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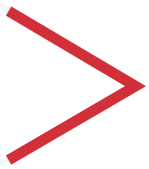
Gas Chromatography/Mass Spectrometry Confirmation of Drugs; Approved Guideline—Second Edition



This document provides guidance on establishing uniform practices necessary to produce quality data for quantitation and identification of a drug or drug metabolite using the gas chromatography/mass spectrometry method. Specific quality assurance criteria for maintaining and documenting optimal instrument performance are also presented.

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

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Gas Chromatography/Mass Spectrometry Confirmation of Drugs; Approved Guideline—Second Edition

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Abstract

Clinical and Laboratory Standards Institute document C43-A2—*Gas Chromatography/Mass Spectrometry Confirmation of Drugs; Approved Guideline—Second Edition* is intended to aid the laboratorian in developing appropriate procedures for the use of gas chromatography/mass spectrometry 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. As a result, it is often necessary or even required that the detection of a drug using a screening procedure be confirmed using a second method based on a different analytical or physical principle possessing greater sensitivity and specificity than the initial method used for screening. The purpose of the confirmation test is to decrease the probability of false-positive results 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, quantitation, 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 continue to move state-of-the-art techniques such as gas- and liquid-phase chemical ionization, tandem mass spectrometry (MS/MS), 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 verified for the purpose and that instruments are operating correctly.

This edition of C43 was revised to clarify concepts and terminology. Some minor content additions were also made, such as MS/MS and time-of-flight (TOF) mass spectrometry.

NOTE: The scope of this document is the use of GC/MS in drug confirmation analyses. By definition, it is assumed that the user is attempting to confirm a screening result obtained using another testing method.

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

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1 Scope

This document is intended to aid the laboratorian in developing appropriate procedures for the use of GC/MS in drug *confirmation* analyses. By definition, it is assumed that the user is attempting to confirm a result obtained using a screening method such as immunoassay. It addresses the instrumental and methodological issues in developing a chromatographic mass spectrometric method, routine performance of the analysis, and continued quality assurance.

Guidance documents exist for laboratories involved in regulatory workplace drug-testing programs and are used in laboratories certified by these programs. Additionally, each laboratory needs to consult its own country's regulatory requirements.[a] However, confirmatory assays are also used in settings outside federal workplace drug testing programs, eg, by laboratories engaged in clinical toxicology, other types of forensic testing, and athletic testing. The present guideline was developed to provide assistance in developing GC/MS confirmation tests that are fit for the analytical purpose in each of these areas.

The chain of custody, although 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 CLSI document C52[1] for recommendations on sample collection and screening testing.

2 Introduction

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, HPLC, or GC. 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. Although this confidence is well founded, the measurement and identification of trace levels of compounds in biological matrices such as urine, hair, blood, bile, or organ tissue present a unique problem due to the complex and variable nature of the matrices. Because GC/MS confirmation tests are applied in areas of clinical and forensic science other than workplace drug testing, it seems appropriate to establish broader criteria.

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 verification of methods and for performance verification in routine analysis.

Two broad uses of drug analysis are performed with GC/MS instrumentation. In the first use, the presence or absence of a drug or drug metabolite is determined using concentration thresholds. These thresholds are based on either scientific criteria or administrative needs. 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

[a]In the United States, 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 US National Laboratory Certification Program provides guidance for laboratories involved in federal workplace drug testing programs.