	International Organization for Standardization
IVD	*in vitro* diagnostic
SD	standard deviation
WHO	World Health Organization

4 Impact of Blood Collection Tubes on Test (Examination) Performance

Laboratory tests (examinations) can be affected by numerous preanalytical (preexamination) variables, including the material used to manufacture the blood collection tube. Blood collection tubes are not inert containers for blood but have several constituents, including anticoagulants, surfactants, and lubricants for rubber stoppers, clot activators, and separator gels that can potentially interfere with assays.

The components used to manufacture the venous and capillary blood collection tube and the collection technique used to fill this tube are assumed not to contribute to the total error or otherwise degrade the performance of the assays for which the tubes are intended for use.

To ensure there is no contribution to measurand interference, laboratories should review clinical literature[17-30] and evaluation information from blood collection tube manufacturers.

Other than increasing vigilance when inspecting laboratory results and improving the feedback between the clinical laboratory and clinicians, clinical laboratories cannot do much to readily detect blood collection tube problems without looking at population means of their assays. Following population means at regular timed intervals can alert the laboratory of potential problems with blood collection tubes.

4.1 Tube Wall

Laboratory tests (examinations) can be affected by numerous preanalytical (preexamination) variables, including the material used to manufacture the blood collection tube. It is important to determine that the interaction of blood specimens with tube material does not change laboratory results. Historically, evacuated blood tubes were made from soda-lime or borosilicate glass.[31-33] Tubes made from soda-lime were found to release trace elements, particularly calcium and magnesium, into solutions. Glass became the reference material for blood collection by evacuated tubes. Over the past two decades, blood collection tubes made from plastic materials have replaced glass blood collection tubes in the clinical laboratory.[33] Types of plastics that can be used to make blood collection tubes include polyethylene terephthalate, polyethylene, polypropylene, polytetrafluoroethylene, polysiloxane, polyvinyl chloride, polyacrylonitrile, and polystyrene.[33,34] The advantages of plastic tubes include (a) increased shock resistance, (b) tolerance of higher centrifugation speeds, and (c) cost and ease of disposal.[34,35] On the other hand, the use of plastic tubes has potential limitations, such as the increased permeability of plastic compared with glass tubes to the movement of gases.[33] Two types of plastic are commonly used to manufacture plastic blood collection tubes, polypropylene and polyethylene terephthalate.[33,36,37] According to the manufacturers of the blood collection tubes, polyethylene terephthalate is virtually unbreakable and is capable of maintaining a vacuum.[33,36,37] Yet polypropylene maintains a better liquid barrier than polyethylene terephthalate, thereby retaining the liquid anticoagulants and the appropriate concentration in the specimen. Liquid within the polyethylene terephthalate tubes tends to evaporate.[33,36,37] Several studies have compared results obtained with glass and plastic tubes for measurands in clinical chemistry,[34,38,39] endocrinology,[40,41] molecular testing,[42] serology,[42] hematology,[43] and coagulation.[35,44-48] Although statistically significant differences between glass and plastic blood collection tubes were found for some measurands in these studies, none of the differences were clinically significant. It was concluded from these studies that switching from glass to plastic tubes could occur without any changes in the interpretation of the result.

4.2 Closures

Blood collection tubes can be closed using either rubber stoppers or plastic screw caps.

Commonly, the stoppers are made from rubber, such as isobutylene-isoprene or chlorinated isobutylene-isoprene. Rubber stoppers require lubricants for maximum functionality (ie, ease of removal and reinsertion).

Some rubber stoppers used in blood collection tubes were found to contain a plasticizer, tris (2-butoxyethyl) phosphate, which can cause the displacement of some drugs, notably, quinidine, propranolol, lidocaine, tricyclic antidepressants, and several phenothiazine drugs, including fluphenazine and chlorpromazine, from α-acid glycoprotein.[49-51] This results in the redistribution of the drug in blood, causing an increase in drug uptake by red blood cells and a decrease in plasma or serum concentration.[50,51]

Most manufacturers have now reformulated their rubber stoppers with low extractable rubber to minimize or eliminate interference from tris (2-butoxyethyl) phosphate.

Certain metals, such as magnesium, aluminum, and zinc, are used in the manufacturing of rubber stoppers, and it is essential that these metals not be extracted to any significant extent with contact of blood specimens.[52-54]

4.3 Closure Lubricant

The application of lubricants such as silicone oils, fluids, or glycerol to the closures of blood collection tubes is desirable to facilitate insertion and removal of stoppers from blood collection tubes. The lubricants applied to the tube closures not only provide lubricity but also minimize the adherence of red blood cells and clots to the closures that may fall into and contaminate the serum or plasma layer. Glycerol should not be used as a lubricant for blood collection tube closures[55] when blood concentrations of glycerol and triglycerides are measured, because the determination of glycerol is used in both assays. Siliconized stoppers are usually preferred because there is less interference by silicone with assays.

4.4 Surfactants

Surfactants are a common component of many immunoassay reagents.[56,57] Surfactants are used to decrease or eliminate nonspecific adsorption, improve stability of the reagents, or modify the solid-phase surface to render it less hydrophobic, thus minimizing the loss of noncovalently bound antibody.[36,37] High concentrations of surfactants may lead to direct loss of passively adsorbed antibody from the solid phase, among other nonspecific effects.[56,57] Little or no information is published on the concentration of surfactant coated on the inner surface and on the rubber stopper of plastic serum blood collection tubes. Previous reports have shown that silicone-coated collection tubes can interfere with ion-specific electrode determinations of ionized magnesium[58-61] and lithium,[62] causing falsely increased concentrations. In addition, the water-soluble silicone polymer coating the interior of serum separator tubes can interfere negatively with avidin-biotin binding in an immunoradiometric assay for thyrotropin, prolactin, and human chorionic gonadotropin.[63] A common tube surfactant used in blood collection tubes was identified to cause falsely elevated triiodothyronine and other measurands in a dose-dependent manner.[64] This surfactant, used for coating the interior of the blood collection tubes, is a member of a family of nonionic silicone surfactants that contain hydrophilic polyoxyalkylene chains. Typically, they exist as homopolymers or copolymers of polyoxyethylene and polyoxypropylene and are attached to a hydrophobic polydimethylsiloxane backbone.[65-68] The molecular structure of the surfactant can be either comb-like, with the polyoxyalkylene chain side grafted on a polydimethylsiloxane backbone, or linear, arranged with either the AB- or ABA-type configuration, with A representing a polyoxyalkylene hydrophile and B a polydimethylsiloxane hydrophobe.[65-68] The polydimethylsiloxane moiety of the surfactant adsorbs to hydrophobic surfaces, such as the plastic (ie, polyethylene terephthalate) in blood collection tube walls, whereas the hydrophilic, polyalkylene oxide moiety faces outward toward the specimen and prevents erythrocyte adherence.[36,65-68] When present in excess amounts in blood collection tubes, this surfactant causes interferences by desorbing the capture antibody. Other studies have shown that silicone formed a complex with C-reactive protein that enhanced the antigen-antibody reaction in this assay and falsely elevated results.[69]

NOTE: It is important to follow the tube manufacturer's recommendations to fill the product to the respective label draw volume to ensure proper additive-to-blood ratios, thus minimizing potential assay interference.

4.5 Clot Activators

Blood collected in venous blood collection tubes and microcollection devices, for the generation of serum, should form a dense clot as rapidly and completely as possible to facilitate clear separation of the

clot from the serum layer by centrifugation.[70] Typically, glass collection tubes do not require clot activators, because the contact of blood with the glass surface initiates clotting. However, plastic tubes require the presence of clot activators, such as diatomaceous earth, particles of inorganic silicates, or biochemicals such as ellagic acid, thrombin, and thromboplastin.[36,37] Some blood collection tubes employ either a carrier, such as polyvinylpyrrolidone,[36] or plastic beads to allow the activator to function. Occasionally, clot activator particles may not pellet completely with the clot in some samples and may thus remain in the serum layer, causing interferences with some assays.[62]

NOTE: It is important to follow the tube manufacturer's recommendations to fill the product to the respective label draw volume to ensure proper additive-to-blood ratios, thus minimizing potential assay interference.

4.6 Anticoagulants

In order to prevent blood from clotting, anticoagulants are used to obtain plasma and whole blood specimens. The most commonly used anticoagulants are ethylenediaminetetraacetic acid (EDTA), heparin, and sodium citrate. Anticoagulants added to specimens in appropriate concentrations to preserve certain measurands may cause problems with the assay of other measurands, frequently by interfering with binding or precipitation of the antigen-antibody complex.

EDTA is a chelating agent that binds calcium and prevents clot generation. It is the anticoagulant of choice for hematology testing. Owing to its chelating properties, EDTA can interfere with some assays. For instance, it can bind metallic ions, such as europium (which is present in immunoassay reagents), or zinc and magnesium, which are cofactors for enzymes used also as immunoassay reagents (such as alkaline phosphatase).[71] Because of this, the blood-to-EDTA ratio is critical for optimal test (examination) results. Elevated EDTA levels in a sample-reagent mixture due to insufficient sample volume can result in the more efficient chelation of magnesium and zinc, and can affect the activity of the alkaline phosphatase enzyme label used in chemiluminescence assays, such as intact parathyroid hormone[72] and adrenocorticotropic hormone (ACTH) measurements.[71] Many proteins contain divalent cation binding sites, and reagent antibodies recognize the configuration held by the cation complex (principally, calcium and magnesium).[49,71] Thus, without these cations, the conformation may change, so the recognition by the antibody may become less efficient in affecting test (examination) results.[49,56,71] EDTA in high concentrations can hypertonically shrink red cells and affect red cell size, causing morphological changes.

Heparin acts primarily through a complex that it forms with antithrombin III.[49,56,71] This complex accelerates the inhibition of thrombin and activated Factor X to prevent clotting or activation of thrombin, which, in turn, prevents the formation of fibrin from fibrinogen. Heparin may interfere with some antibody-antigen reactions.[49,56,71] The use of heparin decreases the rate of reaction of some antibodies, particularly at the precipitation step in second-antibody systems; however, the use of solid-phase systems has minimized this problem.[49,56,71] Heparin can precipitate cryofibrinogen; therefore, this anticoagulant should not be used for cryoprotein investigation.[49,56,71] The influence of exogenously administered heparin on serum levels of thyroid hormones and other measurands was investigated.[49,56,71] Heparin was shown to cause *in vivo* stimulation of lipoprotein lipase with subsequent release of nonesterified fatty acids.[49,56,71] The nonesterified fatty acids inhibited the binding of radiolabeled thyroxine to thyroid-binding globulin with an apparent increase in the thyroxine result.[49,56,71]

Sodium citrate is another calcium chelating agent and is the anticoagulant of choice for coagulation testing (refer to CLSI document H21[73] for additional details). It acts as an inhibitory agent for certain enzymes (aspartate aminotransferase and alkaline phosphatase). Sodium citrate is also a component of other anticoagulants, such as acid citrate dextrose (ACD) and citrate theophylline adenosine dipyridamole (CTAD).

Potassium oxalate is another anticoagulant used to chelate calcium. Potassium oxalate causes shrinkage of erythrocytes by drawing water from the cells into the plasma, thus causing a reduction in hematocrit values by as much as 10%. Oxalate also inhibits several enzymes, such as acid and alkaline phosphatase, amylase, and lactate dehydrogenase.[74] The most common application of potassium oxalate is as an anticoagulant used in conjunction with antiglycolytic additives.

A subset of anticoagulants includes antiglycolytic agents, such as sodium fluoride and sodium iodoacetate.

Sodium fluoride inhibits the enzyme systems involved in glycolysis, resulting in the preservation of, for example, glucose and alcohol. Samples collected into tubes containing sodium fluoride may be unsuitable for some enzymatic immunoassay methods due to inhibition of the enzyme activity by fluoride.[74]

Sodium iodoacetate inhibits creatine kinase and appears to have no other significant effects on clinical tests (examinations).[74]

Owing to the anticoagulant and antiglycolytic properties, plasma generated from specimens collected with particular anticoagulants and antiglycolytic agents may not be used for certain assays. Assay manufacturers should specify the source of plasma validated for use with their systems. The clinical laboratory should also verify the performance of plasma tubes on their assay and instrument platform.

NOTE: It is important to follow the tube manufacturer's recommendations to fill the product to the respective label draw volume to ensure proper additive-to-blood ratios, thus minimizing potential assay interference.

Many additives used today are used in a spray-dried form found on the tube walls; however, some are still used in their liquid state. Liquid additives can lead to specimen dilution, which does not cause an interference, but could affect measurand recovery, reference intervals, and medical decision points.

4.7 Separator Gel

Separator gels are widely used in blood collection tubes to separate serum from clotted whole blood or plasma from cells. Usually, the separator gel is made from materials such as viscous liquid,[37,62,65] fillers,[37,62,65] or tackifiers.[37,62,65] It is well known that the separator gel in some serum separator tubes can bind to and decrease the concentration of certain hydrophobic drugs, leading to falsely low results.[50,75-81] Pieces of separator gel or droplets of oil may be seen on or within the separated serum in some gel-containing blood collection tubes. The gel or oil droplets can interfere with the sample probe, coat tubes, and cuvettes, and cause physical interference with binding in the solid phase immunoassay systems.[49,56,71] It is important to follow the tube manufacturer's recommendation by not using the tubes at excessive temperature, inappropriate centrifugation speeds, or unusual orientation, to minimize the assay interference from separator gels.[49,56,71]

4.8 Trace Metals

Trace metal contamination is a problem for blood specimens tested for trace metals. Studies have shown that some evacuated blood collection tubes contribute trace elements to blood.[82-84] Some tube manufacturers offer collection tubes specifically designed for trace metal analysis.

