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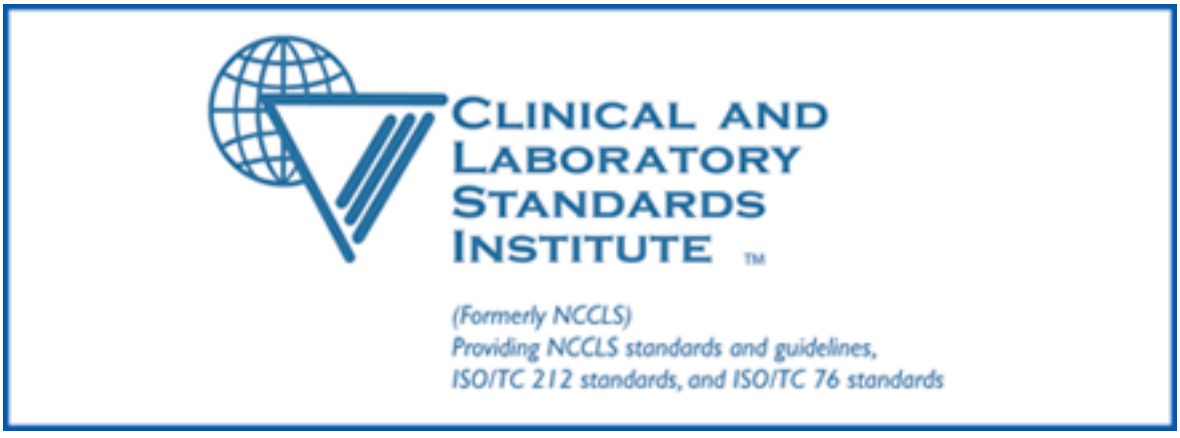
Urine Drug Testing in the Clinical Laboratory; Approved Guideline



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.

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Urine Drug Testing in the Clinical Laboratory; Approved Guideline

Abstract

NCCLS document T/DM8-A— *Urine Drug Testing in the Clinical Laboratory; Approved Guideline*, is designed to aid the clinical laboratorian in developing procedures for the efficient and reliable analysis of urine to qualitatively determine the presence of certain controlled substances. This guideline addresses drug testing in the workplace and other environments such as the criminal justice system and rehabilitation facilities. Its primary objective is to assure that high quality standards are maintained within this important area of clinical laboratory analysis, where test results may affect a person's reputation, employment status, or freedom, as well as the nonemergency diagnosis and treatment of substance abuse problems.

This document conforms to the objective by addressing specimen collection and processing, methods of analysis, quality assurance, and the reporting and interpretation of results. Because the results of drug abuse detection analyses have obvious potential for use as evidence in legal proceedings, information is provided relating to forensic procedures used to safeguard the identity of the specimen, document the chain-of-custody, and assure proper use of analytical results.

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Urine Drug Testing in the Clinical Laboratory; Approved Guideline

Volume 19 Number 6

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Foreword

For purposes of this guideline, it is necessary to initially define what is meant by the term “drug.” In this context, the term "drug" will refer to substances whose manufacture, possession, and usage is regulated by government mandates. Nonprescription medications, tobacco, organic nitrites, solvents, anabolic steroids, or other substances with abuse potential that are not generally included in urine drug testing services offered by clinical laboratories are beyond the scope of this document and will not be addressed. Similarly, alcohol will not be discussed in this guideline, even though interest in detecting its presence in urine appears to be increasing. Because procedures for determining alcohol in urine are somewhat different than those for detecting other drugs, and the implications of its presence are not the same as they are for controlled substances, it is best treated in a separate guideline.

In addition to limiting the drugs to those regulated by government mandate, the discussion contained in this guideline will be further restricted to testing performed to identify persons who use drugs to affect their mood, feelings, or behavior. Testing performed on medically compromised patients to diagnose drug overdoses or exposure to toxic substances will not be addressed.

Within the parameters defined, this guideline will focus on testing conducted to detect abusers of controlled substances so that actions can be initiated to curtail this destructive behavior in order to reduce economic losses and prevent these persons from injuring themselves and others. It is now well established that employee drug abuse prevention programs, which include urine drug testing, are cost justified based on the experiences of numerous organizations. These experiences include decreased absenteeism, increased productivity, and decreased use of medical benefits. Therefore, in this document, consideration will also be given to drug testing in the workplace and other environments, such as the criminal justice system and rehabilitation facilities.

Further, when the results of urine drug testing can affect an individual’s reputation, job status, or freedom, forensically acceptable analytical procedures must be utilized and the findings must be legally defensible. This guideline provides helpful information for laboratorians concerned with developing a specimen processing procedure that meets medico-legal requirements, from specimen collection through the reporting of results.

The Subcommittee on Urine Drug Testing developed this guideline in response to the frequently expressed need for information that addresses issues related to the testing of urine to identify persons who abuse controlled substances. Comments and suggestions for future editions of this guideline are welcomed.

Foreword (Continued)

Key Words

Abused drugs, addiction, controlled substances, drug abuse, drug screen, drug testing, drugs, intoxication, substance abuse, toxicology, urine drug testing.

Acronyms

AAB	American Association of Bioanalysts
AACC	American Association for Clinical Chemistry
CAP	College of American Pathologists
CDC	Centers for Disease Control and Prevention
CI	chemical ionization
DAWN	Drug Abuse Warning Network
DEA	United States Drug Enforcement Administration
DHHS	Department of Health and Human Services
EAP	employment assistance program
ECOCS	External chain-of-custody system
EDDP	2-ethylidene-1, 5-dimethyl-3, 3-diphenylpyrrolidine
FTIR	Fourier transform infrared spectroscopy
GC/AES	gas chromatography/atomic emission spectroscopy
GC/FTIR	gas chromatography/Fourier transform infrared spectroscopy
GC/IR	gas chromatography/infrared spectrography
GC/MS	gas chromatography/mass spectrometry
HB_SAg	hepatitis-B surface antigen
HIV	human immunodeficiency virus
HPTLC	high-performance thin-layer chromatography
ICOCS	Internal chain-of-custody systems
IV	intravenous
LC/MS	liquid chromatography/mass spectrometry
MRO	Medical Review Officer
MS/MS	mass spectrometry/mass spectrometry
PCP	phencyclidine
RIA	radioimmunoassay
SAMHSA	Division of Workplace Programs, Substance Abuse, and Mental Health Services Administration
SIM	selected ion monitoring
TLC	thin layer chromatography
USPS	United States Postal Service

Urine Drug Testing in the Clinical Laboratory; Approved Guideline

1 Introduction

1.1 Applicable Abused Drugs

Traditionally, drug abuse was defined as excessive and persistent use, usually by self-administration, of any drug. By present standards, however, even one-time or occasional use is considered abusive, particularly if it poses a safety or health hazard to the user or other persons. The term "drug," in this context, will be limited to a certain substance whose manufacture, distribution, and use is regulated by government mandates. Other substances such as alcohol, tobacco, inhalants, and caffeine, which have abuse potential but are not listed in the schedules established by the Controlled Substances Act, will not be considered. Likewise, anabolic-androgenic steroids, recently classified as controlled substances will not be addressed, even though their abuse is widespread. This distinction, while somewhat artificial on the basis of abuse, is appropriate when one considers the substances that are included in a "urine drug test" as performed by most clinical laboratories.

1.2 Standard Precautions

Because it is often impossible to know which might be infectious, all patient blood specimens are to be treated with standard precautions. For specific precautions for preventing the laboratory transmission of bloodborne infection from laboratory instruments and materials; and recommendations for the management of bloodborne exposure, refer to NCCLS document M29—*Protection of Laboratory Workers from Instrument Biohazards and Infectious Disease Transmitted by Blood, Body Fluids, and Tissue*.

1.3 Populations to be Tested

In recent years, the use of urine drug testing to identify persons with drug-abuse problems has become a widespread practice. This technique has also been used to monitor people who must remain drug free. Some areas in which urine drug testing is being used for initial detection or monitoring purposes include:

- pre-employment drug testing to detect job applicants with substance abuse problems;
- testing employees to detect persons whose drug use may present a safety or security hazard and adversely affect an employer's products or services;
- testing arrestees, prisoners, and persons on probation or parole, because these people have a high probability of resuming criminal activities if they are abusing drugs;
- testing persons in drug rehabilitation programs to verify claims of drug dependency and to monitor their progress during treatment;
- testing athletes for controlled substances as part of a more comprehensive program to detect substances that may affect performance in sporting events;
- testing school students in voluntary programs designed to provide incentives not to abuse drugs;
- testing patients suspected of being abusers of controlled substances; some patients may require more extensive laboratory studies if the presence of other toxic substances is suspected.

2 Application of Urine Drug Testing

2.1 Purpose

The use of drug testing as discussed in the context of this document is limited to applications in which it is necessary to know if a person has recently taken certain specified controlled substances. Because this information is used in many areas to identify drug abusers, it has become a major activity of many clinical laboratories. This type of testing may not, however, be used for purposes of establishing the degree of impairment at a particular time, as would be required in accident investigations or drunk driving prosecutions.

2.2 Test Specimens

Urine is the most frequently used specimen for substance abuse testing.

2.2.1 Advantages

The advantages of urine as the specimen for testing are as follows.

- Urine may be collected using noninvasive procedures.
- Urine is available in ample amounts for testing.
- Drugs and drug metabolites found in urine are usually stable.
- Drugs and drug metabolites are often present in higher concentrations in urine than in other biological materials.
- Drugs and drug metabolites are detectable for relatively long periods of time.
- Proteins and cellular materials are usually not present in great quantities, thus simplifying the analysis.
- The presence of metabolites in addition to the parent drug provides further evidence of drug use.
- Urine is readily preserved by refrigerating or freezing.
- Commercial reagents and testing systems are available for analyzing urine.

2.2.2 Disadvantages

Some disadvantages of urine as the specimen for testing are as follows.

- Drug concentrations may vary widely depending on a person's fluid intake, voiding pattern, and the time lapse since drug intake.
- Drug concentrations in urine do not correlate well with levels in other body fluids.
- Urine drug excretion continues after the physiological effect of the drug ceases, resulting in a lack of correlation of drug concentration with degree of impairment.
- The presence of metabolites only may prevent differentiation of the parent drug if it is a member of a structurally similar series of substances.
- If the test subject cannot void upon request, the specimen may be difficult to collect.
- Unless the collection is observed, urine specimens may be easily substituted, diluted, or adulterated.
- Observation of a person while he or she is urinating is an invasion of privacy.
- Urine will decompose if it is not properly handled and stored.

2.3 Testing Procedures

Substance abuse testing should be a two-stage process. The first stage consists of a screen or series of initial tests designed to distinguish specimens that test negative from those that are presumed to be positive. In situations where it is not necessary to verify the accuracy of results, testing may end at the conclusion of the first stage (see Section 4). The second stage is a confirmatory analysis to further substantiate the identity of the drug or drug metabolite whose presence is presumptively indicated by the screening procedure. The analytical method used for confirmatory testing must be based on physical or chemical principles that differ from those used in the screening test. Confirmatory procedures must be at least as sensitive toward the drug or metabolite of interest as the initial test.

2.3.1 Screening Procedures

In urine drug testing, screening procedures are initially performed analyses that are designed to distinguish those specimens which may contain the substances of interest (drugs or metabolites) from those specimens which are truly negative and do not contain these substances. Caution must be exercised in interpreting screening results which often utilize

"cutoff levels" for decision-making purposes. If the test system indicates an analyte concentration at or above the cutoff level, a presumptive positive result is recorded, and the specimen is reserved for further testing to verify the finding if it is deemed necessary. On the other hand, if an analyte concentration less than the cutoff level is found, the specimen is considered negative even though a detectable amount of a drug or metabolite of interest may be present. Due to the putative nature of screening results, they have limited clinical utility. Further corroborative testing is generally required if the findings are to be used for diagnostic purposes.

Ideally, methods selected for initial screening should be inexpensive, rapid, easily automated, and uncomplicated. They should produce objective, easily interpreted results that are not difficult to store and retrieve. Because immunoassay procedures best meet these requirements, they are most frequently employed, especially in laboratories that analyze a large number of specimens. Thin-layer chromatography is also widely employed. Even though it does not possess most of the desirable qualities listed above, thin-layer chromatography is capable of detecting more drugs and metabolites than immunoassay procedures. It is particularly useful in laboratories where the number of specimens analyzed is relatively low and where analytes are encountered for which immunoassays are not available. Performance characteristics for screening procedures are summarized in the following sections.

The discussion of performance characteristics which follows is specific to urine drug testing and is not intended to define these parameters or replace definitions contained in documents which specifically address terminology. For authoritative definitions of the terminology which follows, please see the most current versions of NCCLS documents *NRSCL8 Terminology and Definitions For Use in NCCLS Documents,* and *GP10 Assessment of the Clinical Accuracy of Laboratory Tests Using Receiver Operating Characteristic (ROC) Plots*. The usage of these terms by persons involved with urine drug testing may not correspond with the definitions contained in those documents. However, the terminology which is currently utilized in urine drug testing should evolve toward and eventually coincide with the established standards.

2.3.1.1 Accuracy

Initial testing results must distinguish specimens that do not contain drugs or metabolites from those that may contain these substances. From an accuracy point of view, it is acceptable for a screening procedure to indicate the presence of the analyte of interest in some specimens in which it is not present (i.e., a false-positive result). This type of error should be detected and corrected by confirmatory testing. When positive screening results are not confirmed, the presumptive finding must be interpreted with the awareness that the response may be due to the presence of a substance other than the analyte of interest. Ideally, a screening procedure has to detect the analyte of interest in any specimen in which it is present at or above the defined screening concentration (i.e., the cutoff concentration). Accuracy is related to specificity, which is discussed in Section 2.3.1.3.

2.3.1.2 Precision

Screening results should be reproducible so that replicate analyses will consistently indicate either the presence or absence of the drug or metabolite. Precision of the method is important in analyses that distinguish positive from negative specimens on the basis of a cutoff concentration. As analyte concentrations approach the cutoff level, replicate analyses will have a higher probability of producing erroneous or equivocal results if that method is not precise.

2.3.1.3 Specificity

In screening procedures, absolute specificity is not required. Many of these methods produce a positive response in the presence of the target substance or other substances that have similar chemical structures. This cross-reactivity is often advantageous for initial testing purposes since the analysis can be used to detect drug classes (e.g., amphetamines, barbiturates, benzodiazepines, opiates), rather than one specific drug. The sensitivity of a procedure may be improved if the assay responds to metabolites as well as the parent drug.

For example, cross-reactivity of an immunochemical assay with both morphine and its glucuronide metabolite enhances the sensitivity of the assay for that target drug without the need for treatment of the specimen before analysis (hydrolysis). Although absolute specificity may not be attainable or desirable in screening procedures, the cross-reactivity of the assay should not be too extensive or the need for confirmatory testing will be unnecessarily increased. Because many immunoassays respond to the parent drug and its metabolites, caution must be exercised in attempting to apply quantitative interpretations to nonspecific screening results.

Further, analysts should understand that even if enough reactive species are present in a specimen to produce a positive response in a screening test, the amount of any one constituent may not be sufficient to produce a positive response in a confirmatory test that is specific for that one particular substance. High specificity for a drug or class of drugs is advantageous in screening tests because it simplifies the interpretation of results and reduces the number of specimens that must be subjected to confirmatory testing.

2.3.1.4 Selectivity

The selectivity of an assay is related to specificity and refers to the ability of a method to respond more readily to one target analyte than to other constituents in the specimen, whether they are target analytes or not. For example, some immunoassays for the detection of amphetamines respond primarily to amphetamine and require much higher concentrations of methamphetamine to produce a similar response.

Response may also be affected by interference, which is a phenomenon related to specificity and selectivity. Interference occurs when a constituent in the specimen other than a target analyte affects the response of the assay. A substance produces a positive interference when it causes a positive response to be recorded for a specimen that does not contain the target analyte or produces a greater response than should result from the amount of target analyte present. Because this type of interference is difficult to distinguish from an actual positive result, manufacturers of test reagents and systems endeavor to develop products that are not subject to this kind of effect. Negative interference occurs when a constituent of the specimen reduces or entirely prevents the response of the assay system to the target analyte in the sample. Many immunoassays are subject to this type of interference. For example, negative interference can occur when adulterants such as bleach or salt are added to a specimen.

2.3.1.5 Cutoff Concentration

The practical operational sensitivity of a procedure should be considered when establishing a cutoff concentration, which is an administrative threshold that separates positive from negative samples.[a] Assay values above the cutoff value are considered to be positive and those below the value are considered negative. Problems can arise from such interpretations unless the laboratory clearly specifies the basis for such designations. Caution must also be exercised in interpreting results obtained from assays that respond to more than one analyte (e.g., parent drug and metabolites) in a specimen. Cutoff levels should be established only after determining the upper limit of assay values for drug-free urine specimens from a representative population of subjects. To ensure the reproducibility of results, the cutoff concentration is generally assigned a value somewhat higher than the detection limit.

