NATIONAL HIGHWAY TRAFFIC SAFETY ADMINISTRATION

Drugs and Human Performance Fact Sheets

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16. Abstract

A panel of international experts on drug-impaired driving met in Seattle during August 2000 to review developments in the field of drugs and human performance over the last 10 years; to identify the specific effects that both illicit and prescription drugs have on driving; and to develop guidance for others when dealing with drug-impaired driving problems. Delegates represented the fields of psychopharmacology, behavioral psychology, drug chemistry, forensic toxicology, medicine, and law enforcement experts trained in the recognition of drug effects on drivers in the field.

These Fact Sheets represent the conclusions of the Panel and include the state of current scientific knowledge in the area of drugs and human performance for the 16 drugs selected for evaluation. The selected drugs include over-the-counter medications such as dextromethorphan and diphenhydramine; prescription medications such as carisoprodol, diazepam and zolpidem; and abused and/or illegal drugs such as cocaine, GHB, ketamine, LSD, marijuana, methadone, methamphetamine, MDMA, morphine, PCP and toluene.

Keyword continuation: illicit and licit drugs and traffic safety, drugs and driving, drug-impaired driving.

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Carisoprodol, cocaine, dextromethorphan, diazepam, diphenhydramine, GHB,ketamine, LSD, marijuana,methadone, methamphetamine,MDMA, morphine, PCP, toluene, zolpidem,	

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Introduction

The use of psychoactive drugs followed by driving has been an issue of continual concern to law enforcement officers, physicians, attorneys, forensic toxicologists and traffic safety professionals in the U.S. and throughout the world. At issue are methods for identifying the impaired driver on the road, the assessment and documentation of the impairment they display, the availability of appropriate chemical tests, and the interpretation of the subsequent results. A panel of international experts on drug-related driving issues met to review developments in the field of drugs and human performance over the last 10 years; to identify the specific effects that both illicit and prescription drugs have on driving; and to develop guidance for others when dealing with drug-impaired driving problems.

This publication is based on the deliberations of the International Consultative Panel on Drugs and Driving Impairment held in Seattle, WA in August 2000. This meeting was sponsored by the National Safety Council, Committee on Alcohol and other Drugs; the State of Washington Traffic Safety Commission; and the National Highway Traffic Safety Administration. Delegates represented the fields of psychopharmacology, behavioral psychology, drug chemistry, forensic toxicology, medicine, and law enforcement experts trained in the recognition of drug effects on drivers in the field. The Fact Sheets reflect the conclusions of the Panel and have been designed to provide practical guidance to toxicologists, pharmacologists, law enforcement officers, attorneys and the general public on issues related to drug impaired driving.

Sixteen drugs were selected for review and include over-the-counter medications, prescription drugs, and illicit and/or abused drugs. The selected drugs are cannabis/marijuana, carisoprodol, cocaine, dextromethorphan, diazepam, diphenhydramine, gamma-hydroxybutyrate, ketamine, lysergic acid diethylamide, methadone, methamphetamine/amphetamine, methylenedioxymethamphetmaine, morphine/heroin, phencyclidine, toluene, and zolpidem.

The Fact Sheets are based on the state of current scientific knowledge and represent the conclusions of the panel. They have been designed to provide practical guidance to toxicologists, pharmacologists, law enforcement officers, attorneys and the general public to use in the evaluation of future cases. Each individual drug Fact Sheet covers information regarding drug chemistry, usage and dosage information, pharmacology, drug effects, effects on driving, drug evaluation and classification (DEC), and the panel's assessment of driving risks. A list of key references and recommended reading is also provided for each drug. Readers are encouraged to use the Fact Sheets in connection with the other cited impaired driving-related texts.

The information provided is uniform for all the Fact Sheets and provides details on the physical description of the drug, synonyms, and pharmaceutical or illicit sources; medical and recreational uses, recommended and abused doses, typical routes of administration, and potency and purity; mechanism of drug action and major receptor sites; drug absorption, distribution, metabolism and elimination data; blood and urine concentrations; psychological and physiological effects, and drug interactions; drug

effects on psychomotor performance effects; driving simulator and epidemiology studies; and drug recognition evaluation profiles. Each Fact Sheet concludes with general statements about the drugs' ability to impair driving performance. The authors strongly believe that all the above information needs to be taken into account when evaluating a drug.

Case interpretation can be complicated by a number of factors and one of the main limitations of the Fact Sheets is that they primarily relate to single drug use. Other factors which influence the risk of effects on driving for any drug include the dose, the dosage frequency, acute and residual effects, chronic administration, route of administration, the concentration of the drug at the site of action, idiosyncrasies of metabolism, drug tolerance or hypersensitivity, and the combined effects of the drug with other drugs or alcohol, to name but a few.

Individual Fact Sheets

Cannabis/Marijuana
Carisoprodol (and Meprobamate)
Cocaine
Dextromethorphan
Diazepam
Diphenhydramine
Gamma-Hydroxybutyrate (GHB, GBL, and 1,4-BD)
Ketamine
Lysergic acid diethylamide (LSD)
Methadone
Methamphetamine (and Amphetamine)
Methylenedioxymethamphetamine (MDMA, Ecstasy)
Morphine (and Heroin)
Phencyclidine (PCP)
Toluene
Zolpidem (and Zaleplon, Zopiclone)

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Disclaimer

The information contained in the Drugs and Human Performance Fact Sheets represents the views of the contributors and not necessarily those of their place of employment or the National Highway Traffic Safety Administration.

Cannabis / Marijuana (Δ^9-Tetrahydrocannabinol, THC)

Marijuana is a green or gray mixture of dried shredded flowers and leaves of the hemp plant *Cannabis sativa*. Hashish consists of resinous secretions of the cannabis plant. Dronabinol (synthetic THC) is a light yellow resinous oil.

Synonyms: Cannabis, marijuana, pot, reefer, buds, grass, weed, dope, ganja, herb, boom, gangster, Mary Jane, sinsemilla, shit, joint, hash, hash oil, blow, blunt, green, kilobricks, Thai sticks; Marinol®

Source: Cannabis contains chemicals called cannabinoids, including cannabinol, cannabidiol, cannabinolidic acids, cannabigerol, cannabichromene, and several isomers of tetrahydrocannabinol (THC). One of these isomers, Δ^9-THC, is believed to be responsible for most of the characteristic psychoactive effects of cannabis. Marijuana refers to the leaves and flowering tops of the cannabis plant; the buds are often preferred because of their higher THC content. Hashish consists of the THC-rich resinous secretions of the plant, which are collected, dried, compressed and smoked. Hashish oil is produced by extracting the cannabinoids from plant material with a solvent. In the U. S. , marijuana, hashish and hashish oil are Schedule I controlled substances. Dronabinol (Marinol®) is a Schedule III controlled substance and is available in strengths of 2.5, 5 or 10 mg in round, soft gelatin capsules.

Drug Class: *Cannabis/Marijuana*: spectrum of behavioral effects is unique, preventing classification of the drug as a stimulant, sedative, tranquilizer, or hallucinogen. *Dronabinol*: appetite stimulant, antiemetic.

Medical and Recreational Uses: *Medicinal*: Indicated for the treatment of anorexia associated with weight loss in patients with AIDS, and to treat mild to moderate nausea and vomiting associated with cancer chemotherapy. *Recreational*: Marijuana is used for its mood altering effects, euphoria, and relaxation. Marijuana is the most commonly used illicit drug throughout the world.

Potency, Purity and Dose: THC is the major psychoactive constituent of cannabis. Potency is dependent on THC concentration and is usually expressed as %THC per dry weight of material. Average THC concentration in marijuana is 1-5%, hashish 5-15%, and hashish oil ≥ 20%. The form of marijuana known as *sinsemilla* is derived from the unpollinated female cannabis plant and is preferred for its high THC content (up to 17% THC). Recreational doses are highly variable and users often titer their own dose. A single intake of smoke from a pipe or joint is called a hit (approximately 1/20th of a gram). The lower the potency or THC content the more hits are needed to achieve the desired effects; 1-3 hits of high potency sinsemilla is typically enough to produce the desired effects. In terms of its psychoactive effect, a drop or two of hash oil on a cigarette is equal to a single “joint” of marijuana. Medicinally, the initial starting dose of Marinol® is 2.5 mg, twice daily.

Route of Administration: Marijuana is usually smoked as a cigarette (‘joint’) or in a pipe or bong. Hollowed out cigars packed with marijuana are also common and are called

`. Joints and blunts are often laced with adulterants including PCP or crack cocaine. Joints can also be dipped in liquid PCP or in codeine cough syrup. Marijuana is also orally ingested.

Pharmacodynamics: THC binds to cannabinoid receptors and interferes with important endogenous cannabinoid neurotransmitter systems. Receptor distribution correlates with brain areas involved in physiological, psychomotor and cognitive effects. Correspondingly, THC produces alterations in motor behavior, perception, cognition, memory, learning, endocrine function, food intake, and regulation of body temperature.

Pharmacokinetics: Absorption is slower following the oral route of administration with lower, more delayed peak THC levels. Bioavailability is reduced following oral ingestion due to extensive first pass metabolism. Smoking marijuana results in rapid absorption with peak THC plasma concentrations occurring prior to the end of smoking. Concentrations vary depending on the potency of marijuana and the manner in which the drug is smoked, however, peak plasma concentrations of 100-200 ng/mL are routinely encountered. Plasma THC concentrations generally fall below 5 ng/mL less than 3 hours after smoking. THC is highly lipid soluble, and plasma and urinary elimination half-lives are best estimated at 3-4 days, where the rate-limiting step is the slow redistribution to plasma of THC sequestered in the tissues. Shorter half-lives are generally reported due to limited collection intervals and less sensitive analytical methods. Plasma THC concentrations in occasional users rapidly fall below limits of quantitation within 8 to 12 h. THC is rapidly and extensively metabolized with very little THC being excreted unchanged from the body. THC is primarily metabolized to 11-hydroxy-THC which has equipotent psychoactivity. The 11-hydroxy-THC is then rapidly metabolized to the 11-nor-9-carboxy-THC (THC-COOH) which is not psychoactive. A majority of THC is excreted via the feces (~65%) with approximately 30% of the THC being eliminated in the urine as conjugated glucuronic acids and free THC hydroxylated metabolites.

Molecular Interactions / Receptor Chemistry: THC is metabolized via cytochrome P450 2C9, 2C11, and 3A isoenzymes. Potential inhibitors of these isoenzymes could decrease the rate of THC elimination if administered concurrently, while potential inducers could increase the rate of elimination.

Blood to Plasma Concentration Ratio: 0.55

Interpretation of Blood Concentrations: It is difficult to establish a relationship between a person's THC blood or plasma concentration and performance impairing effects. Concentrations of parent drug and metabolite are very dependent on pattern of use as well as dose. THC concentrations typically peak during the act of smoking, while peak 11-OH THC concentrations occur approximately 9-23 minutes after the start of smoking. Concentrations of both analytes decline rapidly and are often < 5 ng/mL at 3 hours. Significant THC concentrations (7 to 18 ng/mL) are noted following even a single puff or hit of a marijuana cigarette. Peak plasma THC concentrations ranged from 46-188 ng/mL in 6 subjects after they smoked 8.8 mg THC over 10 minutes. Chronic users can have mean plasma levels of THC-COOH of 45 ng/mL, 12 hours after use; corresponding

THC levels are, however, less than 1 ng/mL. Following oral administration, THC concentrations peak at 1-3 hours and are lower than after smoking. Dronabinol and THC-COOH are present in equal concentrations in plasma and concentrations peak at approximately 2-4 hours after dosing.

