



C49-A

Analysis of Body Fluids in Clinical Chemistry; Approved Guideline

This document provides guidance for the application of widely available measurement procedures for testing body fluids and for reporting and interpreting those results. It emphasizes defining the common clinical situations for this use; acceptable practice for measuring analytes without extended method verification for abnormal body fluid; influence of biologic and analytic variation on interpretation of results; and variability in comparing results between different instrument manufacturers. This document does not consider serum, plasma, whole blood, or fluids for which assays typically have performance claims in the measurement procedure documentation.

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Analysis of Body Fluids in Clinical Chemistry; Approved Guideline

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Abstract

Clinical and Laboratory Standards Institute document C49-A—*Analysis of Body Fluids in Clinical Chemistry; Approved Guideline* provides guidance to the clinical laboratory director for the application of widely available measurement procedures for testing body fluids and for reporting and interpreting those results. It emphasizes defining the common clinical situations for this use; acceptable practice for measuring analytes without extended method verification for abnormal body fluids; influence of biologic and analytic variation on interpretation of results; and variability in comparing results between different instrument manufacturers. This document does not consider serum, plasma, whole blood, or fluids for which assays typically have performance claims in the measurement procedure documentation.

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Foreword

Measurements of analytes in body fluids other than plasma or serum almost never have performance claims from a method provider, despite occasional clinical need to perform these analyses in abnormal body fluids (e.g., peritoneal, pleural, drainage) to detect specific organ involvement or injury that caused the fluid formation. Such measurements for a number of analytes are widely available, automated, and reasonably inexpensive. Furthermore, the information they provide is unique, frequently definitive, and may not be available from any other noninvasive procedure.

Strict interpretation of laboratory regulations would rule out the performance of analyses on these abnormal body fluids, because:

- manufacturers usually do not have performance claims for measurements in fluids other than serum, plasma, or urine;
- clinical laboratories do not generally have the resources to perform complete method verifications for such samples; and consequently,
- clinical laboratories have not established reference ranges for analytes in those fluids.

Furthermore, matrix effects from proteins and other constituents in serum or plasma and body fluids can be expected to alter measurement of analytes. Because concentrations of these constituents can vary several-fold in body fluids, the matrix effects may be unpredictable in any given fluid. Accordingly, a comparison between measured values from a body fluid and serum or plasma has inherent uncertainty due to this influence on analytic variability.

Nevertheless, clinicians can successfully use the results from fluids in direct comparison with concurrent results in serum or plasma to establish whether the fluid has a very high concentration of the analyte or a very low one (i.e., similar to that in serum or plasma). A high concentration of the analyte in a body fluid suggests direct involvement of the suspect organ; a concentration in the fluid similar to that in serum or plasma indicates no involvement of the organ.

This document provides guidance to clinical diagnostic laboratories for applying widely available measurement procedures to body fluids and for reporting and interpreting those results. Emphasis is placed on:

- the common clinical situations for this use;
- acceptable practice for measuring analytes without extended method verification for abnormal body fluids;
- influence of biologic and analytic variation on interpretation of results;
- variability in comparing results between different instrument manufacturers; and
- recommended reporting format.

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, ISO, and CEN documents; and that legally required use of terms, regional usage, and different consensus timelines are all challenges to harmonization. In light of this, CLSI recognizes that harmonization of terms facilitates the global application of standards and deserves

immediate attention. Implementation of this policy must be an evolutionary and educational process that begins with new projects and revisions of existing documents.

In order to align the usage of terminology in this document with that of ISO, the following terms are used in C49-A:

The term *accuracy*, in its metrological sense, refers to the closeness of the agreement between the result of a (single) measurement and a true value of a measurand, and comprises both random and systematic effects. *Trueness* is used in this document when referring to the “closeness of the agreement between the average value from a large series of measurements and a true value of a measurand”; the measurement of trueness is usually expressed in terms of *bias*. *Precision* is defined as the “closeness of agreement between independent test/measurement results obtained under stipulated conditions.” As such, it cannot have a numerical value, but may be determined qualitatively as high, medium, or low. For its numerical expression, the term *imprecision* is used, which is the “dispersion of results of measurements obtained under specified conditions.” In addition, a different component of precision is defined in C49-A, namely, *reproducibility*, i.e., “the closeness of the agreement between the results of measurements of the same measurand carried out under changed conditions of measurement.”