2.3.2 Confirmatory Procedures

Selection of methods for verifying the presence of drugs or metabolites in a specimen will depend on the purpose of the testing. If results are to be used as a guide in diagnosis or treatment and will not otherwise adversely affect the test subject, it may not be necessary to conclusively establish the presence of the initially detected substances. In such instances, it may be acceptable to further substantiate the initial finding by performing a second "presumptive" determination. This may involve repeating the screening test that was performed initially or, when practical, performing a second determination that utilizes a different chemical or physical principle. This does not substitute

[a] In the U.S., cutoff values that were established by SAMHSA are currently used in many laboratories that conduct urine drug testing.

for confirmatory testing. Therefore, if the initial test were an immunoassay, the second test could be based on chromatography (e.g., gas chromatography). Additional testing of this type would reduce errors that are responsible for false-positive results. These errors are the result of antibody nonspecificity in immunoassays and, in chromatographic procedures, spurious sub-stances that have the same retention values as the target analytes. Testing in this manner improves the reliability of results in situations where exhaustive proof of drug content is not necessary. It also reduces the time and expense required to conduct verifications using more definitive procedures. The utilization of more than one presumptive determination when screening specimens will decrease the probability of error, but is not rigorous confirmatory analysis.

In situations where the reputation, employment status, or freedom of the person tested may be jeopardized, or when forensic quality results are needed for evidentiary purposes, the confirmatory technique used to verify presumptive findings must be capable of withstanding scientific and legal challenges. Therefore, the analysis technique employed should, ideally, produce sufficient data relating to each analyte to permit it to be uniquely characterized. In reality, this goal is often approached, but it is usually not completely achieved. Of the widely available techniques, gas chromatography/mass spectrometry (GC/MS), when performed in the full scan mode, best meets this requirement.

When mass spectrometric analysis is performed using selected ion monitoring (SIM) or chemical ionization (CI) techniques, the data produced may or may not be sufficient to permit definitive identification. Although less conclusive findings are produced, these operational modes are indispensable when the amount of analyte present is not sufficient for a full-scan spectrum to be obtained. Other methods, such as mass spectrometry/mass spectrometry (MS/MS), liquid chroma-tography/mass spectrometry (LC/MS), gas chromatography/infrared spectrography (GC/IR), and gas chromatography/atomic emission spectroscopy (GC/AES) may eventually comple-ment or supplant GC/MS. In contrast to initial screening procedures, definitive confirmatory analysis involves expensive, sophisticated instrumentation that requires a highly trained analyst to operate and maintain. To determine what drugs or metabolites are present requires a qualified individual who has the knowledge and experience necessary to properly interpret the data produced in these analyses. These factors tend to reduce the number of specimens that can be processed in a given time period and to increase the cost of analysis.

The performance characteristics described in Section 2.3.1 for screening procedures also apply to confirmatory procedures. They do, however, differ in certain important aspects, which are described in the following sections. Again, we are not attempting to define these terms in this document as discussed in Section 2.3.1 and refer the user to NRSCL8 and related NCCLS documents for definitions of these terms.

2.3.2.1 Accuracy

The ideal confirmatory testing method would unequivocally verify the presence or absence of suspected substances in specimens and it would not produce any false-positive or false-negative results. Unfortunately, this theoretical goal cannot always be achieved because of low analyte concentrations and limitations in testing procedures.

2.3.2.2 Specificity

In confirmatory procedures where the target analyte must be conclusively identified if it is present, the method employed must produce sufficient data to enable the laboratorian to distinguish the substance of interest from known interferents and positively identify it. This may be possible in certain situations, such as when the concentration of the drug or me-tabolite is high enough to permit a complete mass or infrared spectrum to be obtained. However, as concentrations decrease, it often is not possible to obtain full spectra, and other methods that provide less data (e.g., SIM) must be used. When this occurs, unless a sufficient amount of information is collected to eliminate other substances that could reasonably be expected to occur in the specimen, the result may not withstand legal challenges. If the adequacy of analytical findings is disputed, it should be incumbent upon those challenging the results to show that at least one other sub-stance that could reasonably occur in the speci-men could produce the same findings.

2.3.2.3 Selectivity

When chromatographic methods are used, the selectivity of the detector depends upon its operating principle. For example, in gas chromatography, the detector may respond to analyte concentrations (e.g., thermal conductivity detector) or mass flow rate (e.g., flame ionization detector). The responses of detectors differ depending on the type of compound. Equal amounts of different compounds do not produce equal responses, and each detector must be calibrated to determine appropriate response factors.

2.3.2.4 Sensitivity

If the screening procedure responds to more than one substance in a specimen (e.g., parent drug and metabolites), the concentration of any one target analyte will be less than the cumulative assay result would indicate. In these cases, the confirmatory assay threshold for the target drug or metabolite (i.e., the cutoff concentration) must be set at a concentration proportionately lower than the screening assay cutoff concentration to lessen the chance of a false-negative finding.

2.3.2.5 Detection Limit

In GC/MS analysis, the detection limit is determined by the technique used to ionize the target substances and the manner in which spectral data is collected. When analyzing quantities of substances that weigh less than 10 ng, selective ion-monitoring or chemical ionization techniques are usually used. These methods monitor fewer ions or fragment peaks and the intensity of the observed peaks is increased. Although these techniques improve sensitivity, if enough data to positively identify the analyte are not obtained, they may compromise the specificity of the method.

2.3.2.6 Resolution

Resolution, when applied to chromatographic procedures, relates to the effectiveness of the system in separating components of a mixture. Substances with similar retention times will elute from a gas chromatography column nearly simultaneously, in which case it will not be possible to distinguish more than one substance when a conventional detector is used. However, when a mass spectrometer is employed as the detector, it is often possible to scan the effluent repeatedly and detect c hanges in composition as the leading edge, middle, and trailing edge of the peak are being recorded. This technique enhances the resolution of GC/MS systems and permits the recognition of mixtures that would appear as a single peak (i.e., one component) if the total ion current of the mass spectrometer were monitored.

2.4 Designing a Drug Testing Program

2.4.1 Test Populations

The subjects to be tested usually consist of people from one of the groups listed in Section 1.3. Pertinent information relative to establishing testing programs in these areas is presented in the following sections.

2.4.1.1 Candidates for Employment

Pre-employment testing is performed before officially offering employment, after an offer has been extended contingent on passing a physical examination, or after successfully completing a probationary period prior to obtaining regular employment status. These precautions help to eliminate high-risk persons from the job pool. To avoid discrimination, applicants for all jobs should be tested. If not, there must be documented, nondiscriminatory reasons for selecting those who are tested, such as application for highly sensitive positions, high-risk positions, or positions involving public safety. To avoid taking inappropriate action against an applicant on the basis of a presumptive result, which could be in error, all positive screening tests obtained on employment candidates should be confirmed.

2.4.1.2 Employees

As a condition of employment, employers may require their personnel to participate in urine drug testing programs for the following reasons:

Reasonable suspicion testing is performed when an employee exhibits inappropriate behavior or work performance problems that might be caused by drug abuse. The drug testing policy must clearly define what constitutes a performance problem. This form of testing may also be required after an on-the-job accident or when signs indicative of drug impairment or intoxi-

cation are exhibited. A uniform policy must be established with provisions for maintaining strict confidentially of the test result; this may include probation with ongoing urinalysis monitoring; referral to treatment; and discipline which may lead to termination.

In the event of a positive initial test result, an employee in a position where safety or security may be jeopardized may be temporarily transferred to another job. Further action should not be instituted until the results of confirmatory testing are received.

Random or neutral selection testing is normally reserved for jobs where safety or security is a factor, or where the public trust is a major concern. All workers in job classifications that warrant random testing must have an equal chance of being tested. In the event of a positive test result, options are the same as those that are available for other kinds of testing.

If routine employee physicals or return-to-work physicals after an illness or leave of absence are required, they can include testing for drugs of abuse as part of the examination. Testing on this basis provides employers with a mechanism for regularly testing employees and it may enable them to identify occasional drug users and persons whose abuse patterns have not yet noticeably affected their job performance.

Periodic monitoring for drug use can be performed on persons who have previously had a positive test result or who have been in drug abuse treatment programs. These persons may be placed on probation for a specified period of time. Monitoring persons who have previously experienced drug abuse problems may deter recidivism by providing the person with positive reinforcement not to resume drug use.

In 1970, the Department of Defense began to test service members for opiates and placed those who tested positive in rehabilitation programs. The "NIDA Guidelines" that are now being used resulted from the Department of Defense Health Affairs directives written in 1982 and 1984 to instruct the Armed Forces Services Surgeons General about how to conduct urine drug testing. Other organizations such as the Southern Pacific Railway, Georgia Power and Light, and New York City Transit Authority, to name but a few, have reported that employee drug abuse prevention programs, which include urine drug testing, are cost justified. These organizations have reported decreased absenteeism, increased productivity, and decreased use of medical benefits among their employees as a result of such programs.

2.4.1.3 Diagnostic Testing

Diagnostic testing is comprised of analyses performed as part of a medical workup. Emergency medicine departments, obstetrics facilities, 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. The consequences of a positive test result may include legal action.

2.4.1.4 Forensic Applications

Forensic applications of urine drug testing include death investigations and the testing of subjects suspected of driving under the influence of drugs. The results of drug testing are now being used in some jurisdictions to determine if arrestees will be given bail or incarcerated until trial. Drug users have been shown to have a much higher probability of continuing criminal activity and fleeing to escape prosecution. Because persons with drug abuse problems frequently become involved in criminal activity, negative urine drug test results are now often required before convicts are released or as a condition for remaining on probation or parole.

2.4.2 Privacy Considerations

When urine drug testing programs are planned, questions frequently arise about the rights of those being tested and the legality of intruding into their private lives. **Each laboratory is responsible for knowing and complying with all applicable rules governing privacy and confidentiality in its jurisdiction.**

While these requirements may vary from state to state, the following sections describe several legal issues that must be considered when conducting a urine drug testing program.

2.4.2.1 General Legal Considerations

The legality of drug testing for an employer in any particular situation is governed by the Americans With Disabilities Act, any applicable

collective bargaining agreement, judicial decisions interpreting the Fourth Amendment, and state law. Each laboratory is well advised to consult with a knowledgeable attorney if it has questions about the applicability of any of these authorities.

2.4.2.2 Confidentiality

Even where drug testing is permissible, disclosure of test results to persons or entities not authorized to receive such results may be unlawful. Therefore, those persons involved in the administration of urine drug testing programs should ensure that test results are treated as confidential information. Some jurisdictions, for example, have clinical laboratory laws that specify that the results of testing are to be considered confidential information and are only to be released to certain authorized persons.[b]

2.4.2.3 Observed Urine Collection

Although there are those who claim that direct observation of urine sample collection is the only way to ensure sample integrity, this method is usually considered to be an unnecessary intrusion. There are other methods that work equally well. Removal of coats and purses before entering the collection facility, placing bluing agents in toilet water, and checking the temperature of freshly voided samples usually eliminates the need for direct observation. However, in some circumstances, such as when the persons's behavior is highly suspicious, observed collection may be the only alternative.

2.4.2.4 Due Process Considerations

Using a reliable testing procedure and performing it properly are both ways to ensure due process. Records should show that proper chain-of-custody and testing procedures were followed. If punitive action is a possible consequence of a positive initial test result, the result should be confirmed. In certain instances such as those cited above, it may be necessary to act on the results of the initial test; however, confirmatory tests should be performed before pursuing punitive action. Test results may be admitted as evidence of drug use in arbitration, administrative hearings, and court cases. Refusal to submit a urine specimen may have the same consequences as a positive test result. For this reason, it is good practice to advise test subjects about the consequences of a positive test result and their right to request retesting if they believe a mistake has been made.

2.4.3 Selecting a Laboratory

When selecting a laboratory to perform tests for drugs of abuse, careful consideration of many important factors is required. Reliable laboratories must meet all statutory requirements for conducting drug analysis and participate in proficiency testing programs required by federal, state, and local regulatory authorities. These facilities may also participate in voluntary survey programs (e.g., such as those conducted in the U.S. by the College of American Pathologists (CAP) or the American Association of Bioanalysts AAB), which provide additional assurance of the quality of testing services.[c] Certification of laboratories provides assurance that these facilities meet minimum performance requirements for performing these analyses. Certified facilities should have efficient and well-defined specimen collection and processing procedures that protect the identity and integrity of specimens. Provisions for documenting the chain-of-custody of forensic specimens should be an integral part of this system.

To minimize the possibility of errors, specimens should be analyzed using recognized techniques, and quality assurance procedures s hould be adhered to rigidly. Unused portions of a specimen should be stored in a secure area; and they should be available for further testing, if necessary. The laboratory may store these specimens under refrigeration for short periods of time or they may be frozen for long-term storage.

The laboratory report should be comprehensive and available on a timely basis. It is generally considered better to inform persons about test

[b] In the U.S., some state constitutions include a stipulation that confers a defined right to privacy. The California Constitution, for example, specifically guarantees the right to privacy, which applies to private and government activities.

[c] In the U.S., the Division of Workplace Programs, Substance Abuse, and Mental Health Services Administration (SAMHSA) of the Department of Health and Human Services (DHHS) and some state health departments certify laboratories to conduct urine drug testing.

results in writing rather than verbally due to the increased potential for misunderstandings about what is being conveyed in spoken communications. Telephone reports should be avoided. In situations where verbal reports must be issued, the person in the laboratory must verify that the person receiving the information is an authorized agent of the organization for whom the testing was performed. This may require calling the requestor back if the laboratorian cannot identify the person from previous conversations. Written agreements between the laboratory and the agency submitting the specimens should be established before verbal reports are made. Copies of the report should be stored in the laboratory and should be readily retrievable if requested later. A qualified staff person should be available to advise about drug testing, the selection of appropriate cutoff values, and the interpretation of results. A staff member should be available to give expert testimony in legal proceedings. Laboratories should provide specimen collection supplies and instructions for collecting and shipping specimens. The laboratory's turn-around times should be minimal.

Inspection of any prospective laboratory may provide valuable insight into its capabilities. Information on selecting a referral laboratory can be obtained from NCCLS document GP9—*Selecting and Evaluating a Referral Laboratory*.

3 Specimen Collection and Processing

3.1 Frequency of Collection

The frequency of urine collection may vary in accordance with the purpose of the testing and the population being tested.

3.1.1 Random Sampling

With random sampling, the person being tested cannot predict when testing will be requested. Before establishing a random sampling protocol, it is advisable to consult federal, state, and local laws to ensure compliance. A random sampling protocol should clearly identify the population to be tested, provide each person with an equal probability of being selected, and ensure that each sampling has no effect on any other sampling.

3.1.2 Regularly Scheduled Sampling

Regularly scheduled sampling allows the person to be given notice before he or she is tested. A drug abuser could arrange drug use based on the testing schedule, and therefore, test negative. For this reason, it is best to give as little notice as possible before testing. Drug testing should always be conducted in an even-handed manner consistent with the employer's written policy guidelines. This practice will help protect against allegations that tests are being administered in an unfair or discriminatory manner.

3.1.3 "For Cause" Sampling

Under a "for cause" sampling policy, a person is tested if there is a reasonable suspicion of drug use or if an incident/accident has occurred. The person should be tested with as little warning and as close to the event that caused suspicion as possible. Drug testing after an accident has generally been accepted legally. This may even be required, according to some regulations.

3.2 Specimen Tampering

Specimen collection is the most vulnerable part of any urine drug testing program. Tampering is most likely to occur when the person providing the sample is permitted to void unobserved in a stall or partitioned enclosure. Specimen tampering methods that have been used by drug abusers seeking to avoid detection are described in the following sections.

3.2.1 Substitution

Liquids such as soda, tea, apple juice, and clean urine (i.e., drug-free) are substituted for the test subject's own urine.

3.2.2 Adulteration

Urine may be adulterated by the addition of foreign material known or thought to invalidate the test. Common substances include soap, household cleaners, salt, bleach, and drain cleaner. The effect of each of these adulterants varies with the test methods used. Adulterants are often detectable at the collection site by visual inspection of the specimen or by smell and abnormal temperatures caused by the chemicals. Other properties such as pH and specific

gravity of the urine may also be affected by addition of adulterants.

3.2.3 Dilution

Dilution reduces the drug concentration in urine to the point that it will not be reported by the drug testing laboratory. This may be done by adding water after the specimen is provided.

Subjects may attempt to dilute their urine by ingesting large amounts of fluid, usually water, in an effort to lower the apparent concentration of any drug present below the cutoff level. The determination of creatinine is used to detect these samples, and specimens with creatinine concentrations below 20 mg/dL (1.8 mmol/L) should be reported as suspect, indicating that another specimen should be submitted.

3.2.4 Other

Drug users have been known to resort to drastic measures to avoid detection. Some have even gone so far as to use catheters to fill their bladders with water or someone else's drug-free urine. (Infections and damaged tissue can result from such practices.) In attempts to reduce the drug concentration in their urine or change the excretion rate of the drug, others have consumed large volumes of water or drunk substances such as vinegar.

3.3 Countermeasures to Prevent Tampering

To deter subjects from attempting substitution or adulteration of a specimen, the following safeguards may be incorporated into the collection procedure. The measures instituted will depend on the reasons for testing. Specimens taken for medical purposes may not require such exacting collection procedures.

3.3.1 Place Bluing Agent (Dye) in the Toilet Bowl

Placing dye in the toilet bowl discourages the subject from adding water to the urine specimen to dilute the drug concentration because the color of the urine would change as a result, which would be an obvious indication of tampering. Alternatively, a water-free system such as a commode or chemical toilet may be used.

3.3.2 Require "Photo" Identification

The collection procedure may require that a test subject present identification that includes a photograph of himself or herself. Use of " photo" identification prevents a person from enlisting another person to take the test in their place.

3.3.3 Leave Coats, Briefcases, or Purses Outside of the Collection Area

To reduce the possibility of concealing drug-free urine specimens or adulterants on the test subject's person, coats, briefcases, or purses should be left outside of the collection area. (Subjects may be allowed to retain their wallets.) If it is suspected that urine or adulterants are being concealed, the person being tested may be asked to change into an examination gown and he or she may be searched before proceeding to the collection area.

3.3.4 Wash and Dry Hands Before Providing a Specimen

By washing and drying their hands before providing a urine specimen, test subjects are prevented from placing substances on their hands that could be transferred to the urine in an attempt to adulterate it.

3.3.5 Observe Collection

The most reliable way to prevent specimen tampering is to observe the collection of the urine. This is usually considered intrusive and it is generally permitted only in situations where the test subject has previously tried to substitute or adulterate specimens. Observed collection may also be warranted when the clinical impression does not agree with the test results, or when it is known that, due to circumstances surrounding the test request, the results will be subjected to severe legal scrutiny.

3.3.6 Take the Temperature of the Urine Within Four Minutes of Collection

If the collection is not observed, taking the temperature of the urine is the most effective method of detecting dilution, adulteration, or substitution.

- The temperature should be in the range of 33 to 37 °C (91 to 98 °F). This allows for

a maximum delay of four minutes during which the specimen temperature must be obtained.

- If the temperature of a specimen is outside this range and there is reason to believe that a subject may have adulterated or substituted a specimen, another specimen should be collected. This could be considered a valid reason for collecting the second sample under direct observation by a collection site person of the same gender.

- It is recommended that a higher level supervisor review and concur in advance with any decision made by collection site personnel to obtain a specimen under direct observation.

- When a second specimen is required, both specimens should be carefully marked to indicate the sequence of collection before they are sent to the laboratory for testing.

- Various kinds of thermometers can be used to determine the temperature of the urine.

  — Liquid crystals:

    • are attached to the side of the container;

    • react to a temperature change within 15 seconds; and

    • cause no contamination problems.

  — Digital thermometers:

    • respond rapidly to temperature changes; and

    • require disposable, one-time use tips to prevent contamination.

  — Standard mercury thermometers should *not* be used because they respond slowly and they may be a source of cross-contamination.

- If the temperature of the specimen falls outside of the prescribed range, a subject may volunteer to have his or her oral temperature taken to provide evidence to counter the belief that the specimen was altered or substituted.

3.4 Collection Procedures

The requirements for specimen collection vary depending on the purpose for which the results will be used. The procedure presented here meets evidentiary requirements.

3.4.1 Before Collection

(1) Determine that collection site facilities are clean, well lighted, secure, and dedicated solely to specimen collection.

(2) Account for the presence of all required specimen-collection personnel and supervisors who should be present at the collection site.

(3) Place bluing agent in the toilet bowl, if applicable.

(4) Ensure that no other source of water exists within the enclosure where urination occurs.

(5) Have all supplies necessary for specimen collection present. Sealed collection kits containing all necessary materials are available from various manufacturers. Sealed kits provide assurance that supplies have not been tampered with before opening. Some laboratories supply their clients with collection kits.

(6) Request "photo" identification from the subject (e.g., an identification badge or driver's license). If the person has no "photo" identification, then identification can be made by an official who can positively identify the person.

(7) Complete the applicable chain-of-custody form and the laboratory requisition form.

3.4.2 Unobserved Collection

(1) Ask the subject to remove any unnecessary outer garments such as a coat or jacket.

(2) Instruct the subject to leave all personal belongings, such as a purse or a briefcase, with the outer garments outside of the stall or partitioned area. (The subject may retain a wallet.)

(3) Instruct the subject to wash, rinse, and dry his or her hands.

(4) Give the subject a urine specimen collection container. Have the subject remain in the presence of the collector; the subject should have no access to fountains, faucets, soap dispensers, or any other materials that could be used to adulterate the urine specimen.

(5) Allow the subject to enter and maintain privacy within the stall or partitioned area. If a public restroom is used, the collector should remain in the restroom, but outside of the stall, until the specimen is collected.

(6) Make a note in the permanent record book that describes any unusual circumstances, behavior, or appearance pertaining to the subject.

(7) Accept the specimen from the subject.

(8) If a subject is unable to provide a specimen, offer fluid until voiding occurs.

3.4.3 Observed Collection

If collection under direct observation is authorized according to policy, all procedures should be conducted in a professional, discreet, and objective manner. The following steps should be taken:

(1) Inform the subject that collection will occur under direct observation.

(2) Accompany the subject into the collection facility. (The collector should be the same gender as the subject.)

(3) Instruct the subject to wash, rinse, and dry his or her hands.

(4) Give the subject a urine collection container. (Only the subject and the collector should be in the collection area.)

(5) The collector should position himself or herself in a manner that facilitates verification that the urine specimen passes directly from the subject's body into the specimen container. (Collection of a urine specimen under direct observation is a highly sensitive topic; no information concerning this event, except that it was performed, shall be released.)

(6) Accept the specimen from the subject.

(7) Document on the chain-of-custody/laboratory requisition form that collection was done under direct observation.

3.4.4 After Collection

(1) Upon receipt of the specimen, the collector should immediately:

(a) Ensure that an adequate volume of urine was collected. If the volume collected is not adequate, additional urine may be collected in a separate container. The temperature of each specimen should be measured and recorded and the collector should keep all specimens in view of the subject. When an adequate total volume has been collected, the specimens should be combined into one container while the test subject observes.

(b) Measure the temperature of the urine specimen within four minutes of urination. (33 to 37 °C or 91 to 98 °F is acceptable.)

(c) Inspect the color and appearance of the urine specimen for any signs of contamination. (Note any unusual findings in the permanent record book.) If adulteration is suspected, this could be considered a valid reason for collecting a second sample (under direct observation by a person of the same gender as the subject). It is recommended that a h igher level supervisor review and concur in advance with any decision by collection site personnel to obtain a specimen under direct observation.

(2) Add no additional substances (e.g., preservatives) to the specimen.

(3) Keep the urine specimen in view of the collector and the subject at all times before it is sealed and labeled.

(4) Pass a tamper proof seal over the bottle cap and down the sides of the bottle. If re-

quired, the collector and/or the test subject should initial the seals.

(5) Label the urine specimen. The label should include the subject's name or code number, the date and time of collection, the approximate volume of urine collected, the collector's initials, and the initials of the person providing the specimen. (To insure correct identification, a unique accession number or bar code should be assigned to each specimen). Having the name of the collection site preprinted on the label may deter the subject from switching labels. Labels should be completed in ink that will not smudge or run if it becomes wet. Placing clear plastic tape over the label is another way of protecting this information. All identification information must be legibly printed or typed on the label.

(6) Enter all information that identifies the specimen on the chain-of-custody/laboratory requisition form. Both the collector and the subject providing the urine specimen should sign the form. The subject's signature certifies that the identified specimen is the specimen that he or she provided.

(7) Splitting samples into two containers, both labeled and sealed as previously described, is sometimes recommended as an additional safeguard. One container is sent for analysis, while the other is retained in storage. If the specimen tests positive and the result is disputed, the portion in the stored container can be tested to give added credibility to the results. The second container can also be used in the event that the first is lost or broken. However, the practice of keeping a portion of the specimen in reserve at the collection site may be undesirable (e.g., because of a lack of adequate storage facilities and a lack of proper storage conditions to assure specimen/drug stability or repeatability of results). In reality, the stored specimen may produce different results than the originally tested portion because of deterioration of the ana-lytes during freezing a nd/or storage. If this system is used, the second aliquot should be stored in a locked freezer at -20 °C or less.

3.5 Shipment to the Testing Laboratory

- If the specimen is not immediately prepared for shipment, it must be appropriately safeguarded during temporary storage. If overnight or weekend storage is required, specimens should be refrigerated (2–8 °C). The specimen must be stored in a locked area with access limited to authorized personnel only.

- If possible, forward urine specimens to the laboratory within 24 h of collection.

- Minimize the number of people handling specimens.

- Document the date and the purpose on the chain-of-custody form each time a specimen is handled or transferred. Identify each person who handled the specimen. Postal employees need not be included in the chain of custody. When courier services are utilized, the time of receipt from the collection site and the line of delivery to the laboratory must be documented on the chain-of-custody form.

- Place specimen containers in shipping cartons designed to minimize damage, and seal them securely to eliminate the possibility of undetected tampering. Sealing both the specimen containers and shipping cartons provides two safeguards against tampering. Security may be enhanced by having the collector sign his or her name across the box and tape. Provide the testing laboratory with a list of acceptable signatures. This discourages tampering attempts by making opening and resealing the container more difficult.

- Ensure that the invoice (request form) a nd/or chain-of-custody form accompanies the appropriate specimens in the shipping container. (See Section 3.6 for details.)

- Mail or deliver the specimens to the testing laboratory. The transportation of samples can be accomplished while maintaining adequate specimen validity if a commercial

courier or postal service is used.[d] If a staff member delivers the specimens, a receipt-of-delivery slip must be issued by the laboratory. The receiving laboratory must record and report to the collection site any apparent tampering with the container or specimens, any discrepancy in number of boxes received, or any discrepancy in the specimens versus the invoice or request forms.

- When shipping potentially biohazardous materials, follow state, local and federal regulations. Also, refer to NCCLS document H5— *Procedures for the Handling and Transport of Domestic Diagnostic Specimens and Etiologic Agents.*[e]

3.6 Chain-of-Custody/Laboratory Request (Invoice) Form

Incorporation of the chain-of-custody and the laboratory request form into one form simplifies the amount of paperwork and reduces the potential for clerical errors.

The following information should be included on this form:

- The submitting organization. Use the mailing address, phone number, and contact person within the organization.
- The collection site, date and time of specimen collection.
- The name and address of the laboratory.
- The authorized person to whom results are to be returned.
- Specimen identification. This may be the name, social security number (strictly voluntary), code number, accession number, or bar code, or a combination of identifiers. All identification information must be legibly printed or typed.
- The drugs to be tested. Different reasons for testing may define different screening panels or confirmatory procedures.
- The certification signature of the collector. The collector should read, sign and date the certification statement attesting that the identification on each specimen container and custody form was verified for accuracy and that the specimens are properly packaged and sealed for shipment.
- The chain-of-custody documentation. The signature and printed name of the releasing person, the receiving person, and the purpose of the change.
- If a consent form signed by the subject is required, this too may be incorporated into the request/chain-of-custody form.

See the Appendix for an example of a chain-of-custody form.

3.7 Collection Site Records

Documentation should record all pertinent data on each specimen collected. The following information should be included for each specimen:

- The date and time of collection.
- The test subject's name and social security number or code number.
- The specimen accession number or bar code label (if either are used).
- The temperature of specimen (within 4 min of voiding).
- Any remarks about unusual test subject behavior or unusual test subject findings noted in the examination of the urine specimen or any other relevant information.
- The collector's signature and printed name.

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[d] In the U.S., a federal appeals court has ruled (Interstate Brands Corp. vs. Local 441 Retail, Wholesale and Department Store Union, 11th Circuit U.S. Court of Appeals, No. 94-6306, Dec. 14, 1994) that only people who actually handle a drug test specimen are considered "in the chain of custody" and are therefore required to sign or initial the custody form. Following the decision, the U.S. Department of Transportation amended its regulations (*Federal Register*, Vol. 59, No 160, Pages 42996-42999, August 19, 1994) to reflect the Courts position.

[e] In the U.S., see the United States Postal Service (USPS) Domestic Mail Manual.

- The signature of the test subject, which certifies that the urine collected is, in fact, the specimen that he or she provided.

4 Laboratory Processing of Specimens

4.1 Requesting Laboratory Services

The intended use of test findings will determine the analytical approach to the processing of test specimens. It is essential, therefore, that the laboratory be properly informed on how the information it produces will be used. Hospital-affiliated laboratories that provide diagnostic support services should establish a working relationship with treating physicians. This way, requirements for toxicological analysis will be established on an ongoing, collaborative basis. Laboratories removed from the physician, on the other hand, generally must act solely on a laboratory analysis requisition.

Decisions regarding the nature of laboratory service are predicated on the exchange of relevant information between the physician and the laboratory. This exchange is generally accomplished by use of a test requisition form. Clearly, test requirements (e.g., chain-of-custody, assay sensitivity and specificity) for an employee drug testing program differ from those of a treatment program, which, in turn, differ from the needs of correctional facilities and probation departments. The requisition form, therefore, should clearly define the levels of toxicology service offered and state, or provide reference to, descriptions of specimen collection and handling requirements. Knowledge of the intended use of test findings will allow the laboratory to determine if the specimen(s) have been properly collected and handled.

The laboratory should also provide educational materials and/or on-site instruction for the proper use of laboratory services. This is of particular importance in the workplace where personnel are not familiar with the precautions that must be exercised in specimen collection and handling. If conditions exist that allow specimen adulteration or substitution and incomplete or inaccurate documentation of specimen identification, then the efforts put forth by the laboratory to ensure the integrity of the test process are nonproductive and the objectivity of the drug testing program is lost. An open line of communication between the laboratory and its client should be in place to address specimen collection and handling concerns. Additionally, the laboratory should provide educational material that addresses analytical issues which are important for the person reviewing the testing results to understand in order to accurately interpret the findings.

4.2 Preanalytical Aspects

4.2.1 Specimen Directing Procedures

To facilitate the processing of urine specimens that require special handling, the laboratory should use an identification system that permits different types of specimens to be distinguished in the receiving area. This system may employ color coding, symbols, or lettering that enables receiving personnel to separate specimens or packages containing specimens on the basis of the manner in which they are to be processed. Some specimen types that may require special designation include:

- medical specimens that require rapid processing so that results are available to physicians for diagnosis and treatment; and

- forensic specimens that require special handling to preserve the chain of custody.

4.2.2 Seals on Shipping Cartons

When packages are delivered in the mail or by a courier service and are labeled as forensic specimens (see Section 4.2.1) or contain visible seals, the condition of the seals should be examined and recorded in the specimen logbook as either "intact" or "disrupted." If the seals are broken and there is an indication that the carton was opened, the person or agency who submitted the specimens should be contacted and informed of the situation.

4.2.3 Specimen Requisition (Invoice) Form

The information contained on this form should be reviewed for completeness and accuracy. Patient demographics may be missing, particularly in cases involving emergency department or clinic patients who may be unable to provide the information immediately upon admittance.

4.2.3.1 Patient's Name

If the patient's name is unknown, provisions must be made to relate the person to the specimen and the laboratory report. The use of arbitrarily selected names, such as Jane or John Doe, may be a convenient method for temporarily designating such patients. However, in settings where more than one person is being treated whose identity is unknown, this can be troublesome; the laboratory may receive more than one Jane or John Doe specimen during a testing period. If that is the case, it is critical that the laboratory accurately record the patient's identification number or affix bar code labels on the specimen container and on pertinent logbook pages and report forms.

4.2.3.2 Requested Analyses

It is important to obtain the attending physician's comments, especially if they refer to the suspected intake of certain drugs. This can assist in the treatment of the patient since the suspected agent can be evaluated first and reported to the physician.

In dealing with forensic specimens, the accompanying documentation should be carefully reviewed to ensure that special requests for a particular analyte or decision level are recognized. If the requested service is not within the laboratory's capabilities, the submitting site should be contacted as soon as possible to discuss possible solutions.

4.2.4 External Chain-of-Custody Form

This document, which may be incorporated into the requisition form for forensic analysis, should be signed by the person who opens the specimen shipping carton. The date and time should also be recorded in the appropriate entry spaces. (A date stamp may be used.) The form should be inspected to ensure that the test subject's name, identification number, or bar code labels coincide with those on the urine specimen container. Any noted discrepancies must be promptly recorded on the chain-of-custody form and in the logbook.

4.2.5 Seals on Specimen Containers

Each specimen container should be inspected to ensure the integrity of its seal. The condition of the seal should be recorded in the specimen log as either "intact" or "disrupted." If the seal is broken, the collection facility should be advised that the integrity of the specimen may have been compromised.

4.2.6 Condition of the Urine Specimen

The urine specimen should be examined with regard to the following:

4.2.6.1 Volume

The volume of the specimen should be recorded. The laboratory should have an established policy with regard to processing specimens whose volume is less than the minimum required. If the amount available is less than is needed for all requested testing, the submitter should be consulted to determine what analytes should receive high priority for testing and to determine if additional urine can be obtained to permit all requested tests to be performed. The volume of each specimen should be recorded when it is received in the laboratory. Their information is particularly important when forensic analyses are to be conducted, in which case the initial volume of the specimen should be recorded and any quantities of urine that are removed for testing should be documented.

4.2.6.2 Organoleptic Properties

The urine specimen should be examined and any abnormalities in appearance or odor should be recorded in the specimen log. Any signs of spoilage or deterioration should also be noted. If a urine specimen is unsuitable for analysis, the submitter should be informed and asked to provide another specimen.

4.2.7 Entry into Laboratory Data System

Before testing, laboratory personnel should affix accessioning and/or bar code labels to the specimen container and forms. A system should be in place to uniquely identify each specimen. The data processing system employed should have the capability to permit rapid entry of "stat" requests and it should not be the cause of delayed testing. Provisions must be made to accommodate data entry throughout the day, including periods of planned computer "downtime" for file maintenance or updating. Additionally, plans should be made to enable specimen processing to continue during periods

of nonscheduled computer "downtime," which may include an independent secondary system into which data could be entered for later transfer into the primary system when it becomes operational again.

4.2.8 Specimen Storage

The specimen should be stored at 2–8 °C in a refrigerator located in an area where access is controlled. Storage under these conditions minimizes deterioration and protects the specimens from tampering. Prior to analysis, urine specimens may be stored under refrigeration for five working days. If specimens cannot be analyzed within five working days or portions remaining after analysis are to be retained for longer periods, storage in a freezer at -5°C or lower is recommended. To minimize degradation of frozen specimens that are stored for longer periods, it is advisable to use a freezer that is not a "frost-free" model. Documentation of storage conditions will be necessary if verification is required that the identity and integrity of the specimens were maintained. Storing specimens below room temperature may result in the formation of insoluble material. The testing protocol should be consulted to determine if such precipitates affect test results and how such specimens should be processed.

4.2.9 Additional Requirements for Forensic Specimens

Testing of specimens under forensic conditions necessitates introducing additional requirements that are above those normally employed as a part of good laboratory practice.

4.2.9.1 Specimen Handling

Forensic testing must be conducted in such a way that subsequent legal review can easily determine the status of the specimen (and aliquots removed from it) at any time. The specimen, therefore, must be kept in the container that was originally submitted to the laboratory, rather than dividing the original volume into portions for use in individual assays. If specimens are stored frozen, care should be exercised to minimize the number of freeze/thaw cycles to which the urine is subjected in order to remove aliquots, since this process may cause specimen degradation. If additional testing is required, each aliquot should be removed as needed. This will provide the proper chronological record documenting the purpose of each withdrawal. Standard laboratory procedures also need to define the technique used to remove portions of the specimen from the original container. To minimize challenges concerning specimen contamination, control measures must be introduced to ensure sample integrity. Documentation must include the volume of urine that is removed from the specimen each time an aliquot is removed for testing purposes.

4.2.9.2 Recordkeeping

In processing urine specimens tested under forensic conditions, two types of documentation are generally used. External chain-of-custody system (ECOCS) refers to documentation initiated at the point of collection and forwarded to the laboratory with the specimen. Internal chain-of-custody systems (ICOCS) are initiated in the laboratory upon receipt of the specimen and the external custody documentation.

The ECOCS is used to record the handling of the specimen by the patient and collection site personnel, as well as the entry of the specimen into the laboratory. It is general practice at this time for the collection site personnel to seal the external chain-of-custody document within a tamper-evident packaging system along with the specimen and forward them to the laboratory. Use of such a system precludes the necessity for each person handling the package to sign the external chain-of-custody form. The laboratory performs the necessary inspection process as indicated below to insure that specimen tampering did not occur.

Functionally, the purpose of the ICOCS is to track the processing of the specimen from the time of receipt to storage and disposal. All specimen handling, including the initial transfer from the ECOCS, should be recorded on the internal document. The ICOCS is used to record removal of specimen aliquots for either screening or confirmatory analyses, transfer of specimens (or portions of specimens) from one analyst to another, and the technical staff involved with interpreting and reviewing test results. The ECOCS form is signed at the end of the testing process and after technical review; thus, the time of completion is recorded for future reference.

4.3 Analysis of Specimens

Most laboratories that offer services for the analysis of urine for the detection of abused substances determine the presence of amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, or phencyclidine (PCP). Reliable procedures are also available for determining the presence of methadone, methaqualone, LSD, and fentanyl, although these are less frequently requested. Trends in drug abuse vary with time and geographic location and testing regimens must be adjusted in response to changes in abuse patterns. Governmental drug law enforcement agencies have systems for collecting information on the availability and use of controlled substances for illicit purposes. In the U.S., these include the Drug Abuse Warning Network (DAWN), which collects information from hospital emergency departments and medical examiners offices concerning substances administered by persons evaluated at these facilities. The DAWN system is limited, however, because it collects data only from metropolitan areas. This information may not reflect substance abuse trends in other areas of the country. Furthermore, DAWN and other programs that rely on patient self-reporting may obtain erroneous information because the actual composition of substances obtained from illicit sources may not be known.

"Designer drugs" are usually analogs or homologs of controlled substances but could potentially be compounds that are not structurally similar to other abused drugs. Fortunately, the sporadic incidents involving these substances have usually been of short duration and confined to the area near the point of manufacture. Designer drugs have been sold as other drugs which can place users in jeopardy if they are not aware of the substitution. For example, when 3-methylfentanyl (China white) was sold as heroin, deaths occurred since the pharmacological properties of this designer drug are different from those of heroin, and lethal doses were administered.[f]

From a laboratory perspective, designer drugs pose a problem primarily in the initial screening portion of the analytical process. If the substance is an analog or homolog of a drug for which immunoassays are available, the responses produced may be weaker than would be produced by a comparable amount of the drug that the assay is designed to detect. Designer drugs which are not structurally similar to drugs for which immunoassays are available would not be detected. If thin layer chromatography (TLC) is employed, the designer drug would probably not be detected unless the analyst happened to utilize a standard or control on the chromatogram which contains the substance. Difficulties may also be encountered in separating designer drugs and their metabolites from urine and concentrating them during the preanalytical phase of laboratory testing.

4.3.1 Initial Screening Tests

Initial screening tests are presumptive analyses performed to distinguish specimens that may contain controlled substances (or their biotransformation products) from specimens that do not contain these analytes. Commercially available urine drug screening products are based on the following techniques.

4.3.1.1 Thin Layer Chromatography

Chromatographic procedures are techniques used to separate mixtures of chemical compounds into individual components based on differences in their relative affinities for two different media. One component is a mobile phase (e.g., a moving solvent), and the other is the stationary or sorbent phase (e.g., a porous solid), which is bound to an inert solid support. In TLC, the stationary phase is a thin layer of adsorbent material (e.g., silica gel) coated on a glass or metal plate. The sample is applied as a small spot at the base of the plate and the plate is made to stand on edge in a solvent. As the solvent rises in the stationary phase by capillary action, the sample components move at different rates and are separated into different spots. The plate is removed from the solvent, dried, and stained to make the components visible. A similar technique is called paper chromatography, in which the thin layer plate is replaced by a specially prepared sheet of filter paper, or a cellulose or fiberglass sheet, that has been impregnated with a sorbent material.

(1) **Reliability**. TLC is a relatively nonspecific technique. With TLC, the distance a substance migrates from its point of application (the *Rf* value) and the reactions it undergoes with

[f] In the U.S., see the United States Postal Service (USPS) Domestic Mail Manual.

chromogenic reagents indicates its presence. Because more than one substance may have similar characteristics in the test system, TLC cannot be used to conclusively identify a particular drug or metabolite in a mixture. However, because the probability of two substances having identical characteristics in the test system is relatively low and the number of substances that may be present is limited, TLC often produces sufficient evidence to presume that a particular analyte is present.

(2) **Advantages**. TLC is capable of separating and identifying a wide variety of chemical substances. This characteristic permits its use in the detection of substances for which other screening procedures are not available. Because it does not require costly instrumentation or equipment, TLC is a relatively inexpensive procedure for drug screening. It is most conveniently applied to testing environments in which the sample volume is low.

(3) **Disadvantages.** TLC is a labor-intensive technique, which is relatively slow and difficult to automate. Therefore, it is not usually the method of choice in laboratories that screen large numbers of samples. TLC is also a subjective method, because the observations of the analyst are the basis for determining if a substance is present. Further, because significant quantities of chemicals are employed in this technique, it is not an ideal method from a health, safety, and waste disposal point of view. Migratory characteristics of analytes are influenced by a variety of factors that are difficult to control and that adversely affect the reproducibility of the technique. These effects can be minimized by employing appropriate quality control specimens on each plate. The reliability of TLC drug screening procedures is dependent on the experience and skill of the analyst, and will vary in direct relation to how carefully the technique is performed. Finally, TLC analysis procedures usually require pretreatment of the specimen to separate analytes of interest from the urine matrix and increase their concentration in the solution to be applied to the TLC plate.

(4) **Detection Limits.** Because analyte detection is dependent on the visual acuity of the analyst, the detection limit will vary from analyst to analyst. Therefore, it is important to have good initial training, consistent continuing education, and participation in outside proficiency training programs. Under favorable conditions, a skilled analyst should be able to detect relatively low drug concentrations, as low as 0.3 to 1.0 μg/mL. In the case of some substances such as Cannabinoid metabolites which are present in urine in ng/mL concentrations, specialized TLC systems are available which permit the detection of these compounds in this reduced concentration range. Recently, the analytical capability of TLC has been enhanced by reducing the size of the sorbent particles and the thickness of the stationary phase. This modified technique has been termed high-performance thin-layer chromatography (HPTLC), because it allows for the separation of drugs and metabolites in much shorter distances and has decreased the analysis time. HPTLC is also a more sensitive method than conventional TLC.

4.3.1.2 Immunoassays

Screening procedures based on immunoassay techniques are used extensively in urine drug testing. These procedures involve antigen-antibody interaction, and they may use fluorescent, radioisotopic, turbidimetric, nephelometric, or enzymatic or agglutination analysis techniques to measure the extent of this reaction. Immunoassays are based on the principle of competitive protein binding. A drug in free or conjugated form in a urine sample competes with a labeled drug in the test system for specific binding sites on the antibody. A portion of a urine sample that may contain a drug in free or conjugated form is added to a mixture containing a labeled drug and antibody. If a drug is present in the urine, it competes with the labeled drug for specific binding sites on the antibody. The proportion of labeled drug molecules bound is inversely proportional to the number of unlabeled drug molecules present in the mixture. The concentration of the drug in the urine can then be determined by measuring the displaced labeled drug or, alternatively, by measuring the quantity of the labeled drug that remains bound to the antibody. Using appropriate instrumentation, the signal produced by the labeled molecules is measured. This is compared with a threshold value obtained by determining the signals produced by specimens containing known amounts of the analyte of interest.

There are two major classifications of immunoassays. One group requires separation

of the free and bound drug before the measurement is conducted (e.g., radioimmunoassays); these are designated heterogeneous immunoassays. The other group does not require a separation step; therefore, it is designated homogeneous immunoassays (e.g., enzyme immunoassays, fluorescence polarization immunoassays and microparticle-based immunoassays).

(1) **Reliability.** As in the case of TLC, immunoassays are not completely specific and a positive test result is not a sufficient basis for stating unequivocally that a drug or metabolite is present in a urine specimen. The specificity of immunoassays is dependent on the characteristics of the antibody. For illustrative purposes, an antibody and a drug molecule are often compared to a lock and key, respectively. Some locks, as a result of their design, will allow many different types of keys to be inserted into them. This corresponds to a relatively nonspecific antibody. Such antibodies will produce positive test results in the presence of drug molecules having relatively few structural similarities in common with the target molecule the assay is designed to detect. An example of a relatively nonspecific immunoassay would be an amphetamine assay that responds to a wide range of β-phenylethylamines. Nonspecificity can be an advantage in certain instances, such as when an assay is required to respond to drug classes (e.g., barbiturates or opiates). Other antibodies may have very specific binding requirements, which corresponds metaphorically to a lock that only accepts keys that are very similar to one another. High antibody specificity distinguishes chiral molecules, which differ only in the arrangement of the component atoms in space, and not in their connectivity. This type of process can be explained using the hand-in-glove analogy: A right hand (specific antibody) can only be placed into a right hand glove (chiral molecule). Molecules of opposite configuration would either not interact or they would bind much less avidly with such an antibody.

The reliability of immunoassays can be compromised if any of the following practices are employed in an attempt to obtain more than the specified number of analyses from a quantity of test reagents:

- Diluting reagents. This refers to the practice of adding solvent or other extenders to test reagents so that more than the specified number of specimens can be tested using an immunoassay test kit. It will result in a diminished response that can still be interpreted, but usually results in an increase in false negative findings.

- Mixing specimens. Mixing portions of two or more specimens for analysis as a single specimen will often dilute a positive specimen to such an extent that the drugs present will not exceed the cutoff concentration and a false negative will occur.

- Mixing reagents. This refers to the practice of combining reagents from two or more assays (e.g. barbiturates and opiates) so that the presence of more than one drug or class of drugs can be detected when a single specimen is analyzed. Such procedural variations can potentially change any of the performance specifications for the test (sensitivity, specificity, and limit of detection). Derivations from the manufacturer's recommended uses will require the laboratory to validate the performance of the modified test system.

These practices are usually instituted in an attempt to reduce costs, but are unacceptable and must not be permitted.

(2) **Advantages.** As opposed to TLC, which has the capability to determine more than one drug per analysis, immunoassays are advantageous in situations where it is necessary to distinguish a particular substance or family of substances (e.g., barbiturates) from a large number of other substances that may be present in the sample. When testing to determine if any one group of drugs in a particular family (e.g., barbiturates) is present, the analyst should be aware that certain drugs (e.g., phenobarbital) may not produce the same response as other members of the group.

The primary advantages to using immunoassays for initial screening procedures are their high sensitivity and small sample volume requirements. They can generally be performed more rapidly than TLC procedures because little or no sample preparation is required and lengthy development periods are not involved.

Immunoassays are easily automated and can be performed on programmable analyzers with a minimum of operator intervention. Results obtained using such equipment are objective because they are derived from instrumental measurements and are not dependent on human observation or judgment.

Numerical results are produced that are readily interpreted and can be stored conveniently in laboratory information management systems. Immunoassays further require minimum quantities of reagents that are usually relatively innocuous compared to those used in TLC. Because of the small amounts of radionuclides involved, waste disposal is usually not a problem, even in the case of radioimmunoassays (RIA).

(3) **Disadvantages.** Although it is not necessarily a disadvantage, separate analyses must be performed for each drug or family of drugs to be determined. This increases the number of analyses that must be performed to screen a specimen and raises the cost of the screening process. Instrumentation used is moderately expensive and adds to the overall cost of the screening process. Reagents used in these procedures are also relatively expensive. Skilled operators are required to maintain equipment in good working order, troubleshoot problems when they occur, and conduct quality control procedures. Although numerical results are produced in many testing systems, these values must be interpreted with caution because more than one species in the urine specimen may be responsible for the signal that is generated.

(4) **Detection Limits.** Due to their high sensitivity, immunoassays can easily detect microgram and nanogram per milliliter concentrations of drugs and metabolites that are encountered in urine drug testing. Because they are also easily automated, immunoassays have become the screening methods of choice in large scale drug abuse detection programs, such as those operated by the Department of Defense; the Department of Transportation; the Nuclear Regulatory Commission; and the Alcohol, Drug Abuse, and Mental Health Administration.

(5) **Non-Instrument Based Immunoassays.** Recently, a number of manufacturers have marketed “self contained” or “unitized” immunoassay systems that do not require instrumentation and that can be used conveniently outside of a traditional laboratory setting. When used according to manufacturer's instructions, these devices are reliable, and they may find wide-scale application in hospitals, rehabilitation centers, criminal justice facilities, and the workplace. These devices are, however, subject to the same limitations as are other immunoassay procedures; they should not be used alone as the basis for making a decision that could adversely affect the person who was tested. Since these devices are usually sold as individually packaged single test units designed to analyze one patient’s specimen, it may be difficult to apply conventional quality control procedures to these drug testing devices. Some manufacturers have attempted to overcome this problem by including quality control materials in each testing unit. The acceptability of these controls will depend on how well they evaluate the performance of the materials in the system that is being used to test the patient’s specimen.

4.4 Confirmatory Tests

Screening tests for drugs are designed to be rapid, inexpensive procedures that provide evidence for the presence or absence of the target compounds. Such tests generally lack the specificity necessary to absolutely prove the presence of the target compound. Considering the potential implications of a positive result in a random or reasonable-suspicion drug test, it is not surprising that regulations covering these types of tests require confirmation of positive results found by the screening procedure. Even in situations where confirmatory testing is not required by law, testing programs should have a means of assuring a low probability of false-positive results. Confirmatory testing, as a part of a well-planned and carefully controlled drug testing program, is the best approach to the required accuracy. Decisions concerning the necessity of confirmatory testing or verification of initial screening results should be made by the agency submitting the specimens in consultation with the laboratory that will perform the analyses. A confirmatory test must provide specificity of detection; that is, it must unequivocally prove the presence of the suspected drug above a cutoff level. Therefore, the cutoff level must be set enough above the detection limit to assure that signals exceeding

the cutoff limit are only from true positive results. To assure that any substances that give false-positive results in the screening test do not also give false-positive results in the confirmatory test, the confirmatory test must rely on a different approach to the detection of the drug.

One of the most common procedures, widely accepted as having the necessary specificity for confirmatory testing, use the combined technique of GC/MS. The combination provides excellent sensitivity and specificity not attainable by either technique alone. Separations that require up to hundreds of thousands of theoretical plates can be accomplished by capillary GC. Nevertheless, in complex mixtures, such as urine extracts, overlapping peaks are often encountered, making unequivocal identifications and accurate quantitation difficult by GC alone. From the mass spectrometer, the pattern of ion abundances measured versus mass, known as the mass spectrum, has been described as a fingerprint of an organic compound. It is a reflection of the structure and bond strength of the molecule. However, mass spectra are sometimes indistinguishable from closely related compounds. Nevertheless, the combination of retention time and mass spectrum can provide the strongest possible evidence for the presence of the commonly tested drugs. Mass spectral information can be acquired in two ways: 1) full scan, in which the entire mass spectrum is recorded and 2) SIM, in which only certain characteristic ions are monitored. For most mass spectrometers, including quadrupole instruments, the latter approach is much more sensitive, but the former provides stronger evidence for the presence of a particular compound, if sufficient material is present. Sensitivity is reported to be excellent in either mode for ion trap mass spectrometers, which are now gaining acceptance in forensic applications.

With appropriate choice of internal standards, GC/MS is an excellent technique for quantitation. The best internal standards are those that most closely match the chemical and physical properties of the analyte and these are isotope-labeled forms of the analyte. This is particularly important when the recovery of the drug from the urine matrix is low.

There are, of course, disadvantages to using GC/MS for drug confirmations. The necessary equipment is expensive to purchase and to maintain. Isotope-labeled internal standards are expensive. Skilled operators are required to assure that the instrumentation is operating properly. Because of the low levels of the drugs or their metabolites in the complex urine matrix, a considerable amount of sample preparation may be required before the sample can be injected into the GC/MS system. Generally, the drugs and their metabolites must be converted to less polar and more volatile derivatives to permit separation by gas chromatography. Such restrictions make GC/MS unsuitable for routine large-scale screening applications.

While other techniques have not been recognized as suitable for confirmatory testing, certain combined techniques such as GC/Fourier transform infrared spectroscopy (FTIR) and LC/MS have the potential sensitivity and specificity for certain applications. However, both have many of the same disadvantages of GC/MS, without some of its capabilities. Sensitivity and applicability to quantitation are often problems with FTIR. With LC/MS, the separations are generally not as good as with GC, and the mass spectra are generally simpler, leading to loss of specificity. This specificity can often be regained by use of the technique of collision-induced dissociation, but it requires more complex mass spectrometers than are necessary for GC/MS. With further development, other analytical techniques may reach the required degree of specificity for certain drugs and they may then be recognized as suitable for confirmatory testing.

4.5 Postanalytical Aspects

4.5.1 Interpretation and Laboratory Reports

Testing performed for forensic or employment purposes is not conducted under the same time constraints as in emergency medical situations. Therefore, additional evaluation can be performed to minimize ambiguities, while not unduly delaying the ultimate decision-making process.

Drug evaluations should, at a minimum, determine if applicable drug classes are present or absent. Each class assay should, therefore, employ calibration specimen(s) containing the

drug, as well as a drug-free urine specimen to serve as a blank. This permits comparison of the patient specimen response to that obtained with the instrument calibration. Patient specimens yielding a response greater than the cutoff are interpreted as positive. Specimens yielding a response less than the cutoff are reported as negative. Laboratories employing systems that produce semiquantitative or quantitative results should not report as positive any specimen below the cutoff level.

Reports of screening assays should indicate which drug classes were evaluated. Since most individual drugs within a class react differently with the immunochemical system, the detection limits for the assay should reflect a range from the most to the least sensitive.

Additional information on the toxicological report should include the following information: date and time received and reported; condition of the urine specimen, if abnormal; and whether any assays were not performed because of an insufficient volume of specimen.

Urine drug screens performed for forensic purposes must be evaluated within the context of a multiple testing format. Whereas the screening methods may be identical for both medical and forensic purposes, when testing forensic specimens, an additional level of confirmation is required before final reports are issued. The confirmatory assays employ more specific techniques, and, when procedures such as GC/MS are employed, can yield information much more quantitative in nature. This factor requires attention in that the response for the screening and confirmatory techniques must complement each other. In comparing the GC/MS confirmatory test to the screening test, the detected analyte must be consistent with the sensitivity of the screening assay. For example, some screening assays exhibit a much greater response to a metabolite, rather than the parent compound of that analyte. If the GC/MS chromatogram does not contain the immunoactive metabolite that yields a positive response in the screening assays, the interpretation should be considered inconclusive at this point and reexamination of the original specimen should be considered.

Additionally, within the forensic testing environment, it is not uncommon to test with specific, established screening and confirmatory cutoff levels. These levels may, particularly with GC/MS confirmatory tests, be considerably above the sensitivity of the assay. If the analyte of interest is detected, but at a concentration below the cutoff level, the assay result should be interpreted as negative. For operational convenience and to comply with regulations, laboratories do not report confirmatory drug testing findings as positive if the value recorded is below the range for which the procedure has been calibrated and controls have been tested to verify the accuracy of the method.

With all forensic drug testing, it is critical that two separate chemical methods be employed before a positive finding is issued. Regardless of the response in the screening assay, if the analyte cannot be confirmed by a second independent method, no positive report should be issued.

4.5.2 Retention of Records

The laboratory should specify, within the overall record retention system, the period of time drug screening documentation is to be stored. Two-to-three-year storage for worksheets, chromatograms, and instrument printouts is generally adequate for most medical situations. Final reports should be maintained so that they may be easily retrieved for an additional period of time. It is not uncommon today to receive inquiries for civil cases where the testing was performed four years ago; therefore, maintaining final reports for this period of time is consistent with those practices.

Specific record retention policies for forensic specimens should take into account the nature of the legal proceedings, where the testing results will be presented. While blanket record retention schedules may be established with agencies using the records, any records presented in a legal proceeding must be maintained for the duration of any possible review. Destruction of these records should be made only after review by the appropriate legal staff.

4.5.3 Confidentiality Considerations

All laboratory testing must be considered confidential. Test results should be reported to a medical review physician for interpretation before information is released for treatment purposes or other actions are initiated.

Inadvertent disclosure of individual test results may lead to severe consequences for the laboratory. An appropriate policy should be developed by the testing organization to ensure patient privacy rights in accordance with state and federal statutes.

For the purposes of assuring confidentiality, telephone reports and electronic transmissions should be avoided. Not only do forensic records require this level of confidentiality, but access to the records should be restricted in a "need to access" manner. This not only includes securing completed records, printouts, and chromatograms, but data bases should also have a secure mechanism so that on-line access to the forensic testing information is restricted to appropriate personnel.

4.5.4 Retention of Specimens

Specimens submitted for urine drug testing should be retained for a time compatible with the use of test results. A laboratory director should determine a policy for the retention of specimens. The College of American Pathologists and the Department of Transportation recommend a minimum of one year for positive specimens. It may be advisable to retain negative specimens for a reasonable timeframe in the event additional testing is requested. Testing conducted in an emergency medical situation usually involves sequelae that resolve in a matter of days. Policies should be established where medical review is completed before specimen disposal. Clients affected by a specimen discard policy should be notified in advance of the details of that policy.

Urine specimens analyzed in a forensic system need to be maintained for a time period sufficient to allow for the proper administration of any possible legal activity. Protocols should be developed for the retention of both positive and negative specimens for a short period (one week) in the event additional testing is requested. Positive specimens are retained for a minimum of one year. If any testing is brought into legal review, the specimen should be maintained for the duration of the proceedings.

When specimens are to be retained for extended periods, storage conditions and the fate of the analytes of interest in urine needs to be considered. For example, the major carboxylic acid metabolite of tetrahydrocannabinol (THC) is known to adsorb onto glassware. Silanizing glassware has been reported to be ineffective in preventing such losses. This can present problems if specimens are stored for long periods before analysis or must be analyzed again after a long period in storage. Losses due to adsorption on container surfaces need to be considered in the case of standards, controls, calibration materials and proficiency testing specimens as well. Some analytes may also concentrate in the sediment which often occurs when urine is stored. In addition to analyte losses attributable to adsorption, some substances such as LSD are known to be light, heat, and acid-labile, and should be stored in the dark under refrigeration and not placed into acid-washed silylated glassware. Significant problems are most likely to occur when substances which are present at low concentrations are being analyzed. It is therefore advisable to test specimens as soon as possible after collection and to be aware that extended storage can result in decreases in analyte concentrations.

5 Quality Assurance

5.1 Internal Quality Assurance Program

5.1.1 Basic Principles

For a laboratory to produce results that are both accurate and defensible, they must have a sound quality assurance program in operation. Within the laboratory, they must have accurate methods, calibrated apparatus and instrumentation, trained personnel, appropriate controls and calibrators, procedures for reviewing control and positive results, procedures for error reduction, and complete documentation to demonstrate that these aspects of quality control are functioning.

Methods used for drug screening and confirmation should be chosen based upon a solid record of performance. Once chosen, a method must be completely documented and its performance tracked over time. A review for problem areas and needed improvements should be made on a regular basis. Particular attention should be paid to the elimination of the problem of carry-over from one sample to the next, a situation that could generate false-positive results.

All volumetric and gravimetric apparatus must be certified and/or carefully calibrated. All instrumentation should have regular, documented maintenance. All operators of the analyses must be thoroughly familiar with the instrumentation and procedures they use, aware of potential problems, and know what action to take when problems arise.

For quality control of the drug screening process, controls must be included with each batch of specimens as specified by the manufacturer, or as indicated by appropriate regulatory agencies. These controls must include the following as a minimum:

- a urine specimen that is certified to be free of the tested drugs;
- a urine specimen with levels below the threshold concentration (50 to 80% of the cutoff level, depending on laboratory requirements) that serves as a negative control; and
- a urine specimen with levels above the threshold concentration (110 to 125% of the cutoff level, or greater, depending on laboratory requirements) that serves as a positive control.

Data from the controls should be processed along with that from the samples. All control data must be carefully reviewed by qualified personnel and then archived to permit complete documentation of the system performance.

A laboratory may wish to prepare its own controls for routine operation. For controls other than blank, known amounts of drug standards are added to a blank urine pool. The purity of the drug standards must be known to assure that control levels are correct. Furthermore, controls should be run along with controls from a reliable source for further validatation.

Quality control of the confirmatory tests is even more critical. The method of choice must have been shown to produce accurate and precise results. The relative recovery of the analyte and the internal standard must be known. Documentation supporting the accuracy of a positive confirmation is imperative. Calibration using accurately prepared standards must be performed with enough frequency and over a sufficient concentration range to assure accurate measurement of all positive results and controls. Calibration verification should be done daily, or more often if needed, to demonstrate the stability of the instrument response. Reference materials with carefully determined concentrations can be useful for evaluating and monitoring the confirmatory tests and the routine control materials.

As with the screening process, controls should be included with every run of samples. NCCLS document C24— *Internal Quality Control Testing: Principles and Definitions*, provides useful guidelines for the use of controls and the evaluation of control data.

Blind reliance on the automatic integration routines of instrument data systems is unacceptable. Peak shapes and integration baselines must be examined for all positive results to assure that all of the analytes peak but that none of any nearby peaks are included in the integrated area. If interfering peaks are frequently encountered, methodological modifications should be considered.

A necessary final component in quality control is a system for error detection. Careful adherence to procedures will reduce errors but not eliminate them. Review of the results for clerical errors and unusual results by conscientious, knowledgeable personnel can significantly reduce errors further.

Because there is the potential for legal challenges, and the consequences of an adverse legal ruling could be devastating for a laboratory, it is imperative that the quality assurance plan be strictly adhered to and fully documented.

5.1.2 Blinded Specimens

At least 1% of the specimens in a batch or a minimum of one specimen per batch, if less than 100 specimens are tested, should be controls disguised as patients' urine. These controls should consist of specimens containing drugs as well as drug-free urine. As a general guideline, approximately 20% of the blinded specimens submitted for analysis should contain one or more of the substances to be determined at concentration above the cutoff level for the procedure being employed.

5.2 Use of Unknown Specimens

5.2.1 Internal

Control specimens whose analyte content is unknown to persons performing the analyses may be purchased or prepared in-house. These controls should be disguised so that they are indistinguishable from routine specimens that are received for analysis. At least one percent of each batch of specimens should be internal controls, with a minimum of one control in each batch. Internal controls are generally introduced during the specimen accessioning process, and depending on the design of the quality assurance program, may evaluate the initial screening only on both the initial screening and the confirmatory testing procedures.

Following completion of analysis of a batch of specimens, internal unknown specimens should be identified, and satisfactory performance in determining their analyte content verified before results on client specimens are accepted. The utilization of internal unknown specimens enables errors to be detected and corrected before results are reported. Data accumulated from the analysis of these specimens documents the reliability of analytical procedures and is an essential component of an effective quality control program. Most accreditation and certification programs require the inclusion of internal unknown specimens in each batch of urines to be analyzed as one of their criteria for approval.

5.2.2 External

Controls disguised as clients' urine specimens and submitted to the laboratory from collection sites are more effective than internal controls since they validate the reliability of the entire analytical process. This includes specimen accessioning and result reporting aspects of the process where errors more frequently occur. These programs provide a better indication of the routine performance of the laboratory in urine drug testing since the specimens cannot be distinguished from urine specimens which are regularly received for analysis.

The incorporation of external unknowns into a quality control program is more complex since the cooperation of specimen submitters is involved. Collection sites must have access to control urines and receive instructions for disguising them so that the laboratory cannot distinguish them from routine specimens. When external controls are submitted for testing, they must be accompanied by appropriately completed analysis request forms and chain of custody forms containing fictitious information so that laboratory personnel will not recognize them as controls and process them as routine specimens. Caution must be exercised in completing these documents to avoid the use of names, social security numbers or other demographic data which will reveal to laboratory employees that the specimens are controls.

If external unknown controls are to be included in a quality control program, an agreement must be established between the specimen submitter and the laboratory regarding who will bear the cost of materials and the laboratory's expenses in processing these specimens. A mechanism also needs to be established for communicating information about performance in this testing back to the laboratory. In this regard, policies need to be developed concerning corrective actions to be instituted when laboratory findings do not correspond with the specified analyte content of these controls.

The employment of external unknown controls in quality assurance programs is a relatively new concept which will be more extensively utilized in the future. At this time, it is required primarily in federally mandated drug testing programs and there are relatively few guidelines and regulations which address this type of control.

5.3 External Quality Assurance Program

5.3.1 Program Sources

Proficiency testing and accreditation programs for laboratories conducting analyses of urine for the presence of drugs of abuse are available from government public health agencies, professional organizations, and manufacturers of testing systems. The number and types of programs in which a laboratory must participate will depend on the source of the specimens, the purpose for which the analyses are performed, analytes being tested, and the jurisdictions to which the laboratory is subject. For example, a laboratory located in a particular state that

receives specimens from federal workers in another state would be required to participate in a certification program acceptable to the DHHS because federal workers are involved. The laboratory may also have to be certified by the state in which it is located, if that state has a certification program. In addition, the laboratory would have to comply with the mandates of the state in which the specimens were collected, if that state required laboratories receiving specimens originating from within its boundaries to participate in a proficiency testing and certification program.

The requirement to participate in more than one certification program is burdensome, and it increases the operating expenses of a laboratory. This problem could be alleviated if states developed uniform criteria for certification to conduct urine drug testing. Reciprocal agreements could then be made between states with equivalent requirements. This would permit laboratories to offer interstate testing services, without participating in the certification program of each state from which specimens are received. Having state governments conduct certification programs is desirable because each agency would evaluate and certify a relatively small number of laboratories, and it could provide consultation, training, and technical support to facilities that require assistance. In addition, to provide assurance that certification programs are operated in a fair and impartial manner, regulatory authority should reside with the government.

An alternative certification process for laboratories that conduct business on an interstate basis would be to have a federal or national agency (e.g., in the U.S., the Centers for Disease Control and Prevention [CDC]) regulate these facilities. Under this type of process, a laboratory would be certified in the jurisdiction where it is located, provided that jurisdiction had a certification process. It would also be certified by the appropriate federal or national agency to offer services on an interjurisdictional basis. At most, this process would require a laboratory to be certified by two government agencies and participate in two proficiency testing programs.

Programs that provide proficiency testing and accreditation may be compulsory or voluntary in nature. Generally, those conducted by government agencies are mandatory for the laboratories they have the authority to regulate. Voluntary certification programs (e.g. such as those conducted by CAP or the American Association for Clinical Chemistry [AACC]) are also available and should be used where government regulation is not in place or does not take precedent. These voluntary programs include proficiency testing surveys and peer group inspections, which provide assurance that a laboratory is meeting minimum performance criteria when no other regulatory process is in effect. Generally, programs conducted by manufacturers are not used for accreditation purposes. They may, however, help laboratory analysts detect deficiencies in testing procedures and improve the quality of their drug analysis services.

5.3.2 Goals of External Quality Assurance Programs

Effective external quality assurance programs contain laboratory improvement, educational, and regulatory components that are vital to optimizing the overall reliability of a urine drug testing laboratory. Laboratory improvement measures are used to help analysts detect deficiencies in testing procedures and correct them. Proficiency testing surveys are the primary technique used to evaluate how reliably a laboratory can perform initial detection and/or confirmatory analysis procedures. The agency conducting the proficiency surveys must be prepared to provide additional test specimens and support services if a laboratory requires them to investigate a deficiency, develop a new method, or improve an existing procedure. For this purpose, it is desirable for the testing agency to be adequately staffed and serve relatively few laboratories so that the needs of the laboratories being surveyed can be efficiently addressed.

The educational facet of proficiency testing is as important as the regulatory and laboratory improvement aspects. Proficiency testing surveys provide a unique opportunity for laboratory analysts to learn about current trends in testing and new approaches to handling existing problems. The proficiency testing agency has an obligation to introduce new substances into test specimens when it is determined that they are being abused by a significant segment of the population. This enables analysts to gain experience determining these substances and to adapt their testing

regimen to accommodate new substances. For example, with the increasing prevalence of abuse of fentanyl and related substances, testing agencies should be incorporating these substances and/or their metabolites into urine test specimens to acquaint laboratorians with their detection and confirmation. Consideration should also be given to anabolic steroids because their abuse appears to extend beyond athletes into a much larger population obsessed with looking better and developing a sense of well-being, which steroids are purported to produce. Further, adding designer drugs and their metabolites to proficiency testing specimens would provide experience in identifying these substances in the event their abuse proliferates.

The testing agency can also introduce substances that have been found to complicate or interfere with urine drug analyses for particular substances. Because new drugs are being introduced into clinical practice each year, it is important for analysts to be aware of those medications whose response in analysis systems may affect the determination of substances of abuse. Sympathomimetic amines, such as phenylpropanolamine, which cannot be distinguished from amphetamine or methamphetamine when using certain screening procedures, should be included in test specimens. Laboratories that cannot differentiate these substances should be given the option of reporting sympathomimetic amines as a drug class for screening purposes.

When introducing drugs of abuse, interfering substances, or their respective metabolites into test samples, care must be taken to place in the urine only those substances that would actually be found in the urine of persons who have taken the agent in question. The ratio of glucuronides or other conjugates to unconjugated drugs should approximate that found in the urine of a typical subject. The same reasoning applies to other biotransformation products whose detection is important for analytical purposes. For example, benzoylecgonine is the primary metabolite of cocaine found in urine following cocaine administration. However, some unchanged cocaine, ecgonine methyl ester, and ecgonine should also be included for analysts seeking to identify these additional substances. The concentrations of substances added to the urine should be in the range in which they would be found in an actual patient's specimen, not set at ever decreasing levels to challenge the technology.

When proficiency testing agencies add new substances to a survey, they should inform the laboratories participating in the survey of the change and allow them adequate time to adjust their procedures and gain testing experience before grading their performance in detecting the new substances. For a testing agency to have the knowledge and experience necessary to make innovative changes in proficiency surveys, it should be involved in actual specimen analysis on a continuing basis and it should have provisions for investigating specimens that laboratories report to be unusual or difficult to analyze. To adequately conduct such studies, the proficiency testing agency should be equipped to conduct the same kinds of procedures that are performed by the laboratories being surveyed. Summary reports of proficiency surveys should include information about how laboratories performed according to methods used for drug analysis. To assure the quality of the program, the proficiency testing agency should also test representative portions of test specimens before and during surveys to verify that the analytes of interest can be determined using techniques employed by the laboratories being evaluated. Additional important education services that proficiency testing agencies should provide are training and consultation to laboratorians who are preparing to conduct urine drug determinations or want to improve the reliability of established procedures. At this time, when errorless performance is being demanded of urine drug testing laboratories, the testing agency and the laboratory must work closely together to detect potential problems and correct them before the quality of client services and certification are affected.

The regulatory aspect of an external quality assurance program usually consists of two primary components. The first is a documentation requirement to verify that the laboratory is properly licensed, capably staffed, adequately equipped, and acceptably housed to conduct urine drug testing in a safe and reliable manner. This requirement includes a review of the analytical procedures used by the laboratory to ascertain that they are based on sound scientific principles and documented in the technical literature.

The second component of the regulatory aspect is the maintenance of a record of satisfactory performance in a proficiency testing program that is acceptable to those who are served by the laboratory to conduct testing. The regulatory component may not be present in external quality assurance programs that do not attempt to distinguish those facilities that can offer services reliably from those who cannot. Some programs conducted by manufacturers of testing systems are of this type. It may not be appropriate for manufacturers of testing systems to certify laboratories because performance of the facilities surveyed is a reflection of the quality of manufacturers' products.

5.3.3 Proficiency Testing Surveys

Specimens used in proficiency testing surveys for the detection of substances of abuse in urine are usually prepared by adding the analytes of interest to drug-free urine. Specimens from drug users have been used in some programs, but this is usually not practical when large numbers of laboratories are being surveyed because of difficulties in obtaining large volumes of such urine with uniform composition and containing adequate concentrations of the drugs or metabolites of interest.

Some proficiency testing agencies also use simulated urine to prepare survey specimens, which is acceptable provided that the analytes added to these matrices are detectable using procedures that are designed for urine. When urine from human donors is used, the donor's blood should be tested for the presence of HIV and hepatitis-B surface antigen (HB_SAg). Only urine from antibody-free donors should be used to prepare test specimens. Despite these precautions, analysts should be advised that test specimens may still contain infectious organisms and should be treated as a potential biohazard. Urine to be used as a matrix for proficiency testing specimens should be filtered through an 0.22 micron filter to remove larger microorganisms and then treated with an appropriate mixture of antibiotics to hinder the growth of remaining microorganisms. A combination of potassium penicillin G (280 units/mL), streptomycin sulfate (0.22 mg/mL), and amphotericin-B (2.8 ug/mL) has been found to be satisfactory for this purpose.

When considering what analytes to place in test specimens, the literature should be consulted to determine how substances of abuse are metabolized in humans and what biotransformation products are excreted in urine. The test specimen should simulate the urine of a person who has actually taken the drug in question to the best extent possible. Because some substances are transformed into many metabolites, it may not be possible to include them all. However, those metabolites that various analytical systems are specifically designed to detect must be included, as well as representative quantities of the unchanged parent drug. For example, small amounts of amphetamine, a metabolite of methamphetamine, must be included in specimens prepared to simulate urine from a methamphetamine abuser because some analysis systems identify urine specimens containing either amphetamine or methamphetamine by detecting the presence of amphetamine.

Proficiency testing programs should evaluate a laboratory's capability to perform initial presumptive screening determinations and confirmatory analyses separately. Since screening determinations are usually conducted using thin-layer chromatographic or immunoassay techniques, the detection requirement may be either to putatively determine the presence of a specific substance such as methadone, or a class of substances such as sympathomimetic amines (amphetamines), barbiturates, benzodiazepines, or opiates. This tentative identification may be based on detection of the parent drug (e.g., methadone) if a sufficient amount is excreted in the urine, or a metabolite (e.g., benzoylecgonine in the case of cocaine), if a parent drug is extensively biodegraded. For certain substances (e.g., propoxyphene), analysts may require the detection of both the parent drug and metabolite (norpropoxyphene) in order to report a positive screening result.

When chromatographic methods are used, it may be possible to presumptively detect the parent drug and/or one or more metabolites. For example, when methadone is determined by TLC, the principal metabolite, 2-ethylidene-1, 5-dimethyl-3, 3-diphenylpyrrolidine (EDDP) is also usually detected. The presumptive detection of more than one substance in urine that can be related to a particular drug provides further evidence that the drug was administered. But, it is not considered to be conclusive proof of

drug administration. It should be remembered that chromatographic techniques are primarily separation procedures and the data that they produce (Rf values, chromogenic reactions, or retention times) are not usually considered to be sufficient to exclude all other substances. They, therefore, cannot be used as the basis for a definitive identification. Caution should also be exercised in the interpretation of immunoassay results. The antibodies employed in drug abuse detection assays are usually specific for a structural category of drugs. These assays tend to be cross-reactive with chemically related substances and therefore do not unequivocally indicate the presence of a particular drug of abuse or drug metabolite. Further, because of the calibration procedures used and the fact that concentrations are derived by interpolation from nonlinear curves, immunoassays for drug abuse detection are usually semiquantitative. Consequently, they should not be used for quantitative analysis, unless the manufacturer provides sufficient calibrators for this purpose and specifies that the procedure produces reliable quantitative results. There is some question about the necessity of conducting quantitative drug abuse detection analyses on urine specimens anyway because urine concentrations cannot be correlated with degree of impairment at a particular time.

Proficiency testing specimens to evaluate confirmatory testing ability should specify the results obtained from screening procedures and request the laboratory to verify what is present. When possible, this should include a definitive identification of the drug or metabolite that is present. The confirmatory testing laboratory should be expected to address the more challenging problems that confront analysts today.

An example of such a problem would be to determine if a person who tested positive for opiates in a screening analysis had taken heroin or merely consumed a food product containing poppy seeds with residual traces of morphine. The confirmatory testing laboratory would be expected to determine if 6-acetylmorphine was present in the urine because this heroin biodegradation product would not be present in the urine of a person who had consumed poppy seeds.

Another example of a problem in confirmatory analysis would be to determine if a person who tested positive for the presence of an amphetamine had taken a controlled substance or used an over-the-counter nasal inhaler containing the R(-) optical isomer of methamphetamine, which is a less powerful central nervous system stimulant and has much less abuse potential.

Errors of a nonanalytical type can also be addressed in proficiency testing surveys. These include errors that result from mistakes in recording information or handling specimens. For example, the identification numbers on specimen containers from two different persons could be transposed, so that the identification numbers on the analysis request forms do not correspond with the numbers on the specimens containers. Laboratories would be graded on their ability to detect such errors and correct them. Another example would involve a specimen for confirmatory analysis for a particular drug such as cocaine. However, another drug, such as amphetamine, would be placed in the test specimen to simulate a situation in which specimens containing cocaine and amphetamine are interchanged after screening is completed. The laboratory being evaluated would be expected to attempt to determine why the screening procedure produced an apparent false-positive finding when the confirmatory result was negative. The laboratory would be graded on its ability to investigate such a problem and correct it. A second specimen for confirmation of the presence of amphetamine, but actually containing cocaine metabolites, could be included in the survey to simulate the other specimen. Testing in this manner obviously increases the demands that are placed on both the testing agency and the laboratory undergoing evaluation. Such testing procedures may not be practical in programs with large numbers of participants or limited budgets.

The determination of acceptable results in proficiency testing surveys requires the assistance of reference laboratories. These are usually facilities with a reputation for excellence in urine drug analysis who will agree to analyze representative portions of survey specimens and report their findings to the proficiency testing agency. It is desirable to have reference laboratories use a variety of procedures so that an independent verification is obtained that the test specimens can be successfully analyzed by all available methods. This is necessary because

the testing agency usually cannot analyze the specimens by every method that is available.

External quality assurance programs that certify laboratories to perform urine drug analyses should have procedures for corrective action when a deficiency is found during an inspection or erroneous findings are reported in a proficiency survey. Although, in many instances, errors in testing cannot be tolerated, a process must nevertheless be available that permits laboratories to investigate problems and take remedial action with minimal disruption of services. Laboratories should develop contingency plans for the efficient referral of specimens to another laboratory during periods in which their certification may be suspended. From a practical point of view, because it is difficult to reduce the probability of errors below a few percent, it is best to require laboratories to maintain a certain minimum score in proficiency surveys in order to be certified to offer testing services. Programs that require a discontinuation of services every time an error occurs often cause unnecessary disruptions in testing, which is inconvenient and expensive for the laboratory, the client being served, and the proficiency testing organization.

6 Use of Results

6.1 Role of the Physician in the Review of Findings

The role of physician in a medical review is as consultant to the employer. A physician consulted for evaluation of a positive drug screen should be knowledgeable in the area of drug abuse evaluation and interpretation of laboratory data.

When an employee is referred for medical evaluation as a result of a urine drug test, the employee should be informed and consent to the release of the physician's findings concerning the use of illicit drugs or abuse of drugs or alcohol to the employer. The consent for release of this information may be made a condition of employment. If the employee does not consent, the employer should be so informed.

The physician should as was emphasized in Section 2.3.1.3, exercise caution when evaluating drug testing results. The physician may contact the laboratory if there are any technical questions or to obtain the quantitative values. Positive test results only show past exposure to the drug and cannot be interpreted to determine usage patterns. If the report does not meet forensic standards, the employer should be notified and no adverse action should be taken against the employee.

The physician should interview the employee to determine whether any prescribed medications were used that would explain the findings. Prescriptions should be verified. If the medications were prescribed and there is no evidence to suspect abuse of those medications, the employer should be notified that there is no evidence of illicit drug use or abuse. If rules exist regarding reporting to work while taking certain prescribed or over-the-counter medications, administrative action may be taken by the employer on that basis.

If morphine and codeine were identified, prescribed codeine is the most common cause. A history of poppy seed ingestion should be sought, which could also explain the findings. Because morphine and codeine may also be found after heroin use, the physician should look for needle tracks and other signs of heroin use. The substance 6-monoacetylmorphine is found only as a metabolite of heroin, and has no legitimate medical use. Its presence is interpreted as evidence of the use of heroine.

Except in rare instances where tetrahydrocannabinol has been permitted to be used in legitimate practice, positive cannabinoid test results are usually associated with marijuana abuse. Persons whose urine produce positive cannabinoid tests frequently claim to have taken ibuprofen in the belief that its presence will be integrated as the cause of a false-positive cannabinoid finding. However, it should be noted that the carboxylic acid moiety in ibuprofen has been separated to compete for certain derivitizing reagents in the GC/MS confirmation which interferes with their detection that does not produce a false-positive result. Passive inhalation of smoke from burning marijuana has been experimentally shown to result in measurable concentrations of cannabinoids in urine. However, in those situations, the concentrations produced were generally low, and not in the range associated with physiological effects. The concentrations of cannabinoids that have been produced by

passive inhalation are below the cutoff levels that are used for substance abuse testing; thus it is not an acceptable defense for a positive test result.

Phencyclidine is a schedule I drug. When found in a urine specimen, it indicates illicit use of the drug.

The commonly used tests do not detect the presence of all possible drugs of abuse. This should be considered in the evaluation and reported to the employer. Additional testing may be recommended.

The physician may present the evidence of illicit drug use or abuse of prescribed drugs to the employee. The employee, at this time, may recognize the seriousness of the problem because it threatens his employment. He or she may then heed advice to enter a rehabilitation or employment assistance program (EAP).

6.2 Role of the Agency Requesting Testing

An agency or employer planning a drug testing program should notify the employees and applicable bargaining groups before instituting a drug testing program. Bargaining groups may be involved in the development of the program. Successful programs have been developed and managed by organized labor with the support of management. Management with a serious commitment to a drug testing program would be well advised to obtain consultation and education for the management staff and supervisors on recognition and understanding of behaviors associated with substance abuse. It is recommended that the program be established with drug deterrence and rehabilitation as primary goals. Medical evaluation and an association with an EAP are strongly recommended. Confidentiality should be a prime consideration. The policy on termination due to substance abuse should be a deterrent to continued abuse. Preemployment, scheduled, random, or "for cause" drug testing should be handled in accordance with forensic standards. Policies and procedures should be enforceable and in compliance with federal, state, and local regulations.

In pre-employment drug testing, it is advisable for the applicant to be notified of the drug testing policy and its role in the hiring process. It is unlikely, with chain-of-custody and other procedures involved in obtaining a suitable specimen for drug screening, that this could be concealed. Pre-employment specimens should be handled in accordance with forensic standards, including confirmation of positive results. Unconfirmed positive immunoassay results should not be the basis for denying employment and should be confirmed even though other factors influenced the decision. It is advisable for confirmed positive test results to be submitted to medical review before denying employment. It is recommended that drug screening test results be received and reviewed by a physician qualified to evaluate whether the applicant uses illicit drugs or has a drug abuse problem. Applicable federal, state, and local regulations should be followed.

In random, scheduled, and "for cause" drug testing programs, the employee should be notified in advance of when, or under what circumstances, drug screening will be required. The employee should be notified of procedures to be followed if test results are positive. If a confirmed positive test result is obtained, the employee should undergo medical evaluation to determine whether a substance was used illicitly or evidence of substance abuse exists. If prescribed or over-the-counter medications are determined to be responsible for the positive test result, and abuse is not determined to be present, no action should be taken. Any policies on reporting to work while using prescribed or over-the-counter substances should be reviewed. If medical evaluation indicates use of an illicit substance or evidence of abuse, the employer should notify the person of the policies and course of action. It is recommended that the policies provide for at least one opportunity for rehabilitation with referral to an EAP or rehabilitation center.

Clients of the judicial system have a high prevalence of illicit substance abuse. Drug testing may be used as a deterrent to criminal activity and to verify compliance with requirements for abstinence from drug use. It is common for such agencies to use a simple, on-site immunoassay procedure. The responsible persons must recognize the limitations of such procedures and understand that positive results are presumptive only. If adverse action is to be taken, the result should be verified following forensic standards.

6.3 Role of Laboratory Personnel

The laboratory director or other designated qualified person should be available for consultation with physicians and clients. The indications for urine drug testing are more variable than almost any other laboratory analysis. The director must be knowledgeable of the various settings the laboratory is serving to provide competent consultation.

Emergency toxicology, chemical dependency units, judicial agencies, death investigation, and employee testing have significantly different needs. The director should be prepared to provide competent consultation and appropriate procedures before accepting specimens.

A physician or other client may request consultation on setting up a drug testing program. The client may need education on drug testing programs or may be seeking a laboratory to do testing. The laboratory role in such consultation should evaluate the technical and forensic needs of the client. Technical support on such matters as specimen collection, witnessing, labeling, sealing, chain-of-custody, and transportation should be included. The consultation should include educating or ensuring that the client understands drug screening, its limitations, the concepts of screening and confirmation, and the forensic nature of such testing. The client should be advised to develop a complete program before instituting drug screening. The laboratory should not accept specimens from a forensic setting if the employer wants inexpensive immunoassay screening without confirmation.