5 Validation and Verification of Venous Blood Collection Tubes

5.1 Preanalytical (Preexamination) Considerations

Many variables can affect the accuracy of a laboratory test (examination) result. These variables are considered preanalytical (preexamination), analytical (examination), or postanalytical (postexamination) variables. Preanalytical (preexamination) variables occur from the time a test (an examination) is ordered until it is analyzed. Analytical (examination) variables occur during testing, while postanalytical (postexamination) variables pertain to result reporting.

Preanalytical (preexamination) variables can be further classified as those that occur before collection, during collection, or after collection (see Table 1).

Table 1. Preanalytical (Preexamination) Variables

Before Blood Collection	During Blood Collection	After Blood Collection
• Proper patient identification • Incorrect tube additive for test • Improper storage conditions • Patient-related variables (eg, age, sex, medications) • Venipuncture site selection • Venipuncture site preparation • Incorrect collection system • Incorrect time of collection	• Prolonged tourniquet time • Improper phlebotomy technique • Improper tube mixing • Incorrect draw volume • Incorrect order of draw[86]	• Incorrect handling of gel separator tubes • Interfering substances • Improper transport • Delay in processing • Exposure to light • Incorrect use of pneumatic tube systems • Incorrect centrifugation speeds and times • Tube-instrument incompatibility

When performing a comparative tube evaluation, it is recommended to follow the tube manufacturer's instructions for use so these variables can be managed properly.[85] Furthermore, this can be accomplished by standardizing phlebotomy, processing, handling, and testing procedures, and ensuring that all employees are trained properly beforehand. For additional details, refer to CLSI documents H01,[4] H03,[86] H18,[87] and H21.[73]

5.2 Determining the Need for Validation and Verification

5.2.1 Risk Analysis

Errors can affect the quality of laboratory test (examination) results. A high level of variability exists with regard to the user, eg, skill and knowledge level, the type of specimen, and the environment. It was estimated that 32% to 75% of laboratory errors occur in the preanalytical (preexamination) phase,[88] which makes blood collection a risk for varying degrees of error. Currently, no mechanism exists to evaluate systematically the influence of preanalytical (preexamination) variables on laboratory test (examination) results. Mentioned below are two tools that can be used to assess risk.

Failure mode and effects analysis (FMEA) is a systematic review of an instrument system or process that examines how failures can affect the instrument system or process. Failure reporting and corrective action systems (FRACAS) is a process whereby a system is tested and failures are observed and classified by severity and frequency of occurrence.

A manufacturer conducts FMEA ideally at the start of product design. The purpose of FMEA is to brainstorm potential errors and to ensure that control measures are implemented in the design. A manufacturer performs FRACAS after initial design but before release to correct the errors.

A clinical laboratory conducts FMEA before an assay or instrument system is implemented. A clinical laboratory conducts FRACAS after an assay is implemented to correct observed errors.

For manufacturers and users (eg, clinical laboratory), FMEA and FRACAS are important techniques to prevent failures. Their use is recommended as follows:

Site	Phase	FMEA	FRACAS
Manufacturer	Product design	√	
	Product testing		√
Clinical laboratory	Product evaluation	√	
	Product in use		√

5.2.2 Accreditation

As part of the accreditation process, some accreditation agencies require documentation that blood collection tubes do not adversely affect preanalytical (preexamination) performance. Laboratories can document this via a combination of direct testing, review of clinical literature, and evaluation of information from tube and instrument/assay manufacturers. Users should consult their local accreditation agencies for specific requirements.

5.2.3 Regulatory Requirements

Facilities should consult regional, national, and local regulatory agencies for current applicable requirements.

5.3 Clinical Evaluation—Planning, Designing, and Conducting the Clinical Evaluation

Whenever a tube manufacturer brings a new or substantially modified blood collection tube to market, analytical and clinical studies are needed to ensure safety and efficacy of the devices. Similarly, when releasing a new or substantially modified assay or instrument, assay or instrument manufacturers need to verify the performance of blood collection tubes with their assay or instrument.

When the clinical laboratory changes a tube within its portfolio (eg, gel, additive, or when changing to a different vendor's tubes), it is recommended that a comparative tube evaluation be performed. A tube comparison study helps determine if the tubes evaluated result in an acceptable performance. If the tubes are found unacceptable, laboratorians are advised to contact their respective tube, assay, or instrument manufacturer for more information. (Refer to Appendix A for a sample protocol for user evaluation of evacuated venous blood collection tubes.)

In order to produce accurate test (examination) results, however, the protocol for a tube comparative study must be properly designed and implemented. A number of important steps should be considered during the design of the study. These steps are important in order to achieve quality test (examination) results.

To assess the trueness of all of the assays required, a method comparison similar to that described in CLSI document EP09[89] is conducted whenever possible. Sample size can vary based on the measurand(s) chosen for evaluation. Some considerations to keep in mind when determining the minimum sample size for any experiment evaluating new tubes are:

- Assay variability
- Analytical measurement range
- Desired statistical power for the study
- Study acceptance criteria

The goal is to demonstrate that difference between assay results under the new tubes compared with control tubes is not excessive. Differences and confidence intervals for difference in the vicinity of clinically important points such as cutoffs are calculated. Applicable guidelines may be chosen to determine what is acceptable.

For precision, compare variability of results from samples collected in evaluation tubes (multiple lots) with the variability of results for samples collected in the control tubes (duplicates).

5.3.1 Manufacturer's Validation Studies

Below is a series of steps to consider when designing tube validation studies by the tube manufacturer.[85]

(1) Design the study to meet local regulatory requirements.

(2) Create a protocol that addresses study design, including acceptability criteria and human subject protection. Always follow local human subject protection policies and procedures.

(3) Establish a familiarization period for health care participants with the protocol and other study-related procedures. Some of these procedures include, but are not limited to, the collection and processing of specimens; the manufacturer's requirements to ensure the proper handling of tubes; and the quality control, calibration, and maintenance required for the instruments used in the study.

(4) Collect and handle specimens according to the manufacturer's instructions for use. In addition, abide by those procedures mandated by the local safety agency for the handling and disposing of sharps and other related medical devices. Always employ standard precautions (see Section 2). Ensure that preanalytical (preexamination) variability is minimized (see Section 5.1).

(5) For trueness, tube manufacturers should obtain an appropriate number of samples, evenly distributed throughout the analytical measurement range of measurands evaluated that will provide sufficient power to conduct one or more statistical analyses of the data. Sometimes, it is not possible to obtain specimens from a particular portion of the analytical measurement range. "Spiking" of samples may be necessary to achieve the needed analytical measurement range of each measurand.

Perform analysis of each measurand on a minimum of two different instrument platforms, if possible, addressing two different measurand methodologies. (**NOTE:** While it is impractical for tube manufacturers to test their tubes on all the various assay platforms, the tested platforms should be noted in the validation documentation.) Multiple measurands can be assessed simultaneously. The total number of measurands included in the objectives of the validation depends on the intended use of the blood collection device. The manufacturer can select representative assays for this purpose. The list of selected assays is determined in conjunction with the regional regulatory agency and the rationale appropriately documented.

(6) To check for lot-to-lot variability, tube manufacturers should test three different lots of evaluation tubes and duplicate control tubes from each subject (five tubes per subject) with different testing methodologies (eg, ion-specific electrode, immunoassay, spectrophotometry), if applicable. Duplicate control tubes are needed to estimate the control tube variability. For within-tube

precision, perform triplicate analyses on each control and evaluation tube. Both objectives can be achieved using specimens from a minimum of 20 apparently healthy subjects.

(7) Create a randomization collection schedule to remove collection order bias (vary the sequence of collection of control and evaluation tubes per subject using the established order of draw criteria per CLSI document H03[86]). Also, randomize the analysis schedule to minimize potential analytical bias due to specimen carryover or drifts.

(8) Analyze each specimen within the defined period of analysis. Ensure that both the control and evaluation tubes are analyzed within the same run. This minimizes instrument and within-laboratory variability.

(9) Perform a preliminary examination of the data as they are generated to detect outliers (between the evaluation and comparative tubes and, if available, within the same tube). Follow recommendations provided in CLSI document EP09[89] and a statistical guidance document[90] to assess outliers.

(10) For specific sample stability claims, stability studies are needed to substantiate the claims. If possible, incorporate this with Step 6 mentioned earlier. If not possible, test a minimum of 20 samples.

(11) Perform data management per regulatory standards, if applicable.

(12) Perform data analysis (see Section 5.4).

NOTE: Evaluation of capillary devices may not be required by certain regulatory agencies; however, manufacturers need to ensure safety and efficacy of these devices before release to the market using simplified analytical and clinical study approaches.

5.3.2 End-User Verification Studies

The total number of assays performed for verification studies will vary by intended use of the blood collection device. Laboratories may select representative assays from different testing methodologies (eg, ion-specific electrode, immunoassay, spectrophotometry). The goal of this study is to demonstrate comparable levels of difference and imprecision in diagnostic assay results for new and currently used devices. When results are discordant, laboratorians should contact manufacturers to further investigate.

Before marketing a new collection device, manufacturers must demonstrate safety and efficacy through analytical and clinical studies. Although it is impractical for manufacturers to test their products on all assay platforms, they should ensure process consistency in the quantity and quality of tube components and additives. Manufacturers should also evaluate new or substantially modified tubes under conditions of maximal interference (eg, reduced specimen volumes and extended contact time with the tube components). Analysis of tube stability is needed to determine appropriate storage and lifetime of the collection device. In addition, the impact of blood collection tube components on clinical assays is considered in the context of the total allowable error; hence, tube components should not increase the total allowable error for a clinical assay, thus invalidating the usefulness of the assay. Similarly, when releasing a new assay or instrument platform, manufacturers should verify performance of blood collection tubes with their diagnostic assay or instrument.

Below is a series of steps to consider when designing tube verification studies in the clinical laboratory (see CLSI document EP15).[91] The scale of the study should be dependent upon the size and complexity of the facility's throughput and the laboratory's capabilities.

Design the study to meet all applicable international, national, local, organizational, and accreditation requirements. If users choose to use products for applications other than those claimed by the manufacturer, the user must validate the product for that use.

NOTE: It is impossible for manufacturers to evaluate all measurands on all instrument platforms. (Refer to CLSI document EP09[89] and CLSI document EP10[92] for additional information.) Also, laboratories that receive specimens in tubes from multiple manufacturers should verify tubes from each manufacturer.

(1) Create a protocol that addresses study design, including acceptability criteria and human subject protection. Always follow the institution's Institutional Review Board or International Ethics Committee policies and procedures.

(2) Establish a familiarization period for health care participants with the protocol and other study-related procedures. Some of these procedures include, but are not limited to, the collection and processing of specimens, the manufacturer's requirements to ensure the proper handling of tubes and the quality control, calibration, and maintenance required for the instruments used in the study.

(3) Collect and handle specimens according to all applicable requirements. In addition, abide by those procedures mandated by the local safety agency for the handling and disposing of sharps and other related medical devices. Always employ standard precautions (see Section 2).

(4) For trueness, laboratories should obtain an appropriate number of samples, evenly distributed throughout the analytical measurement range of measurands evaluated that will provide sufficient power to conduct one or more statistical analyses of the data. It is not always possible to obtain specimens from a particular portion of the analytical measurement range. Multiple measurands can be assessed simultaneously. "Spiking" of samples may be necessary to achieve the needed analytical measurement range of each measurand. The total number of measurands for verification depends on the intended use of the blood collection device. Based on the laboratory's risk analysis and requirement from the local accreditation agencies, the laboratory can select representative assays for this purpose. The list of selected assays is determined by the institution and the rationale appropriately documented.

(5) For within-tube precision, perform duplicate analyses on each type of comparative and evaluation tube. This can be achieved using specimens from a minimum of 20 subjects or by performing duplicate testing in the accuracy study.

(6) Create a randomization collection schedule to remove collection order bias. (Vary the sequence of collection of comparative and evaluation tubes per subject using the established order of draw criteria per CLSI document H03.[86]) Also, randomize the analysis schedule to minimize potential analytical error due to specimen carryover or drifts.

(7) Analyze each specimen according to the laboratory's standard operating procedure. Ensure that both the comparative and evaluation tubes are analyzed within the same run. This minimizes instrument and within-laboratory error. If possible, avoid storing specimens unless sample stability is evaluated. It is recommended that each institution ensures sample stability as part of their operating procedures. For more information related to analyte stability, refer to CLSI documents H03,[86] H04,[93] H18,[87] and H21,[73] and the applicable manufacturer's package insert.

