Clinical Drug Testing in Primary Care Part 1

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Audience for the TAP

This Technical Assistance Publication (TAP), *Clinical Drug Testing in Primary Care*, is for clinical practitioners—physicians, nurse practitioners, and physician assistants—who provide primary care in office settings and community health centers. The publication provides information that practitioners need when deciding whether to introduce drug testing in their practices and gives guidance on implementing drug testing.

The TAP does not address drug testing for law enforcement or legal purposes, nor does it include testing for the use of anabolic steroids or performance-enhancing substances. This TAP describes some of the ways that drug testing can contribute to the assessment, diagnosis, and treatment of patients seen in primary care, the management of the treatment of chronic pain, and the identification and treatment of substance use disorders.

Organization of the TAP

This chapter briefly describes the role of drug testing in primary care settings and its historical roots in workplace testing. Chapter 2 defines the terms and practices used in drug testing. Chapter 3 presents the mechanics of testing and describes the steps that primary care practitioners can take to prepare themselves, their staffs, and their office spaces for drug testing. Chapter 4 provides information about implementing testing in clinical practice. Important aspects of urine drug testing for specific drugs are presented in Chapter 5. Appendices A–H include the bibliography; overviews of technical information on specific tests used for initial or screening tests, confirmatory tests, and specimen validity tests; a glossary of terms; the members of the expert panel, consultants, and field reviewers; and acknowledgments.

Reasons To Use Clinical Drug Testing in Primary Care

The term *drug testing* can be confusing because it implies that the test will detect the presence of all drugs. However, drug tests target only specific drugs or drug classes and can detect substances only when they are present above predetermined thresholds (cutoff levels). The term *drug screening* can also be deceptive because it is often used to describe all types of drug testing. However, *drug screening* is usually used in forensic drug testing to refer to the use of immunoassay tests to distinguish specimens that test negative for a drug and/or metabolite from positive specimens. For the purpose of this TAP, the term drug testing is used.

When used appropriately, drug testing can be an important clinical tool in patient care. The types of clinical situations in which clinical drug testing can be used include pain management with opioid medications, office-based opioid treatment, primary care, psychiatry, and other situations when healthcare providers need to determine alcohol or other substance use in patients. Drug testing is also used to monitor patients' prescribed medications with addictive potential. Patients sometimes underreport drug use to medical professionals (Chen, Fang, Shyu, & Lin, 2006), making some patients' self-reports unreliable. Drug test results may provide more accurate information than patient self-report. Although drug testing can be a useful tool for making clinical decisions, it should not be the only tool. When combined with a patient's history, collateral information from a spouse or other family member (obtained with permission of the patient), questionnaires, biological markers, and a practitioner's clinical judgment, drug testing provides information that:

- Can affect clinical decisions on a patient's substance use that affects other medical conditions.
- Can affect clinical decisions about pharmacotherapy, especially with controlled substances.
- Increases the safety of prescribing medications by identifying the potential for overdose or serious drug interactions.
- Helps clinicians assess patient use of opioids for chronic pain management or compliance with pharmacotherapy for opioid maintenance treatment for opioid use disorders.
- Helps the clinician assess the efficacy of the treatment plan and the current level of care for chronic pain management and substance use disorders (SUDs).
- Prevents dangerous medication interactions during surgery or other medical procedures.
- Aids in screening, assessing, and diagnosing an SUD, although drug testing is not a definitive indication of an SUD.
- Identifies women who are pregnant, or who want to become pregnant, and are using drugs or alcohol.
- Identifies at-risk neonates.
- Monitors abstinence in a patient with a known SUD.
- Verifies, contradicts, or adds to a patient's self-report or family member's report of substance use.
- Identifies a relapse to substance use.

Primary Care and Substance Use Disorders

Practitioners can use drug testing to help monitor patients' use of prescribed scheduled medications, as part of pharmacovigilance, and to help identify patients who may need an intervention for SUDs.

For the purpose of this TAP, *substances* refers to alcohol and drugs that can be abused. As defined by the *Diagnostic and Statistical Manual of Mental Disorders,*

Fourth Edition, Text Revision (DSM-IV-TR; American Psychiatric Association [APA], 2000), a *substance-related disorder* is a disorder related to the consumption of alcohol or of a drug of abuse (APA, 2000). *Substance use disorders* (SUDs) includes both substance dependence and substance abuse (APA, 2000). *Substance dependence* refers to "a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues use of the substance despite significant substance-related problems. There is a pattern of repeated self-administration that can result in tolerance, withdrawal, and compulsive drug-taking behavior" (APA, 2000). *Substance abuse* refers to "a maladaptive pattern of substance use manifested by recurrent and significant adverse consequences related to the repeated use of substances" (APA, 2000). In this TAP, the term *substance abuse* is sometimes used to denote both *substance abuse* and *substance dependence* as they are defined in the DSM-IV-TR (APA, 2000).

SUDs can have serious medical complications and serious psychosocial consequences and can be fatal. Treatment of other medical disorders (e.g., HIV/AIDs, pancreatitis, hypertension, diabetes, liver disorders) may be complicated by the presence of an SUD. As the front line in health care, medical practitioners are ideally situated to identify substance use problems. The 2009 National Survey on Drug Use and Health (Substance Abuse and Mental Health Services Administration [SAMHSA], 2010a) found that 23.5 million (9.3 percent) persons ages 12 or older needed treatment for an illicit drug[1] or alcohol use problem. Of this population, only 2.6 million (1.0 percent) persons ages 12 or older (11.2 percent of those who needed treatment) received treatment at a specialty facility. Thus, 20.9 million (8.3 percent) of the population age 12 or older needed substance abuse treatment but did not receive it in the past year (SAMHSA, 2010a). Therefore, a visit to a primary care practitioner may be an excellent opportunity for such people to be diagnosed with SUDs. Moreover, the number of people ages 12 or older seeking help for SUDs from a doctor in private practice increased from 460,000 in 2005 to 672,000 in 2008 (SAMHSA, 2006; SAMHSA, 2009).

Despite the potential benefits of drug testing (such as monitoring pain medication) to patient care, few primary care practitioners use it. For example, a small study conducted on the medical management of patients with chronic pain in family practices found that only 8 percent of physicians surveyed used drug testing (Adams et al., 2001).

Development of Drug Testing

Drug testing performed for clinical reasons differs substantially from workplace drug testing programs. However, clinical drug testing draws on the experience of Federal Mandatory Workplace Drug Testing and, to understand drug testing, a review of workplace drug testing may be helpful. An important reason for clinical practitioners to become familiar with Federal Mandatory Workplace Drug Testing is that the majority of drug testing is done for workplace purposes. For this reason, most laboratories and many point-of-care tests (POCTs) use the cutoff concentrations established by the Mandatory Guidelines for Federal Workplace Drug Testing Programs, discussed in Chapter 2.

There are three categories of drug testing: (1) federally regulated for selected Federal employees (including military personnel and those in safety-sensitive positions); (2) federally regulated for non-Federal employees in safety-sensitive positions (i.e., airline and railroad personnel, commercial truckers, school bus drivers); and (3) nonregulated for non-Federal employees. Commercial truck drivers, railroad employees and airline personnel make up the largest group of individuals being drug tested.

The purpose of both Federal (always regulated) and non-Federal (may be nonregulated) workplace drug testing is to

[1] Includes the nonmedical use of prescription-type pain relievers, tranquilizers, stimulants, and sedatives.

ensure safety in the workplace by preventing the hiring of individuals who use illicit drugs and identifying employees who use illicit drugs.

Workplace Drug Testing

Drug-testing methods have been available for approximately 50 years (Reynolds, 2005). Because of drug use in the U.S. military, by 1984, the military established standards for laboratories and testing methods and created the first system for processing large numbers of drug tests under strict forensic conditions that could be defended in a court of law.

In 1986, an Executive Order initiated the Federal Drug-Free Workplace Program that defined responsibilities for establishing a plan to achieve drug-free workplaces. In 1987, Public Law 100-71 outlined provisions for drug testing programs in the Federal sector. In 1988, Federal mandatory guidelines set scientific and technical standards for testing Federal employees. In 1989, the U.S. Department of Transportation (DOT) issued regulations requiring the testing of nearly 7 million private-sector transportation workers in industries regulated by DOT.

The Federal mandatory guidelines included procedures, regulations, and certification requirements for laboratories; outlined the drugs for which testing was to be performed; set cutoff concentrations; and stated reporting requirements that included mandatory medical reviews by a specially trained physician Medical Review Officer (MRO). Because a positive result does not automatically identify an employee or job applicant as a person who uses illicit drugs, the MRO interviews the donor to determine whether there is an alternative medical explanation for the drug found in the specimen. The Federal mandatory guidelines recommended that the initial screening test identify the presence of the following commonly abused drugs or their metabolites (SAMHSA, 2008):

- Amphetamines (amphetamine, methamphetamine)
- Cocaine metabolites
- Marijuana metabolites
- Opiate metabolites (codeine, morphine)
- Phencyclidine (PCP)

These substances are generally called the "Federal 5," but over the years they have also been called the "NIDA 5" and "SAMHSA 5." The Federal mandatory guidelines have been updated and revised over the years to reflect technological and process changes (Exhibit 1-1). The guidelines, last updated in 2008 (effective May 1, 2010), are available at http://edocket.access.gpo.gov/2008/pdf/E8-26726.pdf.

Revisions for testing of other matrixes (e.g., hair, oral fluid, sweat) and the use of POCTs were proposed in 2004 (SAMHSA, 2008), but have not been finalized.

Although Federal agencies are required to have drug-free workplace programs for their employees, private-sector employers that do not fall under Federal regulations can establish their own drug-free workplace programs and establish their own regulations, testing matrices, and testing methods. Non-Federal employees can be tested for a broader range of drugs than the federally mandated drugs. Many States have laws and regulations that affect when, where, and how employers can implement drug-free workplace programs (see http://www.dol.gov/asp/programs/drugs/workingpartners/regs/regs.asp).

Laboratories are accredited by the National Laboratory Certification Program (NLCP) to meet the minimum requirements of the Federal mandatory guidelines. This program resides in SAMHSA in the Department of Health and Human Services (HHS).

Exhibit 1-1. U.S. Department of Health and Human Services Federal Mandatory Workplace Guidelines Cutoff Concentrations for Initial and Confirmatory Drug Tests in Urine

Initial Test Analyte	Federal Cutoff Concentrations (ng/mL)
Marijuana metabolites	50
Cocaine metabolites	150
Opiate metabolites (codeine/morphine[1])	2,000
6-Acetylmorphine (6-AM)	10
Amphetamines[2] (Amphetamine /methamphetamine)	500
Phencyclidine (PCP)	25
Methylenedioxymethamphetamine (MDMA)	500
Confirmatory Test Analyte	**Federal Cutoff Concentrations (ng/mL)**
Amphetamine	250
Methamphetamine[3]	250
MDMA	250
Methylenedioxyamphetamine (MDA)	250
Methylenedioxyethylamphetamine (MDEA)	250
Cannabinoid metabolite (delta-9-tetrahydrocannabinol-9-carboxylic acid)	15
Cocaine metabolite (benzoylecgonine)	100
Codeine	2,000
Morphine	2000
6-Acetylmorphine (6-AM)	10
PCP	25

Source: SAMHSA (2008).
[1] Morphine is the target analyte for codeine/morphine testing.
[2] Methamphetamine is the target analyte for amphetamine/methamphetamine testing.
[3] To be reported positive for methamphetamine, a specimen must also contain amphetamine at a concentration equal to, or greater than, 100 ng/mL.

Drug Testing in Substance Abuse Treatment and Healthcare Settings

Substance abuse treatment programs use drug testing extensively. Drug testing for patient monitoring in SUD treatment programs began considerably before workplace drug testing and has become an integral part of many drug treatment programs for patient evaluation and monitoring. By 1970, the Federal Government implemented specific mandatory testing requirements for treatment programs that were licensed by the U.S. Food and Drug Administration to dispense methadone or that received Federal funds. During the 1970s, Federal agencies developed a program to monitor laboratories performing drug testing for drug treatment programs under Federal mandates.

Drug testing in SUD treatment is:

- Part of the initial assessment of a patient being evaluated for a diagnosis of an SUD;
- A screen to prevent potential adverse effects of pharmacotherapy (e.g., opioid screen prior to starting naltrexone);
- A component of the treatment plan for an SUD;
- A way to monitor the patient's use of illicit substances or adherence to pharmacotherapy treatment for SUDs; and
- A way to assess the efficacy of the treatment plan (i.e., level of care).

Drug testing can also be used to document abstinence for legal matters, disability determinations, custody disputes, or reinstatement in certain professions (e.g., lawyers, healthcare providers, airline pilots).

Drug testing is also useful in healthcare settings:

- For determining or refuting perinatal maternal drug use;
- As an adjunct to psychiatric care and counseling;
- For monitoring medication compliance during pain treatment with opioids;
- For monitoring other medications that could be abused or diverted; and
- To detect drug use or abuse where it may have a negative impact on patient care in other medical specialties.

See Chapter 4 for more information about the use of drug testing in clinical situations.

Differences Between Federal Workplace Drug Testing and Clinical Drug Testing

Important distinctions exist between drug testing in Federal workplace settings and drug testing in clinical settings (Exhibit 1-2). Despite the differences, Federal workplace drug-testing guidelines and cutoff concentrations continue to influence clinical drug testing. For example, many laboratories and POCT devices test either for the federally mandated drugs or for the same drugs, but using modified cutoff concentrations as the default drug-testing panel. These panels are not suitable for clinical drug testing because these panels do not detect some of the most commonly prescribed pain medications, such as synthetic opioids (e.g., hydrocodone) and anxiolytics (e.g., benzodiazepines, such as alprazolam), or other drugs of abuse. Initial screening test cutoffs may not be low enough for clinical practice in some instances (e.g., cannabinoids, opiates, amphetamines).

Caution

Trends in drug use and abuse change over time and can necessitate a change in drug testing panels. The technology for drug testing evolves quickly, new drug-testing devices become available, and old tests are refined. Although this TAP presents current information, readers are encouraged to continue to consult recent sources. Wherever possible, the TAP refers readers to resources that provide up-to-date information.

Exhibit 1-2. Comparison of Federal Workplace Drug Testing and Clinical Drug Testing

Component	Federal Workplace Testing	Clinical Testing
Specimen	• Urine	• Primarily urine, some oral fluid tests
Collection Procedures	• Federal regulations stipulate specimen collection procedures. • Policies minimize mistaken identity of specimens and specimen adulteration. For example, in criminal cases, chain-of-custody policies require identification of all persons handling specimen packages. In administrative cases (e.g., workplace testing), specimen packages may be handled without individual identification. Only those persons handling the specimen itself need to be identified.	• Practitioners and clinical staff (hospital or clinical laboratory) follow procedures for properly identifying and tracking specimens. • In general, rigorous protocols are not used. Chain of custody usually is not required; however, laboratories under College of American Pathologists accreditation and/or State licensure should have specimen collection, handling, and storage protocols in place.
Specimen Validity Testing	• Extensive testing verifies that specimen substitution or adulteration has not occurred.	• In general, laboratories do not conduct the same validity testing as is required for Federal workplace testing. • Validation often is not required with clinical use of POCT. • Some laboratories record the temperature of the specimen and test for creatinine and specific gravity of urine specimens. • Pain management laboratories may have specimen validity testing protocols that involve creatinine with reflexive specific gravity, pH, and/or oxidants in place.
Confirmatory Methods	• Gas chromatography/mass spectrometry (GC/MS)	• GC/MS, liquid chromatography/mass spectrometry (LC/MS), liquid chromatography/mass spectrometry/mass spectrometry LC/MS/MS.
Testing for Predetermined Substances	• Testing is for the federally mandated drugs.	• No set drug testing panel. • Drugs tested vary by laboratory and within laboratories. • Clinicians may specify which drugs are tested for and usually select panels (menus) that test for more than the federally mandated drugs. Various panels exist (e.g., pain).
Cutoff Concentrations	• Cutoff concentrations have been established for each drug. • A test detecting a concentration at or above the cutoff is considered to be a positive result; a test detecting nothing, or a concentration below the cutoff, is considered to be a negative result.	• Cutoff concentrations vary. • In some circumstances, test results below the cutoff concentration may be clinically significant. • Urine and oral fluid drug concentrations are usually not well correlated with impairment or intoxication, but may be consistent with observed effects.
Laboratory Certification	• Testing must be conducted at an HHS, SAMHSA-certified laboratory.	• Laboratories do not need HHS certification. However, clinical laboratories in the United States and its territories must be registered with Clinical Laboratory Improvement Amendments (CLIA) and comply with all State and local regulations concerning specimen collection, clinical laboratory testing, and reporting. • POCT using kits calibrated and validated by manufacturers does not require CLIA certification.
Medical Review	• A physician trained as an MRO must interpret and report results.	• MRO review is not required.

Chapter 2—Terminology and Essential Concepts in Drug Testing

In This Chapter

- Drug Screening and Confirmatory Testing
- Testing Methods
- Test Reliability
- Window of Detection
- Cutoff Concentrations
- Cross-Reactivity
- Drug Test Panels
- Test Matrix
- Point-of-Care Tests
- Adulterants
- Specimen Validity Tests

Drug Screening and Confirmatory Testing

Traditionally, drug testing usually, but not always, involves a two-step process: an initial drug screen that identifies potentially or presumptively positive and negative specimens, followed by a confirmatory test of any screened positive assays.

Screening tests (the initial tests) indicate the presence or absence of a substance or its metabolite, but also can indicate the presence of a cross-reacting, chemically similar substance. These are qualitative analyses—the drug (or drug metabolite) is either present or absent. The tests generally do not measure the quantity of the drug or alcohol or its metabolite present in the specimen (a quantitative analysis). Screening tests can be done in a laboratory or onsite (point-of-care test [POCT]) and usually use an immunoassay technique. Laboratory immunoassay screening tests are inexpensive, are easily automated, and produce results quickly. Screening POCT immunoassay testing devices are available for urine and oral fluids (saliva). Most screening tests use antigen–antibody interactions (using enzymes, microparticles, or fluorescent compounds as markers) to compare the specimen with a calibrated quantity of the substance being tested for (Center for Substance Abuse Treatment, 2006b).

