CLINICAL AND LABORATORY STANDARDS INSTITUTE®

3rd Edition

EP07

Interference Testing in Clinical Chemistry

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

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

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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.[1]

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Foreword

Interferents can be a significant source of error in medical laboratory measurements.[2-4] 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.[5]

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.[6] 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.[7,8] Comprehensive literature surveys of the analytical and physiological effects of drugs and other substances have also been published.[3,4,9,10]

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,[1] 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 interferents on measurement procedures results by providing information on:
  - Relevant interferents and concentrations to be tested
  - Likely effects of the interferent 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 interferents by:
  - Defining a systematic investigation strategy
  - Specifying data collection and analysis procedures
  - Promoting greater cooperation between laboratory scientists and manufacturers so that new interferents 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 interferents using this guideline.

EP07 and its supplement, CLSI document EP37,[1] are not meant to include a complete list of interferents to be tested and do not stipulate that all potential interferents included in CLSI document EP37[1] are to be tested. However, EP07 and CLSI document EP37[1] 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).

This guideline does not cover potential interference from physiological conditions (eg, pregnancy, diurnal effects) or effects from environmental conditions (eg, heat, sunlight).

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.[11] 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.[12]

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.

Within this guideline, the terms "specimen" and "sample" are differentiated as follows: the term "specimen" refers to the component taken directly from the body, with or without anticoagulants and preservatives, that has not been physically or chemically changed, except that it may have been centrifuged (ie, blood cells have been separated from the serum or plasma); the term "sample" is used to denote a specimen that has been physically or chemically changed from its original state, as in having been spiked with a potential interferent.

The term "manufacturer," for the purpose of this guideline, is used to mean any person or organization that develops a measurement procedure for use in a medical laboratory, including *in vitro* diagnostic device manufacturers and laboratories that make laboratory-developed tests.

IMPORTANT NOTE:

This guideline does not cover potential interference from physiological conditions or effects from environmental conditions.