CLINICAL AND LABORATORY STANDARDS INSTITUTE®

2nd Edition

C49

Analysis of Body Fluids in Clinical Chemistry

This guideline provides information for the medical laboratory for evaluating measurement procedures, as well as a strategy to characterize assay performance, when applied to body fluid matrixes. Key concepts that apply to the entire test cycle, including preexamination, examination, and postexamination phases of body fluid testing, are discussed.

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

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Analysis of Body Fluids in Clinical Chemistry

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Abstract

Clinical and Laboratory Standards Institute guideline C49—*Analysis of Body Fluids in Clinical Chemistry* provides guidance to the medical laboratory for evaluating measurement procedures, as well as a strategy to characterize assay performance, when applied to body fluid matrixes. Key concepts that apply to the entire test cycle, including preexamination, examination, and postexamination phases of body fluid testing are discussed. This guideline does not consider serum, plasma, whole blood, or fluids for which measurement procedures typically have performance claims in the measurement procedure documentation. Appendix A provides didactic content on the anatomy, physiology, and pathophysiology of fluid accumulation. Appendix B provides the medical rationale for quantifying measurands in body fluids and the interpretation of results in the context of disease. Appendix C provides the user with a quick reference guide to the suggested utility of fluid and measurand combinations.

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Foreword

Since C49's original publication, regulatory requirements for laboratories performing body fluid testing have changed. In addition, the number of publications in peer-reviewed journals as well as single case studies documenting the diagnostic need to test a number of measurands in body fluids has increased substantially. To comply with regulatory requirements when choosing to offer body fluid testing, medical laboratories should determine which fluid types are appropriate to accept for testing through collaborating with the requesting clinical areas, characterizing measurement procedure suitability, and understanding performance limitations of methods not designated for use on body fluids by *in vitro* diagnostics manufacturers. This information is critical to ensure the accuracy of reported results, because physicians use these data for patient management.

Overview of Changes

This guideline replaces the previous edition of the approved guideline, C49-A, published in April 2007. This second edition of C49 provides medical laboratories with a strategy to evaluate method performance, as well as guidance on which measurands have clinical relevance when measured in body fluid matrixes. Several changes were made in this edition, including:

- Providing medical laboratories with a workflow that:
  - Outlines important preexamination conditions to consider when validating and performing body fluid testing (see Chapter 3)
  - Discusses key concepts for body fluid matrix considerations and measurement procedure selection (see Chapter 4)
  - Offers strategies for developing a measurement procedure validation plan to provide meaningful and accurate results for appropriate and timely patient management (see Chapter 5)
  - Offers recommendations for reporting body fluid tests to aid in the diagnostic interpretation of results (see Chapter 6)
  - Covers general laboratory QA activities to support ongoing body fluid testing (see Chapter 7)
- Assisting laboratories in minimizing patient risk and maximizing diagnostic return by:
  - Providing general information related to body fluid composition and pathogenic processes that lead to accumulation of body fluids (see Appendix A)
  - Defining the measurands and their expected concentrations that have diagnostic utility when measured in body fluids (see Appendix B)

NOTE: The content of this guideline is supported by the CLSI consensus process and does not necessarily reflect the views of any single individual or organization.

Key Words

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

Analysis of Body Fluids in Clinical Chemistry

Chapter 1: Introduction

This chapter includes:

- Guideline's scope and applicable exclusions
- Standard precautions information
- "Note on Terminology" that highlights particular use and/or variation in use of terms and/or definitions
- Terms and definitions used in the guideline
- Abbreviations and acronyms used in the guideline

1.1 Scope

C49 provides guidance to medical laboratories for the appropriate application of measurement procedures for body fluid testing and for reporting results. This guideline primarily focuses on the recommended practice for verification of measurement procedures for measurands in body fluids and is applicable for laboratory testing requests on body fluids that do not have performance claims in the manufacturer's package insert or an equivalent validated laboratory-developed test. C49 does not cover serum, plasma, whole blood, urine, or fluids (eg, cerebrospinal fluid) for which measurement procedures typically have performance claims in the manufacturer's package insert.

1.2 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 bloodborne pathogens. Published guidelines are available that discuss the daily operations of diagnostic medicine in humans and animals while encouraging a culture of safety in the laboratory.[1] 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 diseases, refer to CLSI document M29.[2]

1.3 Terminology

1.3.1 A Note on Terminology

CLSI, as a global leader in standardization, is firmly committed to achieving global harmonization whenever 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 different countries and regions and that legally required use of terms, regional usage, and different consensus timelines are all important considerations in the harmonization process. CLSI recognizes its important role in these efforts, and its consensus process

focuses on harmonization of terms to facilitate the global application of standards and guidelines. Table 1 is provided to clarify the intended interpretations of the following terms.

