

C52

Toxicology and Drug Testing in the Medical Laboratory

This guideline provides an overview of drug testing by medical laboratories, including testing for drugs of abuse. It discusses the preexamination, examination, and postexamination considerations for specimen collection, methods of analysis, and the reporting and interpretation of results.

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

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Toxicology and Drug Testing in the Medical Laboratory

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Abstract

Clinical and Laboratory Standards Institute guideline C52—*Toxicology and Drug Testing in the Medical Laboratory* helps medical laboratories develop procedures for analyzing drugs of abuse and other compounds. C52 provides guidance on clinical toxicology testing from the initial consultation through final result reporting and interpretation, and includes a variety of specimen types, analytical procedures, and instrumentation.

This guideline discusses the most common purposes for clinical toxicology testing, including the support of emergency medicine, obstetrics and gynecology, neonatology, pediatrics, psychiatry, pain management, and addiction medicine. The primary objective is to ensure high-quality standards are maintained throughout the entire testing process, from specimen collection, processing, and analysis, through results reporting and interpretation.

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C52, 3rd ed.

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Foreword

For the purposes of this guideline, it is necessary to initially define “drug.” In the broadest sense, a drug is any chemical or compound administered to produce a physiological effect. From a legal perspective, “drug” often refers to substances for which the manufacture, possession, and use are regulated by government mandates, including drugs of abuse and prescription drugs. This guideline provides an overview of the analysis of scheduled drugs, nonprescription drugs, synthetic designer drugs, and other nonscheduled compounds. Substances medical laboratories do not typically analyze, such as solvents and anabolic steroids, are beyond this guideline’s scope.

This guideline discusses the detection and quantitation of drugs and compounds in biological specimens for medical purposes. Readers should be aware that clinical toxicology and drug testing results may be used in a court of law as part of the medical record and, inadvertently, become medico-legal results. However, formal forensic testing is also outside this guideline’s scope.

This guideline provides helpful information about preexamination, examination, and postexamination procedures for both screening and definitive testing that meet clinical needs. Each laboratory needs to determine medical staff’s and patients’ expectations and support the relevant extent of testing. Every laboratory cannot reasonably be expected to test for the same drugs or offer analyses for all drugs for which analytical procedures are available. In fact, laboratories should not offer drug tests simply because the measurement procedures are readily available. Laboratory directors need to determine the appropriate offering for drug testing.

Toxicology testing has traditionally been performed in medical laboratories, and this continues to be the case for most testing. However, many point-of-care testing devices, especially screening devices for drugs of abuse, are now available.^{1,2}

Many sources provide information about how to conduct drug testing. After extracting general information from this guideline, users should consult more specific and detailed textbooks, peer-reviewed professional journal papers, websites, and other sources. Readers need to use discretion when adapting this guideline’s recommendations to suit specific purposes and circumstances.

Clinical drug testing is readily distinguished from forensic drug testing because clinical specimens are not collected using a documented chain of custody. Clinical toxicology specimens are collected and processed following the same procedures used for other clinical specimens. Many clinical toxicology measurement procedures are quantitative, but qualitative screening tests may also be used. The results of rapid screening tests may be clinically useful, but their results may not always be confirmed by more specific methods.

Forensic testing is not usually conducted in most medical laboratories or only takes place infrequently and under unusual circumstances. However, there is the potential for situations in which the distinction between clinical and forensic testing becomes blurred. For example, a pregnant woman who undergoes drug testing as a patient but who screens positive for a drug of abuse could be referred to the authorities for prosecution for use or endangering the fetus. Testing of emergency room patients for ethanol may have forensic implications, eg, in the case of a motor vehicle accident with fatalities. It may not be possible for a laboratory to foresee all potential scenarios that can arise, and it may not have a standard operating procedure that covers all eventualities.

Guidelines for conducting drug testing in medical laboratories are presented using any number of organizational schemes. The approach in this guideline follows laboratory preexamination, examination, and postexamination workflow processes for both screening and definitive toxicology testing. This approach is consistent with other guidance documents that seek to ensure the entire laboratory testing process’s quality, from the time a test is ordered until a result is reported.

Clinical and analytical toxicology are rapidly changing sciences. Although efforts have been made to include the most common issues, not all measurands, instruments, or scenarios could be included in this guideline. Therefore, these recommendations may not be applicable to all circumstances, analytical methods, or scenarios.

