



CLINICAL AND  
LABORATORY  
STANDARDS  
INSTITUTE®

3rd Edition

# EP07

## Interference Testing in Clinical Chemistry

Sample

This guideline provides background information, guidance, and experimental procedures for investigating, identifying, and characterizing the effects of interferences on clinical chemistry test results.

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

## Interference Testing in Clinical Chemistry

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### Abstract

Clinical and Laboratory Standards Institute guideline EP07—*Interference Testing in Clinical Chemistry* is intended to promote uniformity in the evaluation of interference characteristics of medical laboratory measurement procedures. EP07 describes procedures to screen potential interferents, quantify interference effects, and confirm interference in patient samples. This guideline also describes procedures for medical laboratories to verify interference claims and investigate discrepant results caused by unsuspected interferents. Detailed examples are given. EP07 also contains background information on interference testing concepts. Tables of recommended test concentrations for potential interferents can be found in the supplement, CLSI document EP37.<sup>1</sup>

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# Contents

Abstract .....	i
Committee Membership .....	iii
Foreword .....	vii
<b>Chapter 1: Introduction .....</b>	<b>1</b>
1.1 Scope .....	2
1.2 Standard Precautions .....	3
1.3 Terminology .....	3
<b>Chapter 2: General Considerations .....</b>	<b>11</b>
2.1 Interference Testing Flow Chart .....	12
2.2 Contributions to Inaccurate Test Results .....	13
<b>Chapter 3: Preparing for Interference Testing .....</b>	<b>17</b>
3.1 Acceptance Criteria for Interference Testing .....	18
3.2 Measurand Concentrations .....	20
3.3 Potential Interferents .....	22
3.4 Interferent Test Concentrations .....	23
<b>Chapter 4: Quality Assurance and Safety .....</b>	<b>25</b>
4.1 Precision Verification .....	26
4.2 Trueness Verification .....	26
4.3 Carryover Assessment .....	26
4.4 Quality Control .....	26
4.5 Safety and Waste Disposal .....	27
<b>Chapter 5: Interference Screening Testing (Paired-Difference Testing) .....</b>	<b>29</b>
5.1 Determining the Number of Replicates .....	31
5.2 Preparing Test Materials .....	34
5.3 Experimental Procedure .....	39
5.4 Worked Example .....	42
<b>Chapter 6: Characterizing Interference Effects (Dose-Response Experiment) .....</b>	<b>45</b>
6.1 Experimental Design .....	46
6.2 Data Analysis .....	49

## Contents (Continued)

<b>Chapter 7: Evaluating Interference Using Patient Calculations</b> .....	<b>65</b>
7.1 Test Group of Patient Specimens .....	67
7.2 Control Group of Patient Specimens .....	67
7.3 Reference or Comparative Measurement Procedure .....	68
7.4 Experimental Procedure .....	68
7.5 Data Analysis .....	69
<b>Chapter 8: Investigating Discrepant Patient Results</b> .....	<b>75</b>
8.1 Verifying Measurement Procedure Performance .....	76
8.2 Evaluating Specimen Quality .....	76
8.3 Confirming the Original Result .....	77
8.4 Identifying Potential Interferents .....	77
8.5 Determining the Probable Interferent .....	78
8.6 Characterizing the Interference .....	79
<b>Chapter 9: Providing Information Regarding Interferences</b> .....	<b>81</b>
9.1 Information Useful for a Medical Laboratory .....	82
9.2 Providing Information to a Medical Laboratory .....	82
<b>Chapter 10: Conclusion</b> .....	<b>85</b>
<b>Chapter 11: Supplemental Information</b> .....	<b>87</b>
<b>References</b> .....	88
<b>Appendix A. Measurand Concentrations for Use in Interference Testing</b> .....	92
<b>Appendix B. Guidelines for Specific Measurement Procedures</b> .....	103
<b>The Quality Management System Approach</b> .....	106
<b>Related CLSI Reference Materials</b> .....	108

## Foreword

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Interferents can be a significant source of error in medical laboratory measurements.<sup>2-4</sup> Such errors can represent a hazard to the patient. Although performance is routinely monitored by internal QC and external quality assessment procedures, and accuracy can, in some cases, be verified by comparison to reference measurements, procedures, or materials (eg, commercial standards or weighed-in concentrations), laboratories cannot easily detect error caused by interferents. Therefore, manufacturers of *in vitro* diagnostic measuring systems need to include evaluation of potential interferents' effects in their risk analyses at the product design stage.

