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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.

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 document EP7-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. EP7 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. EP7 also contains background information on interference testing concepts, tables of recommended test concentrations for analytes and potential interferences, and data collection and analysis worksheets.

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Foreword

Interfering substances can be a significant source of error in clinical laboratory measurements.[1-3] Such errors may, in some cases, represent a hazard to the patient. While precision is routinely monitored by internal quality control, and accuracy can be verified by comparison to reference materials or procedures, laboratories cannot easily detect error caused by interfering substances. Therefore, manufacturers of *in vitro* diagnostic (IVD) analytical systems must include evaluation of the effects of the potentially interfering substances in their risk analyses at the design stage.

Although continuously improving the specificity of measurement procedures is a desirable goal, compromise is sometimes necessary to meet the needs of clinical laboratories. The purpose of this document is to enable manufacturers and laboratories to evaluate interfering substances in the context of medical needs and to inform their customers of known sources of medically significant error. This guideline identifies potential hazards to be evaluated in the risk management process described in ISO 14971.[4]

To accommodate the variety of existing and future measurement procedures, we provided guidance instead of rigid protocols. The subcommittee struck a balance between consistency of structured protocols and flexibility to accommodate the technology being evaluated. Laboratorians and manufacturers need to understand the scientific concepts, make informed choices, and work together toward the common goal of improving patient care. Clearly, identifying an interference effect, evaluating its medical significance, determining its underlying cause, and ultimately improving the measurement procedure requires close cooperation between laboratory and manufacturer.

Background information is included to explain key chemical and statistical concepts. Please note that this document focuses on interference with analytical processes. It does not address physiological effects caused by drugs and their metabolites. The IFCC has issued a series of recommendations on drug effects[5-7] that have been published as a compendium.[8] Comprehensive literature surveys of the analytical and physiological effects of drugs and other substances have been published.[9-11]

The basic substance of EP7-A2 remains unchanged. A thorough review of the exogenous and endogenous compounds recommended for testing was performed. Each drug or drug metabolite was systematically categorized into specific drug classes. This guideline was developed to inform the reader and provide a logical approach to complete the evaluation of the effects of potentially interfering compounds on the measurement procedure test results. The guideline is intended to make the decision easier by basing it on reasonable, objective criteria. We now ask the reader to give us comments and suggestions. Each comment and suggestion will be considered carefully at the next revision.

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 pathological 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 obstacles to harmonization. Despite these obstacles, CLSI recognizes that harmonization of terms facilitates the global application of standards and is an area that needs 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 EP7-A2:

The term *trueness* has replaced the term *accuracy* when referring to the closeness of agreement between the *average value* obtained from a large series of test results and an accepted reference value. *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, thus comprising both random and systematic effects.

The term *measurement procedure* has replaced the terms *method*, *analytical method,* and *analytical system* for a set of operations used in the performance of particular measurements according to a given method. The term *assay* has been replaced by *method, measurement procedure, measurement, analyze,* and *analysis* as appropriate. At this time, due to user unfamiliarity, the term *examination* is not used in this edition of EP7.

The terms *specimen* and *sample* are both used in this document, with *specimen* reserved for material collected directly from the patient, and *sample* reserved for aliquots of the patient specimen and for processed materials (e.g., PT samples, reference materials).

The term *analyte* is used appropriately in this document. The term a*nalyte* is used to represent the particular component of interest to the patient diagnosis, while the term *measurand* is used to describe the specific quantity that is measured by a particular measurement procedure (i.e., the measurand describes what is actually causing the result of the measurement). This important difference can be subtle, since it can be due to the detection of different measurands in the procedures being compared. The term *precision* is a measure of "closeness of agreement between independent test/measurement results obtained under stipulated conditions."[12] The terms in this document are consistent with uses defined in the ISO 3534 and ISO 5725 series of standards.

At this time, due to user unfamiliarity and for the sake of the practicability of the guideline, it is important to point out that the working group has chosen not to replace the term *interfering substance* or *interferent* with the VIM (*International Vocabulary of Basic and General Terms in Metrology*) term *influence quantity* (i.e., quantity that is not the measurand but that affects the result of the measurement). The users of EP7 should understand that the fundamental meanings of the terms are identical, and to facilitate understanding, the terms are defined along with their ISO counterparts in the guideline's Definitions section.

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

Evaluation, hazard analysis, interference, interferent, matrix effects, performance claims, risk management, specificity, validation, verification

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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: