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Gas Chromatography/Mass Spectrometry (GC/MS) Confirmation of Drugs; Approved Guideline

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Abstract

NCCLS document C43-A— *Gas Chromatography/Mass Spectrometry (GC/MS) Confirmation of Drugs; Approved Guideline* is intended to aid the laboratorian in developing appropriate procedures for the use of GC/MS in confirmation analyses. Its primary objective is to establish uniform practices necessary for producing quality data for quantitation and identification of a drug or drug metabolite. To support the scientific basis of the uniform practices, a brief overview of the techniques is provided. Specific quality assurance criteria for maintaining and documenting optimal instrument performance are presented.

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Foreword

The detection of a drug in the biological fluid of an individual can have serious professional, financial, and social consequences. It is generally accepted that detection of a drug by a screening procedure must be confirmed by a second method based on a different analytical or physical principle. The purpose of the confirmation test is to decrease the probability of false-positives and to provide additional information and assurance about the identity of the detected compound.

Gas chromatography/mass spectrometry (GC/MS) is widely accepted in both scientific and legal arenas as one of the most powerful analytical techniques for the separation, quantification, and identification of drug analytes, especially at low concentrations. Technological advances have allowed introduction of bench-top GC/MS instrumentation into forensic and clinical toxicology laboratories. Further advances will continue to move state-of-the-art techniques such as gas- and liquid-phase chemical ionization, tandem mass spectrometry, high-resolution mass spectrometry, and high-performance liquid chromatography/mass spectrometry (HPLC/MS) into routine laboratory operation. Appropriate application of these analytical tools requires that the methods used are fit for their purpose and the instruments are operating correctly.

The Division of Workplace Programs, Substance Abuse and Mental Health Services Administration of the United States Department of Health and Human Services oversees the best-known drug testing program. The U.S. National Laboratory Certification Program has issued guidance documents for laboratories involved in the federal workplace drug-testing program. A similar program is under consideration in the European Union. Confirmatory assays are also used in clinical toxicology, forensic toxicology, and athletic drug testing. Currently available guidelines are not appropriate for all drug confirmation testing. The present guideline was developed to provide assistance in developing confirmation tests that are fit for the analytical purpose in each of these areas.

This guideline addresses the instrumental and methodological issues in developing a chromatographic - mass spectrometric method, routine performance of the analysis, and continued quality assurance. The chain of custody, while an important part of any test result to be submitted to the judicial system, is not discussed here. Guidelines for sample collection and screening testing have been published. Refer to the most current edition of NCCLS document T/DM8—*Urine Drug Testing in the Clinical Laboratory* for recommendations on sample collection and screening testing.

Key Words

Athletic drug testing, clinical toxicology, drugs of abuse, forensic toxicology, gas chromatography, magnetic sector mass spectrometer, mass spectrometry, quadrupole mass spectrometer, tandem mass spectrometry

A Note on Terminology

NCCLS, as a global leader in standardization and harmonization, 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. NCCLS 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 NCCLS, 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, NCCLS 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.

Of particular note in C43-A, are several terms whereby NCCLS intends to eliminate confusion over time, through its commitment to harmonization. For instance, the term "accuracy" comprises three different concepts that ISO documents capture with three distinct terms; i.e., "accuracy," "trueness," and "bias." Also in the context of this guideline, the term "precision" is defined the way ISO defines "uncertainty." To facilitate understanding, all ISO terms are defined in the guideline's "Definitions" section under the terms "accuracy" and "precision."

All terms and definitions will be reviewed for consistency with international use, and revised appropriately during the next scheduled revision of this guideline.

The Quality System Approach

NCCLS subscribes to a quality 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 through a gap analysis. The approach is based on the model presented in the most current edition of NCCLS HS1—*A Quality System Model for Health Care*. The quality 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. 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:

QSEs	
Documents & Records	Information Management
Organization	Occurrence Management
Personnel	Assessment
Equipment	Process Improvement
Purchasing & Inventory	Service & Satisfaction
Process Control	Facilities & Safety

C43-A addresses the following quality system essentials (QSEs):

Documents & Records	Organization	Personnel	Equipment	Purchasing & Inventory	Process Control	Information Management	Occurrence Management	Assessment	Process Improvement	Service & Satisfaction	Facilities & Safety
					X						

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

A path of workflow is the description of the necessary steps to deliver the particular product or service that the organization or entity provides. For example, GP26-A2 defines a clinical laboratory path of workflow which consists of three sequential processes: preanalytical, analytical, and postanalytical. All clinical laboratories follow these processes to deliver the laboratory’s services, namely quality laboratory information. The arrow depicts the sequence, from left to right, that any clinical laboratory follows. In addition, the necessary steps or subprocesses are listed below them.

Gas Chromatography/Mass Spectrometry (GC/MS) Confirmation of Drugs; Approved Guideline

1 Introduction

Gas chromatography/Mass spectrometry (GC/MS) is generally accepted as the “gold standard” for identification and quantitation of drug analytes. As such, it is frequently used to confirm presumptive positive drug screening tests performed by immunoassay, thin-layer chromatography, high-performance liquid chromatography, or gas chromatography. The confidence in the ability of GC/MS to provide unequivocal analytical data is based on recognition of its reproducibility, repeatability, specificity, and trace detection capabilities. While this confidence is well founded, the measurement and identification of trace levels of compounds in complex biological matrices such as urine, hair, blood, bile, or organ tissue present a unique problem. Since GC/MS confirmation tests are applied in areas of clinical and forensic science other than drugs of abuse testing, it seems appropriate to establish broader criteria.

2 Scope

In drug analysis, GC/MS is used either to increase confidence in the identification of an unknown compound or to improve the limits of detection or quantitation through increased analytical specificity. Because of this unique combination of identification and quantitation capabilities, GC/MS methods, particularly confirmation methods, require a specific set of criteria for validation of methods and for performance verification in routine analysis.

There are two broad classes of drug analysis performed with GC/MS instrumentation. For some compounds, quantitative concentration thresholds have been established, on scientific and administrative grounds, to determine the presence of the drug or drug metabolite. When the threshold concentration, threshold ratio of amounts, or other defined parameter is exceeded, the compound is deemed to be present or to be present in nonphysiological amounts. In these cases, the performance of the method and instrument at the threshold has particular importance. The best-known example of the threshold approach was the development of specific administrative threshold concentrations and criteria for identification of five drugs of abuse for the federal drug-testing program.¹ For some other drugs or drug metabolites, however, detection at any documentable concentration is of concern. For these nonthreshold compounds, performance criteria for identification may be more important than the ability to quantify.

Although bench top GC/MS instrumentation has become more available and easier to use, a uniform practice must be established and maintained to provide acceptable evidence in an administrative appeal hearing or legal setting. Continuing improvements in theory and instrumentation will facilitate the use of new techniques, such as GC/MS/MS, in routine analysis. Thus, there is a need to define uniform practices not only for routine GC/MS methods, but also for the application of these more sophisticated approaches.

3 Standard Precautions

Because it is often impossible to know what might be infectious, all human blood specimens are to be treated as infectious and handled according to “standard precautions.” Standard precautions are new guidelines that combine the major features of “universal precautions and body substance isolation” practices. Standard precautions cover the transmission of any pathogen and thus are more comprehensive than universal precautions which are intended to apply only to transmission of blood-borne pathogens. Standard precaution and universal precaution guidelines are available from the U.S. Centers for Disease Control and Prevention (*Guideline for Isolation Precautions in Hospitals*. Infection Control and Hospital Epidemiology. CDC. 1996;Vol 17;1:53-80), (MMWR 1987;36[suppl 2S]2S-18S), and (MMWR 1988;37:377-382, 387-388). For specific precautions for preventing the laboratory transmission of blood-borne infection from laboratory instruments and materials and for recommendations for the management

Related NCCLS Publications*

- EP6-P2** **Evaluation of the Linearity of Quantitative Analytical Methods: A Statistical Approach; Proposed Guideline—Second Edition (2001).** This document provides guidelines for characterizing the linearity of a method during a method evaluation; for checking linearity as part of routine quality assurance; and for determining and stating a manufacturer's claim for linear range.
- M29-A2** **Protection of Laboratory Workers from Occupationally Acquired Infections – Second Edition; Approved Guideline (2001).** This document provides guidance on the risk of transmission of hepatitis viruses and human immunodeficiency viruses in any laboratory setting; specific precautions for preventing the laboratory transmission of bloodborne infection from laboratory instruments and materials; and recommendations for the management of bloodborne exposure.
- NRSCL8-A** **Terminology and Definitions for Use in NCCLS Documents; Approved Standard (1998).** This document provides standard definitions for use in NCCLS standards and guidelines, and for submitting candidate reference methods and materials to the National Reference System for the Clinical Laboratory (NRSCL).
- T/DM6-A** **Blood Alcohol Testing in the Clinical Laboratory; Approved Guideline (1997).** This document provides technical and administrative guidance on laboratory procedures related to blood alcohol testing, including specimen collection, methods of analysis, quality assurance, and reporting of results.
- T/DM8-A** **Urine Drug Testing in the Clinical Laboratory; Approved Guideline (1999).** This guideline addresses the development of procedures for analysis of urine to determine the presence of certain controlled substances; for specimen collection and processing; for methods of analysis; for quality assurance; and for the reporting and interpretation of results.

* Proposed- and tentative-level documents are being advanced through the NCCLS consensus process; therefore, readers should refer to the most recent editions.