Although continually improving the selectivity of measurement procedures is a desirable goal, compromise is sometimes necessary to meet medical laboratories' needs. This guideline assists manufacturers and laboratories with evaluating interferents, determining the extent of interfering effects in the context of medical needs, and informing customers of known sources of medically significant error, in order to avert such errors. This guideline identifies many potential interferents to be evaluated in the risk management process.<sup>5</sup>

Manufacturers and medical laboratories are responsible for ensuring that measurement procedures are specific enough to meet the medical caregivers' needs. Laboratories should also investigate discrepant results for possible interferents and provide objective feedback to the manufacturers who supply their measuring systems.

To accommodate the variety of existing and future measurement procedures, this guideline is intended to provide recommendations instead of rigid protocols. The document development committee strived to achieve a balance between consistency of structured protocols and flexibility to accommodate the technology being evaluated. Laboratory scientists and manufacturers need to understand the scientific concepts, make informed choices, and work together toward the common goal of safeguarding patient care. Identifying an interference effect, evaluating its medical significance, determining its underlying cause, and ultimately improving the measurement procedure necessitates close cooperation between the laboratory and the manufacturer.

Background information is included to explain key chemical and statistical concepts.<sup>6</sup> It is important to note that this guideline focuses on interference with the examination portion of the measurement procedure. It does not include information on physiological effects caused by drugs and their metabolites. A series of recommendations on drug effects has been previously published as a compendium.<sup>7,8</sup> Comprehensive literature surveys of the analytical and physiological effects of drugs and other substances have also been published.<sup>3,4,9,10</sup>

## Overview of Changes

This guideline replaces the previous edition of the approved guideline, EP07-A2, published in 2005. Several changes were made in this edition, including:

- Improved the process for conducting drug screening and characterization to make it simpler and easily performed
- Reviewed and updated the statistics used in determining interference
- Updated the appendixes, including clarifying their purpose and function
- Moved former Appendixes C (Interferent Test Concentrations) and D (Interference Test Concentrations for Endogenous Analytes) to the new supplement, CLSI document EP37,<sup>1</sup> so they may be updated more frequently

**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

Evaluation

Interference

Interferent

Matrix effect

Risk management

Selectivity

Validation

Verification

# 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





# Interference Testing in Clinical Chemistry

## 1 Introduction

### 1.1 Scope

This guideline is intended for manufacturers and medical laboratories, for two purposes:

- Assist manufacturers and other developers of laboratory measurement procedures in characterizing the effects of potential interferences on measurement procedures results by providing information on:
  - Relevant interferences and concentrations to be tested
  - Likely effects of the interference on the concentration of the measurand of interest (ie, no effect, positive effect, or negative effect)
  - Scientifically valid experimental designs
  - Appropriate data analysis and interpretation
  - Stating meaningful interference claims
- Assist medical laboratories in investigating discrepant results that may be due to interferences by:
  - Defining a systematic investigation strategy
  - Specifying data collection and analysis procedures
  - Promoting greater cooperation between laboratory scientists and manufacturers so that new interferences are identified, disclosed, and ultimately eliminated

Any measurement procedure, quantitative or qualitative, may be subject to interference. This guideline is written for a broad spectrum of measurement procedures and measuring systems, with primary focus on quantitative methods and qualitative methods with interpretation based on numeric values. Modification may be necessary to accommodate the particular characteristics of the procedure being evaluated. Measurement procedures that use serum, plasma, whole blood, cerebrospinal fluid, urine, and most other body fluids can be evaluated for interferences using this guideline.

EP07 and its supplement, CLSI document EP37,<sup>1</sup> are not meant to include a complete list of interferences to be tested and do not stipulate that all potential interferences included in CLSI document EP37<sup>1</sup> are to be tested. However, EP07 and CLSI document EP37<sup>1</sup> are intended to provide a solid starting point for assessing interference effects. This guideline is limited to testing potential interference from chemical substances that may be exogenous (eg, drugs) or endogenous changes in concentrations of substances caused by disease processes (eg, bilirubin, lipoproteins).