It is inadvisable to try and predict effects based on blood THC concentrations alone, and currently impossible to predict specific effects based on THC-COOH concentrations. It is possible for a person to be affected by marijuana use with concentrations of THC in their blood below the limit of detection of the method. Mathematical models have been developed to estimate the time of marijuana exposure within a 95% confidence interval. Knowing the elapsed time from marijuana exposure can then be used to predict impairment in concurrent cognitive and psychomotor effects based on data in the published literature.

Interpretation of Urine Test Results: Detection of total THC metabolites in urine, primarily THC-COOH-glucuronide, only indicates prior THC exposure. Detection time is well past the window of intoxication and impairment. Published excretion data from controlled clinical studies may provide a reference for evaluating urine cannabinoid concentrations; however, these data are generally reflective of occasional marijuana use rather than heavy, chronic marijuana exposure. It can take as long as 4 hours for THC-COOH to appear in the urine at concentrations sufficient to trigger an immunoassay (at 50ng/mL) following smoking. Positive test results generally indicate use within 1-3 days; however, the detection window could be significantly longer following heavy, chronic, use. Following single doses of Marinol®, low levels of dronabinol metabolites have been detected for more than 5 weeks in urine. Low concentrations of THC have also been measured in over-the-counter hemp oil products – consumption of these products may produce positive urine cannabinoid test results.

Effects: Pharmacological effects of marijuana vary with dose, route of administration, experience of user, vulnerability to psychoactive effects, and setting of use.
Psychological: At recreational doses, effects include relaxation, euphoria, relaxed inhibitions, sense of well-being, disorientation, altered time and space perception, lack of concentration, impaired learning and memory, alterations in thought formation and expression, drowsiness, sedation, mood changes such as panic reactions and paranoia, and a more vivid sense of taste, sight, smell, and hearing. Stronger doses intensify reactions and may cause fluctuating emotions, flights of fragmentary thoughts with disturbed associations, a dulling of attention despite an illusion of heightened insight, image distortion, and psychosis.
Physiological: The most frequent effects include increased heart rate, reddening of the eyes, dry mouth and throat, increased appetite, and vasodilatation.

Side Effect Profile: Fatigue, paranoia, possible psychosis, memory problems, depersonalization, mood alterations, urinary retention, constipation, decreased motor coordination, lethargy, slurred speech, and dizziness. Impaired health including lung damage, behavioral changes, and reproductive, cardiovascular and immunological effects have been associated with regular marijuana use. Regular and chronic marijuana smokers may have many of the same respiratory problems that tobacco smokers have (daily cough

and phlegm, symptoms of chronic bronchitis), as the amount of tar inhaled and the level of carbon monoxide absorbed by marijuana smokers is 3 to 5 times greater than among tobacco smokers. Smoking marijuana while shooting up cocaine has the potential to cause severe increases in heart rate and blood pressure.

Duration of Effects: Effects from smoking cannabis products are felt within minutes and reach their peak in 10-30 minutes. Typical marijuana smokers experience a high that lasts approximately 2 hours. Most behavioral and physiological effects return to baseline levels within 3-5 hours after drug use, although some investigators have demonstrated residual effects in specific behaviors up to 24 hours, such as complex divided attention tasks. Psychomotor impairment can persist after the perceived high has dissipated. In long term users, even after periods of abstinence, selective attention (ability to filter out irrelevant information) has been shown to be adversely affected with increasing duration of use, and speed of information processing has been shown to be impaired with increasing frequency of use. Dronabinol has an onset of 30-60 minutes, peak effects occur at 2-4 hours, and it can stimulate the appetite for up to 24 hours.

Tolerance, Dependence and Withdrawal Effect: Tolerance may develop to some pharmacological effects of dronabinol. Tolerance to many of the effects of marijuana may develop rapidly after only a few doses, but also disappears rapidly. Marijuana is addicting as it causes compulsive drug craving, seeking, and use, even in the face of negative health and social consequences. Additionally, animal studies suggests marijuana causes physical dependence. A withdrawal syndrome is commonly seen in chronic marijuana users following abrupt discontinuation. Symptoms include restlessness, irritability, mild agitation, hyperactivity, insomnia, nausea, cramping, decreased appetite, sweating, and increased dreaming.

Drug Interactions: Cocaine and amphetamines may lead to increased hypertension, tachycardia and possible cardiotoxicity. Benzodiazepines, barbiturates, ethanol, opioids, antihistamines, muscle relaxants and other CNS depressants increase drowsiness and CNS depression. When taken concurrently with alcohol, marijuana is more likely to be a traffic safety risk factor than when consumed alone.

Performance Effects: The short term effects of marijuana use include problems with memory and learning, distorted perception, difficultly in thinking and problem-solving, and loss of coordination. Heavy users may have increased difficulty sustaining attention, shifting attention to meet the demands of changes in the environment, and in registering, processing and using information. In general, laboratory performance studies indicate that sensory functions are not highly impaired, but perceptual functions are significantly affected. The ability to concentrate and maintain attention are decreased during marijuana use, and impairment of hand-eye coordination is dose-related over a wide range of dosages. Impairment in retention time and tracking, subjective sleepiness, distortion of time and distance, vigilance, and loss of coordination in divided attention tasks have been reported. Note however, that subjects can often “pull themselves together” to concentrate on simple tasks for brief periods of time. Significant performance impairments are

usually observed for at least 1-2 hours following marijuana use, and residual effects have been reported up to 24 hours.

***Effects on Driving*:** The drug manufacturer suggests that patients receiving treatment with Marinol® should be specifically warned not to drive until it is established that they are able to tolerate the drug and perform such tasks safely. Epidemiology data from road traffic arrests and fatalities indicate that after alcohol, marijuana is the most frequently detected psychoactive substance among driving populations. Marijuana has been shown to impair performance on driving simulator tasks and on open and closed driving courses for up to approximately 3 hours. Decreased car handling performance, increased reaction times, impaired time and distance estimation, inability to maintain headway, lateral travel, subjective sleepiness, motor incoordination, and impaired sustained vigilance have all been reported. Some drivers may actually be able to improve performance for brief periods by overcompensating for self-perceived impairment. The greater the demands placed on the driver, however, the more critical the likely impairment. Marijuana may particularly impair monotonous and prolonged driving. Decision times to evaluate situations and determine appropriate responses increase. Mixing alcohol and marijuana may dramatically produce effects greater than either drug on its own.

DEC Category: Cannabis

DEC Profile: Horizontal gaze nystagmus not present; vertical gaze nystagmus not present; lack of convergence present; pupil size normal to dilated; reaction to light normal to slow; pulse rate elevated; blood pressure elevated; body temperature normal to elevated. Other characteristic indicators may include odor of marijuana in car or on subject's breath, marijuana debris in mouth, green coating of tongue, bloodshot eyes, body and eyelid tremors, relaxed inhibitions, incomplete thought process, and poor performance on field sobriety tests.

Panel's Assessment of Driving Risks: Low doses of THC moderately impair cognitive and psychomotor tasks associated with driving, while severe driving impairment is observed with high doses, chronic use and in combination with low doses of alcohol The more difficult and unpredictable the task, the more likely marijuana will impair performance.

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Carisoprodol (and Meprobamate)

Carisoprodol is a white, crystalline powder. Meprobamate is a white powder. Both are available in tablet form.

Synonyms: *Carisoprodol*: N-isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate; Soma®, Sodol®, Soprodol®, Soridol®. *Meprobamate*: Miltown®, Equanil®, Equagesic®, Meprospan®.

Source: Carisoprodol and meprobamate are available by prescription only. Carisoprodol itself is not a federally scheduled compound, while meprobamate is a Schedule IV drug. Soma® is available as a 350 mg strength round, white tablet; Soma® Compound is a 250 mg strength two-layered, white and light orange round tablet (also contains aspirin); and Soma® Compound with Codeine is a 250 mg strength two-layered, white and yellow oval tablet (also contains aspirin and codeine phosphate) and is a schedule III controlled substance. Miltown® is available as a 200 mg and 400 mg strength white tablet; Equanil® is a 200 mg and 400 mg strength tablet; and Equagesic® is a 200 mg strength two-layered, pink and yellow, round tablet (also contains aspirin).

Drug Class: *Carisoprodol*: muscle relaxant, CNS depressant; *Meprobamate*: antianxiety, CNS depressant.

Medicinal and Recreational Uses: Carisoprodol is a centrally acting skeletal muscle relaxant prescribed for the treatment of acute, musculoskeletal pain. Meprobamate is a major metabolite of carisoprodol, and is a CNS depressant in its own right, indicated for the management of anxiety disorders or for short-term treatment of anxiety symptoms. Use of these drugs begins with prescription for muscular pain or anxiety, and abuse develops for their sedative-hypnotic effects, resulting in increased dosage without medical advice, or continued use after pain or anxiety has subsided.

Potency, Purity and Dose: Carisoprodol is present as a racemic mixture. During treatment, the recommended dose of carisoprodol is for one 350 mg tablet taken three times daily and at bedtime (1400 mg/day). The usual dose for meprobamate is one 400 mg taken four times daily, or daily divided doses of up to 2400 mg. To control chronic pain, carisoprodol is often taken concurrently with other drugs, particularly opiates, benzodiazepines, barbiturates, and other muscle relaxants.

Route of Administration: Oral.

Pharmacodynamics: The pharmacological effects of carisoprodol appear to be due to the combination of the effects of carisoprodol and its active metabolite, meprobamate. Meprobamate is equipotent to carisoprodol. There is some evidence suggesting carisoprodol is a $GABA_A$ receptor indirect agonist with CNS chloride ion channel conductance effects. In animals, carisoprodol produces muscle relaxation by blocking interneuronal activity and depressing transmission of polysynaptic neurons in the descending reticular formation and spinal cord. It is unknown if this mechanism of action is also present in humans. In addition to the desired skeletal muscle relaxing effects,

carisoprodol and meprobamate produce weak anticholinergic, antipyretic and analgesic properties.

Pharmacokinetics: Carisoprodol is rapidly absorbed from the gastrointestinal tract and rapidly distributed throughout the CNS. Protein binding is approximately 60%. Carisoprodol is predominantly dealkylated to meprobamate in the liver, and to a lesser extent hydroxylated to hydroxycarisoprodol and hydroxymeprobamate, followed by conjugation and excretion. The half-life of carisoprodol is approximately 100 minutes. Some individuals have impaired metabolism of carisoprodol, and exhibit a half life of 2-3 times that in normal subjects. The half-life of meprobamate is many times longer, between 6 and 17 hours. As a result of the significantly longer half-life of meprobamate relative to carisoprodol, accumulation of meprobamate during chronic therapy may occur.

Molecular Interactions / Receptor Chemistry: The cytochrome P450 2C19 isoenzyme is responsible for the conversion of carisoprodol to meprobamate. Potential inhibitors of the 2C19 isoenzyme could decrease the rate of drug elimination if administered concurrently, while potential inducers of the 2C19 isoenzyme could increase the rate of elimination.

Blood to Plasma Concentration Ratio: Data not available for carisoprodol; 3.3 to 5.0 for meprobamate.

Interpretation of Blood Concentrations: Following therapeutic doses of carisoprodol, blood concentrations are typically between 1 and 5 mg/L for carisoprodol, and between 2 and 6 mg/L for meprobamate. A single oral dose of 350 mg carisoprodol produced average peak plasma concentrations of 2.1 mg/L carisoprodol at one hour, declining to 0.24 mg/L at 6 hours. Following a single oral dose of 700 mg, average peak plasma concentrations of carisoprodol were 3.5 mg/L at 45 minutes, and meprobamate concentrations of 4.0 mg/L were obtained in 220 minutes. A single oral dose of 700 mg carisoprodol has also produced peak plasma concentrations of 4.8 mg/L carisoprodol. Following administration of meprobamate in the treatment of anxiety, concentrations are typically around 10 mg/L, but can range between 3 and 26 mg/L. A single oral dose of 1200 mg meprobamate produced concentrations of 15.6 mg/L at 4 hours. Plasma meprobamate concentrations of greater than 100 mg/L have been associated with deep coma; light coma between 60 and 120 mg/L; and patients with levels below 50 mg/L are invariably conscious.

Interpretation of Urine Test Results: Both drugs are excreted into the urine and are likely be detectable for several days following cessation of use. Less than 1% of a single oral dose of carisoprodol is excreted unchanged in the 24 hour urine, with meprobamate accounting for 4.7% of the dose. Following administration of meprobamate, up to 11% of a single dose is excreted in the urine in 24 hours.

Effects:
Psychological: Dizziness, drowsiness, sedation, confusion, disorientation, slowed thinking, lack of comprehension, drunken behavior, obtunded, coma.

Physiological: CNS depression, nystagmus (becoming more evident as concentrations increase), loss of balance and coordination, sluggish movements, slurred speech, bloodshot eyes, ataxia, tremor, sleep disturbances.

Side Effect Profile: Agitation, tremor, paresthesia, irritability, depression, facial flushing, headache, vertigo, postural hypotension, fainting, weakness, loss of balance and coordination, impairment of visual accommodation, tachycardia, nausea, vomiting, and stomach upset. In abuse or overdose, subjects are consistently sedated and obtunded, frequently becoming comatose. Overdose symptoms may include shallow breathing, clammy skin, dilated pupils, weak and rapid pulse, paradoxical excitement and insomnia, convulsions, and possible death. Meprobamate overdose can produce drowsiness, ataxia, severe respiratory depression, severe hypotension, shock, heart failure, and death.

Duration of Effects: The effects of carisoprodol begin within 30 minutes of oral administration, and last for up to 4-6 hours. In overdose, coma may last from several hours to a day or more. Meprobamate has a much longer duration of effect than carisoprodol due to a much longer half-life.

Tolerance, Dependence and Withdrawal: Development of abuse and moderate physical and psychological dependence can occur with chronic use of both carisoprodol and meprobamate. Abrupt discontinuation of long-term use can be followed by mild withdrawal symptoms such as anxiety, abdominal cramps, insomnia, headache, nausea, vomiting, ataxia, tremor, muscle twitching, confusion, and occasionally chills, convulsions and hallucinations. Onset of withdrawal from meprobamate occurs within 12-48 hours following cessation of use, and can last a further 12-48 hours. Carisoprodol has been shown to produce cross-tolerance to barbiturates.

Drug Interactions: Alcohol enhances the impairment of physical abilities produced by carisoprodol, and increased sedation, extreme weakness, dizziness, agitation, euphoria and confusion may be observed. Alcohol also inhibits the metabolism of meprobamate and produces an additive depressant effect on the CNS that includes sleepiness, disorientation, incoherence and confusion. The concurrent administration of other centrally acting drugs such as opiates, benzodiazepines, barbiturates, and other muscle relaxants can contribute to impairment. Meprobamate may enhance the analgesic effects of other drugs.

Performance Effects: Very limited studies are available for carisoprodol, however, single oral doses of 700 mg have not been shown to affect psychomotor and cognitive tests within 3 hours of dosing, to a significant degree. In contrast, single doses of meprobamate are capable of causing significant performance impairment. Performance effects include impaired divided attention, impaired coordination and balance, slowed reflexes and increased reaction time. With chronic dosing of either drug, it is likely that decrements in psychomotor performance would be even more pronounced.

Effects on Driving: The drug manufacturer suggests patients should be warned that carisoprodol and meprobamate may impair the mental and/or physical abilities required

for the performance of potentially hazardous tasks, such as driving a motor vehicle. Reported signs of psychomotor and cognitive impairment in subjects found to be driving under the influence of carisoprodol/meprobamate include poor perception, impaired reaction time, slow driving, confusion, disorientation, inattentiveness, slurred or thick speech, slow responses, somnolence, lack of balance and coordination, unsteadiness, and difficulty standing, walking or exiting vehicles.

Logan et al., 2000 describes 21 driving under the influence cases where carisoprodol and/or meprobamate were the only drugs detected. The mean carisoprodol and meprobamate concentrations were 4.6 mg/L (range 0-15 mg/L) and 14.5 mg/L (range 1-36 mg/L), respectively. Signs of impairment were noted at blood concentrations as low as 1 mg/L of meprobamate, however, the most severe driving impairment and the most overt symptoms of intoxication occurred in drivers whose combined carisoprodol and meprobamate blood concentrations were greater than 10 mg/L. Signs consistent with CNS depression were typically observed, including poor balance and coordination, horizontal gaze nystagmus, slurred speech, dazed or groggy appearance, depressed reflexes, slow movements, disorientation to place and time, and a tendency to dose off or fall asleep. Many subjects were involved in accidents, and other observed driving behaviors included extreme lane travel and weaving, striking other vehicles and fixed objects, slow speed, and hit and run accidents where the subject appeared unaware they had hit another vehicle.

DEC Category: CNS depressant

DEC Profile: Horizontal gaze nystagmus present; vertical gaze nystagmus may be present in high doses; lack of convergence present; pupil size normal to dilated; reaction to light slow; pulse rate normal to down; blood pressure normal to down; body temperature normal to down. Other characteristic indicators may include slurred speech, drowsiness, disorientation, drunken behavior without the odor of alcohol, and poor performance on field sobriety tests.

Panel's Assessment of Driving Risks: A single therapeutic dose of carisoprodol is unlikely to cause significant performance impairment. However, single therapeutic doses of meprobamate and chronic doses of carisoprodol may produce moderate to severe impairment of psychomotor skills associated with safe driving.

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Cocaine

Cocaine hydrochloride is a white to light brown crystalline powder, shiny rather than dull in appearance. Cocaine base is white to beige in color; waxy/soapy to flaky solid chunks.

Synonyms: Methylbenzoylecgonine. *Cocaine hydrochloride*: coke, snow, flake, blow, cane, dust, shake, toot, nose candy, white lady. *Cocaine base*: crack, rock, free-base.

Source: Naturally derived CNS stimulant extracted and refined from the leaves of the coca plant (*Erythroxylon coca*), grown primarily in the Andean region of South America and to a lesser extent in India, Africa and Indonesia. The picked coca leaves are dried in the open air and then "stomped" as part of the process to extract the alkaloid, resulting in coca paste and eventually cocaine hydrochloride. It is illegal to possess and sell cocaine in the U.S. and cocaine is a Schedule II controlled substance. "Crack" is the street name given to cocaine that has been processed from cocaine hydrochloride. It is prepared by adding baking soda to aqueous cocaine hydrochloride and heating it until the free-base cocaine precipitates into small pellets. The mixture is cooled and filtered, and then the "rocks" are smoked in a crack pipe.

Drug Class: CNS stimulant, local anesthetic.

Medical and Recreational Uses: Minor use as a topical local anesthetic for ear, nose and throat surgery. Traditionally, the coca leaves are chewed or brewed into a tea for refreshment and to relieve fatigue. Recreationally, cocaine is used to increase alertness, relieve fatigue, feel stronger and more decisive, and is abused for its intense euphoric effects.

Potency, Purity and Dose: In ear, nose and throat surgery cocaine is commercially supplied as the hydrochloride salt in a 40 or 100 mg/mL solution. Depending on the demographic region, street purity of cocaine hydrochloride can range from 20-95%, while that of crack cocaine is 20-80%. The hydrochloride powder is often diluted with a variety of substances such as sugars for bulk (lactose, sucrose, inositol, mannitol), other CNS stimulants (caffeine, ephedrine, phenylpropanolamine), or other local anesthetics (lidocaine, procaine, benzocaine). Commonly abused doses are 10-120 mg. Repeated doses are frequently taken to avoid the dysphoric crash that often follows the initial intense euphoric effects. Cocaine is frequently used in combination with other drugs; injected with heroin ("speedball") or taken with alcohol to reduce irritability; smoked with phencyclidine ("tick"); and smoked in marijuana blunts ("turbo").

Route of Administration: Topically applied for use as a local anesthetic. Recreationally, coca leaves can be chewed, however, cocaine abusers typically smoke "crack" in a glass pipe or inject the hydrochloride salt intravenously. Cocaine hydrochloride can be smoked to some effect but this is very inefficient as the powder tends to burn rather than vaporize. Snorting (insufflation/intranasal) is also popular. Subcutaneous injection (skin-popping) is rarely used.

Pharmacodynamics: Cocaine is a strong CNS stimulant that interferes with the reabsorption process of catecholamines, particularly dopamine, a chemical messenger associated with pleasure and movement. Cocaine prevents the reuptake of dopamine by blocking the dopamine transporter which leads to increased extracellular dopamine, resulting in chronic stimulation of postsynaptic dopamine receptors. This results in the euphoric 'rush'. When dopamine levels subsequently fall, users experience a dysphoric 'crash'. Similarly, cocaine interferes with the uptake of norepinephrine and serotonin (5-HT), leading to accumulation of these neurotransmitters at postsynaptic receptors. As a local anesthetic, cocaine reversibly blocks the initiation and conduction of the nerve impulse. Cocaine additionally produces vasoconstriction and dilated pupils.

Pharmacokinetics: Cocaine is rapidly absorbed following smoking, snorting and intravenous administration. Bioavailability is 57% following snorting and ~70% following smoking. Cocaine is 91% bound in plasma. Cocaine is extensively metabolized to a variety of compounds: benzoylecgonine, ecgonine, and ecgonine methyl ester are the major metabolites and are centrally inactive. Benzoylecgonine is produced upon loss of the methyl group and is the major urinary metabolite. Norcocaine is a very minor metabolite, but is active and neurotoxic. Cocaethylene, formed following concurrent ingestion of cocaine and alcohol, is also active and is equipotent to cocaine in blocking dopamine reuptake. The apparent half-life for cocaine is short, approximately 0.8 ± 0.2 hours, while the half-life of benzoylecgonine is 6 hours.