Overview of Changes

This guideline replaces the previous edition of the approved guideline, C52-A2, published in 2007. Several changes were made in this edition, including:

- Focusing the guideline exclusively on clinical toxicology testing (in contrast to previous editions of C52, which focused extensively on clinical and forensic testing for drugs of abuse)
- Removing forensic testing, to avoid redundancy with forensic testing recommendations published by forensic organizations

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

Abused drugs, clinical toxicology, controlled substances, drug abuse, drug screen, drug testing, drugs, drugs of abuse, emergency toxicology, ethanol, forensic toxicology, intoxication, overdose, serum drug testing, substance abuse, therapeutic drugs, toxicology, urine drug testing

Toxicology and Drug Testing in the Medical Laboratory

Chapter 1: Introduction

This chapter includes:

- Guideline's scope and applicable exclusions
- Background information pertinent to the guideline's content
- 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

1.1 Scope

This guideline provides laboratories with basic and general toxicology testing information for medical purposes. The guideline discusses the most common specimen types used for toxicology testing, which include urine, serum, plasma, blood, oral fluid, hair, meconium, sweat, and breath. Other matrixes that can be used for toxicology testing include, but are not limited to, gastric contents, umbilical cord and cord blood, amniotic fluid, breast milk, nails, dried blood spots, and placental tissue. However, these other matrixes are not discussed in this guideline.

The measurands considered in this guideline include drugs of abuse, therapeutic drugs, over-the-counter (OTC) medications, ethanol, and miscellaneous substances. Test methodologies include rapid screening measurement procedures designed to produce only positive or negative results (qualitative tests), routine semiquantitative and quantitative tests, and more complex definitive measurement procedures.

C52 also provides useful guidance when performing drug testing for measurands other than those specifically included and for purposes and situations not covered.

This guideline is primarily applicable to drug testing performed in medical laboratories. The information is likely applicable for drug testing performed in physician office laboratories, clinics, satellite laboratories, and other facilities, but may be less applicable in other testing venues, such as large specialized reference laboratories, dedicated forensic laboratories, and the various sites in which point-of-care "field testing" may occur.

1.2 Background

1.2.1 Purposes of Clinical Toxicology Testing

Clinical toxicology testing is performed for medical reasons. The specimens are collected from patients to diagnose, monitor, and treat pathological conditions. Clinical toxicology testing often involves the following situations:

- Evaluating unexplained symptoms
- Determining substance abuse
- Investigating unusual responses to treatment
- Monitoring addictive medications
- Managing patients in chronic pain

In cases for which immunoassay screening is part of the analytical process, confirmation testing for drugs of abuse is highly desirable. Whether to confirm or not confirm a particular drug or drug class is a decision each laboratory and requesting health care provider makes. Some laboratories have opted to use definitive testing in lieu of immunoassay screening.

Purposes for drug testing and the implications of qualitative and quantitative drug testing are discussed in the scenarios that follow. The terms “qualitative” and “quantitative” are not intended to be analogous to “screening” and “confirmation.” Qualitative testing may involve screening methods or definitive methods with qualitative results. Quantitative testing typically targets specific analytes, but may not provide definitive results.

Purpose 1: Detecting drugs, medications, and chemicals in the setting of toxic ingestion

Qualitative testing: Although clinicians are trained to recognize physiological features associated with specific drug classes, knowing which compounds are present can provide valuable information when treating the comatose, seizing, or obtunded patient. This is especially true during instances of polydrug overdoses, which often present with a variety of symptoms that do not fit a single toxidrome.

Conversely, qualitative testing in emergent situations is not recommended because:

- It does not confirm or rule out significant poisoning.
- It may not provide information that leads to a meaningful change in acute clinical management.
- Many drugs contribute to common clinical symptoms seen in an emergency department that are not detected by some methods (eg, immunoassay screening tests).
- Testing (immunoassays) may not be specific (ie, there are multiple false-positive results, which then need explanation and perhaps investigations).
- A positive result does not mean the detected drug is what is contributing to the patient’s symptoms.³⁻¹³

Quantitative testing: Some clinicians prefer quantitative over qualitative testing using serum, plasma, or blood. Quantitative drug levels offer valuable information to the clinician treating the acutely toxic patient. This is especially true during instances of polydrug overdose in which a variety of symptoms may confuse the clinician. However, developing quantitative measurement procedures for the thousands of available drugs, medications, and compounds is not practical or realistic. Toxicologists should work closely with clinicians to determine which compounds are the most appropriate candidates for quantitative measurement procedures. It should be noted that quantitative analysis in urine is of questionable clinical value due to variable urine output.

