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3rd Edition

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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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

result shows positivity for amphetamines, this is discussed at the visit. However, a qualitative immunoassay amphetamine result may not always detect illegal methamphetamine. The patient may have taken a legal amphetamine, an OTC product, or an unrelated prescribed drug that reacted with the immunoassay.[15]

Detection of an opiate and a benzodiazepine in a specimen from a patient prescribed an opiate medication and a benzodiazepine may be an indicator of medication compliance. However, qualitative immunoassay testing will not provide answers to questions such as, which opiate is the patient taking? Is the patient taking more than one benzodiazepine? Is the patient taking the drug as prescribed?[16-18] On the other hand, qualitative testing with definitive methods may identify specific compounds and allow clinicians to objectively verify patient compliance. However, definitive methods such as mass spectrometry (MS) often need significantly more time to produce results compared to immunoassay screening.

Quantitative testing: Quantitative drug testing may identify the medication(s) or drug(s) the person has taken. In addition, quantitative urine testing with creatinine-corrected results may provide more appropriate monitoring over time. However, as for qualitative testing, quantitative testing does not ensure the patient is taking the drug as prescribed.

Purpose 3: Identifying noncompliant patients who use ethanol, take nonprescribed medications, or use illicit or recreational substances

Qualitative testing: Qualitative testing using immunoassays or definitive testing can show that a patient is positive for an illicit or recreational substance or for a class of drugs the treating clinician did not prescribe. A negative result for a prescribed medication may indicate noncompliance. However, qualitative immunoassay drug testing is considered preliminary, incomplete, and not definitive. For example, a patient has taken the medication several days earlier as prescribed and is in compliance, but the drug concentration in the specimen is below the qualitative cutoff level, indicating noncompliance.

Quantitative testing: Quantitative testing can determine which medications, drugs, or chemicals the patient has taken, including multiple drugs within a drug class. Differentiating the origin of drugs that have overlapping illicit and commercial uses needs to be evaluated carefully with the assistance of quantitative drug levels, parent drug and metabolite ratios, patient history, and, in some cases, chiral analysis. Quantitation of drug concentrations can help to identify incidental use of OTC medications, ingestion of drug-containing foods vs use of illicit, treatment-prohibited substances, or ingestion of nonprescribed medications such as poppy seed–containing food products that can produce marginally positive opiate results.[19,20]

For example, detection of carboxy-tetrahydrocannabinol (THC) in urine demonstrates marijuana use. Quantitative testing helps to identify new THC use in patients being monitored and treated for addiction. Creatinine-corrected urine THC values determined over several days should not increase by specific amounts when the patient is compliant.[21,22]

Purpose 4: Identifying medication noncompliance

Qualitative testing: Positive qualitative immunoassay results do not always indicate medication compliance. Patients who divert their medications use several ways to avoid detection. One way involves depositing a portion of the medication (tablet, capsule, or liquid) into the urine collection cup, resulting in a positive immunoassay result. The patient may successfully deceive the clinician and continue to obtain prescriptions for opioids or other medications that the patient then sells for recreational use. This deception should be suspected when excessively high parent drug concentrations relative to appropriate metabolites are detected, or when metabolites are absent (see “Quantitative testing,” below).

Quantitative testing: This testing is used to determine abnormal parent-to-metabolite ratios. However, quantitative testing does not ensure the patient is taking the drug as prescribed.

Purpose 5: Providing a better understanding of unexpected findings of the presence of ethanol or medications

Qualitative testing: One unexpected finding involves a patient testing positive for ethanol but claiming compliance with the opioid contract or treatment plan. Blood ethanol tests are not likely to produce false-positive results. However, false-positive results can occur in urine due to glucose fermentation in the presence of bacteria or yeast,[23,24] which occurs more frequently when specimens stand at room temperature for extended periods, such as in referral laboratories or nonemergent testing.

Quantitative testing: Quantitative drug testing can positively identify ethanol use. The presence of ethanol through fermentation may be ruled out by the absence of ethanol metabolites such as ethyl glucuronide or ethyl sulfate. For patient use of OTC products containing ethanol, such as cough syrups and hand sanitizers, concentrations of ethanol metabolites would be much lower compared to consumption of alcoholic beverages. However, exceptions include using rubbing alcohol compounds and some mouthwashes with high ethanol concentrations.[25,26]

Purpose 6: Identifying abnormal or unexpected drug metabolism

Qualitative testing: Absence of an expected metabolite or presence of unexpected metabolites may indicate a patient's abnormal or varied drug metabolism. In some cases, metabolism variances expose the patient to great risk. For example, some patients treated with opiate medications do not experience relief from their symptoms with normal doses of medication, or they experience severe side effects such as respiratory depression. Qualitative immunoassay testing is not likely to identify abnormal drug metabolism because this would be situation specific and would depend on the measurement procedure's cutoff concentrations and metabolite cross-reactivity.

Quantitative testing: Quantitative measurement of parent drugs and metabolites is helpful because the ratios of some drugs to their respective metabolites in certain dosing regimens can indicate "normal" or "accepted" metabolism. Unusual quantitative drug test results provide clinicians with information that supports the clinical picture of how the patient is responding to a medication.

1.2.2 Drug Testing Programs

A laboratory should clearly define the drug testing program's purpose before implementation, and provide detailed guidance for how the program will be conducted, including instructions for resolving any unusual situations. Due to the potential for medico-legal issues, hospital management should approve drug testing policies and request legal review, although drug testing is only intended for clinical purposes.

NOTE: Although not included in this guideline, most hospital laboratories are expected to provide some level of toxicology testing, at least to support the emergency department, obstetrics and gynecology, and pain management clinics.