The laboratory quality assurance program should include continuing education of the client and physicians as to the pertinent information regarding urine drug testing. This may take the form of newsletters or other forms of continuing education. If the laboratory identifies a problem in the client's procedures (e.g., leaking containers, poor labeling, or an insufficient amount of specimen), the client should be notified. The laboratory should be prepared to discuss results with the physician or client. Credible depositions and testimony should be available for any analysis, including chain-of-custody, assay procedures, quality control, and interpretation.

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Appendix (Part 1). Example Chain-of-Custody Form

1. Submitting Agency 2. Collection Site & Data					3. Laboratory Name & Address	4. Return Results To
No.	5. Submitting Agency's Specimen Ident.	6. Social Security Number of Person Providing Sample	7. Type Test	8. Drugs Tested	A. Laboratory Accession Number	B. Laboratory Results
01						
02						
03						
04						
05						
06						
07						
08						
09						
10						
11						
12						

9. I certify that I received all specimens and verified for accuracy both the identification on each sample bottle and the Chain-of-Custody document. --- Signature of Collection Official (Date)	C. Specimens Received From	D. Received By (Date)	E. Condition ☐ Undamaged ☐ Damaged* *Describe
	F. Comments/Discrepencies/Reasons Not Tested		
10. I received specimens from the collection official, properly packaged, sealed, and released for shipment. --- Signature of Releasing Official (Date)	G. I certify that the findings noted above accurately report testing results. --- Name, Signature, and Title of Certifying Official (Date)		
	H. Discarded by --- Name, Signature (Date)		

Appendix (Part 2). Instructions for Example Chain-of-Custody Form

INSTRUCTIONS

SUBMITTING AGENCY Block Number:

INSTRUCTIONS

1. Name of submitting agency
2. Location of collection site and date
3. Testing laboratory mailing address
4. Address, telephone, fax to which results are sent
5. Specimen number assigned to each specimen (bar code label permitted)
6. Full Social Security number of person from whom specimen was obtained
7. Enter code for type of test as follows:
   - AT = Applicant Testing
   - RT = Random Testing
   - RS = Reasonable Suspicion Testing
   - RA = Counseling/Rehabilitation Testing
   - SA = Safety, Mishap, Accident Testing
   - VT = Voluntary Testing
8. Enter letter designations as follows:
   - A = THC, cocaine, amphetamines, phencyclidine, opiates
   - B = THC and cocaine
   - C = Other drugs (specify in remarks section)
9. Name, signature of collection official, and date certified
10. Name, signature of official releasing specimen(s) for shipment, and date shipped
11. Indicate means of shipment (e.g., United States Postal Service or commercial courier)

LABORATORY INSTRUCTIONS Block Number:

A. Sequential assigned laboratory accession
B. Indicate laboratory result
C. Indicate the accountable mode of transportation utilized in shipping the specimen
D. Name/signature of laboratory official receiving the shipment and date received
E. Indicate condition of shipping container. If damaged, describe damage in Block F
F. Self-explanatory
G. Printed name, signature, title of certifying official, and date certified
H. Name/signature of laboratory official discarding the specimen and date discarded.

REMARKS:

CHAIN-OF-CUSTODY

DATE	RELEASED BY	RECEIVED BY	PURPOSE OF CHANGE/REMARKS
	SIGNATURE	SIGNATURE	
	NAME	NAME	
	SIGNATURE	SIGNATURE	
	NAME	NAME	
	SIGNATURE	SIGNATURE	
	NAME	NAME	
	SIGNATURE	SIGNATURE	
	NAME	NAME	
	SIGNATURE	SIGNATURE	
	NAME	NAME	

Summary of Comments and Subcommittee Responses

T/DM8-P Urine Drug Testing in the Clinical Laboratory; Proposed Guideline

General

1. Laboratories "certified" as NIDA labs should be required to demonstrate proficiency and licensing/certification in order to perform "other than NIDA" analyses. Laboratories should not be allowed to perform analysis for which they have no procedures and have not demonstrated proficiency.

- **NCCLS guidelines are documents developed through a consensus process and are not intended to be regulatory in nature. State or local government agencies with regulatory authority over clinical laboratories within their jurisdictions should determine if they will accept NIDA certification in lieu of their own requirements. From a regulatory perspective, it is probably better if a regulatory agency subjects all laboratories within its jurisdiction to uniform requirements. Participation in the NIDA program is no guarantee that a laboratory s results will be more reliable than findings obtained by laboratories subject to state or local regulations. NIDA certification has been used by some laboratories as a marketing tactic to attempt to convince potential clients that they are better than laboratories that are not NIDA certified.**

2. Persons submitting to testing, for any reason, should be required to submit, in advance, a confidential list of all medications (over-the-counter and prescription) taken within the two weeks prior to the specimen donation.

- **Confidentiality issues arise if persons submitting specimens for drug abuse testing are required to provide information about all medications which they are taking. Particularly when testing is related to employment, employees may not want employers to know they are taking medications which are used in the treatment of certain diseases or conditions since employers could use this information to make decisions about whether to hire, promote, or assign work to a person. It may therefore be less intrusive not to require this information beforehand and only request it if a positive test result is obtained (e.g. a person with epilepsy taking phenobarbital).**

3. For forensic specimens, "for cause" specimens, and all positive specimens documentation of destruction should be included in file. Date, method of disposal, and person performing this task should be recorded. Some labs save all positive specimens in a freezer indefinitely. Lab directors should give careful consideration and have a written procedure for disposal.

- **Forensic specimens collected in accordance with a particular mandate should be preserved for whatever period of time is specified in the statute or regulations promulgated pursuant to it. When a time period is not specified, positive specimens should be preserved until the legal action to which they relate has been resolved. Laboratories providing services to agencies requiring forensic testing should develop an agreement with them concerning how long specimens should be maintained in storage. Due to storage space limitations and the questionable integrity of specimens that are stored for long periods, it is generally recommended that specimens not be stored for more than two years. This period may have to be considerably shorter for laboratories that process many specimens and have a high percentage of positive results. When specimens are discarded, the date, method of disposal and person completing this task should be recorded to complete the chain of custody.**

  Section 4.5.4 has been modified to provide some guidance to laboratory directors who are responsible for establishing a specimen retention policy. Additionally, date discarded was added to the chain of custody form in Appendix A.

4. The following statement should be added to the guideline: "NOTE: No results should be faxed to an unsecured fax machine. All information should be faxed to a machine with limited access in order to assure confidentiality."

- **Confidentiality of results must be safeguarded regardless of the method that is used to report this information. Results should be forwarded to a reviewing officer who should interpret the findings before the information is released for treatment purposes or so that other actions can be initiated.**

  Section 4.5.3 was revised to state, For the purposes of assuring confidentiality, telephone reports and electronic transmissions should be avoided.

5. No results should ever be given over the telephone (even if the laboratorian knows the individual) without the laboratorian calling the requestor back at a number preapproved by the purchaser of services. Approval should be given in writing to the laboratory director by the requestor for specific individuals at this number to receive results.

- **It is generally considered better to inform persons about test results in writing rather than verbally due to the increased potential for misunderstandings about what is being conveyed in spoken communications. In situations where verbal reports must be issued, the person in the laboratory must verify that the person receiving the information is an authorized agent of the organization for whom the testing was performed. This may require calling the requestor back if the laboratorian cannot identify the person from previous conversations. Written agreements between the laboratory and the agency submitting the specimens should be established before verbal reports are made.**

  Section 2.4.3 has been revised to address this commentor s concern.

6. *Should* appears at least 121 times! No *should* in it! *Should* is only suggestive and means there are little or no consequences to result if one does or does not follow the should. You are doing a disservice to inexperienced followers of your guideline if you do not point out that court cases will be lost if *should* is interpreted in its permissive sense. In these days of word processors I will most strongly suggest that these 121 *shoulds* be replaced with *shall*, *must*, or *will*. An alternative could be a warning to followers of the guideline that if *should* is not followed, then dire legal outcomes will follow and that laboratory risks its legal and scientific reputation for doing legally defensible work. Maybe I have been around the Army and state government too long, but stronger phraseology is required.

- **Consistent with NCCLS s definitions of a standard and guideline, mandatory terms such as shall and must are appropriate for standards. In a guideline, such as T/DM8, the term should is used to convey the subcommittee s recommended course of action. NCCLS standards and guidelines are not intended to take the place of statutes or regulations. Therefore, the use of stronger terms such as shall, must, or will, which compel that certain actions be taken, may be inappropriate for these documents.**

Foreword

7. The document "Foreword" claims the guidelines do not address "Testing performed on medically compromised patients to diagnose drug overdoses..." However, the document abstract states the primary objective is to assure that high quality standards are maintained...where test results may affect a person's...medical diagnosis and treatment. These statements seem to contradict one another. I would suggest the abstract reference to medical diagnosis and treatment be deleted.

- **The Abstract in T/DM8-A was revised to clarify the scope of issues presented in the guideline. The phrase at the end of the last sentence in the first paragraph of the Abstract has been**

reworded to read: As well as the nonemergency diagnosis and treatment of substance abuse problems.

Section 1.1

8. I would suggest adding the underlined text to the following sentence. "By present standards, however, even one-time or occasional *nonprescription drug* use is considered abusive, particularly if it poses a safety or health hazard to the user or other persons."

- **As pointed out in Section 1.1, this document addresses substances regulated under the Controlled Substances Act which are either prescription drugs or substances whose use is not permitted in legitimate medical practice. The subcommittee is not concerned with the improper use of nonperscription drugs in this context which is generally referred to as drug misuse as opposed to drug abuse.**

Section 2.2.1

9. To the third bullet, add "usually" before "stable."

- **The subcommittee agrees with the reviewer and recommends that usually be added before stable.**

Section 2.3.1.1

10. The document states "Initial testing results must be correct and they must distinguish specimens that do not contain drugs or metabolites from those that may contain these substances...it is acceptable for a screening procedure to indicate the presence of the analyte of interest in some specimens in which it is not present." These statements appear contradictory. I would suggest the following wording, "Final testing results must be correct..."

- **The subcommittee agrees with the reviewer s comment, and has deleted the words must be correct and they from the first sentence of this section.**

Section 2.3.1.3

11. The document states "...caution must be exercised in attempting to apply a quantitative interpretation to results." There are literature references to use of quantitative results over time in rehabilitation programs. Therefore, the text should be reworded, "...caution must be exercised in attempting to apply a quantitative interpretation to a single analytical result."

- **The subcommittee agrees with the reviewer s comment. The seventh, eighth and ninth sentences of this section were revised to read, Because many immunoassays respond to the parent drug and its metabolites, caution must be exercised in attempting to apply quantitative interpretations to nonspecific screening results. Further, analysts should understand that even if enough reactive species are present in a specimen to produce a positive response in a screening test, the amount of any one constituent may not be sufficient to produce a positive response in a confirmatory test that is specific for that one particular substance. High specificity for a drug or class of drugs is generally required in screening tests because it simplifies the interpretation of results and reduces the number of specimens that must be subjected to confirmatory testing.**

Section 2.3.1.4

12. This section states "For example, negative interference occurs when salt or other adulterants are added to a specimen." This statement implies all immunoassays are affected by the addition of salt to a urine sample. This is incorrect. I would recommend the guideline use the following

wording, "...negative interference occurs when bleach or other adulterants..". Bleach affects all immunoassays negatively, hence it may be a better example.

- **The subcommittee concurs with the reviewer and revised the last sentence in this section to read, For example, negative interference can occur when adulterants such as bleach or salt are added to a specimen.**

Section 2.3.1.5

13. The document states "The practical operational sensitivity of a procedure is commonly used to establish a 'cutoff' concentration,...". This statement is misleading as it only applies to some manufacturer's assays. Other manufacturer's immunoassays have demonstrated operational sensitivities (95% confidence level) well below the "administrative threshold." Therefore I would suggest the sentence be reworded to state "The 'cutoff' concentration is an administrative threshold that separates positive from negative samples."

- **The subcommittee disagrees with the reviewer s comment. The word commonly in the sentence in question implies that the practical operational sensitivity of a procedure is frequently, generally, or on a widespread basis used to establish cutoff concentrations. It does not imply that it is universally used or that it necessarily applies to all procedures. However, in order to clarify the definitions of sensitivity and detection limit, Sections 2.3.1.5 and 2.3.1.6 have been combined and rewritten to better explain these related terms.**

Section 2.3.2

14. This section states that "...sophisticated instrumentation that requires a highly trained analyst to operate and maintain. To determine what drugs or metabolites are present, the analyst must have the knowledge and experience necessary to interpret complicated data."

    A highly trained analyst is needed to operate and maintain the GC-MS, but it should not be necessary that the same analyst do the analysis and interpretation of the data. The latter responsibility should or could be assigned to a higher qualified individual.

- **The subcommittee concurs with the reviewer and has revised the next to the last sentence in the third paragraph of this section read: To determine what drugs or metabolites are present requires a qualified individual who has the knowledge and experience necessary to properly interpret the data produced in these analyses.**

Section 2.3.2.2

15. The last sentence states, "...it should be incumbent upon those challenging the results to show that at least one other substance that could reasonably occur in the specimen could produce the same findings." Biochemists ask WHY? There could be many compounds interfering and not all compounds are known.

- **The subcommittee does not agree with this reviewer s comments. The subcommittee is not attempting to use the limited amount of information that is available to provide for scientific purposes that the substance specified to be present is the only substance, from the entire universe of possible substances, which could be present. Instead, the subcommittee is stating that, for legal purposes, the substance which was identified has a high probability of being present unless it can be shown that another substance, which could reasonably be expected to be present in the sample, could have produced the positive result. It is unreasonable to expect chemists to eliminate all substances which could produce a specific result. However, it is not unreasonable to expect an attorney to find at least one substance that could produce results similar to those of the drug whose presence is being disputed.**

Section 2.3.2.2 has been modified to indicate that the method should allow the laboratorian to distinguish the substance of interest from its known interference.

Section 2.4.1.1

16. The last paragraph should mention the Department of Defense (DOD). DOD started back in the withdrawal from Viet Nam (fall 1970) to test service members for opiates and place them in rehabilitation programs. Both the NIDA guidelines that you list as a reference, were written from 1982 and 1984 DOD Health Affairs directives instructing the Armed Services Surgeons General how to conduct urine drug testing.

- **The subcommittee revised the beginning of the last paragraph of Section 2.4.1.2 to read: In 1970, the Department of Defense began to test service members for opiates and placed those who tested positive in rehabilitation programs. The NIDA Guidelines that are now being used resulted from Department of Defense health Affairs directives written in 1982 and 1984 to instruct the Armed Forces Services Surgeons General about how to conduct urine drug testing. Other organizations such as the Southern Pacific Railway, ...**

Section 2.4.2.4

17. The fifth sentence should be clarified as follows, "If punitive action is a possible consequence of a positive initial test result, the result **must** be confirmed by an alternative **specific** method."

- **With the lower cutoff levels that are currently being used to distinguish positive from negative specimens, it is often not possible to utilize relatively low cost thin layer chromatography (TLC) procedures to screen or verify the presence of drugs in urine due to the insensitivity of these methods. Testing programs with limited budgets may not be able to support more costly chromatographic testing methods such as GLC, HPLC, or GC-MS. The only alternative available to such programs may be to screen specimens using an immunoassay procedure, and retest specimens which produce positive results in the initial screen using either the same or a different immunoassay. Proceeding in this manner provides further assurance that the initial test was correct if the second test is also positive. However, it does not eliminate the possibility that both tests are in error since they would have either the same or parallel specificities. When immunoassays are used for both screening and verification purposes, the person whose specimen was tested should be confronted with the testing results and further action initiated if the individual admits to administering the drug that was detected. On the other hand, if the person denies abusing drugs, preliminary security measures can be initiated with final disposition being dependent on the results of more definitive testing such as GC-MS. Therefore, the fifth sentence in this section was revised as follows: If punitive action is a possible consequence of a positive initial test result, the result should be confirmed.**

Section 2.4.3

18. The statement, "Telephone reports should be avoided." Should be stronger. Results should not be given by telephone.

- **The subcommittee disagrees with the reviewer s recommendations. In some cases, it may be necessary to report findings by telephone. Section 2.4.3 has been revised to clarify this issue.**

19. The statement, "laboratory personnel should be able to advise about drug testing, the selection of appropriate cutoff values,..." should identify that a qualified staff member should be available to comply with these responsibilities. The term laboratory personnel is too broad.

- **The subcommittee concurs with the reviewer s recommendation and has reworded the sentence to say, A qualified staff person should be available to advise about drug testing, the selection of appropriate cutoff values, and the interpretation of results.**

Section 3.5

20. It is my experience that postal employees may be excluded from the chain-of-custody; however, specimens delivered by a courier (bonded or otherwise) must be documented. Time of receipt from collection site and time of delivery to laboratory should be on the chain-of-custody. Many of these specimens go to court (loss of employment, "for cause" tests, etc.) and a blank time or long unaccounted time period can result in the case being thrown out of court.

- **The subcommittee agrees with the reviewer s recommendation and has revised the last sentence in Section 3.5 (4) to read: Postal employees need not be included in the chain of custody. When courier services are utilized, the time of receipt from the collection site and the time of delivery to the laboratory must be documented on the chain of custody form.**

21. Items (4) and (7) don't seem to agree. If a courier doesn't have to sign a chain-of-custody, what is the purpose of having a receipt?