Molecular Interactions / Receptor Chemistry: The cytochrome P450 3A4 isoenzyme is responsible for the N-demethylation of cocaine to norcocaine. Potential inhibitors of the 3A4 isoenzyme could decrease the rate of drug elimination if administered concurrently, while potential inducers could increase the rate of drug elimination. Cocaine itself is an inhibitor of the CYP2D6 isoform.

Blood to Plasma Concentration Ratio: averages ~ 1.0

Interpretation of Blood Concentrations: The presence of cocaine at a given blood concentration cannot usually be associated with a degree of impairment or a specific effect for a given individual without additional information. This is due to many factors, including individual levels of tolerance to the drug and artifactual changes in cocaine concentrations on storage. There is a large overlap between therapeutic, toxic and lethal cocaine concentrations and adverse reactions have been reported after prolonged use even with no measurable parent drug in the blood. Typical concentrations in abuse range from 0-1mg/L, however, concentrations up to 5mg/L and higher are survivable in tolerant individuals. After single doses of cocaine, plasma concentration typically average 0.2-0.4 mg/L. Repeated doses of cocaine may result in concentrations greater than 0.75 mg/L.

Following intranasal administration of 106 mg, peak plasma concentrations of cocaine averaged 0.22 mg/L at 30 minutes, while benzoylecgonine concentrations averaged 0.61 mg/L at 3 hours. Oral administration of 140 mg/70 kg cocaine resulted in peak plasma concentrations averaging 0.21 mg/L of cocaine at 1 hour. Single 32 mg intravenous doses of cocaine produced an average peak plasma concentration of 0.31 mg/L of cocaine within 5 minutes. Smoking 50 mg of cocaine base resulted in peak

plasma cocaine concentrations averaging 0.23 mg/L at ~ 45 minutes and 0.15 mg/L of benzoylecgonine at 1.5 hours.

Interpretation of Urine Test Results: Urinary excretion is less than 2% for unchanged cocaine, 26-39% for benzoylecgonine, and 18-22% for ecgonine methyl ester. 64-69% of the initial dose is recovered after 3 days. Very low concentrations of cocaine may be detected in urine during the initial few hours, however, benzoylecgonine persists in urine at detectable concentrations from 2-4 days. Chronic, heavy use of cocaine can result in detectable amounts of benzoylecgonine in urine for up to 10 days following a binge.

Effects:
Early phase – Psychological: Euphoria, excitation, feelings of well-being, general arousal, increased sexual excitement, dizziness, self-absorbed, increased focus and alertness, mental clarity, increased talkativeness, motor restlessness, offsets fatigue, improved performance in some simple tasks, and loss of appetite. Higher doses may exhibit a pattern of psychosis with confused and disoriented behavior, delusions, hallucinations, irritability, fear, paranoia, antisocial behavior, and aggressiveness.
Physiological: Increased heart rate and blood pressure, increased body temperature, dilated pupils, increased light sensitivity, constriction of peripheral blood vessels, rapid speech, dyskinesia, nausea, and vomiting.
Late phase - Psychological: Dysphoria, depression, agitation, nervousness, drug craving, general CNS depression, fatigue, insomnia. *Physiological*: Itching/picking/scratching, normal heart rate, normal pupils.

Side Effect Profile: Nervousness, restlessness, tremors, anxiety, and irritability. Chronic use may lead to personality changes, hyperactivity, psychosis, paranoia, and fear. Cocaine overdose can be characterized by agitation, enhanced reflexes, hostility, headache, tachycardia, irregular respiration, chills, nausea, vomiting, abdominal pain, rise in body temperature, hallucinations, convulsions, delirium, unconsciousness, seizures, stroke, cerebral hemorrhage, heart failure, and death from respiratory failure. Cocaine excited delirium is a syndrome often caused by excessive cocaine use, and is associated with a dissociative state, violence to persons and property, exaggerated strength, hyperthermia, cardiorespiratory arrest and sudden death.

Burnt lips and fingers from crack pipes are frequently seen, as are rashes and skin reddening from scratching. Smokers may suffer from acute respiratory problems including cough, shortness of breath, and severe chest pains with lung trauma and bleeding. Prolonged cocaine snorting can result in ulceration of the mucous membrane of the nose. The injecting drug user is at risk for transmitting or acquiring HIV infection/AIDS if needles or other injection equipment are shared.

Duration of Effects: The faster the absorption the more intense and rapid the high, but the shorter the duration of action. Injecting cocaine produces an effect within 15-30 seconds. A hit of smoked crack produces an almost immediate intense experience and will typically produce effects lasting 5-15 minutes. Similarly, snorting cocaine produces effects almost immediately and the resulting high may last 15-30 minutes. The effects

onset more slowly after oral ingestion (~1 hour). General effects will persist for 1-2 hours depending on the dose and late phase effects following binge use may last several days.

Tolerance, Dependence and Withdrawal Effects: Cocaine is a powerfully addictive drug of abuse and an appreciable initial tolerance to the euphoric high may develop. Cocaine is psychologically addicting, particularly with heavy or frequent use, and possibly physically addicting as well. The short duration of effects is one reason leading to probability of addition. As effects wear off, more drug is frequently administered and a pattern of repeated use occurs. Following binge use of cocaine, the "crash" can last from 9 hours to 4 days and may consist of agitation, depressed moods, insomnia to hypersomnolence, and initial drug craving. Withdrawal symptoms can typically last from 1-3 weeks and may consist of alternating low and high drug craving, low to high anxiety, paranoia, dysphoria, depression, apathy, irritability, disorientation, hunger, fatigue, bradycardia, and long periods of sleep.

Drug Interactions: The combined use of cocaine and ethanol forms cocaethylene in the body, a substance which intensifies cocaine's euphoric effects while possibly increasing the risk of sudden death. In laboratory studies, cocaine has been shown to partially reverse some of the adverse effects of alcohol, but may contribute to the detrimental effects of marijuana.

Performance Effects: Most laboratory-based studies have been limited by the low doses of cocaine that were allowed. At these single low doses, studies have shown performance enhancement in attentional abilities and increased behavioral and cortical arousal, but have no enhancement of effects on learning, memory, and other cognitive processes. Faster reaction times and diminished effects of fatigue have been observed. Improvements were greatest in behaviorally impaired subjects (e.g. sleep deprived, fatigued, or concurrent use of ethanol) and least improvements were observed in well-rested, healthy subjects. More deleterious effects are expected after higher doses, chronic ingestion and during drug withdrawal, and include agitation, anxiety, distress, inability to focus on divided attention tasks, inability to follow directions, confusion, hostility, time distortion, and poor balance and coordination. Laboratory studies have also demonstrated increased risk taking (rapid braking or steering) and deleterious effects on vision related to mydriasis. Self-reported increases in sensitivity to light, seeing halos around bright objects, flashes or movement of light in peripheral field, difficulty focusing, blurred vision, and glare recovery problems have been reported.

Effects on Driving: Observed signs of impairment in driving performance have included subjects speeding, losing control of their vehicle, causing collisions, turning in front of other vehicles, high-risk behavior, inattentive driving, and poor impulse control. As the effects of cocaine wear off subjects may suffer from fatigue, depression, sleepiness, and inattention. In epidemiology studies of driving under the influence cases, accidents, and fatally injured drivers, between 8-23% of subjects have had cocaine and/or metabolites detected in their blood. An examination of 253 fatally injured drivers in Wayne County, Michigan between 1996-1998, found that 10% of cases were positive for blood cocaine and/or metabolites. On review of accident and witness reports, aggressive

driving (high speed and loss of vehicle control) was revealed as the most common finding. Ethanol was detected in 56% of these cases, and all of these drivers lost control of their vehicles. In Memphis, Tennessee in 1993, 13% of 150 drivers stopped for reckless driving were determined to be driving under the influence of cocaine based on observations of behavior and appearance, performance on field sobriety tests, and positive urine cocaine tests.

A 25 year-old male driver, who made an improper turn against oncoming traffic, had a blood cocaine concentration of 0.04 mg/L and 0.06 mg/L of benzoylecgonine, 2 hours after the collision. A 30 year-old female caused an accident after failing to stop at a traffic light; the driver admitted to ingesting a large amount of cocaine ~ 2.5 hours prior to the collision, and 0.32 mg/L cocaine was detected in her blood 1 hour post accident.

DEC Category: CNS stimulant.

DEC Profile: Horizontal gaze nystagmus not present; vertical gaze nystagmus not present; lack of convergence not present; pupil size dilated; reaction to light slow; pulse rate elevated; blood pressure elevated; body temperature elevated. Other characteristic indicators may include excessive activity, increased alertness, talkativeness, irritability, argumentativeness, nervousness, body tremors, anxiety, redness to nasal area and runny nose.

Panel's Assessment of Driving Risks: Single low doses of cocaine may improve mental and motor performance in persons who are fatigued or sleep deprived, however, cocaine does not necessarily enhance the performance of otherwise normal individuals. Cocaine may enhance performance of simple tasks but not complex, divided-attention tasks such as driving. Most laboratory studies have been limited by the low single doses of cocaine administered to subjects. At these low doses, most studies showed performance enhancement in attentional abilities but no effect on cognitive abilities. Significant deleterious effects are expected after higher doses, chronic ingestion, and during the crash or withdrawal phase.

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Dextromethorphan

Dextromethorphan is a white powder. Available primarily in tablet, capsule and liquid form.

Synonyms: 3-methoxy-17-methyl-9α, 13α, 14 α-morphinan hydrobromide monohydrate; dextromethorphan hydrobromide, DXM, "robbo tripping"; Anaplex-DM®, Diabe-Tuss DM™, Benylin®, Pertussin®, Delsym®, Sucrets®, Bromfed-DM®, Robitussin®, Vicks Formula 44, etc.

Source: Synthetic analog of codeine and *d*-isomer of 3-methoxy-N-methymorphinan. Available as lozenges, capsules, tablets, and cough syrups, in a variety of prescription medications and over-the-counter cough and cold remedies. Products contain dextromethorphan alone or in combination with guaifenesin, brompheniramine, pseudoephedrine, phenylephrine, promethazine, codeine, acetaminophen, and/or chlorpheniramine. For example, Diabe-Tuss DM™ syrup contains 15 mg dextromethorphan; Benylin® Adult and Pediatric contain 15 mg and 7.5 mg dextromethorphan, respectively; and Anaplex-DM® contains 30 mg dextromethorphan, 4 mg brompheniramine and 60 mg pseudoephedrine.

Drug Class: Non-opioid antitussive, cough suppressant, CNS depressant (in high doses).

Medical and Recreational Uses: Used as an antitussive for temporary relief of coughs caused by minor throat and bronchial irritation. Recreationally used for effects ranging from mild stimulation and intoxication, to dissociation.

Potency, Purity and Dose: As an antitussive, the recommended dosage for adults and children aged 12 years and older is 60-120 mg daily in divided doses; for children aged 6-12 years, 30-60 mg daily in divided doses; and for children aged 2-6 years, 15-30 mg daily in divided doses. Each brand contains different quantities of dextromethorphan, generally 20-30 mg per dose, and the majority contain other drugs as previously mentioned. Approximate recreational doses are: threshold dose 80-90 mg; light 100-200 mg; common 200-400 mg; strong 400-600; and heavy dose 600-1500 mg.