(8) Perform a preliminary examination of the data as they are generated to detect outliers (between the evaluation and comparative tubes and, if available, within the same tube) (see CLSI document EP09).[89] Follow recommendations in CLSI document EP09[89] and a statistical guidance document[90] to assess outliers.

(9) Record the data and check for acceptability based on previously established criteria.

(10) Determine if the number of results is adequate and the range of results is acceptable.

(11) Perform data analysis (see Section 5.4).

NOTE: Evaluation of capillary devices is not a standard of practice; however, it is suggested that laboratories ensure preanalytical (preexamination) performance of these devices in their institutions before use, applying practical analytical and clinical study approaches.

5.4 Data Analysis

The goal of the evaluation should be to demonstrate that using the tubes under study results in an acceptable performance. In other words, show that using the new tubes does not increase the total error (defined as the combination of bias and imprecision) or otherwise degrade the performance of the assays for which the tubes are intended.

Upon completion of the assessment conducted on the new blood collection tube, laboratories can use the following data analysis measures to assess the concordance between results: implications of diverging from the manufacturer's guidance for tube processing and handling; lot-to-lot variability; and an audit program to look at lot changes over time.

Record the data in a logical manner, allowing the ability to plot and assess the data both visually and statistically for relative linearity, adequate range, and uniform scatter. Based on the results of the data examination, several statistical methods can be used to estimate the expected bias and the confidence interval for that bias.

5.4.1 Method for Analysis of Trueness

If single tubes are used, create an X, Y scatter plot with the results obtained from the currently used tube on the horizontal axis (X), vs the results from the same patient, gathered using the type of tube evaluated on the vertical axis (Y), and a line drawn with a slope of one going through the origin. If duplicate tubes are obtained, see CLSI document EP09.[89] For additional types of data presentation such as Bland-Altman plots, see CLSI document EP09.[89]

Apply linear regression analysis of Y vs X to estimate the slope (proportional error) and intercept (constant error) with 95% confidence intervals. Use a regression method appropriate for the error structure in the data and taking into account duplicate tubes, if obtained (see CLSI document EP09[89]).

Obtain an average difference with 95% confidence intervals from a regression method to judge the magnitude of the average systematic difference at clinical decision levels as determined by the medical director or designee of the institution.

If a constant difference (systematic difference) is observed throughout the analytical measurement range and differences at clinical decision levels are similar, a method to estimate a systematic difference (bias) that is valid throughout the range can be used, such as a two-sided confidence interval from a paired t-test.

5.4.2 Method for Analysis of Precision

For the tube manufacturer (validation), the data obtained from the evaluation tube can be used to estimate the within-tube (repeatability) and lot-to-lot standard deviation (SD) using a variance component additive model from a statistical software package. Similarly, the data obtained from the control tube can be used

to estimate the within-tube (repeatability) and tube-to-tube (if only one lot is used) or lot-to-lot (if two lots are used) SD. An example of a method for analysis of precision is provided in Appendix B.

For the end-user verification, repeatability SDs for each of the evaluated tubes and comparative tubes are derived from the following formula:

$$S_r = \sqrt{\frac{\sum_{i=1}^{N}(y_{i1} - y_{i2})^2}{2N}}, \quad (1)$$

where
N = total number of subjects,
y_{i1} = result for replicate 1 of subject i,
y_{i2} = result for replicate 2 of subject i.

For comparing the repeatability in the evaluation and control tubes, the ratio of the evaluation tube SD squared to the control tube SD squared, with 95% confidence interval, may be calculated:

$$\left(\frac{s_r^2(evaluation)}{s_r^2(control)} F_{.025}^{(N,N)}, \frac{s_r^2(evaluation)}{s_r^2(control)} \frac{1}{F_{.025}^{(N,N)}} \right), \quad (2)$$

where
$F_{.025}^{(N,N)}$ represents the 2.5th percentile of an F distribution with N and N degrees of freedom (for example, $F_{.025}^{(20,20)} = 0.4058$). A ratio of 1 suggests equality between evaluation and control tube repeatability.

If the within-subject repeatability is dependent on the size of the measurements, the above-mentioned calculations could be inaccurate. An approach that may be used to address this problem is to perform the SD calculations in equation (1) with the natural log-transformed data.[94] If SD is the SD of the natural log-transformed variable, an approximation to the percent CV is obtained as $100 \times \sqrt{\left(e^{s_r^2} - 1\right)}$. Alternatively, the range may be subdivided into regions analyzed separately; however, sample size in each region will be reduced unless additional data are collected.

5.5 Clinical Acceptance Criteria

Do not rely solely on statistical significance. Sometimes, there are circumstances in which a statistical significance is detected when there is no clinical significance. Conversely, a possible clinically significant difference may not be statistically significant. (For example, a larger than expected variation may result in a confidence interval for a difference overlapping both zero and the clinical acceptance criteria.)

Clinical acceptance criteria are used to determine if the performance of a tube is acceptable for use in a clinical setting. This performance can be evaluated by applying acceptance limits within which a test result is likely considered clinically equivalent. These acceptance limits are determined by the laboratory staff or clinicians in each institution in conjunction with their medical staff or technical literature.

Some examples of acceptance criteria are:

- Evaluation of data using the formula for imprecision of replicates
- Biological variation for a measurand
- Published data

Clinical acceptance criteria can also be used to assess the clinical performance of new blood collection tubes as compared with a predicate device by tube manufacturers.

Two blood collection tubes are considered clinically equivalent when the difference in their performance is not likely to affect health care decisions on diagnosis or patient management. If the clinical acceptance criteria are not met, review the results to assess the medical risk of the nonequivalence. The outcome of this review is used to document tube validation, verification, and implementation.

6 Conclusion

Numerous preexamination variables, including the material used to manufacture the blood collection tube, may affect laboratory examinations. Therefore, laboratories should evaluate venous and capillary blood collection tubes to ensure there is no contribution to measurand interference or impact on examination performance.

The information presented in this document should be considered by laboratories and tube manufacturers before conducting these types of clinical evaluation studies.

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Appendix A. Sample Protocol for User Evaluation of Evacuated Venous Blood Collection Tubes

A1. How to Use This Protocol

Use the following steps to determine the design of the user assessment, and then use either the generic protocol as a template for a more formal record of the evaluation or the sample checklist provided as Table A1 to capture the essence of the evaluation.

(1) Select the subject groups of interest for testing. For example, consider a mixture of the following:

- Samples for emergency testing
- Samples from particular patient populations, eg, dialysis patients
- Apparently healthy subjects with values within the normal reference interval
- Subjects with pathological values outside the normal reference interval

NOTE: Select subjects to cover a clinically meaningful range for the measurand.

(2) Select measurands of interest for testing.

(3) Consider whether any visual observation of the sample is recorded.

NOTE: Observations such as serum yield, gel barrier formation, fibrin, and hemolysis may be of interest.

(4) Choose the instrument(s) and method(s) for use in testing.

(5) Consider use of duplicate or single tubes.

NOTE: Differences exist between plasma and serum values for certain measurands.[1]

- Run one control and one evaluation. With this design, one can determine whether the mean difference between the control and evaluation is acceptable and ideally within predefined criteria.

- Run two controls and two evaluations. With this design, in addition to the comparison of the mean differences, one can compare the variation in both tube designs. This design increases the statistical power, and it is good to use if there are no issues with collecting a larger quantity of blood.

(6) Randomization is an important scientific principle that is applicable to all aspects of evaluations. For example, it is important to ensure that the order of tube collection is randomized. If the same tube is always drawn first, it may contain lysed cells due to the initial trauma of the venipuncture that could lead to elevated potassium results or other deviations. An example of this randomization is as follows:

Subject	1st Tube	2nd Tube
One	Control Tube	*Evaluation Tube*
Two	*Evaluation Tube*	Control Tube
Three	Control Tube	*Evaluation Tube*

Appendix A. (Continued)

(7) The purpose of the evaluation is to understand how much the blood collection tube affects the test (examination) results. To achieve this, it is important that the preanalytical (preexamination) variables are standardized for all tubes collected and blood samples analyzed. For example, standardize variables such as blood collection procedures, mixing, transportation of the blood to the laboratory, and centrifugation as far as possible.

(8) One may be interested in the effect of time on the measurand for each tube type. For example, some samples are stored under refrigeration. Whenever considering the testing over a time period, ensure that the tube manufacturers' instructions for use or literature on the stability of samples are referenced.

(9) Determine the number of subjects required. For statistical validity, typically 20 to 30 subjects are sufficient for most measurands. Some agencies provide guidance on this, such as the US Food and Drug Administration (FDA) and the World Health Organization (WHO), where 40 subjects is the norm.

(10) Determine whether informed consent or ethics committee approval is required at the institution. For this type of user evaluation, there may already be approval under any general agreement the institution has for method comparisons or other laboratory-based evaluations with the institution. Ensure compliance with applicable regulations.

(11) Determine the clinical acceptance limit (CAL) for the selected measurands. CALs can be generated based on:

- Discussions with institutions
- External journal publications
- Laboratory medicine textbooks
- Data and consensus from international scientific conferences and opinion groups
- Expert medical opinion

(12) Enter the details of the patient population, instrument, method, or sample size that is used during the evaluation into the evaluation design (see Table A2).

(13) Enter the details of the specimen collection devices used in Table A3.

(14) Use the evaluation method suitable as determined by the institution or laboratory director.

(15) Create the appropriate data report forms (DRFs). (See Table A4 for an example.)

(16) When analyzing the blood sample, maintain the randomization created for the blood draw for the analysis on the instrument. As with the preanalytical (preexamination) variables, it is important to ensure that the analytical (examination) variables are also standardized. For example, test both control and evaluation specimen collection devices in the randomized order on the same run/batch using the same instrument, reagent lot, and calibration settings. Run quality control materials before and after testing.

(17) Record the data on the DRF.

(18) Analyze the data.

Appendix A. (Continued)

Table A1. Sample Evaluation Checklist

<table>
<tr><td colspan="2">Tube for: _____
Compiled by: _____ Date:_____</td></tr>
<tr><td>Control tube lot number:
Evaluation tube lot number:</td><td>Control tube product number:
Evaluation tube product number:</td></tr>
<tr><td>Control tube expiration date:
Evaluation tube expiration date:</td><td>Control tube draw volume:
Evaluation tube draw volume:</td></tr>
<tr><td>One or two control tubes/subject?</td><td>One or two evaluation tubes/subject?</td></tr>
<tr><td>Pathological samples?</td><td>Number of subjects:</td></tr>
<tr><td>Phlebotomy device: Needle/line/wing set</td><td>Draw order randomized?</td></tr>
<tr><td colspan="2">Tourniquet application time (CLSI recommendation < 1 minute[2]):</td></tr>
<tr><td>Number of inversions for control:
Tube manufacturer recommendation</td><td>Number of inversions for evaluation:
Site recommendation or tube manufacturer recommendations</td></tr>
<tr><td>Minimum clotting time for control:
Tube manufacturer recommendation</td><td>Minimum clotting time for evaluation:
Site recommendation or tube manufacturer recommendations</td></tr>
<tr><td rowspan="2">Centrifugation:
Time _____
Speed _____
Temperature _____</td><td>Tube manufacturer recommendations: List and recommendation</td></tr>
<tr><td>Centrifuged within two hours of collection?</td></tr>
<tr><td colspan="2">Visual analysis for fibrin/hemolysis/barrier formation?</td></tr>
<tr><td>Instrumentation:</td><td>Specimen storage temperature?</td></tr>
<tr><td>Method:</td><td>Tested within two hours of centrifugation?</td></tr>
<tr><td>Reagents:</td><td>Fresh or frozen specimen?</td></tr>
<tr><td>Cap piercing or open tube?</td><td>Primary tube sampling or aliquot?</td></tr>
<tr><td>Stability testing time points:</td><td>Singlet or replicate testing?</td></tr>
<tr><td colspan="2">Measurands tested and CALs:</td></tr>
<tr><td colspan="2">When analyzing the blood sample, maintain the randomization created for the blood draw for the analysis on the instrument. As with the preanalytical (preexamination) variables, it is important to ensure that the analytical (examination) variables are also standardized. For example, test both control and evaluation specimen collection devices in the randomized order on the same run/batch using the same instrument, reagent lot, and calibration settings. Run quality control materials before and after testing.</td></tr>
<tr><td colspan="2">Comments:</td></tr>
</table>

Appendix A. (Continued)

Table A2. Evaluation Design Overview

Evaluation Design Overview				
Measurand	**Number of Subjects**	**Testing Time Points***	**Instruments Used**	**Method**

*Testing time points should be in accordance with CLSI document H03.[2]

Table A3. Details of the Specimen Collection Devices

Blood Collection Tubes			
Tube Type	**Reorder Number**	**Lot Number**	**Expiration Date**
Collection Tube 1			
Collection Tube 2			
Collection Tube 3			
Collection Tube 4			
Collection Tube 5			

Appendix A. (Continued)

Table A4. Example of Data Report Form

Clinical Data Analysis							
Hospital Name							
Investigator Name							
Date							
Control Tube	Description						
Evaluation Tube	Description						
Stability Time Points							
Stability Temperature							
Instrument							
		CAL	0.5	20%			
		Units	mmol/L	U/L			
Sample number	Tube	Time point	K*	LDH†	Measurand 3	Measurand 4	Measurand 5
1	Control	T0					
2	Control	T0					
3	Control	T0					
4	Control	T0					
5	Control	T0					
6	Control	T0					
7	Control	T0					
8	Control	T0					
9	Control	T0					
10	Control	T0					
1	Control	T24					
2	Control	T24					
3	Control	T24					
4	Control	T24					
5	Control	T24					
6	Control	T24					
7	Control	T24					
8	Control	T24					
9	Control	T24					
10	Control	T24					
1	Evaluation	T0					
2	Evaluation	T0					
3	Evaluation	T0					
4	Evaluation	T0					
5	Evaluation	T0					
6	Evaluation	T0					
7	Evaluation	T0					
8	Evaluation	T0					
9	Evaluation	T0					
10	Evaluation	T0					
1	Evaluation	T24					
2	Evaluation	T24					
3	Evaluation	T24					
4	Evaluation	T24					
5	Evaluation	T24					
6	Evaluation	T24					
7	Evaluation	T24					
8	Evaluation	T24					
9	Evaluation	T24					
10	Evaluation	T24					

*K = potassium.
†LDH = lactate dehydrogenase.

