

# EP07-A2

## Interference Testing in Clinical Chemistry; Approved Guideline—Second Edition

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

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

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## Interference Testing in Clinical Chemistry; Approved Guideline— Second Edition

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### Abstract

Clinical and Laboratory Standards Institute document EP07-A2—*Interference Testing in Clinical Chemistry; Approved Guideline—Second Edition* is intended to promote uniformity in the evaluation of interference characteristics of clinical laboratory measurement procedures. EP07 describes procedures for manufacturers to screen potentially interfering substances, to quantify interference effects, and to confirm interference in patient samples. This document also describes procedures for clinical laboratories to verify interference claims, and to investigate discrepant results caused by unsuspected interfering substances. Detailed examples are given. EP07 also contains background information on interference testing concepts, tables of recommended test concentrations for analytes and potential interference, and data collection and analysis worksheets.

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# Interference Testing in Clinical Chemistry; Approved Guideline—Second Edition

## 1 Scope

This document is intended to serve two purposes:

- 1) to assist manufacturers and other developers of laboratory measurement procedures in characterizing the susceptibility of measurement procedures to interfering substances, by offering scientifically valid experimental designs, by specifying the relevant substances and concentrations to be tested, and by clarifying appropriate data analysis and interpretation, so that potential hazards can be evaluated and meaningful interference claims may be provided to users; and
- 2) to assist clinical laboratories in investigating discrepant results due to interfering substances, by defining a systematic investigation strategy, by specifying data collection and analysis requirements, and by promoting greater cooperation between laboratory users and manufacturers, so that new interferences can be identified, disclosed, and ultimately eliminated.

This guideline is intended for manufacturers of *in vitro* diagnostic medical devices and clinical laboratories.

Manufacturers and other developers of laboratory measurement procedures are responsible for characterizing the analytical performance of their procedures and analyzing hazards to patients caused by errors due to interfering substances. Manufacturers are required to provide information about interference susceptibility to those who use their systems. **NOTE:** The term “manufacturer,” for the purpose of this document, is used to mean anyone that develops a measurement procedure for use in a clinical laboratory.

Clinical laboratories are responsible for ensuring that measurement procedures are specific enough to meet the needs of their physician clients. Laboratories should also investigate discrepant results, identify interfering substances, and provide objective feedback to the manufacturers who supply their analysis systems.

## 2 Introduction

### 2.1 Measurement Procedures

Any measurement procedure, quantitative or qualitative, may be subject to interference. This document is written for a broad spectrum of measurement procedures and analyzers. Modification may be necessary to accommodate the particular characteristics of the procedure being evaluated. Two specific method principles (i.e., separation techniques and immunochemical measurement procedures) are discussed in Appendix A.

#### 2.1.1 Specimen Type

Interferences with measurement procedures that use serum, plasma, whole blood, cerebrospinal fluid, urine, and most other body fluids may be evaluated using this guideline.

#### 2.1.2 Interfering Substances

Potentially interfering substances may originate from the following endogenous and exogenous sources:

- metabolites produced in pathological conditions, such as diabetes mellitus, multiple myeloma, cholestatic hepatitis, etc.;
- compounds introduced during patient treatment, such as drugs, parenteral nutrition, plasma expanders, anticoagulants, etc.;
- substances ingested by the patient, such as alcohol, drugs of abuse, nutritional supplements, various foods and drink, etc.;
- substances added during sample preparation, such as anticoagulants, preservatives, stabilizers, etc.;
- contaminants inadvertently introduced during sample handling from sources such as hand cream, powdered gloves, serum separators, collection tube stoppers, etc.; and
- the sample matrix itself, such as chemical and physical properties that differ from the ideal fresh sample.<sup>13-16</sup>

## 2.2 Concepts and Scientific Principles

### 2.2.1 Contribution of Interference to Inaccuracy

Inaccuracy (total analytical error) consists of three principal contributors: imprecision, method-specific bias, and sample-specific bias.<sup>17,18</sup> Measurement procedure evaluations frequently estimate only the first two. Sample-specific bias (i.e., interference) is often viewed as an isolated problem with specific samples, rather than as a quantifiable characteristic of the procedure. From the standpoint of an evaluation, susceptibility to interference causes both systematic and random error, both of which can be quantified statistically as components of inaccuracy (total analytical error).<sup>19,20</sup>

- For a given *patient population*, the average concentration of interfering substances in the samples may cause a systematic bias, which will be included in the estimate of bias. Individual deviations from this average bias contribute to the total random error observed in a comparison to a more specific measurement procedure. For some procedures, random interference effects exceed imprecision as the dominant source of random error.
- For an *individual patient*, interfering substances cause a bias dependent on their concentrations in the patient's specimen. The bias changes as the interferent concentration changes (e.g., due to clearance or metabolism). The resulting change in bias could be erroneously interpreted as a change in patient condition.

### 2.2.2 Clinical Relevance

In laboratory medicine, interference has to be viewed from a clinical perspective. Clinical relevance determines whether an analytical effect is considered interference. The form of the analyte intended to be measured and its concentration basis must be clearly defined.

Paradoxically, analytical results from some measurement procedures may reflect the true analyte concentrations, but not necessarily the clinically relevant values. For example, flame photometry and indirect potentiometry correctly measure the total concentration of sodium in an aliquot of plasma, regardless of the lipid concentration. However, if the lipid concentration is high, these procedures will falsely indicate hyponatremia in a patient with proper electrolyte balance. Direct potentiometry correctly reports normal sodium in this case, because it responds to sodium activity in the plasma water fraction, which is what the body regulates. Thus, overestimating the total sodium in the sample is appropriate from



### The Quality System Approach

Clinical and Laboratory Standards Institute (CLSI) subscribes to a quality management system approach in the development of standards and guidelines, which facilitates project management; defines a document structure via a template; and provides a process to identify needed documents. The approach is based on the model presented in the most current edition of CLSI/NCCLS document 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<br>Organization<br>Personnel | Equipment<br>Purchasing & Inventory<br>Process Control | Information Management<br>Occurrence Management<br>Assessment | Process Improvement<br>Service & Satisfaction<br>Facilities & Safety |
|--|--|---|--|

EP07-A2 addresses the quality system essentials (QSEs) indicated by an “X.” For a description of the other 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 C3 C24 EP5 EP9 EP14						

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

**Related CLSI/NCCLS Publications\***

- C3-P4**      **Preparation and Testing of Reagent Water in the Clinical Laboratory; Proposed Guideline—Fourth Edition (2005).** This document provides guidance on water purified for clinical laboratory use; methods for monitoring water quality and testing for specific contaminants; and water system design considerations.
- C24-A2**      **Statistical Quality Control for Quantitative Measurements: Principles and Definitions; Approved Guideline—Second Edition (1999).** This guideline provides definitions of analytical intervals, planning of quality control procedures, and guidance for quality control applications.
- EP5-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.
- EP9-A2**      **Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline—Second Edition (2002).** 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.
- 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 measurement procedures are compared.
- HS1-A2**      **A Quality Management System Model for Health Care; Approved Guideline—Second Edition (2004).** This document provides a model for providers of healthcare services that will assist with implementation and maintenance of effective quality management systems.

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\* 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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