Confirmatory tests either verify or refute the result of the screening assay. With recent improvements in confirmation technology, some laboratories may bypass screening tests and submit all specimens for analysis by confirmatory tests. It is the second analytical procedure performed on a different aliquot, or on part, of the original specimen to identify and quantify the presence of a specific drug or drug metabolite (Substance Abuse and Mental Health Services Administration [SAMHSA], 2008). Confirmatory tests use a more specific, and usually more sensitive, method than do screening tests and are usually performed in a laboratory. Confirmatory tests usually:

- Provide quantitative concentrations (e.g., ng/mL) of specific substances or their metabolites in the specimen.
- Have high specificity and sensitivity.

- Require a trained technician to perform the test and interpret the results.
- Can identify specific drugs within drug classes.

In clinical situations, confirmation is not always necessary. Clinical correlation is appropriate. For example, if the patient or a family member affirms that drug use occurred, a confirmation drug test is not usually needed.

A POCT, performed where the specimen is collected, is a screening test. A confirmatory drug test is usually more technically complex and provides definitive information about the quantitative concentrations (e.g., ng/mL) of specific drugs or their metabolites in the specimen tested. However, the term *drug screening* or *testing* is misleading in that it implies that all drugs will be identified by tests, whereas the drug or drug metabolites detected by a test depend on the testing method and the cutoff concentration.

In Federal workplace testing, all positive initial screening test results must be followed by a confirmatory test (SAMHSA, 2008). In clinical settings, however, confirmatory testing is at the practitioner's discretion. Laboratories do not automatically perform confirmatory tests. When a patient's screening test (either a POCT or laboratory test) yields unexpected results (positive when in substance use disorder (SUD) treatment, or negative if in pain management treatment), the practitioner decides whether to request a confirmatory test. In addition, a confirmatory test may not be needed; patients may admit to drug use or not taking scheduled medications when told of the drug test results, negating the necessity of a confirmatory test. However, if the patient disputes the unexpected findings, a confirmatory test should be done. Chapter 4 provides information that can be helpful in deciding whether to request a confirmatory test.

Testing Methods

Conventional scientific techniques are used to test specimens for drugs or drug metabolites. Most commonly, immunoassay testing technology is used to perform the initial screening test (Meeker, Mount, & Ross, 2003). Appendix B, Laboratory Initial Drug-Testing Methods, briefly describes these methods.

The most common technologies used to perform the confirmatory test are gas chromatography/mass spectrometry, liquid chromatography/mass spectrometry, and various forms of tandem mass spectrometry. Information about these methods and other confirmatory testing methods are in Appendix C, Laboratory Confirmatory Drug-Testing Methods. Other testing methods are used to detect adulteration or substitution. Appendix D, Laboratory Specimen Validity-Testing Methods, provides a short explanation of methods for specimen validity testing.

Test Reliability

Both POCTs and laboratory tests are evaluated for reliability. Two measures of test reliability are *sensitivity* and *specificity*, which are statistical measures of the performance of a test. The *sensitivity* indicates the proportion of positive results that a testing method or device correctly identifies. For drug testing, it is the test's ability to reliably detect the presence of a drug or metabolite at or above the designated cutoff concentration (the true-positive rate). *Specificity* is the test's ability to exclude substances other than the analyte of interest or its ability not to detect the analyte of interest when it is below the cutoff concentration (the true-negative rate). It indicates the proportion of negative results that a testing method or device correctly identifies.

Tests are designed to detect whether a specimen is positive or negative for the substance. Four results are possible:

- True positive: The test correctly detects the presence of the drug or metabolites.
- False positive: The test incorrectly detects the presence of the drug when none is present.
- True negative: The test correctly confirms the absence of the drug or metabolites.
- False negative: The test fails to detect the presence of the drug or metabolites.

Confirmatory tests must have high specificity. Generally, screening tests have relatively low specificity. Screening tests are manufactured to be as sensitive as possible, while minimizing the possibility of a false-positive result (Dolan, Rouen, & Kimber, 2004). Notable exceptions from common manufacturers of laboratory-based or point-of-care immunoassay kits are cannabinoids, cocaine metabolite, oxycodone/oxymorphone, methadone, and methadone metabolite (EDDP, or 2-ethylidine-1,5-dimethyl-3,3-diphenylpyrrolidine). Other examples may exist. With the exceptions noted previously, they cannot reliably exclude substances other than the substance of interest (the analyte), and they cannot reliably discriminate among drugs of the same class. For example, a low-specificity test may reliably detect morphine, but be unable to determine whether the drug used was heroin, codeine, or morphine.

Generally, the cutoff level for initial screening tests is set to identify 95–98 percent of true-negative results, and 100 percent of true-positive results. Confirmatory test cutoff concentrations are set to ensure that more than 95 percent of all specimens with screened positive results are confirmed as true positives (Reynolds, 2005). However, confirmation rates are highly dependent upon the analyte. For cannabinoids and cocaine metabolite, the confirmatory rate usually exceeds 99 percent. The clinically important point is that false positives are rare for cocaine metabolite or cannabinoids.

Window of Detection

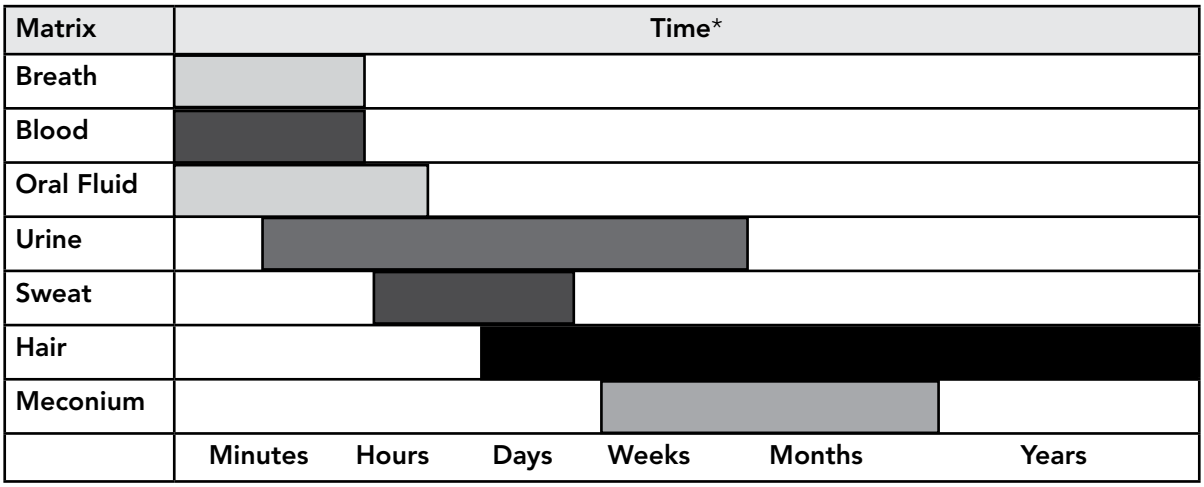
The *window of detection*, also called the detection time, is the length of time the substances or their metabolites can be detected in a biological matrix. It part, it depends on:

- Chemical properties of the substances for which the test is being performed;
- Individual metabolism rates and excretion routes;
- Route of administration, frequency of use, and amount of the substance ingested;
- Sensitivity and specificity of the test;
- Selected cutoff concentration;
- The individual's health, diet, weight, gender, fluid intake, and pharmacogenomic profile; and
- The biological specimen tested.

All biological matrices may show the presence of both parent drugs and their metabolites (Warner, 2003). Drug metabolites usually remain in the body longer than do the parent drugs. Blood and oral fluid are better suited for detecting the parent drug; urine is most likely to contain the drug's metabolites. Exhibit 2-1 provides a comparison of detection periods used for various matrices.

Many factors influence the window of detection for a substance. Factors include, but are not limited to, the frequency of drug use (chronic or acute), the amount taken, the rate at which the substance is metabolized (including pharmacogenomic abnormalities, such as mutations of CYP2D6 and other drug-metabolizing enzymes [White & Black, 2007]), the cutoff concentration of the test, the patient's physical condition and, in many cases, the amount of body fat.

Exhibit 2-1. Window of Detection for Various Matrices



*Very broad estimates that also depend on the substance, the amount and frequency of the substance taken, and other factors previously listed.
†As long as the patch is worn, usually 7 days.
‡7–10 days after use to the time passed to grow the length of hair, but may be limited to 6 months hair growth. However, most laboratories analyze the amount of hair equivalent to 3 months of growth.

Sources: Adapted from Cone (1997); Dasgupta (2008).

Cutoff Concentrations

The administrative *cutoff* (or *threshold*) of a drug test is the point of measurement at or above which a result is considered positive and below which a result is considered negative. This level is established on the basis of the reliability and accuracy of the test and its ability to detect a drug or metabolite for a reasonable period after drug use (see Test Reliability).