Purpose 2: Ensuring medication compliance

Qualitative testing: Studies have shown that patients tested for their respective drugs by any method are more likely to be compliant than those not tested.¹⁴ Qualitative drug testing serves this purpose and provides clinicians with immediate results to use during the office visit. For example, when a patient’s drug test

The Quality Management System Approach

Clinical and Laboratory Standards Institute (CLSI) subscribes to a quality management system (QMS) approach in the development of standards and guidelines, which facilitates project management; defines a document structure using a template; and provides a process to identify needed documents. The QMS approach applies a core set of “quality system essentials” (QSEs), basic to any organization, to all operations in any health care service’s path of workflow (ie, operational aspects that define how a particular product or service is provided). The QSEs provide the framework for delivery of any type of product or service, serving as a manager’s guide. The QSEs are as follows:

Organization	Personnel	Process Management	Nonconforming Event Management
Customer Focus	Purchasing and Inventory	Documents and Records	Assessments
Facilities and Safety	Equipment	Information Management	Continual Improvement

C52 covers the QSEs indicated by an “X.” For a description of the other documents listed in the grid, please refer to the Related CLSI Reference Materials section.

Organization	Customer Focus	Facilities and Safety	Personnel	Purchasing and Inventory	Equipment	Process Management	Documents and Records	Information Management	Nonconforming Event Management	Assessments	Continual Improvement
		M29			C24 EP19	X C24 C43 C62 EP12 EP19	X EP19	X		EP19	

Path of Workflow

A path of workflow is the description of the necessary processes to deliver the particular product or service that the organization or entity provides. A laboratory path of workflow consists of the sequential processes: preexamination, examination, and postexamination and their respective sequential subprocesses. All laboratories follow these processes to deliver the laboratory’s services, namely quality laboratory information.

C52 covers the medical laboratory path of workflow processes indicated by an “X.” For a description of the other documents listed in the grid, please refer to the Related CLSI Reference Materials section.

Examination ordering	Preexamination			Examination			Postexamination	
	Sample collection	Sample transport	Sample receipt and processing	Examination	Results review and follow-up	Interpretation	Results reporting and archiving	Sample management
	X	X	X	X C24 EP19	X	X	X	X

Related CLSI Reference Materials*

- C24** **Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions. 4th ed., 2016.** This guideline provides definitions, principles, and approaches to laboratory quality control design, implementation, and assessment.
- C43** **Gas Chromatography/Mass Spectrometry Confirmation of Drugs. 2nd ed., 2010.** 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.
- C62** **Liquid Chromatography-Mass Spectrometry Methods. 1st ed., 2014.** This document provides guidance to the clinical laboratorian for the reduction of interlaboratory variance and the evaluation of interferences, assay performance, and other pertinent characteristics of clinical assays. This guideline emphasizes particular areas related to assay development and presents a standardized approach for method verification that is specific to mass spectrometry technology.
- EP12** **User Protocol for Evaluation of Qualitative Test Performance. 2nd ed., 2008.** This document provides a consistent approach for protocol design and data analysis when evaluating qualitative diagnostic tests. Guidance is provided for both precision and method-comparison studies.
- EP19** **A Framework for Using CLSI Documents to Evaluate Clinical Laboratory Measurement Procedures. 2nd ed., 2015.** This report uses the “measurement procedure lifecycle” framework to aid users of CLSI evaluation protocols documents during establishment and implementation of measurement procedures developed by both commercial manufacturers and clinical laboratories, ie, for laboratory-developed tests.
- M29** **Protection of Laboratory Workers From Occupationally Acquired Infections. 4th ed., 2014.** Based on US regulations, this document provides guidance on the risk of transmission of infectious agents by aerosols, droplets, blood, and body substances in a laboratory setting; specific precautions for preventing the laboratory transmission of microbial infection from laboratory instruments and materials; and recommendations for the management of exposure to infectious agents.

* CLSI documents are continually reviewed and revised through the CLSI consensus process; therefore, readers should refer to the most current editions.

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