Route of Administration: Oral.

Pharmacodynamics: Dextromethorphan acts centrally to elevate the threshold for coughing, and has no significant analgesic or sedative properties at antitussive doses. It is proposed that dextromethorphan is a glutamate and NMDA antagonist, and blocks the dopamine reuptake site. It may also increase $5HT_{1A}$ activity possibly via NMDA antagonism.

Pharmacokinetics: Dextromethorphan is rapidly absorbed from the gastrointestinal tract and peak plasma concentrations are reached in approximately 2.5 hours. Dextromethorphan is widely distributed, and is rapidly and extensively metabolized by the liver. Dextromethorphan is demethylated to dextrorphan, an active metabolite, and to

3-methoxymorphinan and 3-hydroxymorphinan. It is primarily excreted as unchanged parent drug and dextrorphan.

Molecular Interactions / Receptor Chemistry: The cytochrome P450 2D6 isoenzyme is responsible for the conversion of dextromethorphan to dextrorphan; and P450 3A4 and 3A5 isoenzymes are responsible for converting dextromethorphan to 3-methoxymorphinan and 3-hydroxymorphinan. Potential inhibitors of these isoenzymes could decrease the rate of dextromethorphan elimination if administered concurrently, while potential inducers could increase the rate of elimination.

Blood to Plasma Concentration Ratio: Data not available.

Interpretation of Blood Concentrations: A single 20 mg oral dose of dextromethorphan produced peak concentrations of 1.8 ng/mL in serum after 2.5 hours. Chronic oral dosing of 120 mg daily, in divided doses, resulted in peak plasma dextromethorphan concentrations of 0.5-5.9 ng/mL (mean 2.4 ng/mL) in extensive metabolizers, and 182-231 ng/mL (mean 207 ng/mL) in poor metabolizers.

Interpretation of Urine Test Results: In a 24 hour period, less than 2.5% of a dose is excreted unchanged in the urine, while up to 30% of the conjugated dextrorphan is excreted.

Effects: At recommended doses, dextromethorphan produces little or no CNS depression. At recreational doses, positive effects may include acute euphoria, elevated mood, dissociation of mind from body, creative dream-like experiences, and increased perceptual awareness. Other effects include disorientation, confusion, pupillary dilation, and altered time perception, visual and auditory hallucinations, and decreased sexual functioning. Recreational doses of approximately 100-200 mg have a mild, stimulant effect (likened to MDA); doses of 200-500 mg produce a more intoxicating effect (likened to being 'drunk and stoned'); 500-1000 mg may result in mild hallucinations and a mild dissociate effect (likened to a low dose of ketamine) and an overall disturbance in thinking, senses and memory; while doses over 1000 mg may produce a fully dissociative effect (likened to a high dose of ketamine). Recreationally abused doses are capable of impairing judgment, memory, language, and other mental performances.

Side Effect Profile: Adverse effects with recommended antitussive doses are rare. However, nausea, other gastrointestinal disturbances, slight drowsiness and dizziness can occur. Following acute doses of between 250-1500 mg, the following clinical and overdose symptoms have been reported: excitation, nausea, vomiting, drowsiness, dizziness, blurred vision, nystagmus, dilated pupils, body itching, rash, ataxia, sweating, hot/cold flashes, fever, hypertension, shallow respiration, urinary retention, diarrhea, opisthotonos (spasm where head and heels are bent back, and torso is bent forward), toxic psychosis (hyperactivity, marked visual and auditory hallucinations), coma, and an increase in heart rate, blood pressure and body temperature. Side effects can be serious if very large doses of the combined preparations are ingested; for example, guaifenesin and

dextromethorphan can cause severe nausea and vomiting; chlorpheniramine and dextromethorphan can cause seizure, loss of consciousness and bleeding.

Duration of Effects: Dextromethorphan exerts its antitussive effects within 15-30 minutes of oral administration. The duration of action is approximately 3-6 hours with conventional dosage forms.

Tolerance, Dependence and Withdrawal Effects: At recommended antitussive doses, addiction does not occur. Mild psychological dependence and depression may occur with regular use of increased doses. Abrupt discontinuation of higher doses may produce insomnia, dysphoria and depression. Poor metabolizers of dextromethorphan have been shown to tolerate lower doses of the drug compared to extensive metabolizers, and report greater sedation, dysphoria and psychomotor impairment. Preliminary evidence also suggests that extensive metabolizers may report a greater dextromethorphan abuse potential due to the increased rate of metabolism to the active metabolite dextrorphan.

Drug Interactions: Should not be taken with Monoamine Oxide Inhibitors (MAOIs) and Selective Serotonin Reuptake Inhibitors (SSRIs) because of an apparent serotonin syndrome (fever, hypertension, arrhythmias). Should be used with caution in atopic children due to histamine release. Additive CNS depressant effects when co-administered with alcohol, antihistamines, psychotropics, and other CNS depressant drugs.

***Performance Effects*:** Minimal at therapeutic levels, however, with high doses one can expect gross cognitive and psychomotor impairment.

***Effects on Driving*:** Little to no effect at therapeutic levels, however with high doses one could expect significant impairment. The drug manufacturer states that the combined preparation of promethazine and dextromethorphan may cause marked drowsiness or impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle. Patients should be told to avoid engaging in such activities until it is known that they do not become drowsy or dizzy. Similar effects could be seen with other combined dextromethorphan preparations.

DEC Category: CNS depressant

DEC Profile: Data not available; however, the profile for a CNS depressant is: horizontal gaze nystagmus present; vertical gaze nystagmus present at high doses; lack of convergence present; pupil size normal to dilated; reaction to light slow; pulse rate down; blood pressure down; body temperature normal. Such effects are more likely to be seen following recreational doses of dextromethorphan.

Panel's Assessment of Driving Risks: Minimal to no risk at therapeutic levels. Potentially mild to moderate driving risk with higher recreational use.

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Diazepam

Diazepam is a colorless, crystalline compound. Available primarily in tablet or liquid form.

Synonyms: 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one; Valium®, Valrelease®, Vazepam®, Diaz Intensol®, Diastat®, Dizac®.

Sources: Diazepam is a Schedule IV controlled substance and is available by prescription in tablet, gel and injectable form. Valium® tablets are white (2 mg), yellow (5 mg) or blue (10 mg) round tabs with a cut out "V" design. Valium® Injectable is available in 5 mg/mL strength liquid.

Drug Class: Tranquilizer, sedative, CNS depressant.

Medical and Recreational Uses: Used medicinally in the management of anxiety disorders, as an adjunct for the relief of skeletal muscle spasm and for convulsive disorders/status epilepticus, and as a minor tranquilizer or sedative. Also used to suppress or dampen acute alcohol withdrawal, and anxiety-related gastrointestinal disorders such as stress ulcers. Diazepam is used recreationally as a sedative or to enhance the effects of alcohol or opioids. For example, administration of diazepam 30 minutes after a dose of oral methadone reportedly produces an augmented high. Diazepam is used by cocaine users to increase seizure threshold and by heroin users to enhance the effects of heroin, and by both of these users to reduce the impact of withdrawal symptoms between doses.

Potency, Purity and Dose: Commonly prescribed doses of Valium® are 5-40 mg daily. For anxiety, 2-10 mg is taken twice to four times daily; for alcohol withdrawal symptoms 10 mg is taken three to four times daily. For the injectable form, 2-20 mg is administered intramuscularly or intravenously. Street doses may consist of several tablets administered at once.

Route of Administration: Usually oral, but intravenous injection is possible after preparing a solution from crushed tablets. Commercially available liquid Valium® can be injected, and gel forms can be rectally administered.

Pharmacodynamics: Diazepam is a 1,4-benzodiazepine, which binds with high affinity to the $GABA_A$ receptor in the brain to reduce arousal and to affect emotions. Diazepam's action causes an increase in affinity of the major inhibitory neurotransmitter, GABA. GABA binds mainly to the α subunit while diazepam binds to the β subunit. The γ subunit is also essential for modulation of chloride transport by benzodiazepines. Diazepam increases chloride transport through ion-channels and ultimately reduces the arousal of the cortical and limbic systems in the CNS. Diazepam depresses the electrical after-discharge in the amygdala and hippocampus regions of the limbic system that affect emotions.

Pharmacokinetics: Diazepam is rapidly absorbed. Oral bioavailability is approximately 100%, and close to 99% is bound in plasma. The half-life of diazepam is 43±13 hours,

but ranges from 40-100 hours if the contribution from active metabolites is included. Diazepam is metabolized to nordiazepam which is an active metabolite with a half-life of 40-99 hours. Temazepam and oxazepam are minor active metabolites of diazepam. Diazepam is excreted in urine mainly as oxazepam conjugate (~33 %), and temazepam conjugate, with only traces of diazepam and nordiazepam.

Molecular Interactions / Receptor Chemistry: Diazepam is demethylated to nordiazepam via P450 2C19 and 3A4; and 3-hydroxylation to temazepam and oxazepam occurs via P450 3A4. Potential inhibitors of 2C19 and 3A4 could decrease the rate of diazepam elimination if administered concurrently, while potential inducers of these isoenzymes could increase the rate of elimination.

Blood to Plasma Concentration Ratio: 0.55 and 0.70 reported; 0.59 for nordiazepam.

Interpretation of Blood Concentrations: Simple interpretation of blood concentrations without any knowledge of drug-taking history is ill advised. Given changing responses with repeated use and variability in response, blood concentrations will not provide a good indication of likely behavioral effects. Additionally, the long half-life of diazepam may cause accumulation to occur with repeated use. Blood concentrations may be several-fold higher after chronic use compared to single use, and there are significant increases in blood levels in the elderly

Therapeutic blood concentrations typically range from 0.1-1.0 mg/L. Single oral doses of 10 mg result in diazepam concentrations of 0.2-0.6 mg/L at 0.5-2 hours, while chronic doses of 30 mg produce steady state diazepam concentrations of 0.7-1.5 mg/L and nordiazepam concentrations of 0.35-0.53 mg/L. Plasma concentrations of 0.3-0.4 mg/L are recommended for anxiolytic effects, and > 0.6 mg/L for control of seizures. Higher concentrations might suggest misuse or abuse.

Interpretation of Urine Test Results: Urine concentrations of metabolites are detectable for several days to weeks after last use. Urinary excretion of unchanged drug is less than 1%.

Effects: At low doses, diazepam is a moderate tranquilizer, causing sleepiness, drowsiness, confusion, and some loss of anterograde memory. At high doses, excitement, disinhibition, severe sedation, and effects on respiration occur, particularly if respiration is impaired by other drugs or by disease. Diazepam can produce a state of intoxication similar to that of alcohol, including slurred speech, disorientation, and drunken behavior.

Side Effect Profile: Side effects may include dry mouth, blurred or double vision, headache, vertigo, urinary retention, excessive perspiration, nausea and vomiting, ataxia, tremor, depression, hypotension and diminished reflexes. The elderly are more likely to develop significant adverse CNS effects from the use of diazepam. In overdose, paradoxical reactions of anxiety, insomnia, stimulation, hallucination, and acute hyperexcited state may occur. Shallow breathing, clammy skin, dilated pupils, weak and rapid pulse, coma, and death are possible.