Before the establishment of the Federal mandatory guidelines, cutoff concentrations for screening tests were determined by the manufacturer of the test or the laboratory. Because the majority of drug testing is done for workplace purposes, most laboratories and many POCTs use the Federal mandatory guidelines for workplace testing cutoff concentrations. However, Federal cutoff concentrations are **not** appropriate for clinical use. Practitioners need to know the cutoff concentrations used in the POCTs, or by the laboratory testing their patients' specimens, and should understand which analyte and at what cutoff the test is designed to detect.

Detection thresholds for Federal, employer, and forensic drug testing panels are set high enough to detect concentrations suggesting drug abuse, but they do not always detect therapeutic concentrations of medications. For example, the threshold for opiates in federally mandated workplace urine drug screening is 2000 ng/mL. The usual screening threshold for opiates in clinical monitoring is much lower, at 300 ng/mL for morphine, hydrocodone, and codeine (Christo et al., 2011) to detect appropriate use of opioid pain medication.

For laboratory tests, practitioners can request lower cutoff concentrations than are commonly used in workplace testing. However, in some cases, the error rate increases as the cutoff concentration decreases.

Cross-Reactivity

Cross-reactivity occurs when a test cannot distinguish between the substances being tested for and substances that are chemically similar. This is a very important concept when interpreting test results.

Drug class-specific immunoassay tests compare the structural similarity of a drug or its metabolites with specially engineered antibodies. The ability to detect the presence of a specific drug varies with different immunoassay tests, depending on the cross-reactivity of the drug with an antibody. For example, a test for opioids may be very sensitive to natural opioids, such as morphine, but may not cross-react with synthetic or semisynthetic opioids, such as oxycodone.

Substances other than the drug to be detected may also cross-react with the antibody and produce a false-positive result. Some over-the-counter (OTC) decongestants (e.g., pseudoephedrine) register a positive drug test result for amphetamine. Phentermine, an anorectic agent, commonly yields a false-positive initial amphetamines test. Dextromethorphan can produce false-positive results for phencyclidine (PCP) in some assays. Cross-reactivity can be beneficial in clinical testing. As an example, a urine test that is specific for morphine will detect only morphine in a patient's urine. The morphine-specific test will miss opioids, such as hydrocodone and hydromorphone. A urine drug test or panel that is reactive to a wide variety of opioids would be a better choice for a clinician when looking for opioid use by a patient. Conversely, the lack of sensitivity to the common semisynthetic opioid, oxycodone, is detrimental to patient care when a clinician is reviewing the results of a "urine drug screen" and sees "opiates negative" when oxycodone abuse is suspected. Thus, cross-reactivity can be a double-edged sword in clinical practice.

To avoid false-positive results caused by cross-reactivity, practitioners should be familiar with the potential for cross-reactivity and ask patients about prescription and OTC medication use.

Drug-testing accuracy continues to improve. For example, newer drug tests may correct for interactions that have been formerly associated with false-positive results. Practitioners can find some of this information in the instructions in the POCT packaging material, or they can talk with laboratory personnel to know exactly what a laboratory's tests will and will not detect.

Drug Test Panels

A *drug test panel* is a list (or menu) of drugs or drug classes that can be tested for in a specimen. These can be ordered to identify drugs of abuse or in pain management. No single drug panel is suitable for all clinical uses; many testing options exist that can be adapted to clinical needs. These panels are designed to monitor adherence to pain treatment plans, to detect use of nonprescribed pain medications, and to screen for use of illicit drugs. Clinical practitioners can order more comprehensive drug test panels to identify drugs or classes of drugs that go beyond the federally mandated drugs for testing. Which drugs are included in the testing menu vary greatly between and within laboratories; laboratories differ in the drugs or metabolites included in their comprehensive panel and have more than one type of panel. Therefore, practitioners should contact their laboratory to determine the capabilities and usual practices of the laboratory. It is just as important for a clinical practitioner to know what a "urine drug screen" will not detect as it is to know what it will detect. Some laboratories have a comprehensive pain management panel for people prescribed opioids for pain (Cone, Caplan, Black, Robert, & Moser, 2008). Panels can be customized for individual practices or patients, but using existing test panels from the laboratory is generally less expensive for patients and less time-consuming for practitioners than ordering tests for many individual substances. However, these panels vary by laboratory and are not standardized. However, it should be noted that laboratories may default to the federally mandated drug tests if a practitioner does not order a different test panel.

Panels are available in various configurations. The more drugs on a panel, the more expensive the test. Substances typically on these panels include, but are not limited to:

- Amphetamine, methamphetamine.
- Barbiturates (amobarbital, butabarbital, butalbital, pentobarbital, phenobarbital, secobarbital).
- Benzodiazepines (alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, flurazepam, lorazepam, oxazepam, temazepam).
- Illicit drugs (cocaine, methylenedioxyamphetamine [MDA], methylenedioxymethamphetamine [MDMA], methylenedioxyethylamphetamine [MDEA], marijuana).
- Opiates/opioids (codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, meperedine, methadone, morphine, oxycodone, oxymorphone, propoxyphene).

The practitioner should consult with the laboratory when determining the preferred test panels.

The test menu for POCTs differs per the manufacturer and the device. Most POCTs screen for drugs included in the federally mandated test panel and other drugs or metabolites. Different devices and manufacturers offer various configurations of drugs tested for in devices.

Test Matrix

A *test matrix* is the biological specimen used for testing for the presence of drugs or drug metabolites. Almost any biological specimen can be tested for drugs or metabolites, but the more common matrices include breath (alcohol), blood (plasma, serum), urine, sweat, oral fluid, hair, and meconium. Depending on its biological properties, each matrix can provide different information about a patient's drug use. For example, the ratio of parent drug to metabolite in each matrix can be decidedly different, and each matrix has a different window of detection. Urine is the most widely used test matrix (Watson et al., 2006). Detailed information about test matrices is in Chapter 3.

Point-of-Care Tests

A *POCT* is conducted where the specimen is collected, such as in the practitioner's office. POCTs use well-established immunoassay technologies for drug detection (Watson et al., 2006).

POCTs:

- Reveal results quickly;
- Are relatively inexpensive ($5–$20, depending on the POCT, the drugs or drug metabolites tested for, and the number of tests purchased);
- Are relatively simple to perform; and
- Are usually limited to indicating only positive or negative results (qualitative, not quantitative).

When reading the test results, it is important to know that how quickly the test becomes positive or the depth of the color do not indicate quantitative results.

A comparison of POCTs and laboratory tests is in Chapter 3.

Adulterants

An *adulterant* is a substance patients can add to a specimen to mask the presence of a drug or drug metabolite in the specimen, creating an incorrect result to hide their drug use. Methods to detect adulterants exist, and most laboratories and some POCTs can detect common adulterants. No one adulterant (with the exception of strong acids, bases, oxidizers, and reducing agents) can mask the presence of all drugs. The effectiveness of an adulterant depends on the amount of the adulterant and the concentration of the drug in the specimen. A specimen validity

test can detect many adulterants. Numerous adulterants are available, especially for urine (see Chapter 5).

Specimen Validity Tests

Specimen validity tests determine whether a urine specimen has been diluted, adulterated, or substituted to obtain a negative result. A specimen validity test can compare urine specimen characteristics with acceptable density and composition ranges for human urine, detect many adulterants (e.g., oxidizing compounds), or test for a specific compound (e.g., nitrite, chromium VI) at concentrations indicative of adulteration. Many laboratories perform creatinine and pH analyses of all specimens submitted for drug testing. An adulteration panel can be ordered that determines the characteristics of the urine sample (e.g., creatinine level with reflexive specific gravity when a low creatinine is encountered) and checks for the presence of common adulterants. POCT devices are available that test for specimen validity, as well.

Although validity testing is not required in clinical settings, it is sometimes advisable if the patient denies drug use. For example, a physician treating a patient for an SUD may want to request validity testing if the patient exhibits signs of relapse, but has negative test results. Point-of-care validity tests are available, and some POCT devices also test for validity at the same time they test for the drug analyte.

Additional information on validity follows:

- The pH for normal urine fluctuates throughout the day, but usually ranges between approximately 4.5 and 9.0. Specimens outside this range are usually reported by the laboratory as invalid. Specimen adulteration should be suspected if the pH level is less than 3.0 or greater than 11.0.
- Creatinine is a normal constituent in urine at concentrations greater than or equal to 20 mg/dL. If the creatinine is less than 20 mg/dL, the specimen is tested for specific gravity.
- *Specific gravity* of urine is a measure of the concentration of particles in the urine. Only specimens whose creatinine is less than 20 mg/dL need to be reflexively tested for specific gravity, although specific gravity may be an integral part of a POCT device's specific validity testing panel. Specimens with a low creatinine and an abnormal specific gravity may be reported as dilute, invalid, or substituted, depending on the laboratory's reporting policies (SAMHSA, 2008).

If the laboratory finds the specimen is dilute, it will report the specimen as dilute. However, the laboratory will also report the positive or negative test results. Depending on the degree of dilution, an analyte may still be detected.

Appendix D provides more information on laboratory specimen validity tests.

Chapter 3—Preparing for Drug Testing

In This Chapter

- Deciding Which Drugs To Screen and Test For
- Choosing a Matrix
- Selecting the Initial Testing Site: Laboratory or Point-of-Care
- Preparing a Specimen Collection Site

Deciding Which Drugs To Screen and Test For

When using drug tests to screen a patient for substance use disorders, the practitioner should test for a broad range of drugs. Decisions about which substances to screen for can be based on:

- The patient, including history, physical examination, and laboratory findings;
- The substance suspected of being used;
- The substances used locally (the Substance Abuse and Mental Health Services Administration's [SAMHSA's] Drug Abuse Warning Network compiles prevalence data on drug-related emergency department visits and deaths; information is available at http://www.dawninfo.samhsa.gov);
- The substances commonly abused in the practitioners' patient population; and
- Substances that may present high risk for additive or synergistic interactions with prescribed medication (e.g., benzodiazepines, alcohol).

Choosing a Matrix

Practitioners can choose among several matrices for drug and alcohol testing for adults: urine, oral fluid, sweat, blood, hair, and breath (alcohol only). Neonates can be tested using meconium. Urine is the most commonly used matrix for drug testing and has been the most rigorously evaluated (Watson et al., 2006); it is discussed at length in Chapter 5. Exhibit 3-1 provides a brief comparison of the advantages and disadvantages of the seven matrices.

Exhibit 3-1. Advantages and Disadvantages of Different Matrices for Drug Testing

Matrix	Advantages	Disadvantages
Urine	• Available in sufficient quantities • Higher concentrations of parent drugs and/or metabolites than in blood • Availability of point-of-care tests (POCTs) • Well-researched testing techniques	• Short to intermediate window of detection • Easy to adulterate or substitute • May require observed collection • Some individuals experience "shy bladder" syndrome and cannot produce a specimen
Oral Fluid	• Noninvasive specimen collection • Easy to collect • Reduced risk of adulteration • Directly observed specimen collection • Parent drug rather than metabolite can be the target of the assay • Able to detect same-day use, in some cases • Availability of POCTs • Detect residual drug in the mouth	• Limited specimen volume • Possibility of contamination from residual drug in mouth that cannot be correlated with blood concentrations • Short window of detection • Requires supervision of patient for 10–30 minutes before sampling • Salivation reduced by stimulant use • Need for elution solvent to efficiently remove drugs adsorbed to collection device • Cannabinoids in oral fluid have been shown to arise from contamination of the oral cavity rather than excretion in saliva from blood
Sweat	• Detects recent use (fewer than 24 hours with a sweat swipe) or allows for cumulative testing with the sweat patch (worn for up to 7–14 days) • Noninvasive specimen collection • Difficult to adulterate • Requires little training to collect specimen • May be an economical alternative to urine	• Few facilities and limited expertise for testing • Risk of accidental or deliberate removal of the sweat patch collection device • Unknown effects of variable sweat excretion among individuals • Only a single sweat collection patch available so multiple analyses cannot be done if needed (i.e., more than one positive initial test) • May be affected by external contaminants • Requires two visits, one for patch placement and one for patch removal
Blood	• Generally detects recent use • Established laboratory test method	• Expensive, except to detect ethanol • Limited window of detection • Invasive specimen collection (venipuncture) • Risk of infection • Requires training to collect specimen • May not be an option for individual with poor venous access

Exhibit 3-1. Advantages and Disadvantages of Different Matrices for Drug Testing, continued

Matrix	Advantages	Disadvantages
Hair	• Longest window of detection • May be able to detect changes in drug use over time (from 7–10 days after drug use to 3 months, depending on length of hair tested) • Directly observed specimen collection • Noninvasive specimen collection • Four tests will cover 1 year • Easy storage and transport • Difficult to adulterate or substitute • Readily available sample, depending on length of hair tested	• Cannot detect use within the previous 7–10 days • Difficult to interpret results • Costly and time consuming to prepare specimen for testing • Few laboratories available to perform testing • No POCTs currently available • Difficult to detect low-level use (e.g., single-use episode) • May be biased with hair color (dark hair contains more of some basic drugs [cocaine, methamphetamine, opioids] due to enhanced binding to melanin in hair) • Possibility of environmental contamination • Specimen can be removed by shaving
Breath	• Well-established method for alcohol testing • Readily available	• Used only for alcohol and other volatiles • Short window of detection • May be difficult to obtain adequate sample, especially with patients who are very intoxicated or uncooperative • Uncommon in clinical setting
Meconium	• Can detect maternal drug abuse and fetal or infant exposure • Wide window of drug detection (third trimester of gestation) • Noninvasive collection from diaper • Generally, adequate specimen amount	• Narrow collection window that can be missed, especially in babies with low birth weight • Testing not available in all laboratories • Requires extra steps (weighing and extraction) • Confirmation assays more difficult than for urine

Sources: Center for Substance Abuse Treatment (2006a); Dolan, Rouen, & Kimber (2004); Kwong & Ryan (1997); Warner (2003).

Once ingested, drugs of abuse are rapidly distributed via the blood to all parts of the body. Abused drugs are generally lipid soluble and are mainly metabolized by the liver to more water-soluble metabolites. These metabolites are removed from blood by the kidneys and excreted in urine. Because many drugs are cleared from the blood rapidly, testing of blood or its components (serum) has short periods of detection, as does breath for testing for alcohol consumption and oral fluids because the drug passes quickly into, and is eliminated from, breath and oral fluids. Depending on the drug itself and previously listed factors that affect metabolism, urine usually has a window of detection that is slightly longer than oral fluid. Urine detection times vary from less than 1 day after ingestion to several weeks. Hair has a longer window of detection, but is best suited for detection of heavy drug use. The cells that generate hair absorb the metabolites that are circulating in the blood at the time the hair is produced; therefore, hair has the longest window of detection, depending on the length of the hair. It is notable that drugs may be incorporated into hair from external sources, such as mechanical contact between the hair and the drug. In utero drug exposure also can be monitored with maternal and neonatal urine and/or hair testing.

Specimen Availability

Some specimens are more easily collected than others. Collection of blood samples requires trained personnel to perform venipuncture and is more invasive than collection of urine, oral fluid, or hair specimens. Collections of oral fluid and hair are less intrusive than urine collection.

Oral Fluid

During the past decade, the use of oral fluid for drug testing has been validated by a large body of scientific literature (Bosker & Huestis, 2009; Cone & Huestis, 2007). The parent drug is usually found in oral fluids, although the metabolite(s) may be present and quite useful. The parent drug is generally found in higher concentrations in oral fluids than are drug metabolites. Compared with urine specimens, oral fluid specimens present fewer opportunities for adulteration or substitution (Dams, Choo, Lambert, Jones, & Huestis, 2007). Use of commercial adulterants or mouthwashes were not found to interfere with the immunoassay (Bosker & Huestis, 2009), or they did not affect test results if the products are used more than 30 minutes before specimen collection (Drummer, 2006; Niedbala, Kardos, & Fries, et al., 2001; Niedbala, Kardos, Fritch, Cannon & Davis, 2001). The window of detection for oral fluid is narrower than it is for urine, and drug concentrations are generally lower (Warner, 2003). In general, drug testing of oral fluids detects drug use during the previous 24–48 hours, regardless of the route of administration (Cone, 2006), although the selection of cutoffs plays an important role in the length of the detection window.

Oral fluid collection devices vary, but the most common version is a swab or absorbent pad on a stick that is placed between the lower cheek and gums to collect fluid and is left in place for a few minutes. It is then inserted into a vial containing a buffer solution for shipment to the laboratory. POCTs are also available for oral fluid testing.

On occasion, dry mouth syndrome can slow oral fluid collection, often requiring several minutes to collect an adequate sample (Drummer, 2006). Some medications and illegal drugs cause a dry mouth, and some oral fluid collection devices assist collection by stimulating oral fluid flow. Patients should not eat immediately before testing because some food tends to inhibit oral fluid production. If blood is present in the patient's oral fluid, collection of an alternative specimen, such as blood or urine, would be needed. Oral fluid limits the number of repeat or confirmatory tests on the specimen because of the small amount of the sample, compared with a urine sample.

Sweat

Several collection devices have been manufactured for collecting sweat specimens. The two most common are the patch and the swipe; however, the sweat patch is the only device approved by the U.S. Food and Drug Administration (FDA). The quantity of sweat collected is determined by the length of time the patch is worn and the physiology of the person wearing the patch. The patch should be worn for at least 3 days, but no longer than 7 days, although most drugs will have been excreted within the first 48 hours (Barnes et al., 2009; Huestis et al., 2008; Kacinko et al., 2005; Schwilke et al., 2006). This ensures that a sufficient amount of sweat is collected for testing. The sweat collected with the patch detects drug use that occurred shortly before the patch was applied and while the device remains on the skin.

The skin should be thoroughly cleaned with soap and water and then swabbed well with alcohol. The patch should then be applied to the skin by a staff member, not the patient (Watson et al., 2006). After 7 days, the patch is removed by the practitioner and sent to the laboratory for analysis.

Mainly the parent drug is found in sweat; however, some drug metabolites also may be detected (Dasgupta, 2008). Drugs and drug metabolites that have been detected

in sweat include tetrahydrocannabinol (THC), amphetamine, methamphetamine, methylenedioxymethamphetamine (MDMA, or "Ecstasy"), codeine, morphine, heroin metabolite, phencyclidine (PCP), and cocaine and its metabolites (e.g., benzoylecgonine, ecgonine methyl ester) (Barnes et al., 2009; Dasgupta, 2008).

Because sweat can be collected only in limited quantities, there may not be sufficient specimen for repeat or confirmatory testing. Sweat is less susceptible to tampering or adulteration than is urine. The accuracy of sweat testing is not standardized. Its accuracy remains somewhat controversial (Chawarski, Fiellin, O'Connor, Bernard, & Schottenfeld, 2007; Watson et al., 2006) and more research is needed (Barnes et al., 2009; Huestis et al., 2008; Kacinko et al., 2005; Schwilke et al., 2006). However, the sweat patch is used extensively in the criminal justice system, and its use to identify relapse or violations of conditions of probation has been upheld by the courts.

Blood

Blood testing detects alcohol or drug use starting shortly after use, depending on the substance and the route of administration. In general, blood has a shorter detection period than urine (Warner, 2003). Blood collection is more invasive than other procedures and requires trained personnel to collect the specimen and perform laboratory testing. For people who inject drugs, or those with poor venous access, drawing blood may be difficult.

Hair

In theory, the presence of drugs in hair is based on a simple principle: Drugs or their metabolites circulate in a person's bloodstream, and the hair follicles absorb the drug and/or metabolites from the bloodstream and from secretions of the sebaceous and sweat glands in the scalp (Cone, 1996; Musshoff & Madea, 2006). Trace amounts of drug become entrapped in the core of the hair as it grows, at a rate of approximately 1 cm per month (Dolan et al., 2004). Drug metabolites can be detected in the hair shaft approximately 7–10 days after drug ingestion. Hair is unique in that it may provide retrospective information on drug use, versus the point-of-time information provided by urine, blood, and breath. (Kintz, Villain, & Ludes, 2004). In some cases, drugs were found to move down the hair shaft via sweat (Henderson, Harkey, Zhou, Jones, & Jacob, 1996), which would disrupt the use of hair testing's ability to determine the historical use. Another unfortunate aspect of interpreting hair test results of drugs and their metabolites is that drugs may be incorporated into hair by simple environmental drug exposure (Ropero-Miller & Stout, 2008; Wang & Cone, 1995).

The hair sample is usually taken from the back of the head, cut with scissors as close to the skin as possible (Wong & Tse, 2005). Hair can be collected from other parts of the body (e.g., face, armpit) of patients who are bald or have shaved heads.

Hair testing appears to be most reliable for detecting prior frequent, heavy use of cocaine, opioids, amphetamine, PCP, and Ecstasy, but is not suited for detection of very recent use, or occasional drug use. Musshoff and Madea (2006) report that hair tests can detect the presence of the THC metabolite, tetrahydrocannabinol carboxylic acid. Hair analysis can often distinguish between heroin and morphine use—a distinction that is sometimes difficult to make with blood or urine analysis (Dolan et al., 2004) because of the short half-life of heroin metabolite in these matrices. Hair testing for alcohol is inappropriate; alcohol does not incorporate into hair. However, the minor metabolites of ethanol, ethyl glucuronide, and ethyl sulfate in hair show promise as markers of alcohol use (Wurst, Skipper, & Weinmann, 2003).

Hair testing is suited to:

- Detecting chronic drug use (Dolan et al., 2004; Warner, 2003);
- Providing a view of the patient's long-term substance use pattern; and
- Indicating periods of abstinence (Pragst & Balikova, 2006).

An advantage of drug testing with hair is the longer window of detection compared with other matrices (Boumba, Ziavrou, & Vougiouklakis, 2006). The detection period for hair is limited only by the length of the hair sample and the degree of deposition in the hair. Cannabinoids have been shown to deposit less readily than basic drugs in hair (Huestis et al., 2007). Some laboratories typically restrict analysis to a hair segment representing about 3 months of growth. However, this long window period is also a disadvantage; hair testing is not useful in substance abuse treatment or monitoring opioid pain or other addictive medications when frequent (weekly or monthly) drug testing is desired. Because the timing of the drug use is difficult to determine by testing hair, it is not very useful clinically.

Disadvantages for testing for drugs in hair are the high costs and the longer time needed to obtain results, compared with the time required by other matrices. Analysis of the hair specimen is a complex process that involves breaking down the hair to free the drugs trapped in it. This chemical process requires a longer time of analyses than other matrixes. It can be done only in a laboratory; no POCTs are available for testing hair samples.

Some questions remain about environmental contamination; a person may claim that the drug is present in the hair because the individual was in a room where others were smoking drugs. Therefore, in preparation for analysis at the laboratory, the hair sample is washed, which may remove the contamination. Unfortunately, this environmental contamination cannot always be differentiated from actual drug use, even if drug metabolites are measured quantitatively in hair (Ropero-Miller & Stout, 2008).

Additional controversies exist about whether biophysical attributes affect hair analysis. Studies have shown that concentrations of drugs in hair can be affected by variations in hair structure, growth rate, melanin content, hygiene, and cosmetic hair treatments, such as bleaching (Dasgupta, 2008). Although there have been a limited number of human clinical controlled studies, data show that higher concentrations of some drugs (e.g., codeine, cocaine, amphetamine) are found in dark hair compared with concentrations found in blond or red hair (SAMHSA, 2004). Cone and Joseph (1996) reviewed several articles and found that hair testing may be biased toward some hair types. Drugs of abuse bind more readily to Africoid and Mongoloid types of hair compared with Caucasoid hair. Cosmetic hair treatments also affect the binding of drugs to hair. For example, bleaching of the hair can reduce drug content, but it also can damage the hair to the extent that bleaching may increase binding of the drug to the hair (Skopp, Pötsch, & Moeller, 1997). Some drugs (i.e., THC) do not differentially distribute into hair based on melanin content (Smeal, 2007). Therefore, hair testing may not be the most equitable drug testing matrix. Hair rinses, bleaches, and shampoos that claim to interfere with drug tests are advertised on the Internet and in magazines.

Breath

Several simple-to-use, but accurate, breath-testing devices are available for detecting very recent alcohol use. Breath also may be employed for the identification and quantitation of a variety of other volatiles, especially in industrial hygiene situations. However, breath testing is commonly used in alcohol treatment programs, but not in primary care.

The body metabolizes alcohol rapidly, but alcohol will be detectable in breath as long as it is present in blood. The detection period for ethyl alcohol itself is hours (not days) after the last alcohol use. The metabolism of alcohol varies considerably by the person's gender, age, physical condition (especially the condition of the liver), and weight.

Easily administered breath alcohol tests are available to confirm alcohol ingestion within the past several hours. When a breath alcohol analyzer test is conducted properly, it gives an accurate measurement of breath alcohol content (BrAC). The BrAC gives an estimate of blood alcohol level (BAL) (Watson et al., 2006). Body temperature and breathing patterns can affect breath alcohol test results. Compared with blood and urine tests, breath tests are less precise. Some evidence suggests that breath tests may underestimate BALs by approximately 8.5 percent (Garriott, 2008).

The breath alcohol analyzer (such as the best-known version, Breathalyzer) is a device that gives an accurate BrAC. The benefits of breath alcohol analyzers are that they:

- Are simple to use;
- Are inexpensive;
- Give instant results; and
- Are noninvasive.

The National Highway Traffic Safety Administration provides a list of breath alcohol analyzer devices that have been tested for accuracy and reliability. The list is available at http://www.dot.gov/ost/dapc/testingpubs/20070131_CPL_ASD.pdf.

Meconium

Meconium is the first few bowel movements of a neonate. Research shows that meconium provides a record of neonate exposure and maternal substance use in the third trimester of gestation (Concheiro et al., 2010; Gray & Huestis, 2007; Kacinko, Jones, Johnson, Choo, & Huestis, 2008). Meconium offers a wide window of drug detection, monitoring drug use primarily over the third trimester of gestation. Because collection of meconium is noninvasive (requiring only the transfer of the specimen or meconium from diaper to specimen container), it is usually easier to collect than urine. Collection of a specimen must be made before the neonate passes the first formed stool; for full-term babies, this generally occurs within 3 days (Gareri, Klein, & Koren, 2006).

However, this is a highly subspecialized area that may be used in connection with a maternal urine drug test. The testing of meconium should be recognized as having potential medicolegal ramifications (i.e., a positive test may result in the State removing the newborn from the new mother's custody).

Potential disadvantages to using meconium exist. Test results vary greatly by substances used and cutoff concentrations because of the unique qualities of meconium. Moreover, laboratory methods of preparing the specimen can affect the test results greatly (Gray & Huestis, 2007). Urine contamination may skew results (Gray et al., 2010).

Selecting the Initial Testing Site: Laboratory or Point-of-Care

Many factors should be considered when deciding to test onsite with a POCT for the initial test or offsite by a laboratory. Exhibit 3-2 compares POCTs and laboratory tests. The sections below explain each method.