The term *measuring range* has replaced *reportable range* when referring to “a set of values of measurands for which the error of a measuring instrument (test) is intended to lie within specified limits.” The term *diagnostic sensitivity* has replaced the term *clinical sensitivity* because in Europe, the term “clinical” often refers to clinical studies of drugs under stringent conditions.

Users of C49-A should understand, however, that the fundamental meanings of the terms are identical in many cases, and to facilitate understanding, terms are defined in the Definitions section of this guideline.

All terms and definitions will be reviewed again for consistency with international use, and revised appropriately during the next scheduled revision of this document.

Key Words

Body fluid, exudate, matrix effect, method validation, organ injury, serous fluid, synovial fluid, transudate

Acknowledgement

This guideline was prepared by CLSI, as part of a cooperative effort with IFCC to work toward the advancement and dissemination of laboratory standards on a worldwide basis. CLSI gratefully acknowledges the participation of IFCC in this project. The IFCC expert for this project is Andrea Griesmacher, MD, University Hospital of Innsbruck, Austria.

Analysis of Body Fluids in Clinical Chemistry; Approved Guideline

1 Scope

CLSI document C49 provides guidance to the clinical laboratory director for the application of measurement procedures for testing body fluids, and for reporting and interpreting those results. The document emphasizes: the most common clinical situations; acceptable practice for measuring analytes without extended method verification for abnormal body fluids; the influence of biologic and analytic variation on interpretation of results; and the variability in comparing results between different instrument manufacturers.

This document does not consider serum, plasma, whole blood, or fluids for which assays typically have performance claims in the measurement procedure documentation.

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 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.¹ For specific precautions for preventing the laboratory transmission of all infectious agents from laboratory instruments and materials and for recommendations for the management of exposure to all infectious disease, refer to the appropriate CLSI document.²

3 Terminology

3.1 Glossary of Body Fluids

cerebrospinal fluid (CSF) – the fluid in the ventricles of the brain, between the arachnoid and the pia mater, and surrounding the spinal cord.

drainage fluid – fluid that drains through the skin from a surgical site, wound, or other penetrating injury; **NOTE 1:** The medical need is typically to determine whether the fluid is produced locally at the cutaneous site or whether it derives from deeper organ injury (e.g., kidney and urinary tract, liver and gall bladder, pancreas, intestine, stomach, esophagus, etc.); **NOTE 2:** Quantitation of organ-specific analytes in a drainage fluid can often provide unique diagnostic information to indicate what organs might need surgical repair.

pericardial fluid – fluid that accumulates in the pericardium, a closed sac of tissue surrounding the heart, often due to inflammation or malignancy.

peritoneal fluid (ascites, ascitic fluid) – fluid that accumulates in the peritoneal cavity of the abdomen, often due to hepatic cirrhosis and less frequently due to malignancy or cardiac failure; a subtype is:

peritoneal dialysis fluid – fluid that is instilled into the abdominal cavity and then removed as a form of dialysis in patients with renal failure.

pleural fluid (pleural effusion) – fluid that accumulates in the pleural cavity surrounding the lungs; various subtypes (which may also be applied to other body fluids) are as follows:

exudate – due to inflammation and characterized by high protein and presence of cells (see the Definitions section).

transudate – due to changes in hemodynamic pressures typically paucicellular and low in protein; often seen in congestive heart failure (see the Definitions section).

hemothorax – blood in the pleural space due to direct hemorrhage from an interrupted blood vessel.

chylothorax – indicates injury to the thoracic (lymphatic) duct with release of fat droplets/chylomicrons into the pleural space.

cholesterol effusion – due to chronic pleural effusion with breakdown of inflammatory cell membranes into cholesterol crystals; **NOTE:** This fluid can appear iridescent and is sometimes referred to as “pseudochylous.”

synovial fluid (joint fluid) – fluid normally present in the joint space that can be increased in amount usually due to inflammatory or septic causes.