Duration of Effects: Dose-dependent, however, with therapeutic doses onset of effects occurs within 30 minutes and significant effects can last for 12-24 hours.

Tolerance, Dependence and Withdrawal Effects: Regular use will produce tolerance to most of the sedative and adverse effects, but tolerance may not occur for the anxiolytic benefits of diazepam. Tolerance may take several weeks or months to develop depending on dose and frequency of administration. Diazepam is capable of causing mild physical and psychological dependence and is regarded as having a significant abuse potential. Abstinence or abrupt withdrawal may produce excitement, restlessness, dysphoria, anxiety, apprehension, fearfulness, dizziness, headache, muscle stiffness, tremors, insomnia, and sensitivity to light and sound. More severe symptoms may include intense rebound nausea, vomiting, abdominal cramps, delirium, hallucinations, hyperthermia, sweating, panic attacks, confusional or paranoid psychoses, tachycardia, increased blood pressure, and occasionally seizures or convulsions.

Drug Interactions: Other benzodiazepines, alcohol, phenothiazines, narcotic analgesics, barbiturates, MAOI's, and other CNS depressants may potentiate action of diazepam. Alcohol enhances such effects as drowsiness, sedation, and decreased motor skills, and can also exacerbate the memory impairing effects of diazepam. Cimetidine delays clearance of diazepam. Valproate may potentiate the CNS depressant effects. Theophylline has an antagonistic action to some of the deleterious effects of diazepam.

Performance Effects*:* Laboratory studies have shown that single doses of diazepam (5-20 mg) are capable of causing significant performance decrements, with maximal effect occurring at approximately 2 hour post dose, and lasting up to at least 3-4 hours. Decreases in divided attention, increases in lane travel, slowed reaction time (auditory and visual), increased braking time, decreased eye-hand coordination, and impairment of tracking, vigilance, information retrieval, psychomotor and cognitive skills have been recorded. Lengthened reaction times have been observed up to 9.5 hours post dose. Lethargy and fatigue are common, and diazepam increases subjective perceptions of sedation. Such performance effects are likely to be exacerbated in the elderly. In drug users, diazepam has greater behavioral changes, including subjects' rating of liking and decrements in psychomotor and cognitive performance. Reduced concentration, impaired speech patterns and content, and amnesia can also be produced, and diazepam may produce some effects that may last for days. Laboratory studies testing the effect of ethanol on subjects already using benzodiazepines demonstrate further increases in impairment of psychomotor and other driving skills, compared to either drug alone.

Effects on Driving: The drug manufacturer suggests patients treated with diazepam be cautioned against engaging in hazardous occupations requiring complete mental alertness such as driving a motor vehicle. Simulator and driving studies have shown that diazepam produces significant driving impairment over multiple doses. Single doses of diazepam can increase lateral deviation of lane control, reduce reaction times, reduce ability to perform multiple tasks, decrease attention, adversely effect memory and cognition, and increase the effects of fatigue. Significant impairment is further increased when diazepam is combined with low concentrations of alcohol (0.05 g/100 mL). A number of

epidemiological studies have been conducted to evaluate the risk of crashes associated with the use of diazepam and other benzodiazepines. These show a range of relative risk, but most demonstrate increases in risk compared to drug free drivers. These increases have been twice to several fold. The elderly may have an increased risk of a motor vehicle crash.

DEC Category: CNS depressant

DEC Profile: Horizontal gaze nystagmus present; vertical gaze nystagmus present in high doses; lack of convergence present; pupil size normal; reaction to light slow; pulse rate down; blood pressure down; body temperature normal. Other characteristic indicators may include behavior similar to alcohol intoxication without the odor of alcohol, staggering and stumbling, lack of balance and coordination, slurred speech, disorientation, and poor performance on field sobriety tests.

Panel's Assessment of Driving Risks: The incidences of diazepam in drivers involved in road crashes and in drivers suspected of being under the influence, suggest an adverse effect of diazepam on road safety. Data are available to demonstrate that single therapeutic doses of diazepam can significantly impair psychomotor skills associated with safe driving, with some effects still observable the morning after a nighttime dose.

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Diphenhydramine

Diphenhydramine is a white, crystalline powder. Available primarily in tablet, capsule and liquid form.

Synonyms: 2-(diphenylmethoxy)-N,N-dimethylethylamine hydrochloride; diphenhydramine hydrochloride; Benadryl®, Unisom® Sleepgels, Dytuss®, Dramamine®.

Source: Available in capsules, tablets, chewable tablets, syrups, elixirs, topical, and injectable forms in a variety of prescription and over-the-counter medications. Products contain diphenhydramine alone or in combination with other drugs such as pseudoephedrine and acetaminophen. Diphenhydramine is also an ingredient in several Tylenol® (i.e., acetaminophen) preparations. Dimenhydrinate (Dramamine®) is a combination of diphenhydramine and 8-chlorotheophylline in equal molecular proportions.

Drug Class: Antihistamine, antiemetic, sleep aid, sedative, CNS depressant.

Medical and Recreational Uses: Used as an antihistamine for the temporary relief of seasonal and perennial allergy symptoms. Diphenhydramine is also used as a sleep aid and a cough suppressant, and has been used as a centrally acting antitussive although the mechanism for this action is unclear. Dramamine is used as a prophylaxis against and for the treatment of motion sickness.

Potency, Purity and Dose: As an antihistamine, recommended doses for adults is 25-50 mg diphenhydramine every 6-8 hours, not to exceed 50-100 mg every 4-6 hours. For children, 12.5-25 mg three or four times daily is recommended. As a sleep aid the dose is 50 mg at bedtime. Adults can be given 10-50 mg intravenously or intramuscularly, up to a maximum daily dose of 400 mg.

Route of Administration: Oral, injected, and topical applications.

Pharmacodynamics: Diphenhydramine is a first generation antihistamine and is a H_1 receptor antagonist. Antagonism is achieved through blocking the effect of histamine more than blocking its production or release. Diphenhydramine inhibits most responses of smooth muscle to histamine and the vasoconstrictor effects of histamine. The antagonism may also produce anticholinergic effects, antiemetic effects, and significant sedative side effects.

Pharmacokinetics: Following oral administration diphenhydramine is well absorbed from the gastrointestinal tract, is widely distributed throughout the body, and is able to pass though the blood-brain barrier. The oral availability is 61%, and 78% is bound in plasma. Peak plasma concentrations are reached in 2-3 hours. Diphenhydramine is metabolized to nordiphenhydramine (active metabolite), dinordiphenhydramine, and diphenylmethoxyacetic acid. The plasma half-life is 8.5±3.2 hours; shorter and longer

half-lives have been reported for children and elderly subjects, respectively. Urinary excretion of unchanged diphenhydramine is 1.9%.

Molecular Interactions / Receptor Chemistry: Diphenhydramine is metabolized via cytochrome P450 2D6 isoenzyme. Potential inhibitors of P450 2D6 could decrease the rate of drug elimination if administered concurrently, while potential inducers could increase the rate of drug elimination.

Blood to Plasma Concentration Ratio: 0.77 and 0.82 reported.

Interpretation of Blood Concentrations: Following a single oral dose of 50 mg, average peak plasma concentrations of 83 ng/mL diphenhydramine were detected at 3 hours, declining to 9 ng/mL by 24 hours. A single oral 100 mg dose resulted in average peak plasma concentrations of 112 ng/mL at 2 hours post dose. Effective antihistamine concentrations are greater than 25 ng/mL, drowsiness can be observed at 30-40 ng/mL, and mental impairment may be observed with concentrations above 60 ng/mL.

Interpretation of Urine Test Results: Less than 2% of an oral dose is excreted in the 24 hour urine as unchanged parent drug, while approximately 11% is eliminated as its glucuronide conjugate.

Effects: First generation H_1 antagonists can both stimulate and depress the CNS. Stimulation results in restlessness, nervousness and inability to sleep, while depressive effects include diminished alertness, slowed reaction time and somnolence. Diphenhydramine is particularly prone to cause marked sedation. Drowsiness, reduced wakefulness, altered mood, impaired cognitive and psychomotor performance may also be observed.

Side Effect Profile: Includes agitation, anticholinergic side effects such as dry mouth, confusion, dizziness, drowsiness, fatigue, disturbed coordination, irritability, paresthesia, blurred vision, and depression. In overdose, symptoms may include excitement, ataxia, tremor, sinus tachycardia, fever, hallucination, athetosis, convulsions or seizures, hypotension, deep coma, cardiorespiratory collapse, and death. Fixed and dilated pupils are also observed. Gastrointestinal symptoms are less with diphenhydramine than with other H_1 antagonists.

Duration of Effects: Dose-dependent, however, following oral administration of therapeutic doses, peak plasma concentrations are reached in 2-3 hours and effects usually last 4-6 hours.

Tolerance, Dependence and Withdrawal Effects: Some tolerance may develop to the sedative effects of diphenhydramine with repeated oral dosing. No reported dependence or withdrawal effects with doses recommended.

Drug Interactions: Effects of diphenhydramine are increased by the presence of alcohol, MAOI's, diazepam, hypnotics, sedatives, tranquilizers, and other CNS

depressants. Alcohol enhances such effects as drowsiness, sedation and decreased motor skills. These decrements in effect are more pronounced in the elderly.
MAOI's prolong and intensify the anticholinergic effects of diphenhydramine.

***Performance Effects*:** All first generation antihistamines, including diphenhydramine, have been demonstrated to diminish cognitive and psychomotor performance in healthy volunteers. Impairment might even be of greater clinical significance in patients when the allergic disorder per se adversely affects CNS function, as suggested in studies in which a reduction in cognitive functioning in patients was exacerbated by diphenhydramine. Laboratory studies have shown diphenhydramine to decrease alertness, decrease reaction time, induce somnolence, impair concentration, impair time estimation, impair tracking, decrease learning ability, and impair attention and memory within the first 2-3 hours post dose. Significant adverse effects on vigilance, divided attention, working memory, and psychomotor performance have been demonstrated. It is important to note that impairment has been shown to occur even in the absence of self-reported sleepiness or sedation. Concurrent use of diazepam and diphenhydramine caused significant performance decrements at 2 hours, and to some degree up to 4 hours.

***Effects on Driving*:** The drug manufacturer states that patients should be warned about engaging in activities requiring mental alertness such as driving a car. Diphenhydramine has repeatedly been shown to severely impair tracking and reaction time performance in actual on-the-road driving tests. Single doses of 50 mg have been shown to cause significant impairment during a 90 km highway test (measuring vehicle following, constant speed and lateral position). In contrast, single 25-100 mg doses caused no significant driving effects during a short 15 minute driving test. Using the Iowa Driving Simulator, Weiler et al, 2000 compared the effects of a single oral dose of 50 mg diphenhydramine to the effects corresponding to a blood alcohol concentration of 0.1 g/100 mL. Diphenhydramine caused significantly less coherence (ability to maintain a constant distance) and impaired lane keeping (steering instability and crossing center line) compared to alcohol. Overall driving performance was the poorest after taking diphenhydramine, and participants were most drowsy after taking diphenhydramine (before and after testing). The authors concluded that diphenhydramine clearly impairs driving performance, and may have an even greater impact than does alcohol on the complex task of operating a motor vehicle.

