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C50-A

Mass Spectrometry in the Clinical Laboratory: General Principles and Guidance; Approved Guideline

This guideline provides a general understanding of mass spectrometry and the principles that dictate its application in the clinical laboratory. It includes guidance, references, and quality assurance markers that will assist with the implementation and correct operation of a mass spectrometry (MS) system for its many applications. Information on maintaining optimum performance, approaches to ensuring accurate and precise mass measurement, verification of methods, quality control of assays within and between instruments, instrument troubleshooting, sample preparation, interpretation of results, and limitations of the technology is included.

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

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NOTE: This document is no longer being reviewed as part of the CLSI consensus process. However, because of its usefulness to segments of the health care community, it is available for its informational content.

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Abstract

Clinical and Laboratory Standards Institute document C50-A—*Mass Spectrometry in the Clinical Laboratory: General Principles and Guidance; Approved Guideline* provides a general understanding of MS and the principles that dictate its application in the clinical laboratory. It includes guidance, references, and quality assurance markers that will assist with the implementation and correct operation of an MS system for its many applications. Information on maintaining optimum performance, approaches to ensuring accurate and precise mass measurement, verification of methods, quality control of assays within and between instruments, instrument troubleshooting, sample preparation, interpretation of results, and limitations of the technology is included. This document is intended to be a basic resource for clinical chemists; health practitioners; instrument manufacturers; and those responsible for developing standards, implementing policy, and teaching.

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Contents

Foreword

Since the early 1900s, mass spectrometry (MS) has been employed as an analytical tool in science (chemistry and physics) and industry (petroleum and pharmaceutical). Gas chromatography-mass spectrometry (GC-MS) was introduced into clinical medicine for the identification of inborn errors of organic acid metabolism; this type of MS analysis has been practiced for more than a quarter century.[1-3] Laboratories adopting this method were often specialized reference- or university-based medical centers, principally because of the complexity of sample preparation and the expertise required for interpretation of the results.

The development of more user-friendly, affordable, and versatile mass spectrometers has since allowed a large increase in the use of MS for clinical applications. This was also facilitated by the availability of stable isotopes that can serve as internal standards, thereby allowing for more accurate quantitation. An excellent history of MS has been published.[4] Most early clinical applications of MS employed GC-MS systems to analyze small biochemical compounds such as amino acids, fatty and organic acids, steroids, and simple carbohydrates; however, over the last two decades, rapid developments in ion sources have provided the opportunity to analyze more water-soluble, polar compounds, including peptides, proteins, oligonucleotides, DNA, and trace elements.[5]

The purpose of this document is to provide accurate and state-of-the-art information and guidance for the appropriate use of MS in the clinical laboratory. However, this document cannot cover all possibilities in this rapidly developing field, and the recommendations made herein should be interpreted in the light of continuing progress.

The greater part of this document focuses on a general understanding of MS and the principles that dictate its application in the clinical laboratory. To illustrate these concepts, portions of methods currently practiced and in widespread use are provided. More specific applications of some methods are provided in the appendix. This document is intended to be a basic resource for clinical chemists; health practitioners; instrument manufacturers; regulatory agencies; and those responsible for developing standards, implementing policy, and teaching. It is hoped that this document will be used to support future guidelines and recommendations for specific clinical applications pertaining to a mass spectrometric method.

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 metrological 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. In light of this, CLSI recognizes that harmonization of terms facilitates the global application of standards and deserves immediate attention. Implementation of this policy must be an evolutionary and educational process that begins with new projects and revisions of existing documents.

In the context of this document, it is necessary to point out that the term *analyte* is used differently in the United States and other countries, notably those in Europe. ISO defines the term *analyte* as a component represented in the name of a measurable quantity; but uses the term *measurand* (a particular quantity subject to measurement) when the term relates to a biological fluid/matrix. In the United States, *analyte* is used to describe both a single component (analyte) as well as the analyte in its specific matrix (measurand).

Also, in order to align the usage of terminology in this document with that of ISO, the following terms are used in C50-A:

The term *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, and comprises both random and systematic effects. *Trueness* is used in this document when referring to the "closeness of the agreement between the average value from a large series of measurements and a true value of a measurand"; the measurement of trueness is usually expressed in terms of *bias.* The term *measuring range* has replaced *reportable range* when referring to "a set of values of measurands (analytes) for which the error of a measuring instrument (test) is intended to lie within specified limits." The term *measurement procedure* has replaced *analytical method* when referring to a set of operations, described specifically, used in the performance of particular measurements according to a given method. The terms *diagnostic sensitivity* and *diagnostic specificity* have replaced the terms *clinical sensitivity* and *clinical specificity* because in Europe, the term "clinical" often refers to clinical studies of drugs under stringent conditions.

Users of C50-A should understand, however, that the fundamental meanings of the terms are identical in many cases, and to facilitate understanding, terms are defined in the Definitions section of this guideline.

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

Biomarker, GC-MS, ionization, isotope, LC-MS, mass spectra, mass spectrometry, mass spectrum, metabolism, proteins

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1 Scope

This document provides an introduction to, and guidance, resources, and references for, the use of mass spectrometry (MS) in the clinical laboratory. It serves to illuminate specific issues in mass spectrometric analyses that must be considered when the technology is applied to clinical testing. This guideline aims to educate both the practitioners of MS and the medical professionals who use the results produced by the instruments for the diagnosis, characterization, or monitoring of disease. Through knowledge of this material, the medical professional will better understand why MS may be preferred for a clinical application. They will also become more informed consumers when selecting a diagnostic laboratory to provide MS services. This document is also intended to be a basic resource for instrument manufacturers; regulatory agencies; and those responsible for developing standards, implementing policy, and teaching.

Selected examples of “routinely utilized clinical assays” are used to describe the fundamental principles of MS. These examples are primarily from tests for small molecules and metabolites. There is also a brief discussion of the MS analysis of other analytes that are either not common in clinical chemistry application at the time of this writing or are highly specialized, warranting their own document. These analytes include elements, peptides, proteins, and other biopolymers, including oligonucleotides.

A description of all current clinical applications of MS is beyond the scope of this document. Therefore, the goal of this guideline is to provide a basic understanding of the technology and how it should be used in the clinical laboratory with an emphasis on:

- advantages and disadvantages;
- precautions required in its use;
- quality control awareness;
- assay verification/validation;
- approaches to reporting results; and
- communication of the data.

Portions of published and validated clinical methods are discussed in more detail to illustrate these concepts when required.

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 infectious agents and thus are more comprehensive than universal precautions which are intended to apply only to transmission of blood-borne pathogens. Standard and universal precaution guidelines are available from the U.S. Centers for Disease Control and Prevention.[6] For specific precautions for preventing the laboratory transmission of all infectious agents from laboratory instruments and materials and for recommendations for the management of exposure to all infectious disease, refer to CLSI document M29.[7]