Appendix A. (Continued)

NOTE: These protocol guidelines are provided for information purposes only, without warranties of any kind. The laboratory should validate the suitability of these protocol guidelines for its own purposes and requirements.

A2. Purpose

The purpose of this evaluation is to compare the performance of one blood collection tube (control) with that of another blood collection tube (evaluation) for chemistry or hematology, on laboratory instruments.

A3. Scope

This evaluation includes (1) a visual inspection of the physical characteristics of the blood collection tube; (2) analytical (examination) performance of the blood collection tube; and (3) a comparison of the analytical (examination) performance over time.

A3.1 Evaluation of the physical characteristics of the blood collection tube is ordinarily limited to a subjective visual examination of the plasma or serum and the gel barrier formed after centrifugation (where appropriate).

A3.2 Analytical (examination) testing assesses accuracy of the blood collection tube when recovered measurand values are compared with the currently used blood collection tubes.

A3.3 Comparing the measurand values for a particular tube at each of the time points specified with the initial value obtained assesses the analytical (examination) performance over time.

A4. Responsibility

The laboratory is responsible for onsite subject/patient solicitation, informed consent (ensure compliance with applicable regulations), specimen collection, and centrifugation of the collected specimens.

The laboratory is responsible for obtaining sufficient reagents to perform this evaluation on the analytical (examination) systems. The laboratory calibrates all selected methods. When samples are available, the laboratory runs patient samples on the selected instruments, collects the data, and analyzes the data.

A5. Supplies and Equipment

- Standard equipment for phlebotomy procedures (tourniquet, alcohol pads, needles, and holder).
- Draw all other tubes according to a randomization schedule.
- A centrifuge capable of spinning multiple specimens according to the manufacturer's centrifugation instructions.

A6. Subject Selection

Select subjects in accordance with the institutional procedures.

Where appropriate, the subjects must be adults (> 18 years old, approximately one half of the participants should be women and one half should be men).

Appendix A. (Continued)

Attempt to select patients whose results should span a clinically meaningful range. This range may extend beyond the reference interval.

A7. Evaluation Methods

Sample collection, transportation, and processing should be in accordance with the CLSI guidelines.

Below is a suggested evaluation method that may require modification to suit the method followed by the institution.

(1) Document the date and time of venipuncture.

(2) Collect blood samples according to a randomization schedule.

(3) Record any difficulties with the blood collection.

(4) Invert tubes according to the manufacturer's recommendations (see CLSI document H18).[3]

(5) Allow blood to clot according to the manufacturer's recommendations (see CLSI document H18).[3]

(6) Centrifuge tubes according to the manufacturer's recommendations (see CLSI document H18).[3]

(7) At the specified time point, perform the tests as outlined in Table A1.

(8) Perform a visual evaluation as described in the following list:

- Visually examine and document the quality and quantity of the serum/plasma and the gel barrier formed after centrifugation.

- Serum yield: Aliquot the serum into vials of known volume to record the serum yield.

- Barrier formation: The notation of "good" (recorded on DRF as 0) indicates that the gel has migrated to form a barrier of even thickness between the blood cells and serum/plasma. The notation of "poor" (1) indicates a thin and uneven barrier formation. Blood cells entrapped within the barrier have no clinical consequences.

- Hemolysis:

  0 = None.
  1 = Trace (very slight pink coloration of serum – compare with a 0 sample).
  2 = Moderate (definite, clearly visible red coloration – no comparison required).
  3 = Gross (deep red coloration).

  Pass: Ratings of 0 or 1 acceptable. Fail: 2 and 3.

- Fibrin: The notation of "none" (recorded on DRF as 0) indicates that there was no visible formation of fibrin above the gel barrier. The notation of "fibrin" (1) indicates that there was visible fibrin formation above the gel barrier.

Appendix A. (Continued)

(9) Perform measurand analysis.

- Timing of testing: Centrifuge samples within two hours of collection. Conduct sample testing over several days. For example, process 10 samples on day 1 of the evaluation, a second set of 10 subjects on day 2 of the evaluation, and so on.

- Sample processing: Process samples on the instrument system as "primary tube" samples, or transfer an aliquot into a sample cup.

- Maintain the randomization created for the order of draw throughout the sample analysis.

(10) If insufficient sample to complete all testing is obtained from any of the participants, exclude the sample set from the evaluation, select a new subject, then redraw and test samples.

(11) As required by institutional procedures, include quality control activities.

A8. Data Analysis

Perform data analysis as described in Section 5.4 of this document or per institutional policy.

A9. Acceptance Criteria

Establish acceptance criteria as described in Section 5.5 of this document or per institutional policy (refer to CLSI document H01[4] for additional details).

References for Appendix A

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[2] 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.

[3] CLSI. *Procedures for the Handling and Processing of Blood Specimens for Common Laboratory Tests; Approved Guideline—Fourth Edition*. CLSI document H18-A4. Wayne, PA: Clinical and Laboratory Standards Institute; 2010.

[4] CLSI/NCCLS. *Tubes and Additives for Venous Blood Specimen Collection; Approved Standard—Fifth Edition*. CLSI/NCCLS document H01-A5. Wayne, PA: NCCLS; 2003.

Appendix B. Example of a Method for Analysis of Precision[1]

Manufacturer Calculations (includes lot-to-lot variation and within-tube precision)

For direct calculations of between-lot variation (evaluation tubes) and within-tube precision (repeatability), the following quantities are needed:

$$S_r = \sqrt{\frac{\sum_{i=1}^{N}\sum_{j=1}^{L}\sum_{k=1}^{R}(y_{ijk} - \bar{y}_{ij.})^2}{2LN}}$$

$$A = \sqrt{\frac{\sum_{i=1}^{N}\sum_{j=1}^{L}(\bar{y}_{ij.} - \bar{y}_{i..})^2}{N(L-1)}}$$

A = the standard deviation of the lot means,
N = total number of subjects,
L = number of tube lots,
R = number of replicate analyses per tube,
y_{ijk} = result of replicate k, from tube lot j, from subject i,
$\bar{y}_{i..}$ = average of all observations for subject i,
$\bar{y}_{ij.}$ = average of replicates for each lot/subject combination.

The within-tube precision (or repeatability SD) is the quantity S_r :

The between lot SD is obtained from:

$$S_{lot}^2 = A^2 - \frac{S_r^2}{R}$$

The above-mentioned estimate is set to 0 if negative. Setting the (possibly) negative variance components to 0 follows a widely used convention in statistics.

The estimate of the evaluation tube's total precision is then calculated with the following SD formula:

$$S_{EvalTube} = \sqrt{S_{lot}^2 + S_r^2}$$

Below is an example of a method for analysis of precision using 20 subjects.

N = total number of subjects = 20
L = number of tube lots = 3
R = number of replicate analyses per tube = 3

Appendix B. (Continued)

Subject	Lot 1			Lot 2			Lot 3			Subject Averages	Sum of Lot Squared Deviations $\sum_{j=1}^{L}(\bar{y}_{ij.}-\bar{y}_{i..})^2$
	Observations y_{i1k} $i = 1…20$ $k = 1…3$	Average $\bar{y}_{i1.}$	Sum of Individual Squared Deviations $\sum_{k=1}^{3}(y_{i1k}-\bar{y}_{i1.})^2$	Observations y_{i2k} $i = 1…20$ $k = 1…3$	Average $\bar{y}_{i2.}$	Sum of Individual Squared Deviations $\sum_{k=1}^{3}(y_{i2k}-\bar{y}_{i2.})^2$	Observations y_{i3k} $i = 1…20$ $k = 1…3$	Average $\bar{y}_{i3.}$	Sum of Individual Squared Deviations $\sum_{k=1}^{3}(y_{i3k}-\bar{y}_{i3.})^2$		
1	116			120			115				
1	117	117	2	119	119	2	115	115	0	$\bar{y}_{1..}$ = 117	8
1	118			118			115				
2	99			101			100				
2	100	100	2	101	101	0	98	99	2	$\bar{y}_{2..}$ = 100	2
2	101			101			99				
3	104			102			102				
3	104	103	6	102	102	0	101	101	2	$\bar{y}_{3..}$ = 102	2
3	101			102			100				
4	113			115			113				
4	113	113	0	114	114	2	112	112	2	$\bar{y}_{4..}$ = 113	2
4	113			113			111				
5	92			93			90				
5	91	91	2	92	92	2	90	90	0	$\bar{y}_{5..}$ = 91	2
5	90			91			90				
6	98			98			98				
6	98	98	0	98	98	0	98	98	0	$\bar{y}_{6..}$ = 98	0
6	98			98			98				
7	99			101			101				
7	101	100	2	102	2	2	101	101	0	$\bar{y}_{7..}$ = 101	2
7	100			103			101				
8	121			121			123				
8	122	122	2	121	22	6	122	122	2	$\bar{y}_{8..}$ = 123	0
8	123			124			121				
9	100			98			96				
9	99	99	2	98	98	0	97	97	2	$\bar{y}_{9..}$ = 98	2
9	98			98			98				
10	101			101			101				
10	101	101	0	100	101	2	101	101	0	$\bar{y}_{10..}$ = 101	0
10	101			102			101				

Appendix B. (Continued)

Subject	Lot 1 Observations y_{i1k} $i = 1…20$ $k = 1…3$	Lot 1 Average $\bar{y}_{i1.}$	Lot 1 Sum of Individual Squared Deviations $\sum_{k=1}^{3}(y_{i1k} - \bar{y}_{i1.})^2$	Lot 2 Observations y_{i2k} $i = 1…20$ $k = 1…3$	Lot 2 Average $\bar{y}_{i2.}$	Lot 2 Sum of Individual Squared Deviations $\sum_{k=1}^{3}(y_{i2k} - \bar{y}_{i2.})^2$	Lot 3 Observations y_{i3k} $i = 1…20$ $k = 1…3$	Lot 3 Average $\bar{y}_{i3.}$	Lot 3 Sum of Individual Squared Deviations $\sum_{k=1}^{3}(y_{i3k} - \bar{y}_{i3.})^2$	Subject Averages	Sum of Lot Squared Deviations $\sum_{j=1}^{L}(\bar{y}_{ij.} - \bar{y}_{i..})^2$
11	108			108			109				
11	108	108	0	109	109	2	110	110	2	$\bar{y}_{11..} = 109$	2
11	108			110			111				
12	97			98			96				
12	98	97	2	97	97	2	96	97	6	$\bar{y}_{12..} = 96$	0
12	96			96			99				
13	111			111			110				
13	111	111	0	112	112	2	110	110	0	$\bar{y}_{13..} = 111$	2
13	111			113			110				
14	93			95			92				
14	95	94	2	95	95	0	93	93	2	$\bar{y}_{14..} = 94$	2
14	94			95			94				
15	89			88			87				
15	89	89	0	88	88	0	88	87	2	$\bar{y}_{15..} = 88$	2
15	89			88			86				
16	99			101			99				
16	101	100	2	100	101	2	99	99	0	$\bar{y}_{16..} = 100$	2
16	100			102			99				
17	117			117			117				
17	117	117	0	117	117	0	118	117	2	$\bar{y}_{17..} = 116$	0
17	117			117			116				
18	86			90			88				
18	89	88	6	89	89	2	86	87	2	$\bar{y}_{18..} = 88$	2
18	89			88			87				
19	110			103			103				
19	106	107	14	105	105	8	103	103	0	$\bar{y}_{19..} = 104$	8
19	105			107			103				
20	110			109			110				
20	110	111	6	109	109	0	110	110	0	$\bar{y}_{20..} = 110$	2
20	113			109			110				
Sum of Individual Squared Deviations Lot 1			50	Sum of Individual Squared Deviations Lot 2		34	Sum of Individual Squared Deviations Lot 3		26		
Sum of All Individual Squared Deviations $\sum_{i=1}^{N}\sum_{j=1}^{L}\sum_{k=1}^{R}(y_{ijk} - \bar{y}_{ij.})^2 = 110$										Sum of Lot Squared Deviations	$\sum_{i=1}^{N}\sum_{j=1}^{L}(\bar{y}_{ij.} - \bar{y}_{i..})^2 = 42$

Appendix B. (Continued)

$$S_r = \sqrt{\frac{\sum_{i=1}^{N}\sum_{j=1}^{L}\sum_{k=1}^{R}(y_{ijk} - \bar{y}_{ij.})^2}{2LN}} = \sqrt{\frac{110}{2 \times 3 \times 20}} = 0.96$$

$$A = \sqrt{\frac{\sum_{i=1}^{N}\sum_{j=1}^{L}(\bar{y}_{ij.} - \bar{y}_{i..})^2}{N(L-1)}} = \sqrt{\frac{42}{20 \times 2}} = 1.025$$

$$S_{lot} = \sqrt{A^2 - \frac{S_r^2}{R}} = \sqrt{1.05 - \frac{0.9167}{3}} = 0.86$$

The estimate of the evaluation tube's total precision is then

$$S_{EvalTube} = \sqrt{S_{lot}^2 + S_r^2} = \sqrt{0.86^2 + 0.96^2} = 1.29$$

Calculate the control tube variability as mentioned above, with L representing the number of control tube lots tested (eg, L = 2 if two control tube lots are drawn from each subject). If the two control tubes are from the same lot, then the control tube-to-tube variation is of interest and S_{tube} replaces S_{lot} in the above-mentioned formulas.