Collection Devices

The collection device must be single use. It will normally be individually packaged with collection aids and a tamper-evident security seal. The collection device must not alter or affect the specimen. The device should have the following features for each specimen matrix:

- **Blood**. Sterile tubes that usually contain sodium fluoride to inhibit breakdown of drugs. The use of "gel" or "serum separator

Exhibit 3-2. Comparison of Laboratory Tests and POCTs

Criterion	Laboratory Test	POCT
Time to Results	Initial test can be available within hours, but the confirmatory test takes days	Minutes
Ease of Use	Requires complex equipment	Relatively simple to use
Training	Requires trained technicians or technologists	Minimal training required
Breadth of Tests	Wide range of test menus	Limited test menu
Interpretation	Objective quantitative results; variations in laboratory cutoff concentrations may influence interpretation	Subjective results; requires interpretation, not quantitative

Sources: Melanson (2005); Watson et al. (2006).

tubes" for specimen collection for any type of drug analysis is highly discouraged.

- **Hair**. Foil or a plastic bag to store the sample with an indication of proximal and distal ends.
- **Oral fluid**. Device that allows accurate determination of the volume collected (usually 1.0±0.1 mL) and that contains an elution solvent to efficiently elute the adsorbed drugs.
- **Sweat**. A patch, placed on the skin, typically composed of an adhesive layer, release liner, and sweat-collection pad.
- **Urine**. A plastic collection container typically with a temperature strip outside the container to determine specimen temperature.

Shipping materials, documentation, and order forms will be needed if the specimen is to be sent to a laboratory.

Laboratory Tests

Laboratories perform screening, confirmatory, and validity tests, using instrumented devices that are operated by trained technical personnel. Laboratory testing is more accurate than POCT and provides quantitative information on what drugs and/or metabolites were detected. Laboratories use high-volume immunoassay tests to separate negative specimens from those that require confirmation testing. Confirmation tests use either liquid chromatography (LC) or gas chromatography (GC) in combination with mass spectrometry (MS) for detection and measurement of drugs and metabolites. Tandem mass spectrometry (MS/MS) is a more sensitive form of MS. These tests provide a laboratory with the ability to identify and measure drugs and/or metabolites in biological fluids at low concentrations. Technical details about these tests and their strengths and limitations are in Appendixes B–D.

Most laboratories usually perform initial drug tests for commonly abused drugs, including 6-acetylmorphine (heroin metabolite), opioids, cocaine, amphetamines, barbiturates, PCP, and THC. Some laboratories offer extended opioid panels; these laboratory tests can detect and confirm several opioids including morphine, codeine, hydrocodone, hydromorphone, oxycodone, and oxymorphone. Some laboratories offer, upon request, panels that will differentiate individual benzodiazepines and their metabolites. Other extended panels include buprenorphine, carisoprodol, methadone, fentanyl, meperidine, and propoxyphene, among others. Not all laboratories are capable of identifying all known benzodiazepines and, where necessary or appropriate, their metabolites. The requirement for additional testing depends in large part on the patient population

served by the facilities using the laboratory (e.g., a methadone clinic or a detoxification facility might require methadone, EDDP [methadone metabolite], burprenorphine/norbuprenorphine, and/or other drug or metabolite analyses). POCTs or laboratory-based tests may be used for the initial testing, but only laboratories can perform confirmatory testing.

Advantages and Disadvantages of Testing in a Laboratory

Advantages. Laboratory tests have several important advantages over POCTs. Laboratory tests:

- Generally have a higher degree of precision.
- May offer quantitation of drugs and/or metabolites and a reasonable estimate of the timeframe in which the drug was used.
- Can provide information on specific drugs used.
- Can be directly sent for confirmatory GC/MS on the same sample.
- Are performed by trained laboratory professionals.

Disadvantages. The disadvantage of laboratory-based tests is turnaround time. The time required for laboratory-based testing may include transportation of the specimen to the laboratory, specimen aliquot preparation, and instrument analysis time—steps that are not required for POCTs. Results from POCT can be available while the patient is still in the office, so the practitioner can immediately discuss them with the patient. Depending on the laboratory, clinical screening results may be available in less than 1 hour after receipt or the next day, unless further testing, such as confirmation or reflexive testing, is required.

Considerations for Selecting a Laboratory

Before selecting a laboratory, practitioners should contact the laboratory and speak directly to the director or toxicologist to (White & Black, 2007):

- Determine the laboratory's analytic capabilities (laboratories may use the Federal Five as the testing menu for drug screens, which may or may not include the clinical drugs of interest);
- Inquire about other panels that test for drugs and drug classes of clinical interest;
- Confirm that the laboratory follows established Federal and State regulations (Exhibit 3-3);
- Determine whether the laboratory's testing procedures are appropriate for clinical use; and
- Ensure that the laboratory provides technical assistance so the practitioner can obtain help with interpreting test results or determining which panel to order.

Exhibit 3-3. Federal and State Regulations

- The Clinical Laboratory Improvement Amendments (CLIA) of 1967 and of 1988 set forth conditions that all laboratories must meet to be certified to perform testing on biological specimens (http://www.cms.hhs.gov/CLIA).
- The U.S. Department of Health and Human Services (HHS) Mandatory Guidelines for Federal Workplace Drug Testing Programs specify the requirements for a laboratory to be certified by the HHS National Laboratory Certification Program. Information is available at http://workplace.samhsa.gov/Dtesting.html
- Private and professional organizations (e.g., College of American Pathologists) have established voluntary laboratory accreditation programs. The American Association of Bioanalysts has private personnel standards.
- State clinical laboratory programs operate under individual State laws; State programs are usually authorized through the Centers for Medicare & Medicaid Services.

Practitioners need to talk to laboratory personnel about:

- Appropriate in-office specimen collection, handling, and storage procedures for each matrix used;
- Each test ordered, at least until the practitioner is thoroughly familiar with the tests and drug panels the laboratory offers (practitioners need to be sure they know exactly what they are ordering and the limitations of any particular test);
- Test results (practitioners should contact the laboratory about unexpected results, whether positive or negative); and
- Referral testing for drugs not offered by the primary testing clinical laboratory.

Point-of-Care Tests

Several different types of POCTs are available. Generally, POCTs:

- Use well-established immunoassay technologies for drug detection;
- Determine the presence of parent drugs or their metabolites;
- Sometimes can determine the validity of a specimen, which is to be highly recommended as an integral part of the testing process;
- Identify drug classes (e.g., opioids, benzodiazepines, barbiturates), single drugs, or metabolites (e.g., benzoylecgonine, a cocaine metabolite); and
- Require a few drops of a specimen.

FDA has approved POCT devices for urine, breath, and oral fluid testing, but devices for urine drug testing are most widely used. Advances are being made in developing POCTs for other matrices, and these may be available in the future.

Various POCTs are available:

- Breath-testing devices, which are rare in primary care practice (the patient blows into the device)
- Cards or cassettes (drops of urine are placed on a card or in wells on a cassette)
- Dipsticks (an absorbent strip is dipped into the specimen)
- Combination collection/test cups (the testing strip is integrated into the collection cup, and results can be read on the outside of the cup)

A few devices double as both collection and testing devices. After the specimen is collected, the tester initiates the test, carefully times the test, and interprets and records the results. The test component of noninstrumented POCTs is an absorbent strip with an antibody-dye complex. The test is done by inserting the absorbent strip, card, or cassette into the specimen or adding the specimen to the testing device. When the strip or cassette comes into contact with the specimen, it reacts to the drug or drug class that the POCT can detect. Generally, a line or dot appears in the zone labeled for a specific drug if the drug is not present (negative test result); no line or dot appears when a specific drug is present (positive test result). A photocopy of the portion of the POCT device that is read can be made and placed in the patient's chart. Enough fluid (urine or oral fluid) should be retained for any reflexive or confirmatory testing that may be required.

It is critical that practitioners read package inserts carefully to know how to perform the test and read the results. Positive POCT results should usually be followed by a laboratory confirmatory test if the patient denies drug use when confronted with the positive results. A confirmatory test must be done if legal or employment ramifications for the patient will result.

Advantages and Disadvantages of POCTs

The principal advantage of POCTs is that the results are available in approximately 10 minutes. This fast turnaround allows practitioners to discuss the results with the patient during that office visit and make clinical decisions and act appropriately that day. This early intervention may prevent other health problems, hospitalization, or treatment episodes. It is also in keeping with behavioral principles: the immediacy of the intervention in relation to a behavior makes reinforcement more useful. Several manufacturers have developed drug-of-abuse assays for POCT that offer similar, but not exact, sensitivity and specificity to the methodologies used by central laboratories (Melanson, 2009). A variety of testing panels with different cutoff concentrations is available for these testing devices, but they are not as varied as laboratory testing. Increasingly, vendors are offering point-of-care devices that test for a wider range of drugs and with more sensitivity and specificity. POCTs are available to test for amphetamine, methamphetamine, barbiturates, benzodiazepines, cocaine, methadone, opioids, PCP, propoxyphene, Ecstasy, oxycodone, tricyclic antidepressants, buprenorphine, and THC acid metabolite (Melanson, 2005).