Table 1. Common Terms or Phrases With Intended Interpretations

Term or Phrase	Intended Interpretation
"Needs to" or "must"	Explains an action directly related to fulfilling a regulatory and/or accreditation requirement or is indicative of a necessary step to ensure patient safety or proper fulfillment of a procedure
"Require"	Represents a statement that directly reflects a regulatory, accreditation, performance, product, or organizational requirement or a requirement or specification identified in an approved documentary standard
"Should"	Describes a recommendation provided in laboratory literature, a statement of good laboratory practice, or a suggestion for how to meet a requirement

1.3.2 Definitions

1.3.2.1 Body Fluid–Specific Definitions

body fluid testing – measurement of measurand(s) in biological specimens for which no performance claims from the measurement procedure's manufacturer are available.

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

chylous effusion – fluid resulting from chronic pleural effusion with breakdown of inflammatory cell membranes into cholesterol crystals; **NOTE 1:** This fluid can appear iridescent and is sometimes referred to as "pseudochylous"; **NOTE 2:** The term "chylothorax" indicates the accumulation of fat droplets or chylomicrons in the pleural space due to thoracic (lymphatic) duct disruption or obstruction.

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 (eg, kidney and urinary tract, liver and gall bladder, pancreas, intestine, stomach, esophagus); **NOTE 2:** Quantitation of organ-specific measurands 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; **NOTE:** The removal of such fluid is performed by pericardiocentesis.

peritoneal 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; also known as ascitic fluid; **NOTE 1:** The pathologic accumulation of fluid in the peritoneal cavity is called ascites and may be identified as ascitic fluid; **NOTE 2:** The removal of such fluid is performed by paracentesis; **NOTE 3:** A subtype is peritoneal dialysis fluid, which is delivered into the abdominal cavity and then removed through dialysis or dialyzed content in patients with renal failure.

Chapter 5: Measurement Procedure Validation

This chapter includes:

- Procedures for validating measurement procedure performance characteristics, including:
  - Accuracy
  - Precision
  - Detection capabilities
  - Linearity and reportable intervals
  - Reference intervals
  - Interfering substances
  - Measurand stability

Once the body fluid type for a particular measurand is identified for validation, each validation component should be considered. Table 2 lists typical components and the applicable CLSI document(s). The list in Table 2 is not all inclusive, and additional studies may be added as needed for a particular measurand or body fluid type. Depending on the method selected, body fluid types, and available volumes, the laboratory director(s) may choose to customize this validation plan based on application and scalability. CLSI document EP19[32] provides a list of CLSI documents useful for validation.

Table 2. Components of Measurement Procedure Validation

Component	Related CLSI Document(s)
Accuracy	EP09[33]
Precision	EP05,[34] EP15[35]
Detection capabilities	EP17[36]
Linearity and reportable interval	EP06[37]
Medical decision limits and reference interval	EP28[38]
Interfering substances	EP07[39]
Measurand stability	Not applicable

5.1 Accuracy

Ideally, accuracy should be traceable to national or international standards and compared with a reference measurement procedure whenever possible (see CLSI document EP09[33]). Although comparative reference measurement procedures might not be available to assess accuracy for a body fluid, comparison with a previously established measurement procedure that is known to be accurate and free of matrix interferences may be used. CLSI document EP09[33] provides a protocol to assess accuracy by measurement procedure comparison and recommends testing a minimum of 40 samples, although this number might not be feasible with limited sample availability for some body fluids. The principal causes of inaccuracy for body fluid analyses are matrix interferences and the effect of altered physicial characteristics, eg, viscosity, on fluid delivery into the measurement system (see Subchapter 4.1). In the absence of suitable method comparisons, evaluation of the body fluid for accuracy can be accomplished by performing any of the studies described in Subchapters 5.1.1 to 5.1.3. The utility of performing spiked recovery studies to verify measurand performance has been demonstrated in a number of body fluid matrixes.[40,41] The laboratory may consider conducting all these accuracy studies.

In the following sets of studies, high-concentration solutions, identified as spiking materials, are needed. There are a number of spiking material options laboratories should consider, shown in Table 3. The measurand concentration in the spiking material is determined using the measurement procedure under evaluation or is based on the assigned concentration from gravimetric preparation of the purified analyte. Avoid diluting the body fluid specimen more than 10% by volume to prevent alteration of the body fluid

Chapter 6: Results Reporting and Interpretation

This chapter includes:

- Reporting and interpreting results

It is good laboratory practice to include pertinent information in an official report when communicating body fluid analysis results. Table 13 shows an example.

Table 13. Example Body Fluid Analysis Laboratory Report*

Information	Description
Fluid type	Pleural fluid
Source	Right lung
Measurand	pH
Result	7.12
Units	Unit
Decision limit	≥7.2
Interpretation	Abnormal

* Refer to Subchapter 5.5.
Abbreviation: pH, the measurement of acidity or alkalinity of a substance.

In addition to reporting specific elements, as indicated in Table 13, providing a general comment on the patient report ensures full disclosure of information related to testing and reporting measurands in body fluids. Any appropriate disclaimers on test limitations should be included in the official report, as well as limitations from applicable regulatory requirements.