***DEC Category*:** CNS depressant

***DEC Profile*:** Data not available; however, the profile for a CNS depressant is: horizontal gaze nystagmus present; vertical gaze nystagmus present at high doses; lack of convergence present; pupil size normal; reaction to light slow; pulse rate normal; blood pressure normal; body temperature normal. Diphenhydramine may produce dilated pupils.

Panel's Assessment of Driving Risks: Single therapeutic doses of diphenhydramine have been shown to significantly impair psychomotor performance during the first 4 hours, and may have a greater impact on driving performance than alcohol.

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Gamma-Hydroxybutyrate (GHB, GBL, and 1,4-BD)

GHB is a clear liquid, or a white powder with a soap-like texture. Precursor drugs such as gamma-butyrolactone (GBL) and 1,4 butanediol (1,4-BD) are clear liquids.

Synonyms:

GHB: Sodium oxybate, Xyrem® oral solution; liquid X, liquid XTC, salt water, scoop, soap, grievous bodily harm, georgia home boy, G, G-caps, easy lay, everclear, vita G, degreaser + lye, smart drug, gamma-OH, Somatomax.

GBL: 2(3)-furanone dihydro; Blue Nitro, G3, Invigorate, Jolt, ReActive, REMForce, RenewTrient, Rest-eze, Revivarant, Verve, V35.

1,4-BD: tetramethylene glycol; Amino Flex, Enliven, FX, GHRE, Inner G, NRG3, Pine Needle Extract, Revitalize, Serenity, SomatoPro, Thunder Nectar, Zen.

Source: GHB was first synthesized in 1960 as an experimental GABA analog, and was classified as a food and dietary supplement and sold in health food stores in early 1990. It was available in tablet, capsule and liquid forms. In late 1990, the FDA banned over-the-counter sales of GHB in the U. S. In 1999, the FDA issued warnings on the dangers of its precursor drugs GBL and 1,4-BD. In early 2000, GHB was federally reclassified as a Schedule 1 controlled substance. GBL and 1,4-BD are not scheduled, however, GBL is classified as a list 1 chemical and a controlled substance analog, while 1,4-BD is listed as a controlled substance analog. GHB can be clandestinely made and the ingredients are available in kit form over the internet. GHB is made from GBL and a base (e.g. lye/NaOH), the mixture is heated, and vinegar is added to reduce the pH. Acetone can then be added and the mixture dried, resulting in GHB powder. GBL and 1,4-BD are commercially available as industrial solvents and are used as ingredients in cleaners, solvents, paint removers, and engine degreasers. They are also sold as "natural supplements" over the internet, and in some health food stores and gymnasiums, and are marketed as natural, non-toxic dietary supplements.

Drug Class: CNS depressant, sedative, anesthetic.

Medical and Recreational Uses: In Europe, GHB is used as an anesthetic adjunct and hypnotic agent, used to treat narcolepsy, and used to suppress symptoms of alcohol-dependence and opiate withdrawal syndrome. In the U. S., medically formulated sodium oxybate (Xyrem®) has been approved as a Schedule III controlled substance for the treatment of cataplexy (sudden loss of muscle tone associated with narcolepsy). Recreationally, GHB is used for its intoxicating effects (euphoria, reduced inhibitions, sedation), and by bodybuilders as an alternative to anabolic steroids. GBL and 1,4-BD rapidly convert to GHB within the human body following oral administration and are taken as GHB substitutes. They are marketed as anti-aging drugs, for weight loss, to treat insomnia, anxiety and depression, and as mood enhancers and energizers.

Potency, Purity and Dose: Clinical doses for alcohol withdrawal syndrome are 25-50 mg/kg every 12 hours (1.7-3.5 g/70 kg); sleep induction 20-30 mg/kg (1.5-2.25 g/70 kg); prolonged deep sleep 75-100 mg/kg (5-7 g/70 kg); and anesthetic induction greater than 100 mg/kg (> 7 g/70 kg). Illicit manufacture often introduces impurities and wide

variations in potency. Recreational use of GHB often involves doses well in excess of one teaspoon (~2.5 g, or 35 mg/kg in a 70 kg adult) of the powder dissolved in water/alcohol, or one capful of liquid GHB, GBL, or 1,4-BD; such doses far exceed therapeutic doses. Chronic use can consist of dosing every few hours, around the clock, for months to years. Up to 100 g GHB has been reportedly used by an individual in one day. GHB and its precursor drugs are often used in combination with alcohol, MDMA, marijuana, methamphetamine, and cocaine.

Route of Administration: Oral, intravenous.

Pharmacodynamics: GHB is a naturally occurring compound present in both mammalian CNS and peripheral tissue. It is also a minor metabolite and precursor of the major inhibitory neurotransmitter GABA. GHB is also the pharmacologically active form of both GBL and 1,4-BD. GHB has weak agonist activity at $GABA_B$ receptors and there appears to be a distinct GHB receptor site in the brain. GHB dose-dependently alters dopaminergic activity; at sub-anesthetic doses there is an initial excitation of dopamine neurons producing elevated levels of synaptic dopamine; at anesthetic doses GHB blocks impulse flow from dopamine neurons resulting in a build-up of dopamine in the nerve terminals. GHB mimics natural physiological sleep, enhances REM sleep, and increases stage 3 and 4 of slow-wave sleep. GHB decreases alcohol consumption and intensity of withdrawals. Beyond the CNS effects, GHB has significant cardiovascular pharmacology, causing bradycardia and dysregulation of blood pressure (hyper- and hypotension). Interestingly, GHB causes a detectable increase in growth hormone and prolactin concentrations with doses as small as 3 g, and this is the basis for its use in body building despite there being no evidence of an actual increase in body mass.

Pharmacokinetics: Oral doses are rapidly absorbed from the gastrointestinal tract and exhibit first pass metabolism. Absorption is capacity limited (an increase in dose results in increased time to peak concentration). There is an increased rate of absorption of GHB on an empty stomach leading to a decreased time to peak concentration and an increased concentration. Accumulation is not known to occur following repeated doses. GHB readily crosses the blood-brain barrier and placental barrier, and is distributed in the brain, cerebrospinal fluid, vitreous, liver, and kidney. The dose-response curve is steep, and a large between and within subject variability is noted. GHB is rapidly eliminated and has a half-life of 27 minutes (range 20-53 minutes) which appears to increase with higher doses, a sign of zero order or saturation kinetics. GHB is metabolized to succinic semialdehyde (SSA) via GHB-dehydrogenase, then to succinic acid via SSA-dehydrogenase. GBL is metabolized to GHB via lactonase; while 1,4-BD is first metabolized to γ-hydroxybutyraldehyde via alcohol dehydrogenase, then to GHB via aldehyde dehydrogenase.

Molecular Interactions / Receptor Chemistry: Metabolism via cytochrome P450 isoenzymes has not been described.

Blood to Plasma Concentration Ratio: 1.2 (N=1)

Interpretation of Blood Concentrations: Peak plasma concentrations are observed at 20-45 minutes. Due to rapid elimination, GHB is undetectable in plasma or blood after 6-8 hours. Following single oral doses of 25 mg/kg GHB in 10 alcoholic dependant patients, mean peak plasma GHB concentrations were 54 mg/L (24-88 mg/L). Single oral doses of 12.5, 25, and 50 mg/kg in 8 healthy subjects produced mean peak plasma GHB concentrations of 23, 46 and 80 mg/L, respectively. Single oral doses of 26-52 mg/kg in 6 narcoleptic patients resulted in mean peak plasma GHB concentrations of 63 mg/L (30-102 mg/L). The same doses were administered to the same subjects 4 hours later, and the mean peak GHB concentrations obtained were 91 mg/L (47-125 mg/L). An intravenous dose of 50 mg/kg in an adult produced a peak blood GHB concentration of approximately 170 mg/L within 15 minutes. Patients presenting to an emergency department with GHB overdose/intoxication, had blood GHB concentrations ranging from 29-432 mg/L (mean 118 mg/L; N = 54).

Although GHB is naturally present in the human body, endogenous blood GHB concentrations are typically well below 1 mg/L in living subjects. In contrast, endogenous postmortem production of GHB can occur, and concentrations of up to 170 mg/L GHB have been reported in non-GHB using subjects. In postmortem analysis the analysis of multiple specimens such as vitreous and urine is recommended.

Interpretation of Urine Test Results: Peak urine concentrations are observed within 4 hours of administration and GHB is undetectable in urine after 10-12 hours. Endogenous concentrations of up to ~7 mg/L GHB have been detected in urine of non-GHB using subjects. It is suggested that a cut-off for urinary GHB be set at 10 mg/L. Similarly, in postmortem urine specimens from non-GHB using subjects, urine concentrations of GHB are typically below 10 mg/L.

Effects:
Psychological: At low doses, effects are similar to those seen with alcohol. Effects include relaxation, reduced inhibitions, euphoria, confusion, dizziness, drowsiness, sedation, inebriation, agitation, combativeness, and hallucinations.
Physiological: Nausea, vomiting, profuse sweating, somnolence, visual disturbances, nystagmus, loss of peripheral vision, short-term amnesia, uncontrolled shaking or seizures, bradycardia, hypothermia, suppression of gag reflex, respiratory depression, and transient or unarousable unconsciousness.

Side Effect Profile: Disorientation, sweating, vomiting, incontinence, apnea, severe ataxia, sinus bradycardia, twitching, seizure-like activity and hypothermia. In overdose, symptoms may include severe respiratory depression, mild acute respiratory acidosis, sinus bradycardia or sinus tachycardia, suppression of gag reflex, acute delirium, combativeness, unarousable unconsciousness, coma, and patients often need to be intubated. Deaths have been reported following overdose from GHB, GBL and 1,4-BD alone, and in combination with other drugs.

Duration of Effects: Onset of effects occurs within 10-20 minutes, peak plasma concentrations are achieved within 20-45 minutes, and effects generally last 2-5 hours. Complete recovery from GHB overdose can occur within 3-6 hours. Sleep induction time

is shortest with GBL and longest with 1,4-BD, as GBL is more lipophilic and is absorbed faster. There is a longer duration of effect following 1,4-BD ingestion as it metabolizes more slowly to GHB than does GBL.

***Tolerance, Dependence and Withdrawal Effects*:** Tolerance can develop to GHB with chronic abuse and even following chronic treatment. Subjects do not become tolerant to all the effects (e.g. tolerance does not develop to the enhanced sleep that GHB produces). Cross-tolerance exists between GHB and ethanol. Severe physical and psychological addiction occurs with chronic abuse. Clinical presentation of withdrawal may include mild clinical anxiety, confusion, agitation, tremor, muscular cramps, insomnia, combativeness, delirium, delusions, paranoia with hallucinations (auditory, tactile and visual), tachycardia, hypotension, and an occasional schizophrenic-like state. The withdrawal syndrome can start as early as 1-2 hours after the last dose in addicted individuals.