Reference for Appendix B

[1] CLSI/NCCLS. *Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline—Second Edition.* CLSI/NCCLS document EP05-A2. Wayne, PA: NCCLS; 2004.

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 Delegate Comments and Subcommittee Responses

GP34-P, *Validation and Verification of Tubes for Venous and Capillary Blood Specimen Collection; Proposed Guideline*

General

1. It is impossible to meet the goals of this document in laboratories that are not staffed by MTs/MLTs, and it is not cost effective.

- **The subcommittee recognizes that for smaller laboratories or laboratories with limited qualified technical personnel or monetary resources, verification of blood collection tubes may be challenging. For this reason, recommendations were made in this document to allow laboratories to conduct testing using smaller sample sizes and/or a limited number of measurands.**

2. There is concern that this is too sophisticated for many small laboratories.

- **The subcommittee recognizes that for smaller laboratories or laboratories with limited qualified technical personnel or monetary resources, verification of blood collection tubes may be challenging. For this reason, recommendations were made in this document to allow laboratories to conduct testing using smaller sample sizes and/or a limited number of measurands.**

3. There is a mix of "commentary style" and "instructive style" text. For example, under Section 5.5, the first sentence is an instruction that reads, "Do not rely on statistical significance." For consistency with most of the remainder of the document, "Statistical significance should not be relied on" may be more appropriate. An "instructional" style is used in Sections 5.3.1 and 5.3.2, but this is in the context of a series of defined steps (instructions). Maybe it is not so important. It would be a fairly large task to wade through the whole document to make the changes.

- **The document was reviewed for consistency. Although both "commentary" and "instructional" styles were used, the subcommittee believes its presentation of information is appropriate.**

Section 3.2, Definitions

4. If "order of draw" is considered as an addition to the document, then a brief definition should be included. Provide a definition for "order of draw."

- **A definition for "order of draw" was added. It reads, "standardized sequence used during the blood collection process for the filling of the blood collection tubes to minimize carryover of tube additives from tube to tube."**

Section 4.1, Tube Wall

5. Last sentence – "It was concluded from these studies that switching from glass to plastic tubes could occur without changes in the interpretation of the result." This may be counterintuitive to the whole document. It does not seem to align with the information provided in paragraph 3 of the Foreword. Although the statement is supported by several references, it may be worth considering removal of this sentence, and even those preceding. When I read this paragraph, I gained the impression that CLSI is saying it is OK to rely on the published literature alone when moving from one tube type to another (in this case, glass to plastic, but maybe readers could extrapolate).

- **The information provided is a summary of the current available knowledge. It is not intended as a position statement; therefore, no change was made.**

6. First paragraph, second sentence, "ascertain" – Break down for simplification. Change to "determine."

- **The term "ascertain" was replaced with the term "determine" as suggested.**

7. The sentence lists the laboratory areas that have been studied regarding glass vs plastic collection tubes, but hematology is not listed. Hematology has been studied and could be added here. Revise the text to include hematology in the listing and add the following supporting reference: Van Cott EM, Lewandrowski KB, Patel S, et al. Comparison of glass K3EDTA versus plastic K2EDTA blood-drawing tubes for complete blood counts, reticulocyte counts, and white blood cell differentials. *Lab Hematol.* 2003;9(1):10-14.

- **The text was revised and the reference was added as suggested.**

Section 4.3, Closure Lubricant

8. Third sentence, "Glycerol should not be used..." – This may be a little confusing to readers. The text may need some rewording to explain that glycerol in the tube would contribute to the total triglyceride value.

- **Glycerol used on the stopper can also contribute to analytical error for triglyceride values. Therefore, the text was maintained as originally presented.**

  A supporting reference was added.

Section 4.4, Surfactants

9. NOTE, Sections 4.4 and 4.5 – Manufacturers are now referring to the accrediting agency. State manufacturers and accrediting agency recommendations.

- **The subcommittee is not aware of accrediting agencies making recommendations for handling and processing of blood collection products. Therefore, the text was maintained as originally presented.**

Section 4.6, Anticoagulants

10. First paragraph, second sentence – There are two types of citrates, sodium citrate used for coagulation tests and for erythrocyte sedimentation rate samples in hematology. Also, acid citrate dextrose (ACD) is used in blood banking and also contains sodium citrate. "Citrate" should be replaced with "citrate(s)" or "sodium citrate."

- **The text was revised to read, "The most commonly used anticoagulants are ethylenediaminetetraacetic acid (EDTA), heparin, and sodium citrate."**

11. I am not sure about the relevance of the EDTA commentary. The focus is on the blood to additive (EDTA) ratio in the context of immunoassays susceptible to interference mediated by chelation of metallic cations. I think this does not require detailed (if any) commentary, as EDTA specimens should not be used for these applications, anyway. In my opinion, the focus should be on blood to additive (EDTA) ratio in the context of hematology testing (EDTA artifact such as red cell size variation, cell morphological changes).

- **The following statement was added: "EDTA in high concentrations can hypertonically shrink red cells and affect red cell size, causing morphological changes."**

12. Third paragraph, sixth sentence, "of exogenously" – Break down for simplification. Delete "of exogenously."

- **The subcommittee believes the text is accurate and understandable. Therefore, the wording was maintained as originally presented.**

13. Fifth paragraph on potassium oxalate – It may be worth adding another sentence stating that the most common application of this additive (potassium oxalate) is as an anticoagulant used in conjunction with antiglycolytic additives.

- **The following sentence was introduced in the fifth paragraph of Section 4.6 for clarity:**

  "The most common application of potassium oxalate is as an anticoagulant used in conjunction with antiglycolytic additives."

14. Seventh paragraph on sodium fluoride – It may be appropriate to add a little more detail on the mode of action of sodium fluoride, given the level of detail afforded to EDTA and heparin in the preceding paragraphs. Maybe add a sentence on the glycolytic pathway and enolase inhibition.

- **The subcommittee believes the subject of sodium fluoride is appropriately addressed.**

15. Eighth paragraph on iodoacetate – As for fluoride, it may be worth adding a line on inhibition of glyceraldehyde-3-phosphate dehydrogenase by iodoacetate.

- **The subcommittee believes the subject of iodoacetate is appropriately addressed.**

16. Entire section – Add a comment that certain anticoagulants lead to specimen dilution, which is not caused by interference, but will affect analyte recovery, reference ranges, medical decision points, and so on.

- **The text was revised as suggested. A paragraph was added to end of Section 4.6 for clarification. It reads, "Many additives used today are used in a spray-dried form found on the tube walls; however, some are still used in their liquid state. Liquid additives can lead to specimen dilution, which does not cause an interference, but could affect measurand recovery, reference intervals, and medical decision points."**

Section 5.1, Preanalytical (Preexamination) Considerations (formerly Preexamination Considerations)

17. This document uses the terminology "examination" rather than "analytical" (eg, preexamination). Other CLSI documents and published quality practice papers more often refer to "preanalytical," "analytical," and "postanalytical." Consider use of "analytical" rather than "examination."

- **To align the use of terminology in this document with that of ISO, the terms preexamination, examination, and postexamination were adopted. For the sake of introduction and to avoid confusion, the subcommittee included the ISO terms parenthetically where the US terms appear. The Note on Terminology in Section 3.1 was revised to this effect.**

18. Table 1, "Before Blood Collection" – Add "Incorrect collection system." Needle size—using a large needle bore can cause hemolysis as with the use of needles that are too fine.

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

19. Table 1, "Before Blood Collection" – Add "Incorrect collection time." The timing of blood collection is an important part of therapeutic drug monitoring due to the cycle of drug absorption, time to reach max. Drug concentration and eventual leveling off of the concentration in the blood is usually before the next dose, so depending on the assay, the timing of sample collection is vital.

- **The table was revised to read "incorrect time of collection."**

20. Table 1 – Order of draw (CLSI standard H03) is done for specific reasons, primarily due to additive crossover (ie, EDTA in lavender top collection tubes is potassium enriched and it also binds calcium, so if a lavender tube was collected before a chemistry tube, then several results including those for potassium and calcium would be inaccurate).

- **The table was revised. "Incorrect order of draw" was included under "During Blood Collection" and CLSI document H03 was added as a reference.**

21. Table 1– The document is thorough and well written. One recommendation I have is the addition of "Incorrect order of draw" to Table 1 under the column "During Blood Collection." If the study involves the collection of several different blood tubes from the same patient at the same draw time, then it is important to prioritize the tubes so that the material from one phlebotomy tube does not contaminate the next one. For example, if an EDTA tube is used before a regular serum tube, the latter tube could become contaminated with trace amounts of EDTA, which may inhibit certain enzymes, such as alkaline phosphatase. Also, include a reference for CLSI document H03.

- **The table was revised. "Incorrect order of draw" was included and CLSI document H03 was added as a reference.**

22. Table 1– If the study involves the collection of several different blood tubes from the same patient at the same draw time, then it is important to prioritize the tubes so that material from one phlebotomy tube does not contaminate the next one. Add "Incorrect order of draw" as a possible preanalytical (preexamination) variable under the column "During Blood Collection."

- **The table was revised. "Incorrect order of draw" was included and CLSI document H03 was added as a reference.**

23. Table 1– There is an omission of a preanalytical (preexamination) variable that can occur during collection. The "During Blood Collection" column should include "Incorrect order of draw."

- **The table was revised. "Incorrect order of draw" was included and CLSI document H03 was added as a reference.**

24. Table 1 – Reference is made to pneumatic tubes. The message some readers may take from this is that these are a "no-no." Consider including a qualifying statement at the bottom of the table. Alternatively, a change to "incorrect use of pneumatic tube systems" may be appropriate.

- **The table was revised to include "Incorrect use of pneumatic tube systems" under "After Blood Collection" as suggested.**

Section 5.3, Clinical Evaluation—Planning, Designing, and Conducting the Clinical Evaluation

25. First paragraph, second sentence, "platform" – Reword for simplification. Omit "platform."

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

26. Fourth paragraph, third and fourth bullets – The bullets are not needed. Omit "statistical power for study" and "study acceptance criteria."

- **Information is key to consider when conducting clinical evaluations. Therefore, the text was maintained as originally presented.**

Section 5.3.1, Manufacturer's Validation Studies

27. Item 9 – This tells the readers what not to do with outliers, but does not tell them what to do. Insert instructions on how to deal with outliers.

- **The text was revised to recommend that users consult CLSI document EP09 for information on outliers, and the applicable reference was added.**

Section 5.3.2, End-User Verification Studies

28. Item 4 – The sixth sentence appears to be redundant given sentence 7. Remove the sentence.

- **The subcommittee believes the text is accurate. Therefore, the text was maintained as originally presented.**

29. Item 8 – This tells readers what not to do with outliers, but does not tell them what to do. Insert instructions on how to deal with outliers.

- **The text was revised to recommend that users consult CLSI document EP09 for information on outliers, and the applicable reference was added.**

Section 5.3.3, Summary

30. I think the second paragraph lacks clarity. Reword it as follows: "Similarly, it is impractical for tube manufacturers to test their tubes on all the various assay platforms. Statistical methods should be used to ensure that during the manufacturing process, there is consistency in the amount and quality of additives applied to the tubes."

- **Section 5.3.3 was deleted.**

31. Last paragraph – The recommendation that diagnostic companies should repeat previous reference range studies with any new sample collection tube is impractical. A demonstration of equivalence of results between new and old tubes will justify transference of previously determined reference ranges. Reword the last paragraph accordingly.

- **Section 5.3.3 was deleted.**

Section 5.4.2, Method for Analysis of Precision

32. The third paragraph, commencing "In both methods" was a little unclear. Which two methods are these? I presume they refer to 'within tube' and 'lot-to-lot' variation (per Appendix B). Clarify this point.