- **The revision resulting from Comment 20 results in an agreement of items (4) and (7) in Section 3.5.**

Section 3.6

22. There absolutely must be a method to assure no specimen identification number repeats. Also, all unused number must be account for.

- **The third sentence in Section 3.4.4(5) has been revised to read: (To insure correct identification, a unique accession number or bar code should be assigned to each specimen.) This section was also revised to provide additional information concerning court decisions that relate to transport systems and chain of custody requirements.**

Section 3.7

23. To the fifth bullet, add "client" before "behavior."

- **The subcommittee agrees with the commenter and has placed test subject before behavior in the fifth bulleted item.**

24. I question the need for a permanent (bound) record book as indicated. If an appropriately comprehensive chain of custody form is employed which calls for all data elements as indicated in 3.7, a permanent record book would not be necessary. The chain of custody form would then be filed as necessary - if the program is a preemployment or employment drug testing program in the employee's permanent personnel file.

- **A permanent (bound) record book may not be required if the required information can be recorded on an appropriate form or in an electronic format. Bound logbooks reduce the possibility of losing information which could occur more easily if information is recorded on forms. Section 3.7 has been revised to reflect this change.**

Section 4.2.6.1

25. This section should state that the volume of specimen should be recorded at time of collection. In drug testing, for any purpose, it is essential to account for all of the specimen.

- **The volume of urine is usually recorded when a specimen is received by a laboratory. This information is particularly important when forensic analyses are to be conducted, in which case the initial volume of the specimen should be recorded and any quantities of urine that are removed for testing should be documented. This section has been revised to address this issue.**

Section 4.2.8

26. This section should recommend a time frame for refrigerator storage and recommend sample freezing after that time period.

- **After reviewing the reviewer s comments relating to specimen storage, Section 4.2.8 was revised to address the concerns that were expressed.**

Section 4.2.9.1.

27. The document recommendations apply to refrigerated samples. If a sample is frozen the freeze/thaw cycles required to further test the sample may cause sample degradation. I would recommend the guideline offer clarification of sample storage conditions and subsequent adjustment in specimen handling recommendations.

- **The subcommittee is not aware of any data that would suggest that freeze/thaw cycles affect the analytes in question.**

28. The document states, "Documentation must include...volume of urine from the specimen that was discarded." This is an unusual procedure. Why is the volume of specimen discarded required information, if the lab is documenting the volume of urine removed from the specimen?

- **The subcommittee concurs with the reviewer. If the volumes of urine removed from the original specimen are recorded, it should not be necessary to document the volume that was discarded.**

Section 4.3.1.2

29. I feel other disadvantages should be included in item (3); specifically, lack of ability to identify specimen on machine except manually and operator error (specimen transfer errors, cup translocation errors, etc.). Also, as most of these types of analyzers print all results on one tape, the ability to store original test data with the individual file is compromised.

- **The subcommittee believes the issues raised are not unique to immunoassay test systems. It would appear that, when specimens are bar coded, as is common practice today, there is no problem identifying specimens on an instrument. Further, if analyzers print out a single tape containing testing results for a group of specimens, copies of this tape can be made for placement in individual patient files. In summary, these do not appear to be significant disadvantages to the use of immunoassays and therefore do not require inclusion in this document.**

30. Item (5) includes the statement, "Because of the manner in which some of these devices are marketed, it is difficult to apply quality assurance procedures to them...." The device marketing may lead the lab to think quality assurance procedures do not need to be applied to the device, but marketing does not make it difficult to apply quality assurance procedures. The sentence should be reworded to state, "Quality assurance procedures should be applied to all devices to verify they are performing according to specifications, regardless of the manner in which the devices are marketed."

- **This comment is valid but requires further clarification. It is really the design of these products and not the manner in which they are marketed that makes it difficult to apply quality control measures to them. Section 4.3.2.1 (5) has therefore been rewritten to more accurately describe these devices and their utilization.**

Section 4.5.1

31. The seventh paragraph states, "If the analyte of interest is therefore detected, but at a concentration below the cutoff level, the assay result must be interpreted as negative." Further explanation of why would be helpful.

- **In order to comply with the reviewer s request, and better explain how results should be interpreted, the last sentence in the second paragraph of Section 4.5.1 has been rewritten. Also, the first two sentences of the fifth paragraph of this section have been rewritten to better express the information the subcommittee wants to convey.**

Section 4.5.4

32. The time limit for storage of confirmed positives should be precise, either 6 months or 1 year, preferably minimum of 1 year.

- **Policies relating to the retention of specimens will vary depending on the purpose for which the testing was conducted, and the requirements of agencies requesting the testing. It is not appropriate for this committee to dictate how long specimens should be stored. However, in order to assist persons seeking guidance concerning specimen retention, additional information was included in this section relating to the policies of some organizations that are involved in drug testing.**

33. In the case of forensic testing, I feel 6 months to 1 year storage of specimens (and test data) is too short. Specimens should be saved a minimum of 3 years and test data a minimum of 7 years to ensure availability if challenged.

- **The subcommittee has modified Section 4.5.4 to be consistent with the requirements of other regulatory and accrediting agencies.**

Section 5.1

34. We agree that controls must include drug-free urine, urine specimens with levels below the threshold as negative controls and above threshold (120 to 200%) as positive. Nevertheless, we consider that controls should also include urine specimens with drug levels at or close to the threshold value, but considered positive.

- **Some laboratories may prefer to include a control at the threshold (cutoff) value and this is an acceptable practice. However, it is more than is required and does not need to be reflected in this document.**

35. No distinction should be made for laboratories using semiquantitative screening methods. We consider that the urine specimen with drug levels at the threshold value should be positive controls.

- **The reviewer s recommendation was accepted by the subcommittee and the statement in question was deleted from the document.**

36. The documents states, "...controls must be included with each run of samples." However, the document never defines a "run." I would suggest a run be defined as a 24-hour period as in the CLIA '88 guidance document.

- **To remove ambiguity associated with the meaning of the word run, this section of the document was revised to remove this term and replace it with better defined terminology.**

Section 5.2.2

37. This section seems to be a bit verbose and too detailed if the readership audience is clinical laboratory personnel.

- **The goals of external quality assurance programs are frequently not understood and unless there is concern about the length of the document it may be best to allow this section to remain in the guideline.The subcommittee believes that the goals of external quality assurance programs are frequently not understood and therefore retained the information for those end-users who may find the information helpful.**

Section 6.1

38. The last sentence of the sixth paragraph states, "However, in those situations it is associated with psychoactive effects; thus, it is not an acceptable defense for a positive test result." Is there evidence for this statement?

- **It appears that the statements relating to passive inhalation are not a correct reflection of the facts. These statements were rewritten as follows: Passive inhalation of smoke from burning marijuana has experimentally been shown to result in measurable concentrations of cannabinoids in urine. However, in those situations, the concentrations produced were generally low and not in the range associated with physiological effects. The concentrations of cannabinoids that have been produced by passive inhalation are below the cutoff levels that are used in substance abuse testing; thus, it is not an acceptable defense for a positive test result.**

Section 6.3

39. The Laboratory Director is an administrative position with extensive responsibilities over the whole functioning of the clinical laboratory to allow direct consultation on such a specialized area. A qualified individual should be identified in order to provide consultation, technical support, education and assurance that the client understands the significance of drug testing.

- **The subcommittee believes this is a valid point. The first paragraph of Section 6.3 was revised in accordance with the reviewer s recommendation.**

Appendix

40. The Appendix allows no place for the tested individual to indicate witnessing the labeling and sealing of the specimen container, any medications he may be taking, signature of the individual who has sealed the specimen or any place to show the signature of analyst and the condition of the tamper-proof seal.

- **The form provided is an example of a form used by one testing organization and is not intended to be universally applicable. Each testing program should design a form which meets their specific needs.**

Summary of Delegate Voting Comments and Responses

T/DM8-A Urine Drug Testing in the Clinical Laboratory; Approved Guideline

General

1. Because of its requirements, employment drug testing should be developed by NCCLS as a separate application, not melted in with criminal justice and treatment/rehab. This is not a contribution to improvement.

- **In accordance with objectives specified by the Area Committee on Clinical Chemistry and Toxicology, and in the project proposal authorized by the Board of Directors, the Subcommittee on Urine Drug Testing prepared a guideline (T/DM8-A) which addresses urine drug testing in the workplace and other environments such as the criminal justice system and rehabilitation facilities. It was generally accepted that the various aspects of testing performed in these diverse environments shared enough similarities to be adequately addressed in one document. On the other hand, it was determined that drug testing performed to diagnose or monitor the treatment of medically compromised patients was beyond the scope of this document and would not be included. The rationale for what is and what is not included in this document is presented in the Foreword.**

2. What about "designer drugs?" Many not yet controlled substances.

- **Concern about designer drugs is valid; therefore, two paragraphs regarding this topic have been added to Section 4.3.**

3. This document is useless, redundant, and ambiguous. Programs doing such testing are regulated specifically and differently by NIDA/SAMHSA standards. Due to the costs and differences from clinical laboratory operations, there is strong opinion that these tests for employee surveillance cannot not be performed by clinical laboratories.

- **This document is not intended to replace the existing regulatory standards; rather, to provide additional guidance for facilities doing such testing. See response to Comment 1.**

Introduction

4. Introduction items 1.2 and 1.3 paragraph 1 for both items should be deleted.

- **These paragraphs are necessary to define drug abuse and introduce approaches to controlling this problem through the use of urine drug testing. Both paragraphs are brief and contain factual information which is not controversial in nature.**

Sections 2.3.2.4 and 2.3.1.3

5. *Sensitivity (2.3.2.4) and specificity (2.3.1.3) seem to be in conflict.*

- **Specificity in Section (2.3.1.3) applies to screening procedures and sensitivity in Section (2.3.2.4) applies to confirmatory procedures. The two terms are interrelated but do not conflict with one another. In screening it is desirable for a procedure to detect a particular substance (e.g. phencyclidine) or a closely related group of substances (e.g. barbiturates). It may be advantageous for a screening procedure to be somewhat non-specific, since responding to both a parent drug and its metabolites which are structurally closely related increases the overall sensitivity of the procedure.**

On the other hand, in confirmatory testing when the procedure detects one specific compound, the sensitivity must be high enough to detect that compound, which may have been a minor component among many substances which produced a combined response in the initial screening procedure.

Section 2.4.3

6. This section on Selecting a Laboratory, does not mention the range of testing and what can be provided in a forensic manner as opposed to those drugs that can only be identified easily by one methodology.

- **The range of testing that most laboratories provide is discussed in Section (4.3) titled Analysis of Specimens. For forensic purposes, most drugs can adequately be identified by GC/MS. If initial screening is performed by immunoassay, only those drugs for which reagent kits are available can be screened. Chromatographic screening techniques (TLC, GLC, and HPLC) can be applied to most drugs if suitable standards are available for comparison purposes.**

Section 3.2.3

7. Requirement of retesting of creatinine <20 mg/dL is not reasonable. Five percent of our samples are in this category.

- **In the last sentence, the words requiring another specimen to the submitted were replaced with indicating that another specimen should be submitted.**

8. Section 3.2.3 mentions creatinine levels below 20 mg/dL as suspect, yet some literature suggests that creatinine values less then 35 mb/dL should also be considered suspect. Which is correct?

- **The creatinine level in urine used to determine whether a urine specimen is suspected of being diluted is somewhat arbitrary. The number of specimens determined as suspect will increase as the cut-off level increases. The level of 20 mg/dL is a compromise that permits adequate detection of diluted specimens without producing an unacceptably high number of specimens that are suspected of being diluted.**

Section 3.4.4

9. Storage of split specimens at collection site is not feasible. The facilities are not equipped for this.

- **The subcommittee is not advocating the use of split specimens. It is merely pointing out the advantages and disadvantages of splitting samples.**

Section 3.5

10. It is not reasonable to include courier as formal part of chain of custody. The couriers are not "handling the specimens" since the seals are kept intact.

- **The seventh bullet contains a footnote which explains that couriers are not part of the chain of custody.**

Section 4.1

11. Section 4.1 should include a mention of educational material discussing analytical issues to the client.

- **At the end of the last paragraph the following sentence has been added: Additionally, the laboratory should provide educational material that addresses analytical issues which it is important for the person reviewing the testing results to understand in order to accurately interpret the findings."**

Section 4.2.7

12. Section 4.2.7 should include the mentions of backup plans for nonscheduled computer down time.

- **At the end of Section 4.2.7, the following sentence has been added: Additionally, plans should be made to enable specimen processing to continue during periods of non-scheduled computer downtime which may include an independent secondary system into which data could be entered for later transfer into the primary system when it becomes operational again."**

Section 4.3.1.1

13. Section 4.3.1.1 (4) mentions TLC LOD of 0.3 to 1.0 mcg/mL, however Toxi-Lab THC methods can detect the THC-COOH metabolite at about 20 ng/mL. So the detection limit for at least some drugs is lower than mentioned.

- **The following sentence has been added to subsection (4): In the case of some substances such as cannabinoid metabolites which are present in urine in ng/mL concentrations, specialized TLC systems are available which permit the detection of these compounds in this reduced concentration range.**

Section 4.3.1.2

14. Regarding reliability, the terms "diluting reagent" and "mixing reagent" are not clearly defined. Preparation of reagents must be according to manufacturer's procedures. Any modification to procedures requires validation by the lab. Additionally, diluting and mixing procedures can affect all test methods, not just immunoassays.

- **In Section 4.3.1.2 (1), the first bullet, the following sentence has been added: This refers to the practice of adding solvent or other extenders to test reagents so that more than the specified number of specimens can be tested using an immunoassay test.**

  Also the following sentence has been added in the third bullet: This refers to the practice of combining reagents from two or more assays (e.g. barbiturates and opiates) so that the presence of more than one drug or class of drugs can be detected when a single specimen is analyzed.

  These practices were addressed only under immunoassays since it is primarily in these screening procedures where they are employed.

15. Regarding non-instrument based immunoassays, the issues regarding within unit quality control materials and built-in procedural controls seems to be left hanging.

- **In Section 4.3.2.1, no further comment was made concerning within-unit quality control materials and built-in procedural controls since this is an area where some controversy exists and no solutions are evident.**

Section 4.4

16. I do not agree that confirmation is required for all clinical specimens. I disagree with the statements on page 25 & 26.

- **In Section 4.4 which discusses confirmatory testing, there is no statement that confirmation is required for all clinical specimens. To emphasize the point that decisions regarding confirmatory testing should be made by the agency submitting the specimens in consultation with the laboratory, the following sentence has be added after the fifth sentence in the first paragraph: Decisions concerning the necessity of confirmatory testing or verification of initial screening results should be made by the agency submitting the specimens in consultation with the laboratory that will perform the analyses.**

Section 4.5.4

17. In Section 4.5.4 no mention is made of storage in containers that can have drug adherence. Regardless of storage condition, some positive samples can become negative if stored in a container that can absorb the drug.

- **A paragraph has been added to Section 4.5.4 to address the commentor s issue.**

Section 5

18. Section 5 seems to show a bias toward GC/MS and quantitative or semiquantitative methods for confirmation of drug presence in the quality control of the confirmation test paragraph.

- **Apparent bias toward GC/MS as a confirmatory technique is unavoidable since this is the most common method of verifying presumptive positive screening results. In situations where screening test s are repeated to verify that the initial presumptive positive result was correct, the quality control measures for those procedures apply.**

Section 5.2.2

19. Section 5.2.2 the second sentence should end “more frequently occur.”

- **The suggested revision has been incorporated.**

Related NCCLS Publications

C24-A2 **Statistical Quality Control for Quantitative Measurements: Principles and Definitions; Approved Guideline Second Edition (1999).** Addresses the principles of statistical quality control (QC), with particular attention to the planning of a QC strategy, the definition of an analytical run, the selection of control materials, and the application of statistical QC in a healthcare laboratory.

GP2-A3 **Clinical Laboratory Technical Procedure Manuals Third Edition; Approved Guideline (1996).** Offers guidelines that address the design, preparation, maintenance, and use of technical procedure manuals in the clinical laboratory.

GP9-A **Selecting and Evaluating a Referral Laboratory; Approved Guideline (1998).** This guideline provides an outline of reasons and criteria for choosing a referral laboratory. A checklist for evaluating potential referral laboratories is included to assist in the decision process.

GP10-A **Assessment of the Clinical Accuracy of Laboratory Tests Using Receiver Operating Characteristic (ROC) Plots; Approved Guideline (1995).** Discusses design of a study to evaluate clinical accuracy of laboratory tests; procedures for preparing ROC curves; glossary of terms; and information on computer software programs.

H5-A3 **Procedures for the Handling and Transport of Domestic Diagnostic Specimens and Etiologic Agents Third Edition; Approved Standard (1994).** *American National Standard*. Gives proper packaging, handling, and transport requirements for medical specimens. Includes federal regulations.

M29-A **Protection of Laboratory Workers from Instrument Biohazards and Infectious Disease Transmitted by Blood, Body Fluids, and Tissue; Approved Guideline (1997).** 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 blood-borne infection from laboratory instruments and materials; and recommendations for the management of blood-borne exposure.

NRSCL8-A **Terminology and Definitions For Use in NCCLS Documents; Approved Standard (1998).** 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 (1997).** 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.

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