A survey of five POCT immunoassay devices for urine testing found that each had a false-negative rate for opioids of less that 1 percent and a false-positive rate less than 0.25 percent for testing for pain management (Crouch, Hersch, Cook, Frank, & Walsh, 2002). Melanson's (2009) review of the literature reviewed studies looking at the analytical performance (sensitivity, specificity, precision, and accuracy) of POCTs for drugs of abuse. Generally, most studies suggested that POCTs are a reliable method to screen for drugs of abuse and that the results are comparable to those from automated immunoassays and GC/MS. However, Melanson (2009) also noted that some studies found inconsistencies, such as:

- Several devices were found to have discrepancies between the claims of the manufacturer and the devices' product performance.
- Some devices deviated from their stated cutoffs showing positive results below the cutoff or negative results above the cutoffs.

However, no POCT device yields perfect agreement with more sophisticated testing, such as GC/MS or high-performance liquid chromatography (Watson et al., 2006). Disagreement between methods was highest for samples near the cutoffs.

Cross-reactivity differs among POCT devices because of differing antibody specificity. The manufacturer provides a list of compounds tested and their degree of cross-reactivity, including those medications outside the drug class, which may cause false-positive results (Melanson, 2009).

George and Braithwaite (2002) caution that the apparent benefit of POCTs—rapid assessment of a patient's drug use—can be detrimental if treatment decisions are based on these rapid, but unconfirmed, results. A disadvantage of noninstrumented POCTs is that most test only for drug classes, not for specific drugs within a class (Gourlay, Caplan, & Heit, 2010), which is what is needed more often in clinical applications. Many POCTs have a limited test menu, compared with laboratory testing and in clinical settings; practitioners may need a more complete panel, or separate tests, to assess for specific drugs. POCT devices do not provide quantitative drug or metabolite information. POCT devices provide presumptive results only; a sample needs to be sent for confirmatory testing at a laboratory. Cutoffs employed by some POCT devices may not provide adequate sensitivity. Result interpretation may also be subjective, making performance operator-dependent (Melanson, 2009).

Considerations for Selecting POCT Devices

Matrices. POCT devices should be FDA approved and usually CLIA-waived to test urine, breath (for alcohol), and oral fluid for substances of abuse. None are available yet for hair, sweat, or blood for drugs of abuse, although some POCT devices do exist for therapeutic drugs in blood or blood products. POCTs for urine remain the most commonly used, despite advances in testing of other matrices. Cutoff levels, cross-reactivity, and other possible interferences have been studied more for POCT urinalysis than for any other matrix (Watson et al., 2006). Most POCT devices are used in an environment that is external to a clinical laboratory.

Regulatory Issues. The use of POCTs is covered by two Federal regulations. The Medical Devices Act requires that all in vitro medical diagnostic devices be evaluated and cleared for use by FDA for commercial distribution before use with patients. CLIA regulates the use of POCTs and requires that medical diagnostic tests and devices be used only in laboratories that meet CLIA standards and are certified to perform those specific tests. However, tests may be waived from CLIA regulatory oversight if they meet certain requirements, primarily if they are simple to use and interpret and have a low error risk.

Practitioners should be aware of the following specific requirements when considering using a POCT device:

- **FDA approval**. FDA has cleared several point-of-care devices for testing drugs of abuse. The FDA Center for Devices and Radiological Health provides information on test categorization and approval or clearance of testing devices (http://www.fda.gov/MedicalDevices/default.htm).
- **Waived tests.** A testing device may have been cleared by FDA for commercial distribution, but may not have been CLIA waived. FDA maintains a list of currently waived tests (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCLIA/testswaived.cfm). POCT manufacturers will also state whether a test is waived by CLIA.
- **Certificate of waiver**. All sites performing waived tests must have a CLIA-waiver certificate and adhere to the manufacturer's instructions for performing the test. Facilities or physicians' offices performing waived tests must enroll in CLIA, pay the applicable fee, and follow the manufacturer's instructions. An explanation of the procedures to obtain a CLIA certificate is available at http://www.cms.hhs.gov/CLIA/08_Certificate_of_%20Waiver_Laboratory_Project.asp.
- **State regulatory issues**. Many States have their own regulations regarding POCTs that practitioners or their designees must learn before they start to test.

Cost. The information on the economics of POCT for drugs and ethanol is limited, although cost issues should be important in deciding to initiate a point-of-care drug-testing program. The fixed unit price of POCTs often exceeds those of laboratory-based test methods. However, the cost of devices also depends in large part on the number of drugs included in the test panel, the difficulty in identifying the substances included in the panel, the number of devices ordered, and the volume of testing. Costs may vary according to location. In general, as the demand for POCTs grows, the cost per device decreases. In addition, the extra staff time and space to perform the test, staff training, quality assurance procedures, and documentation need to be taken into account when considering the cost. Then again, staff already collect specimens and perform POCTs to test for other conditions in many physician practices. These costs should be carefully reviewed prior to initiating POCT for drug testing.

Other Considerations. Practitioners should research the point-of-care devices being considered for use in terms of (Melanson, 2005):

- **Analytic performance**. Seemingly minor differences in sensitivity, specificity, and accuracy among the available POCT devices may or may not be clinically important and must be evaluated.
- **Cross-reactivity**. Some devices may not be able to distinguish between the substance being tested for and other chemically similar substances.
- **Validation studies**. Lot-specific evaluation information is usually summarized in package inserts, with more extensive verification documentation available on request. A POCT manufacturer may have additional credentials documenting that the testing device and the manufacturing processes meet quality control and quality assurance standards (e.g., certification by the International Organization for Standardization).
- **Ease of use**. Most POCT devices can be operated by an individual with little laboratory experience. However, some devices may entail following fairly complex instructions for use, which can contribute to human errors that will affect test results. Even test operators with technical or scientific backgrounds can make errors using these devices because of lack of training or unfamiliarity with new devices.
- **Ease of reading and interpreting the results**. Most devices require visual interpretation of a color response. Clear, distinguishable results are necessary for accurate interpretation. It is also necessary to know which substances will cross-react and produce a false-positive result (e.g., pseudoephedrine giving an "amphetamines" positive) or a false negative result (e.g., oxycodone and its active metabolite oxymorphone, both of which are opiates, giving a negative opiates result when either or both are present in the patient's specimen).
- **Quality assurance and control procedures**. Devices differ in the amount of time needed for staff to learn quality control procedures, such as completing documentation to ensure adherence to the manufacturer's instructions for maintenance (if any) and assay of the appropriate control specimens at the required intervals. Maintenance and quality control procedures also must meet CLIA, State, and local regulations. Positive and negative quality control samples must be included to verify accurate testing, but the frequency of analysis of quality control is dependent upon State regulations or regulatory agency.
- **Laboratory testing for verification**. It is suggested that a percentage (i.e., 5 percent) of specimens that screen negative or positive be sent to a laboratory to verify accurate performance of POCT results, and that all positive results that are contested by patients be submitted to a laboratory for confirmation testing.

Implementing Point-of-Care Testing

Based on surveys of sites holding CLIA waivers, Howerton, Anderson, Bosse, Granade, and Westbrook (2005) suggest that practitioners consider the following questions when deciding whether to use any type of POCT device:

- Who will manage and be accountable for testing oversight? Can this person receive the appropriate training?
- Are there sufficient personnel to conduct testing?
- How will testing affect workflow?
- How will staff be trained to conduct a POCT?
- Can the site adequately comply with Federal, State, and local regulations regarding the POCT?
- What are the safety considerations for both personnel and patients?

- Can personnel reasonably follow quality control procedures?
- Does the site meet physical requirements for testing (e.g., space for collection, testing, storage, security)?
- What are the benefits and costs of POCTs to the practitioner?
- How will testing records be maintained? What written documentation is needed?
- What are the plans for quality control testing and quality assurance?

Preparing Clinical and Office Staffs for Testing

Once a practitioner has decided which matrices and types of tests to use, the clinical and office staffs need to be prepared to begin testing. Preparation may include:

- Obtaining a CLIA waiver;
- Developing written policies and procedures for testing, including ongoing staff training, and establishing quality control procedures;
- Developing and implementing testing protocols, including guidelines for specimen collection, use of POCT, confirmatory testing, and laboratory technical assistance;
- Establishing confidentiality safeguards;
- Training staff in use of the selected POCT devices and in collecting specimens for laboratory testing;
- Establishing recordkeeping procedures;
- Preparing appropriate storage sites for completed POCTs and laboratory tests; and
- Arranging pickup or transportation for laboratory tests.

Preparing a Specimen Collection Site

The collection site is a designated area where a patient provides the specimen for a drug test. Collection of most specimen matrices does not require special arrangements. Urine collection in primary care settings needs to be configured for privacy while a patient provides a specimen if direct observations are not required. Water for drinking needs to be available in the event the patient cannot provide sufficient urine (shy bladder). In substance abuse treatment and workplace testing, measures need to be taken to prevent adulteration or substitution, such as putting a bluing agent in the toilet, not providing access to soap and water in the collection room, and directly observing specimen provision. These actions are needed in clinical situations only if adulteration or substitution is suspected. Once specimens are collected and labeled, there must be space and proper conditions for securely and appropriately storing them. A refrigerator is a convenient, appropriate storage place, especially when samples are picked up by a laboratory courier on a daily or less frequent basis.

Substance Abuse and Mental Health Services Administration. (2012).
Clinical drug testing in primary care. Technical Assistance Publication (TAP) 32. HHS Publication No. SMA 12-4668.
Rockville, MD: Substance Abuse and Mental Health Services Administration.

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