- **The first sentence of the third paragraph was revised for clarity. It reads, "In both methods, if the within-subject repeatability is dependent on the size of the measurements (as seen by the plot of differences vs average showing a change in the amount of variation with the magnitude of the measurements), the above-mentioned calculations could be inaccurate."**

33. Fourth paragraph, first sentence, statement in parentheses at end of sentence – It can be inaccurate. Delete the text in parentheses.

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

Section 5.5, Clinical Acceptance Criteria

34. Third paragraph, second sentence – Reword for simplification, ie, "Nonequivalence change to difference."

- **The subcommittee believes that changing the wording would imply that laboratories may assess the data for statistical difference only and not consider the clinical significance of any change noted. Therefore, the text was maintained as originally presented.**

References

35. Would it be possible to include yet another relevant reference? Fiebig EW, Etzell JE, Ng VL. Clinically relevant differences in prothrombin time and INR values related to blood sample collection in plastic vs glass tubes. *Am J Clin Pathol*. 2005;124:902-909.

- **The suggested reference was added to the "Additional References" section of the guideline.**

Appendix A, Sample Protocol for User Evaluation of Evacuated Venous Blood Collection Tubes; and Table A1

36. Table A1, Number of Inversions – The wording concerning the number of inversions for the evaluation tube could be confused as suggesting that the site use their own recommendation. During an evaluation, it must be clear that the site use the manufacturer's recommendation as stipulated in the Instructions for Use, since the site

will have no to limited experience with the tube to determine this. Revise to "Number of inversions for evaluation: Tube manufacturer recommendation."

- **The text was revised to read: "Site recommendation or tube manufacturer recommendations."**

37. Step 16 and Table entry above comment space – It is not clear to me what is meant by "With controls, run before and after testing." Clarify.

- **The last sentence in Step 16 and the text in Table 1 were revised for clarity. Both sentences read, "Run quality control materials before and after testing."**

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

GP34-A 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 and Records	Organization	Personnel	Equipment	Purchasing and Inventory	Process Control	Information Management	Occurrence Management	Assessment —External and Internal	Process Improvement	Customer Service	Facilities and Safety
				H03	X EP05 EP09 EP10 EP15 EP21 H01 H03 H04 H18 H21 M15 M40 M47			EP10			H03 M29

Adapted from CLSI 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 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.

GP34-A 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 H01							
H03	H03 H04	H03	H03	H03	H03			
		H18	H18	H18				
	H21	H21						
	M15	M15 M40	M15	M15	M15	M15		
	M47	M47	M47	M47	M47	M47	M47	

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

Related CLSI Reference Materials*

EP05-A2 **Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline—Second Edition (2004).** This document provides guidance for designing an experiment to evaluate the precision performance of quantitative measurement methods; recommendations on comparing the resulting precision estimates with manufacturers' precision performance claims and determining when such comparisons are valid; as well as manufacturers' guidelines for establishing claims.

EP09-A2-IR **Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline—Second Edition (Interim Revision) (2010).** This document addresses procedures for determining the bias between two clinical methods, and the design of a method comparison experiment using split patient samples and data analysis.

EP10-A3 **Preliminary Evaluation of Quantitative Clinical Laboratory Measurement Procedures; Approved Guideline—Third Edition (2006).** This guideline provides experimental design and data analysis for preliminary evaluation of the performance of a measurement procedure or device.

EP15-A2 **User Verification of Performance for Precision and Trueness; Approved Guideline—Second Edition (2005).** This document describes the demonstration of method precision and trueness for clinical laboratory quantitative methods using a protocol designed to be completed within five working days or less.

EP21-A **Estimation of Total Analytical Error for Clinical Laboratory Methods; Approved Guideline (2003).** This document provides manufacturers and end users with a means to estimate total analytical error for an assay. A data collection protocol and an analysis method that can be used to judge the clinical acceptability of new methods using patient specimens are included. These tools can also monitor an assay's total analytical error by using quality control samples.

H01-A5 **Tubes and Additives for Venous Blood Specimen Collection; Approved Standard—Fifth Edition (2003).** This document contains requirements for venous blood collection tubes and additives, including technical descriptions of ethylenediaminetetraacetic acid (EDTA), sodium citrate, and heparin compounds used in blood collection devices.

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.

H18-A4 **Procedures for the Handling and Processing of Blood Specimens for Common Laboratory Tests; Approved Guideline—Fourth Edition (2010).** This document includes criteria for preparing an optimal serum or plasma sample and for the devices used to process blood specimens.

H21-A5 **Collection, Transport, and Processing of Blood Specimens for Testing Plasma-Based Coagulation Assays and Molecular Hemostasis Assays; Approved Guideline—Fifth Edition (2008).** This document provides procedures for collecting, transporting, and storing blood; processing blood specimens; storing plasma for coagulation testing; and general recommendations for performing the tests.

M15-A **Laboratory Diagnosis of Blood-borne Parasitic Diseases; Approved Guideline (2000).** This document provides guidance on specimen collection, optimum timing for preparing blood films, blood film preparations, staining procedures, examination of specimens, and identification of parasites.

* CLSI documents are continually reviewed and revised through the CLSI consensus process; therefore, readers should refer to the most current editions.

Related CLSI Reference Materials (Continued)

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.

M40-A **Quality Control of Microbiological Transport Systems; Approved Standard (2003).** This document provides criteria to assist manufacturers and end users of transport devices in providing and selecting dependable products for the transport of microbiological clinical specimens.

M47-A **Principles and Procedures for Blood Cultures; Approved Guideline (2007).** This document provides recommendations for the collection, transport, and processing of blood cultures as well as guidance for the recovery of pathogens from blood specimens taken from patients who are suspected of having bacteremia or fungemia.

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Beckman Coulter, Inc.
bioMérieux, Inc.
College of American Pathologists
Diagnostica Stago
GlaxoSmithKline
Ortho-Clinical Diagnostics, Inc.
Roche Diagnostics, Inc.

Professional Members

AAMI
American Association for Clinical Chemistry
American Association for Laboratory Accreditation
American Association for Respiratory Care
American Medical Technologists
American Society for Clinical Laboratory Science
American Society for Clinical Pathology
American Society for Microbiology
American Type Culture Collection
Association of Public Health Laboratories
Associazione Microbiologi Clinici Italiani (AMCLI)
British Society for Antimicrobial Chemotherapy
Canadian Society for Medical Laboratory Science
COLA
College of American Pathologists
College of Medical Laboratory Technologists of Ontario
College of Physicians and Surgeons of Saskatchewan
Critical Path Institute
ESCMID
Family Health International
Hong Kong Accreditation Service Innovation and Technology Commission
International Federation of Biomedical Laboratory Science
International Federation of Clinical Chemistry
Italian Society of Clin. Biochem. and Clin. Molec. Biology
JCCLS
The Joint Commission
The Korean Society for Laboratory Medicine
National Society for Histotechnology, Inc.
Nova Scotia Association of Clinical Laboratory Managers
Ontario Medical Association Quality Management Program-Laboratory Service
RCPA Quality Assurance Programs Pty Limited
SIMeL
Sociedad Española de Bioquímica Clínica y Patología Molec.
Sociedade Brasileira de Patologia Clinica
World Health Organization

Government Members

Armed Forces Institute of Pathology
BC Centre for Disease Control
CAREC
Centers for Disease Control and Prevention
Centers for Disease Control and Prevention - Namibia
Centers for Disease Control and Prevention - Tanzania
Centers for Disease Control and Prevention RETRO-CI CDC/PEPFAR
Centers for Medicare & Medicaid Services
Centers for Medicare & Medicaid Services/CLIA Program
Chinese Committee for Clinical Laboratory Standards
Chinese Medical Association (CMA)
Danish Institute for Food and Veterinary Research
Department of Veterans Affairs
DFS/CLIA Certification
FDA Center for Biologics Evaluation and Research
FDA Center for Devices and Radiological Health
FDA Center for Veterinary Medicine
Health Canada
Institut Pasteur de Côte d'Ivoire
Institute of Tropical Medicine Dept. of Clinical Sciences
Laboratoire National de la Sante Publique
MA Dept. of Public Health Laboratories
Malaria Research Training Center
Meuhedet Central Lab
Ministry of Health and Social Welfare - Tanzania
Namibia Institute of Pathology
The Nathan S. Kline Institute
National Cancer Institute, OBBR, NIH
National Center for Disease Control and Public Health
National Health Laboratory Service C/O F&M Import & Export Services
National HIV & Retrovirology Lab Public Health Agency of Canada
National Institute of Standards and Technology
National Pathology Accreditation Advisory Council
New York State Dept. of Health
NJ State Department of Health and Senior Services
Ontario Agency for Health Protection and Promotion
Pennsylvania Dept. of Health
SA Pathology
SAIC Frederick Inc NCI-Frederick Cancer Research & Development Center
Saskatchewan Health-Provincial Laboratory
Scientific Institute of Public Health
State of Alabama
University of Iowa, Hygienic Lab
US Naval Medical Research Unit #3
USAMC - AFRIMS
Virginia Department of Agriculture - Animal Health Laboratories

Industry Members

3M Medical Division
Abbott
Abbott Diabetes Care
Abbott Point of Care Inc.
Access Genetics
Aderans Research
AdvaMed
Akonni Biosystems
Ammirati Regulatory Consulting
Anapharm, Inc.
AspenBio Pharma, Inc.
Astellas Pharma
AstraZeneca Pharmaceuticals
Ativa Medical
Axis-Shield PoC AS
Bayer Healthcare, LLC Diagnostic Division
BD
BD Biosciences - San Jose, CA
BD Diagnostic Systems
BD Vacutainer Systems
Beaufort Advisors, LLC
Beckman Coulter Cellular Analysis Business Center
Beckman Coulter, Inc.
Beth Goldstein Consultant
Bio-Rad Laboratories, Inc.
Bio-Rad Laboratories, Inc. - France
Bio-Reference Laboratories
Bioanalyse, Ltd.
BioDevelopment S.r.l.
Biohit Oyj.
Biomedia Laboratories SDN BHD
bioMérieux, Inc.
Blaine Healthcare Associates, Inc.
The Clinical Microbiology Institute
BRI Consultants Limited
Calloway Laboratories
Canon U.S. Life Sciences, Inc.
Cempra Pharmaceuticals, Inc.
Cepheid
The Clinical Microbiology Institute
Compliance Insight, Inc.
Constitution Medical Inc
Controllab
Copan Diagnostics Inc.
Crescendo Bioscience
Cubist Pharmaceuticals, Inc.
Dahl-Chase Pathology Associates PA
Diagnostica Stago
Docro, Inc.
DX Assays Pte Ltd.
Eiken Chemical Company, Ltd.
Elanco Animal Health
Elkin Simson Consulting Services
Emika Consulting
Enigma Diagnostics
Eurofins Medinet
Evidia Biosciences Inc.
Gen-Probe
Genzyme Diagnostics
GlaxoSmithKline
Greiner Bio-One Inc.
Habig Regulatory Consulting
HandyLab Inc.
Himedia Labs Ltd
HistoGenex N.V.
Icon Laboratories, Inc.
Innovotech, Inc.
Instrumentation Laboratory
Integrated BioBank
IntelligentMDx, Inc.
Intuity Medical
Japan Assn. of Clinical Reagents Industries
Johnson & Johnson Pharmaceutical Research & Develop., L.L.C.
Kaiser Permanente
KoreaBIO
Krouwer Consulting
Lab PMM
Laboratory Specialists, Inc.
LifeLabs
LifeScan, Inc.
Liofilchem SRL
LipoScience, Inc.
Maine Standards Company, LLC
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Medical Device Consultants, Inc.
The Medicines Company
Merck & Company, Inc.
Merial Limited
Micromyx, LLC
Nanosphere, Inc.
Nihon Kohden Corporation
Nissui Pharmaceutical Co., Ltd.
NJK & Associates, Inc.
NorDx - Scarborough Campus
NovaBiotics
Novartis Institutes for Biomedical Research
OncoMethylome Sciences S.a.
Optimer Pharmaceuticals, Inc.
Ortho-Clinical Diagnostics, Inc.
Ortho-McNeil, Inc.
Paratek Pharmaceuticals, Inc.
PathCare Pathology Laboratory
PerkinElmer Genetics, Inc
Pfizer Animal Health
Pfizer Inc
Pfizer Italia Srl
Phadia AB
Philips Healthcare Incubator
PPD
ProteoGenix, Inc.
QML Pathology
Quality Regulatory Solutions
Quotient Bioresearch Ltd.
Radiometer America, Inc.
Roche Diagnostics GmbH
Roche Diagnostics, Inc.
Roche Molecular Systems
Sanofi Pasteur
Sarstedt, Inc.
Seventh Sense Biosystems
Siemens Healthcare Diagnostics Inc.
Siemens Healthcare Diagnostics Products GmbH
Soloy Laboratory Consulting Services, Llc
Sphere Medical Holding Limited
Streck Laboratories, Inc.
Super Religare Laboratories Ltd
Sysmex America, Inc.
Sysmex Corporation - Japan
TheraDoc
Therapeutic Monitoring Services, LLC
Theravance Inc.
Thermo Fisher Scientific
Thermo Fisher Scientific, Oxoid Products
Thermo Fisher Scientific, Remel
Transasia Bio-Medicals Limited
Trek Diagnostic Systems
Tulip Group
Ventana Medical Systems Inc.
Veracyte, Inc.
Vivacta
Watson Pharmaceuticals
Wellstat Diagnostics, LLC
XDx, Inc.