1.2.3 Drug Testing Practice and Consultation

Major stakeholders of drug testing practice include the laboratory, medical staff, and other appropriate disciplines with vested interests in drug screening outcomes. Communication between the laboratory and medical staff is essential to ensure appropriate use of drug testing services. Laboratories should serve as consultants to the medical staff at every stage of the testing process, from designing testing schemes through interpreting results. These consultations should encompass the entire spectrum of the testing program.

Issues to be resolved with all stakeholders include:

- Distinction between clinical and forensic testing
- Test menu in the main facility vs point-of-care testing (POCT)
- Specimen-specific test menus
- Specimen collection
- Turnaround time for stat and routine tests
- Use of confirmation testing

1.2.4 Specimen Selection

Specimen selection depends on the medical purpose and circumstances. Serum, plasma, or blood is used when there is a relationship between drug concentration and toxicity. Urine is commonly used because it has been well characterized, sample volume is usually sufficient, and collection is noninvasive. However, urine may not be available due to "shy bladder syndrome," renal insufficiency, or facility limitations. Therefore, alternative sample types that are collected noninvasively with less likelihood for adulteration and for which collection can be witnessed include oral fluid, hair, sweat, breath, meconium, and umbilical cord and cord blood.

1.2.5 Laboratory Personnel

The laboratory director is responsible for ensuring personnel are properly trained and are qualified to conduct the various types of drug testing performed. The testing needs to comply with national, regional, and local regulations and requirements for testing personnel's eligibility and credentials. In many circumstances, routine drug testing, such as POCT, may be performed by nonlaboratory personnel; however, laboratories should take an active role in managing drug testing quality and ensuring applicable staff's competency.

1.3 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 known infectious agents and thus are more comprehensive than universal precautions, which are intended to apply only to transmission of bloodborne pathogens. Published guidelines are available that discuss the daily operations of diagnostic medicine in humans and animals while encouraging a culture of safety in the laboratory.[27] For specific precautions for preventing the laboratory transmission of all known infectious agents from laboratory instruments and materials and for recommendations for the management of exposure to all known infectious diseases, refer to CLSI document M29.[28]

1.4 Terminology

1.4.1 A Note on Terminology

CLSI, as a global leader in standardization, is firmly committed to achieving global harmonization whenever 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 different countries and regions, and that legally required use of terms, regional usage, and different consensus timelines are all important considerations in the harmonization process. CLSI recognizes its important role in these efforts, and its consensus process focuses on harmonization of terms to facilitate the global application of standards and guidelines.

NOTE: Mandates are generally reserved for CLSI standards, but are occasionally allowed in CLSI guidelines. In CLSI guidelines, use of the term "must" is either 1) based on a requirement or 2) indicative of a necessary step to ensure patient safety or proper fulfillment of a procedure. The document development committee evaluated use of the term "must" and deemed it appropriate.

1.4.2 Definitions

accuracy (of measurement) – closeness of agreement between a measured quantity value and a true quantity value of a measurand[29]; **NOTE 1:** In drug testing, accuracy also refers to a test's ability to detect a measurand when it is present at a concentration equal to or above a specified cutoff value; **NOTE 2:** Due to their inherent limitations, immunoassays are expected to produce some false-positive and false-negative screening results, thus definitive testing is warranted.

adulterant/adulteration – urine drug donors may add a substance (adulterant) to their specimens that will cause it to test negative on initial screening (adulteration); **NOTE:** Use of adulterants to avoid detection in forensic testing is considered to be even more serious than drug abuse itself.

aliquot – a portion of an original specimen collected by or submitted to a laboratory for testing; **NOTE 1:** Aliquots are removed from the specimen and tested, and aliquotting from a specimen should be done in a manner that preserves the integrity of the original specimen; **NOTE 2:** A sample is an aliquot of a specimen.

chain of custody – a forensic document that unequivocally identifies the donor of a specimen and tracks its handling from the time of collection to the completion of testing and disposal; **NOTE:** The chain of custody must not be broken and must account for the history of the specimen with no gaps. The chain of custody must be retained in the laboratory for a specified period of time after completion of testing and the reporting of results.

clinical testing – diagnostic testing that is performed as part of a medical procedure; **NOTE:** Emergency departments, most hospital wards, and drug treatment programs are typical environments for this type of testing. In these situations, test results are needed to establish diagnoses, institute treatment, and monitor patient progress. Although a positive drug test result may lead to some type of legal action, clinical testing is not intended for forensic purposes.

cocktail immunoassay testing – a practice in which multiple specimens are combined and tested as one, or multiple antibodies to different drug classes are combined in an effort to reduce the total number of analytical tests; **NOTE 1:** If any cocktailed specimens are positive then the original specimens are retested to determine which particular specimen(s) is positive; **NOTE 2:** If any cocktailed reagent produces a positive result for a particular specimen, then the original specimen(s) is retested with an individual reagent(s) to determine which specific drug is present.

compliance – the act or process of complying to a desire, demand, proposal, or regimen, or to coercion[30]; **NOTE:** In C52, compliance refers to 1) patient adherence to a clinician's prescription for a drug regimen, and 2) patient adherence to his or her pain management "contract" that he or she signs with the clinician.

cross-reactivity – the ability of a drug, metabolite, a structurally similar compound other than the primary measurand, or even an unrelated compound to affect the measurement procedure; **NOTE:** See **specificity.**

cutoff – the test response point below which a qualitative and quantitative test result is determined to be negative and at or above which the result is determined to be positive.

definitive testing//confirmation analysis – a procedure that is based on a different, more specific, physicochemical method than the original screening assay, and is used to confirm positive results; definitive tests can be qualitative or quantitative; **NOTE:** A definitive test determines whether a specimen result is