3.2 Definitions

accuracy (of measurement) – closeness of the agreement between the result of a measurement and a true value of the measurand (VIM93).³

analyte – component represented in the name of a measurable quantity (ISO 17511)⁴; **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)⁴; **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).⁵

bias – the difference between the expectation of the test results and an accepted reference value (ISO 3534-1).⁶

diagnostic sensitivity – the proportion of patients with a well-defined clinical disorder whose test values are positive or exceed a defined decision limit (i.e., a positive result and identification of the patients who have a disease); **NOTE 1:** The clinical disorder must be defined by criteria independent of the test under consideration; **NOTE 2:** The term **diagnostic sensitivity** (Europe) is equivalent to **clinical sensitivity** (US).

exudate – the accumulation of a fluid having a high concentration of protein in a body cavity caused by increased capillary permeability usually secondary to inflammation.⁷

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

matrix effect – influence of a property of the sample, other than the analyte, on the measurement, and thereby on the value of the measurable quantity (EN 12287⁸); **NOTE:** The physicochemical effect(s) (e.g., interference) of the matrix on the measurement procedure’s ability to accurately measure an analyte.

measurand – particular quantity subject to measurement (VIM93)³; **NOTE 1:** For example, vapor pressure of a given sample of water at 20 °C (VIM93)³; **NOTE 2:** The specification of a measurand may require statements about quantities such as time, temperature, and pressure (VIM93)³; **NOTE 3:** In the example above, the measurand includes not only the entity being measured (water), but the particular

The Quality Management System Approach

Clinical and Laboratory Standards Institute subscribes to a quality management system approach in the development of standards and guidelines, which facilitates project management; defines a document structure via a template; and provides a process to identify needed documents. The approach is based on the model presented in the most current edition of CLSI/NCCLS document HS1—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 healthcare service’s path of workflow (i.e., 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 quality system essentials (QSEs) are:

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

C49-A addresses the quality system essentials (QSEs) indicated by an “X.” For a description of the other Clinical and Laboratory Standards Institute documents listed in the grid, please refer to the Related CLSI/NCCLS Publications section on the following page.

Documents & Records	Organization	Personnel	Equipment	Purchasing & Inventory	Process Control	Information Management	Occurrence Management	Assessment	Process Improvement	Service & Satisfaction	Facilities & Safety
					X EP10 EP14				EP10		

Adapted from CLSI/NCCLS document HS1—A *Quality Management System Model for Health Care*.

Related CLSI/NCCLS Publications*

- C34-A2** **Sweat Testing: Sample Collection and Quantitative Analysis; Approved Guideline—Second Edition (2000).** This document addresses appropriate methods of collection and analysis, quality control, and the evaluation and reporting of test results.
- EP10-A2** **Preliminary Evaluation of Quantitative Clinical Laboratory Methods; Approved Guideline—Second Edition (2002).** This guideline provides experimental design and data analysis for preliminary evaluation of the performance of an analytical method or device.
- EP14-A2** **Evaluation of Matrix Effects; Approved Guideline—Second Edition (2005).** This document provides guidance for evaluating the bias in analyte measurements that is due to the sample matrix (physiological or artificial) when two analytical methods are compared.
- M29-A3** **Protection of Laboratory Workers From Occupationally Acquired Infections; Approved Guideline—Third Edition (2005).** Based on U.S. 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.
- X5-R** **Metrological Traceability and Its Implementation; A Report (2006).** This document provides guidance to manufacturers for establishing and reporting metrological traceability.

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



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