Associate Active Members

31st Medical Group SGSL (AE)
3rd Medical Group (AK)
48th Medical Group/MDSS RAF Lakenheath (AE)
55th Medical Group/SGSAL (NE)
59th MDW/859th MDTS/MTL Wilford Hall Medical Center (TX)
81st MDSS/SGSAL (MS)
Academisch Ziekenhuis-VUB UZ Brussel (Belgium)
ACL Laboratories (IL)
ACL Laboratories (WI)
Adams County Hospital (OH)
Adena Regional Medical Center Hospital (OH)
Affiliated Laboratory, Inc. (ME)
The AGA Khan University Hospital (Pakistan)
Akron Children's Hospital (OH)
Al Noor Hospital (United Arab Emirates)
Al Rahba Hospital (United Arab Emirates)
Alameda County Medical Center (CA)
Albany Medical Center Hospital (NY)
Albemarle Hospital (NC)
Alberta Health Services (Alberta, Canada)
All Children's Hospital (FL)
Allegiance Health (MI)
Alpena General Hospital (MI)
Alta Bates Summit Medical Center (CA)
Alverno Clinical Laboratories, Inc. (IN)
American University of Beirut Medical Center (NJ)
Anand Diagnostic Laboratory (India)
Anne Arundel Medical Center (MD)
Antech Diagnostics (CA)
Antelope Valley Hospital District (CA)
APP - Unipath (CO)
Appalachian Regional Healthcare System (NC)
Arkansas Children's Hospital (AR)
Arkansas Dept of Health Public Health Laboratory (AR)
Arkansas Methodist Medical Center (AR)
Artemis Health, Inc. (CA)
Asan Medical Center (Republic of Korea)
Asante Health System (OR)
Asiri Group of Hospitals Ltd. (Sri Lanka)
Aspen Valley Hospital (CO)
Aspirus Wausau Hospital (WI)
Associated Regional & University Pathologists (UT)
Atlantic City Regional Medical Center (NJ)
Atrium Medical Center (OH)
Auburn Regional Medical Center (WA)
Augusta Health (VA)
Aultman Hospital (OH)
Avera McKennan Hospital (SD)
AZ Sint-Jan (Belgium)
Azienda Ospedale Di Lecco (Italy)
Azienda Ospedaliera Padova (Italy)
Azienda Ospedaliera Verona (Italy)
Azienda Policlinico Umberto I Di Roma (Italy)
Baptist Hospital for Women (TN)
Baptist Hospital of Miami (FL)
Baptist Memorial Hospital (MS)
Baptist Memorial Hospital East (TN)
Barnes-Jewish Hospital (MO)
Baton Rouge General (LA)
Baxter Regional Medical Center (AR)
BayCare Health System (FL)
Baylor Health Care System (TX)
Bayou Pathology, APMC (LA)
BC Biomedical Laboratories (BC, Canada)
Beloit Memorial Hospital (WI)
Berg Diagnostics (MA)
Blanchard Valley Hospital (OH)
Blanchfield Army Community Hospital (KY)
Bon Secours Health Partners (VA)
Bonnyville Health Center (AB, Canada)
Boston Medical Center (MA)
Boulder Community Hospital (CO)
Boyce & Bynum Pathology Labs (MO)
Brant Community Healthcare System/Brant General Hospital (Ontario, Canada)
Bremerton Naval Hospital (WA)
Bridgeport Hospital (CT)
Brooke Army Medical Center (TX)
The Brooklyn Hospital Center (NY)
Broward General Medical Center (FL)
Cadham Provincial Laboratory-MB Health (MB, Canada)
Calgary Laboratory Services (AB, Canada)
California Department of Public Health (CA)
California Pacific Medical Center (CA)
Cambridge Health Alliance (MA)
Camden Clark Memorial Hospital (WV)
Canadian Science Center for Human and Animal Health (MB, Canada)
Cape Fear Valley Medical Center Laboratory (NC)
Capital Coast Health (New Zealand)
Capital Health - Regional Laboratory Services (AB, Canada)
Capital Health System Mercer Campus (NJ)
Carilion Labs Charlotte (NC)
Carl R. Darnall Army Medical Center Department of Pathology (TX)
Carolinas Healthcare System (NC)
Carpermor S.A. de C.V. (D.F.) (Mexico)
Catholic Health Initiatives (KY)
Cedars-Sinai Medical Center (CA)
Central Baptist Hospital (KY)
Centre Hospitalier Anna-Laberge (Quebec, Canada)
Chaleur Regional Hospital (NB, Canada)
Chang Gung Memorial Hospital (Taiwan)
Changhua Christian Hospital (Taiwan)
The Charlotte Hungerford Hospital (CT)
Chatham - Kent Health Alliance (ON, Canada)

CHC Labs (FL)
Chester County Hospital (PA)
Children's Healthcare of Atlanta (GA)
Childrens Hosp.- Kings Daughters (VA)
Children's Hospital & Research Center At Oakland (CA)
Childrens Hospital Los Angeles (CA)
Children's Hospital Medical Center (OH)
Children's Hospital of Central California (CA)
Children's Hospital of Philadelphia (PA)
Childrens Hospital of Wisconsin (WI)
Children's Hospitals and Clinics (MN)
Children's Medical Center (TX)
Children's Medical Center (OH)
Children's Memorial Hospital (IL)
The Children's Mercy Hospital (MO)
Christiana Care Health Services (DE)
CHU - Saint Pierre (Belgium)
CHU Sainte-Justine (Quebec, Canada)
CHUM Hopital Saint-Luc (Quebec, Canada)
CHW-St. Mary's Medical Center (CA)
City of Hope National Medical Center (CA)
Clarian Health - Clarian Pathology Laboratory (IN)
Clearstone Central Laboratories (ON, Canada)
Cleveland Clinic (OH)
Cleveland Heartlab, LLC (OH)
Clinical Hospital Merkur (Croatia)
Clinical Labs of Hawaii (HI)
Clinton Memorial Hospital (OH)
Colchester East Hants Health Authority (NS, Canada)
Colegio De Tecnologos Medicos De Puerto (PR)
College of Physicians and Surgeons of Alberta (AB, Canada)
Collingwood General & Marine Hospital (ON, Canada)
Columbia Regional Hospital (MO)
Commonwealth of Virginia (DCLS) (VA)
Community Hospital (IN)
Community Hospital of the Monterey Peninsula (CA)
Community Medical Center (NJ)
Community Memorial Hospital (WI)
Complexe Hospitalier de la Sagamie (Quebec, Canada)
Consultants Laboratory of WI LLC (WI)
Contra Costa Regional Medical Center (CA)
Cook Children's Medical Center (TX)
The Cooley Dickinson Hospital, Inc. (MA)
Corniche Hospital (United Arab Emirates)
Cornwall Community Hospital (ON, Canada)
Corona Regional Medical Center (CA)
Covance CLS (IN)
The Credit Valley Hospital (ON, Canada)
Creighton Medical Lab (NE)
Creighton University Medical Center (NE)
Crozer-Chester Medical Center (PA)
Cumberland Medical Center (TN)
Darwin Library NT Territory Health Services (NT, Australia)
David Grant Medical Center (CA)
Daviess Community Hospital (IN)
Deaconess Hospital Laboratory (IN)
Dean Medical Center (WI)
DHHS NC State Lab of Public Health (NC)
DiagnoSearch Life Sciences Inc. (Maharashtra, India)
Diagnostic Laboratories (CA)
Diagnostic Laboratory Services, Inc. (HI)
Diagnostic Services of Manitoba (MB, Canada)
Dimensions Healthcare System Prince George's Hospital Center (MD)
DMC University Laboratories (MI)
Drake Center (OH)
Driscoll Children's Hospital (TX)
DUHS Clinical Laboratories Franklin Site (NC)
Dynacare Laboratory (WI)
Dynacare NW, Inc - Seattle (WA)
DynaLIFE (AB, Canada)
E. A. Conway Medical Center (LA)
East Georgia Regional Medical Center (GA)
Eastern Health - Health Sciences Centre (NL, Canada)
Eastern Health Pathology (Victoria, 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)
Exeter Hospital (NH)
Exosome Diagnostics, Inc. (MN)
Federal Medical Center (MN)
Fletcher Allen Health Care (VT)
Florida Hospital (FL)
Fort Loudoun Medical Center (TN)
Fort St. John General Hospital (BC, Canada)
Forum Health Northside Medical Center (OH)
Fox Chase Cancer Center (PA)
Franciscan Skemp Medical Center (WI)
Fraser Health Authority Royal Columbian Hospital Site (BC, Canada)
Fresenius Medical Care/Spectra East (NJ)
Gamma-Dynacare Laboratories (ON, Canada)
Garden City Hospital (MI)
Garfield Medical Center (CA)
Gaston Memorial Hospital (NC)
Geisinger Medical Center (PA)
Genesis Healthcare System (OH)
George Washington University Hospital (DC)
Ghent University Hospital (Belgium)
Golden Valley Memorial Hospital (MO)
Good Shepherd Medical Center (TX)
Grana S.A. (TX)
Grand River Hospital (ON, Canada)
Grey Bruce Regional Health Center (ON, Canada)
Gundersen Lutheran Medical Center (WI)
Guthrie Clinic Laboratories (PA)
Haga Teaching Hospital (Netherlands)
Halton Healthcare Services (ON, Canada)
Hamad Medical Corporation (Qatar)
Hamilton Regional Laboratory Medicine Program - St. Joseph's (ON, Canada)
Hanover General Hospital (PA)
Harford Memorial Hospital (MD)
Harris Methodist Fort Worth (TX)
Harrison Medical Center (WA)
Hartford Hospital (CT)
Health Network Lab (PA)
Health Sciences Research Institute (Japan)
Health Waikato (New Zealand)
Heart of Florida Regional Medical Center (FL)
Heartland Health (MO)
Heidelberg Army Hospital (AE)
Helen Hayes Hospital (NY)
Henry Ford Hospital (MI)
Henry M. Jackson Foundation for the Advancement of Military Medicine-MD (MD)
Hi-Desert Medical Center (CA)
Highlands Medical Center (AL)
Hoag Memorial Hospital Presbyterian (CA)
Holy Cross Hospital-Lab (MD)
Holy Name Hospital (NJ)
Holy Spirit Hospital (PA)
Hopital du Haut-Richelieu (PQ, Canada)
Hopital Maisonneuve-Rosemont (PQ, Canada)
Hopital Santa Cabrini Ospedale (PQ, Canada)
Horizon Health Network (NB, Canada)
The Hospital for Sick Children (ON, Canada)
Hospital of St. Raphael (CT)
Hospital Sacre-Coeur de Montreal (Quebec, Canada)
Hotel Dieu Grace Hospital Library (ON, Canada)
Hunter Area Pathology Service (Australia)
Hunterdon Medical Center (NJ)
IBT Reference Laboratory (KS)
Imelda Hospital (Belgium)
Indian River Memorial Hospital (FL)
Inova Central Laboratory (VA)
Institut fur Stand. und Dok. im Med. Lab. (Germany)
Institut National de Santé Publique Du Quebec Centre de Doc. - INSPQ (PQ, Canada)
Institute of Clinical Pathology and Medical Research (Australia)
Institute of Laboratory Medicine Landspitali Univ. Hospital (Iceland)
Institute of Medical & Veterinary Science (SA, Australia)
Integrated Regional Laboratories South Florida (HCA) (VA)
Intermountain Health Care Lab Services (UT)
International Health Management Associates, Inc. (IL)
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Jackson Purchase Medical Center (KY)
Jessa Ziekenhuis VZW (Belgium)
John C. Lincoln Hospital - N. MT. (AZ)
John F. Kennedy Medical Center (NJ)
John H. Stroger, Jr. Hospital of Cook County (IL)
John Muir Health (CA)
Johns Hopkins Medical Institutions (MD)
Johns Hopkins University (MD)
Johnson City Medical Center Hospital (TN)
JPS Health Network (TX)
Kailos Genetics (AL)
Kaiser Permanente (MD)
Kaiser Permanente (OH)
Kaiser Permanente Medical Care (CA)
Kaleida Health Center for Laboratory Medicine (NY)
Kantonsspital Aarau AG (AG) Switzerland
Kenora-Rainy River Reg. Lab. Program (ON, Canada)
King Abdulaziz Hospital, Al Ahsa Dept. of Pathology & Laboratory Medicine (Al-hasa, Saudi Arabia)
King Abdulaziz Medical City - Jeddah National Guard Health Affairs (WR, Saudi Arabia)
King Fahad National Guard Hospital KAMC - NGHA (Saudi Arabia)
King Fahad Specialist Hospital-Dammam, K.S.A. (Eastern Region) Saudi Arabia
King Faisal Specialist Hospital (MD)
King Faisal Specialist Hospital & Research Center (Saudi Arabia)
King Hussein Cancer Center (Jordan)
Kings County Hospital Center (NY)
King's Daughters Medical Center (KY)
Kingston General Hospital (ON, Canada)
Lab Medico Santa Luzia LTDA (Brazil)
Labette Health (KS)
Laboratory Alliance of Central New York (NY)
Laboratory Corporation of America (NJ)
LabPlus Auckland District Health Board (New Zealand)
LAC/USC Medical Center (CA)
Lafayette General Medical Center (LA)
Lakeland Regional Medical Center (FL)
Lancaster General Hospital (PA)
Landstuhl Regional Medical Center (AE)
Langley Air Force Base (VA)
Laredo Medical Center (TX)
LeBonheur Children's Medical Center (TN)
Legacy Laboratory Services (OR)
Lewis-Gale Medical Center (VA)
L'Hotel-Dieu de Quebec (PQ, Canada)
Licking Memorial Hospital (OH)
LifeLabs Medical Laboratory Services (BC, Canada)
Loma Linda University Medical Center (LLUMC) (CA)
Long Beach Memorial Medical Center-LBMMC (CA)
Long Island Jewish Medical Center (NY)
Louisiana Office of Public Health Laboratory (LA)
Louisiana State University Medical Ctr. (LA)
Lourdes Hospital (KY)
Lower Columbia Pathologists, P.S. (WA)
Maccabi Medical Care and Health Fund (Israel)
Madigan Army Medical Center (WA)
Mafraq Hospital (United Arab Emirates)
Magnolia Regional Health Center (MS)
Main Line Clinical Laboratories, Inc. (PA)
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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)
Mary Washington Hospital (VA)
Massachusetts General Hospital (MA)
Mater Health Services - Pathology (Australia)
Maxwell Air Force Base (AL)
Mayo Clinic (MN)
MCG Health (GA)
Meadows Regional Medical Center (GA)
Medecin Microbiologiste (Quebec, Canada)
Medical Center Hospital (TX)
Medical Center of Louisiana At NO-Charity (LA)
Medical Centre Ljubljana (Slovenia)
Medical College of Virginia Hospital (VA)
Medical University of South Carolina (SC)
Memorial Hermann Healthcare System (TX)
Memorial Hospital at Gulfport (MS)
Memorial Medical Center (PA)
Memorial Medical Center (IL)
Memorial Regional Hospital (FL)
Mercy Franciscan Mt. Airy (OH)
Mercy Hospital & Medical Center (IL)
Methodist Dallas Medical Center (TX)
Methodist Hospital (PA)
Methodist Hospital (TX)
Methodist Hospital Park Nicollet Health Services (MN)
Methodist Hospital Pathology (NE)
MetroHealth Medical Center (OH)
Metropolitan Hospital Center (NY)
Metropolitan Medical Laboratory, PLC (IA)
Miami Children's Hospital (FL)
The Michener Inst. for Applied Health Sciences (ON, Canada)
Middelheim General Hospital (Belgium)
Middlesex Hospital (CT)
Minneapolis Medical Research Foundation (MN)
Mississippi Baptist Medical Center (MS)
Mississippi Public Health Lab (MS)
Monongalia General Hospital (WV)
Montreal General Hospital (Quebec, Canada)
Mt. Carmel Health System (OH)
Mt. Sinai Hospital (ON, Canada)
Mt. Sinai Hospital - New York (NY)
Naples Community Hospital (FL)
Nassau County Medical Center (NY)
National B Virus Resource Laboratory (GA)
National Cancer Center (Republic of Korea)
National Institutes of Health, Clinical Center (MD)
National Naval Medical Center (MD)
National University Hospital Department of Laboratory Medicine (Singapore)
National University of Ireland, Galway (NUIG) (Ireland)
Nationwide Children's Hospital (OH)
Nationwide Laboratory Services (FL)
Naval Hospital Great Lakes (IL)
The Naval Hospital of Jacksonville (FL)
Naval Medical Center Portsmouth (VA)
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NB Department of Health (NB, Canada)
The Nebraska Medical Center (NE)
New England Baptist 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)
Nor-Lea General Hospital (NM)
North Carolina Baptist Hospital (NC)
North District Hospital (China)
North Mississippi Medical Center (MS)
North Shore Hospital Laboratory (New Zealand)
North Shore-Long Island Jewish Health System Laboratories (NY)
Northridge Hospital Medical Center (CA)
Northside Hospital (GA)
Northwest Texas Hospital (TX)
Northwestern Memorial Hospital (IL)
Norton Healthcare (KY)
Ochsner Clinic Foundation (LA)
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Ohio Valley Medical Center (WV)
Onze Lieve Vrouwziekenhuis (Belgium)
Ordre Professionnel Des Technologistes Médicaux Du Québec (Quebec, Canada)
Orebro University Hospital (Sweden)
Orlando Regional Healthcare System (FL)
Ospedale Casa Sollievo Della Sofferenza - IRCCS (Italy)
The Ottawa Hospital (ON, Canada)
Our Lady's Hospital For Sick Children (Ireland)
Palmetto Baptist Medical Center (SC)
Parkland Health & Hospital System (TX)
Pathlab (IA)
Pathology and Cytology Laboratories, Inc. (KY)
Pathology Associates Medical Lab. (WA)
Peace River Regional Health Center (FL)
Penn State Hershey Medical Center (PA)
Pennsylvania Hospital (PA)
The Permanente Medical Group (CA)
Peterborough Regional Health Centre (ON, Canada)
Piedmont Hospital (GA)
Pitt County Memorial Hospital (NC)
Potomac Hospital (VA)
Prairie Lakes Hospital (SD)
Presbyterian Hospital - Laboratory (NC)
Presbyterian/St. Luke's Medical Center (CO)
Prince County Hospital (PE, Canada)
Princess Margaret Hospital (Hong Kong, China)
Providence Alaska Medical Center (AK)
Providence Health Care (BC, Canada)
Providence Health Services, Regional Laboratory (OR)
Providence Medford Medical Center (OR)
Provincial Health Services Authority (BC, Canada)
Provincial Laboratory for Public Health (AB, Canada)
Queen Elizabeth Hospital (P.E.I, Canada)
Queen Elizabeth Hospital (China)
Queensland Health Pathology Services (Australia)
Queensway Carleton Hospital (ON, Canada)
Quest Diagnostics JV (OH)
Quest Diagnostics, Incorporated (CA)
Quintiles Laboratories, Ltd. (GA)
Rady Children's Hospital San Diego (CA)
Ramathibodi Hospital (Thailand)
Redington-Fairview General Hospital (ME)
Regions Hospital (MN)
Reid Hospital & Health Care Services (IN)
Renown Regional Medical Center (NV)
Research Medical Center (MO)
Response Genetics, Inc. (CA)
Rex Healthcare (NC)
River Valley Health-Chalmers Regional Hospital (NB, Canada)