# The Quality Management System Approach

Clinical and Laboratory Standards Institute (CLSI) subscribes to a quality management system (QMS) approach in the development of standards and guidelines that facilitates project management, defines a document structure using a template, and provides a process to identify needed documents. The QMS 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:

Organization	Personnel	Process Management	Nonconforming Event Management
Customer Focus	Purchasing and Inventory	Documents and Records	Assessments
Facilities and Safety	Equipment	Information Management	Continual Improvement

EP07 covers the QSE indicated by an “X.” For a description of the other documents listed in the grid, please refer to the Related CLSI Reference Materials section.

Organization	Customer Focus	Facilities and Safety	Personnel	Purchasing and Inventory	Equipment	Process Management	Documents and Records	Information Management	Nonconforming Event Management	Assessments	Continual Improvement
						X					
						C24					
						EP05					
						EP12					
						EP14					
						EP15					
						EP25					
						EP30					
						EP37					
						GP40					
		M29									

## Path of Workflow

A path of workflow is the description of the necessary processes to deliver the particular product or service that the organization or entity provides. A laboratory path of workflow consists of the sequential processes: preexamination, examination, and postexamination and their respective sequential subprocesses. All laboratories follow these processes to deliver their services, namely quality laboratory information.

EP07 covers the medical laboratory path of workflow process indicated by an "X." For a description of the other documents listed in the grid, please refer to the Related CLSI Reference Materials section.

Preexamination				Examination			Postexamination	
Examination ordering	Sample collection	Sample transport	Sample receipt and processing	Examination	Results review and follow-up	Interpretation	Results reporting and archiving	Sample management
				X		EP14		
				EP37	EP37	EP37		

## Related CLSI Reference Materials\*

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- C24** **Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions. 4th ed., 2016.** This guideline provides definitions, principles, and approaches to laboratory quality control design, implementation, and assessment.
- EP05** **Evaluation of Precision of Quantitative Measurement Procedures. 3rd ed., 2014.** This document provides guidance for evaluating the precision performance of quantitative measurement procedures. It is intended for manufacturers of quantitative measurement procedures and for laboratories that develop or modify such procedures.
- EP12** **User Protocol for Evaluation of Qualitative Test Performance. 2nd ed., 2008.** This document provides a consistent approach for protocol design and data analysis when evaluating qualitative diagnostic tests. Guidance is provided for both precision and method-comparison studies.
- EP14** **Evaluation of Commutability of Processed Samples. 3rd ed., 2014.** This document provides guidance for evaluating the commutability of processed samples by determining if they behave differently than unprocessed patient samples when two quantitative measurement procedures are compared.
- EP15** **User Verification of Precision and Estimation of Bias. 3rd ed., 2014.** This document describes the estimation of imprecision and of bias for clinical laboratory quantitative measurement procedures using a protocol that can be completed within as few as five days.
- EP25** **Evaluation of Stability of *In Vitro* Diagnostic Reagents. 1st ed., 2009.** This document provides guidance for establishing shelf-life and in-use stability claims for *in vitro* diagnostic reagents such as reagent kits, calibrators, and control panels.
- EP30** **Characterization and Qualification of Commutable Reference Materials for Laboratory Medicine. 1st ed., 2010.** This document provides information to help material manufacturers in the production and characterization of commutable reference materials, as well as to assist assay manufacturers and laboratorians in the appropriate use of these materials for calibration and trueness assessment of *in vitro* diagnostic medical devices.
- EP37** **Supplemental Tables for Interference Testing in Clinical Chemistry. 1st ed., 2018.** This document includes recommended testing concentrations for analytes and endogenous substances that may interfere in clinical chemistry measurement procedures and is intended for use with the evaluation procedures in the Clinical and Laboratory Standards Institute guideline EP07.

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\* 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)

- GP40**     **Preparation and Testing of Reagent Water in the Clinical Laboratory. 4th ed., 2012.** This document provides guidelines on water purified for clinical laboratory use; methods for monitoring water quality and testing for specific contaminants; and water system design considerations.
- M29**     **Protection of Laboratory Workers From Occupationally Acquired Infections. 4th ed., 2014.** 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.

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