Riverside County Regional Medical Center (CA)
Riverside Health System (VA)
Riverside Methodist Hospital (OH)
Riyadh Armed Forces Hospital, Sulaymainia (Saudi Arabia)
Riyadh National Hospital (Saudi Arabia)
Rockford Memorial Hospital (IL)
Royal Victoria Hospital (ON, Canada)
Sacred Heart Hospital (WI)
Sacred Heart Hospital (FL)
Sahlgrenska Universitetssjukhuset (Sweden)
Saint Francis Hospital & Medical Center (CT)
Saint Mary's Regional Medical Center (NV)
Saints Memorial Medical Center (MA)
Salem Memorial District Hospital (MO)
Sampson Regional Medical Center (NC)
Samsung Medical Center (Republic of Korea)
San Francisco General Hospital-University of California San Francisco (CA)
Sanford USD Medical Center (SD)
Santa Clara Valley Medical Center (CA)
SARL Laboratoire Caron (France)
Scott & White Memorial Hospital (TX)
Seattle Children's Hospital/Children's Hospital and Regional Medical Center (WA)
Seoul National University Hospital (Republic of Korea)
Seoul St. Mary's Hospital (Republic of Korea)
Sheik Kalifa Medical City (United Arab Emirates)
Shiel Medical Laboratory Inc. (NY)
Shore Memorial Hospital (NJ)
Singapore General Hospital (Singapore)
South Bend Medical Foundation (IN)
South County Hospital (RI)
South Miami Hospital (FL)
Southern Community Laboratories (Canterbury) New Zealand
Southern Health Care Network (Australia)
Southern Maine Medical Center (ME)
Spectrum Health - Blodgett Campus (MI)
St. Agnes Healthcare (MD)
St. Anthony Hospital (OK)
St. Barnabas Medical Center (NJ)
St. Christopher's Hospital for Children (PA)
St. Elizabeth Community Hospital (CA)
St. Eustache Hospital (Quebec, Canada)
St. Francis Hospital (SC)
St. John Hospital and Medical Center (MI)
St. John's Hospital & Health Ctr. (CA)
St. John's Mercy Medical Center (MO)
St. John's Regional Health Center (MO)
St. Joseph Hospital (IN)
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. Luke's Hospital (PA)
St. Luke's Hospital (IA)
St. Mary Medical Center (CA)
St. Mary of Nazareth Hospital (IL)
St. Mary's Hospital (WI)
St. Tammany Parish Hospital (LA)
Stanford Hospital and Clinics (CA)
Stanton Territorial Health Authority (NT, Canada)
State of Connecticut Department of Public Health (CT)
State of Ohio/Corrections Medical Center Laboratory (OH)
State of Washington Public Health Labs (WA)
Stillwater Medical Center (OK)
Stony Brook University Hospital (NY)
Stormont-Vail Regional Medical Ctr. (KS)
Strong Memorial Hospital (NY)
Sudbury Regional Hospital (ON, Canada)
Sunbury Community Hospital (PA)
Sunnybrook Health Sciences Centre (ON, Canada)
Sunrise Hospital and Medical Center (NV)
Sutter Roseville Medical Center (CA)
Swedish Edmonds Hospital (WA)
Swedish Medical Center (CO)
Sydney South West Pathology Service Liverpool Hospital (NSW, Australia)
T.J. Samson Community Hospital (KY)
Taichung Veterans General Hospital (Taiwan)
Taipei Veterans General Hospital (Taiwan)
Taiwan Society of Laboratory Medicine (Taiwan)
Tallaght Hospital (Ireland)
Tartu University Clinics (Estonia)
Temple Univ. Hospital - Parkinson Pav. (PA)
Texas Children's Hospital (TX)
Texas Department of State Health Services (TX)
Texas Health Presbyterian Hospital Dallas (TX)
Timmins and District Hospital (ON, Canada)
Tokyo Metro. Res. Lab of Public Health (Japan)
The Toledo Hospital (OH)
Touro Infirmary (LA)
Tri-City Medical Center (CA)
Trident Medical Center (SC)
Trinity Medical Center (AL)
Tripler Army Medical Center (HI)
Tuen Mun Hospital, Hospital Authority (China)
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)
UMC of El Paso - Laboratory (TX)
UMC of Southern Nevada (NV)
UNC Hospitals (NC)
Union Clinical Laboratory (Taiwan)
United Christian Hospital (Kowloon, Hong Kong)
United Clinical Laboratories (IA)
United Medical Center (DC)
United States Air Force School of Aerospace Medicine / PHE (TX)
Unity HealthCare (IA)
Univ. of Pennsylvania Health System (PA)
Università Campus Bio - Medico Di Roma (IT) Italy
Universitair Ziekenhuis Antwerpen (Belgium)
University College Hospital (Ireland)
University Hospital (GA)
University Hospital Center Sherbrooke (CHUS) (Quebec, Canada)
University Medical Center At Princeton (NJ)
University of Alabama Hospital Lab (AL)
University of Chicago Hospitals Laboratories (IL)
University of Colorado Health Sciences Center (CO)
University of Colorado Hospital (CO)
University of Illinois Medical Center (IL)
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University of MS Medical Center (MS)
University of Pittsburgh Medical Center (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)
UPMC Bedford Memorial (PA)
UZ-KUL Medical Center (Belgium)
VA (Asheville) Medical Center (NC)
VA (Bay Pines) Medical Center (FL)
VA (Central Texas) Veterans Health Care System (TX)
VA (Chillicothe) Medical Center (OH)
VA (Cincinnati) Medical Center (OH)
VA (Dayton) Medical Center (OH)
VA (Decatur) Medical Center (GA)
VA (Durham) Medical Center (NC)
VA (Hampton) Medical Center (VA)
VA (Indianapolis) Medical Center (IN)
VA (San Diego) Medical Center (CA)
VA (Tampa) Hospital (FL)
Valley Health / Winchester Medical Center (VA)
Vancouver Coastal Health Regional Laboratory (BC, Canada)
Vancouver Island Health Authority (SI) (BC, Canada)
Vanderbilt University Medical Center (TN)
Via Christi Regional Medical Center (KS)
Virginia Beach General Hospital (VA)
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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 Penn Allegheny Health System-Allegheny General Hospital (PA)
West Shore Medical Center (MI)
West Valley Medical Center Laboratory (ID)
Westchester Medical Center (NY)
Western Baptist Hospital (KY)
Western Healthcare Corporation (NL, Canada)
Wheaton Franciscan Laboratories (WI)
Wheeling Hospital (WV)
Whitehorse General Hospital (YT, Canada)
William Beaumont Army Medical Center (TX)
William Beaumont Hospital (MI)
William Osler Health Centre (ON, Canada)
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