Drug Interactions: Potential additive effects between GHB and other sedating CNS depressants, including alcohol, antidepressants, antipsychotics, antihistamines and muscle relaxants. In rats, ethanol has significant synergistic effects on the sedative, behavioral and toxic effects of GHB, GBL and 1,4-BD. Ethanol also delays the conversion of 1,4-BD to GHB, because both 1,4-BD and ethanol utilize alcohol-dehydrogenase in their metabolic pathways. Several drugs have been shown to inhibit GHB-dehydrogenase and it is not known clinically what effects these drugs would have if administered concurrently. These drugs include valproate, ethosuximide, salicylate, amobarbital, phenytoin, disulfiram and cyanide.

Performance Effects: Oral GHB doses of 1-2 g have been shown not to deteriorate reactive, attentive and co-ordination skills related to driving, nor increase the effects of low dose alcohol. Similarly, oral doses of 12.5-25 mg/kg GHB had no effect on attention, vigilance, alertness, short-term memory or psychomotor coordination; although dizziness or dullness were experienced in 50-66% of subjects. It is important to note, however, that doses used in laboratory studies to date have been well below both recreational and abused doses of GHB.

Effects on Driving: Signs of behavioural effects and impaired performance have been reported in several driving case reports. In 13 driving under the influence cases where GHB was detected, the reported symptoms were generally those of a CNS depressant. The subjects were typically stopped because of erratic driving, such as weaving, ignoring road signs, and near-collisions. Common signs of impairment included confusion and disorientation, incoherent speech, short-term memory loss, dilated pupils, lack of balance and unsteady gait, poor coordination, poor performance of field sobriety tests, copious vomiting, unresponsiveness, somnolence, and loss of consciousness. GHB concentrations in blood specimens collected between 1-3.5 hours of the arrest ranged from 26-155 mg/L (median 95 mg/L). In another 11 cases of driving under the influence of GHB, concentrations of GHB in blood and urine specimens ranged from 81-360 mg/L and 780-2380 mg/L, respectively. Circumstances of their arrest, observed driving behavior and signs of impairment were similar to the previous study. Other reported symptoms have

included dizziness, drowsiness, agitation, loss of peripheral vision, slow responses, slow and slurred speech, and transient unconsciousness.

DEC Category: CNS depressant

DEC Profile: Horizontal gaze nystagmus present; vertical gaze nystagmus present in high doses; lack of convergence present; pupil size generally dilated; reaction to light slow; pulse rate normal; blood pressure normal; body temperature generally down. Other characteristic indicators include vomiting, sweating, slurred speech, somnolence or transient unconsciousness, poor balance and coordination, and poor performance on field sobriety tests. Note that while pulse rate and blood pressure may decrease after GHB ingestion, both parameters may be elevated during drug withdrawal.

Panel's Assessment of Driving Risks: Given the ability of GHB to induce sleep and unconsciousness, recreational use of GHB or its precursor drugs have the potential to produce moderate to severe driving impairment.

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Ketamine

Ketamine is a white, crystalline powder or clear liquid.

***Synonyms*:** (+/-)-2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone; Ketalar®, Ketaject®, Ketaset®, Vetalar®; K, Special K, Vitamin K, Lady K, Jet, Super Acid, Bump, Special LA Coke, KitKat, Cat Valium.

***Source*:** Available by prescription only, and is commercially available as a veterinary anesthetic. It is difficult to synthesize clandestinely and is usually stolen from veterinarian offices or diverted from legitimate pharmaceutical sources in liquid form. Ketamine is currently a schedule III controlled substance in the US.

***Drug Class*:** Dissociative anesthetic, hallucinogen, psychotomimetic.

***Medical and Recreational Uses*:** Primarily used in veterinary applications as a tranquilizer. Also used as an anesthetic induction agent for diagnostic and surgical procedures in humans, prior to the administration of general anesthetics. Occasionally used as a short-acting general anesthetic for children and elderly patients. Recreationally used as a psychedelic and for its dissociative effects.

***Potency, Purity and Dose*:** Ketamine is available as a racemic mixture with the S-(+)- isomer being more potent than the R-(-)- isomer. Commercially supplied as the hydrochloride salt in 0.5 mg/mL and 5 mg/mL ketamine base equivalents. For induction of 5-10 minutes surgical anesthesia, a dose of 1.0-4.5 mg/kg is intravenously administered; 6.5-13 mg/kg is given intramuscularly for 12-25 minutes of surgical anesthesia. The liquid from injectable solutions can be gently heated to evaporate the water, leaving a white powder (ketamine hydrochloride) which can be snorted or orally ingested. Recreational doses are highly variable. Common doses are 25-50 mg intramuscularly, 30-75 mg snorting, and 75-300 mg oral. Snorting a small line ("bump", 30-50 mg) usually results in a dreamy effect. "K-hole" can be obtained following a dose of 60-125 mg intramuscularly, or by snorting 100-250 mg. Impurities are rarely seen, although ketamine hydrochloride itself can be used as a heroin adulterant.

***Route of Administration*:** Injected, snorted, orally ingested, and rectally administered. Similar to phencyclidine (PCP), ketamine can be added to tobacco or marijuana cigarettes and smoked.

***Pharmacodynamics*:** Involves analgesia, anesthetic and sympathomimetic effects that are mediated by different sites of action. Non-competitive NMDA receptor antagonism is associated with the analgesic effects; opiate receptors may contribute to analgesia and dysphoric reactions; and sympathomimetic properties may result from enhanced central and peripheral monoaminergic transmission. Ketamine blocks dopamine uptake and therefore elevates synaptic dopamine levels. Inhibition of central and peripheral cholinergic transmission could contribute to induction of the anesthetic state and hallucinations. Ketamine is structurally similar to PCP, but 10-50 times less potent in blocking NMDA effects.

Pharmacokinetics: Bioavailability following an intramuscular dose is 93%, intranasal dose 25-50%, and oral dose 20±7%. Ketamine is rapidly distributed into brain and other highly perfused tissues, and is 12% bound in plasma. The plasma half-life is 2.3 ± 0.5 hours. Oral administration produces lower peak concentrations of ketamine, but increased amounts of the metabolites norketamine and dehydronorketamine. Ketamine and its metabolites undergo hydroxylation and conjugation. Norketamine produces effects similar to those of ketamine. There are no significant differences between the pharmacokinetic properties of the S-(+) and R-(-)-isomers.

***Molecular Interaction / Receptor Chemistry*:** Cytochrome P450 3A4 is the principal enzyme responsible for ketamine N-demethylation to norketamine, with minor contributions from CYP2B6 and CYP2C9 isoforms. Potential inhibitors of these isoenzymes could decrease the rate of ketamine elimination if administered concurrently, while potential inducers could increase the rate of elimination

***Blood to Plasma Concentration Ratio*:** Data not available.

***Interpretation of Blood Concentrations*:** There is no direct correlation between ketamine concentrations and behavior. Drowsiness, perceptual distortions and intoxication may be dose related in a concentration range of 50 to 200 ng/mL, and analgesia begins at plasma concentrations of about 100 ng/mL. During anesthesia, blood ketamine concentrations of 2000-3000 ng/mL are used, and patients may begin to awake from a surgical procedure when concentrations have been naturally reduced to 500-1000 ng/mL.

Interpretation of Urine Test Results: Urinary excretion of unchanged drug is 4±3%, and ketamine use can be detected in urine for about 3 days. Concentration ranges for ketamine in urine have been reported as low as 10 ng/mL and up to 25,000 ng/mL.

***Effects*:** Users have likened the physical effects of ketamine to those of PCP, and the visual effects to LSD.
Psychological: Decreased awareness of general environment, sedation, dream-like state, vivid dreams, feelings of invulnerability, increased distractibility, disorientation, and subjects are generally uncommunicative. Intense hallucinations, impaired thought processes, out-of-body experiences, and changes in perception about body, surroundings, time and sounds. Delirium and hallucinations can be experienced after awakening from anesthesia.
Physiological: Anesthesia, cataplexy, immobility, tachycardia, increased blood pressure, nystagmus, hypersalivation, increased urinary output, profound insensitivity to pain, amnesia, slurred speech, and lack of coordination.

***Side Effect Profile*:** High incidence of adverse effects, including anxiety, chest pain, palpitations, agitation, rhabdomyolysis, flashbacks, delirium, dystonia, psychosis, schizophenic-like symptoms, dizziness, vomiting, seizures, and paranoia.

Duration of Effects: Onset of effects is within seconds if smoked, 1-5 minutes if injected, 5-10 minutes if snorted and 15-20 minutes if orally administered. Effects generally last 30-45 minutes if injected, 45-60 minutes if snorted, and 1-2 hours following oral ingestion. Ketamine is often readministered due to its relatively short duration of action. Some subjects may experience dreams 24 hours later. Marked dissociative effects, schizotypal symptoms and impaired semantic memory are found in some recreational users days after drug use.

Tolerance, Dependence and Withdrawal Effects: In long-term exposure, high tolerance, drug craving, and flashbacks are described. Little evidence of a physiological withdrawal syndrome unless abrupt discontinuation in chronic users.

Drug Interactions: Midazolam attenuates altered perception and thought processes. Lorazepam may decrease ketamine-associated emotional distress but does not decrease cognitive or behavioral effects of ketamine. Acute administration of diazepam increases the half-life of ketamine. Lamotrigine significantly decreases ketamine-induced perceptual abnormalities, but increases the mood elevating effects. Haloperidol may decrease impairment by ketamine in executive control functions, but does not affect psychosis, perceptual changes, negative schizophrenic-like symptoms, or euphoria. Alfentanil is additive to ketamine in decreasing pain and increasing cognitive impairment. Physostigmine and 4-aminopyridine can antagonize some pharmacodynamic effects of ketamine.

***Performance Effects*:** Broad spectrum of cognitive impairments and marked dissociative effects. Increased distractibility and intensely visual or polysensual hallucinations. Impairment of immediate and delayed recall, and verbal declarative memory. Memory impairment is associated with encoding or retrieval processes, and not accounted for by decreased attention. Impaired language function, failure to form and use memory traces of task relevant information. Overall decreased awareness, increased reaction time, distorted perceptions of space, non-responsiveness, and blurred vision. The S-(+) isomer impairs psychomotor function 3-5 times more than the R-(-) isomer.

***Effects on Driving*:** The drug manufacturer suggests that patients should be cautioned that driving an automobile should not be undertaken for 24 hours or more following anesthesia. No driving studies have been performed.

***DEC Category*:** Phencyclidine.

***DEC Profile*:** Horizontal gaze nystagmus present; vertical gaze nystagmus present; lack of convergence present; pupil size normal; reaction to light normal; pulse rate elevated; blood pressure elevated; body temperature elevated. Other characteristic indicators may include rigid muscles, cyclic behavior, and lack of response to painful stimuli.

***Panel's Assessment of Driving Risks*:** The use of ketamine is not conceivably compatible with the skills required for driving due to its moderate to severe psychomotor, cognitive, and residual effects.

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Lysergic acid diethylamide (LSD)

LSD is a white powder or a clear, colorless liquid.

Synonyms: *d*-lysergic acid diethylamide; acid, animal, barrels, beast, blotter, 'cid, dots, kool aid, LSD-25, lysergide, microdots, panes, sandoz, tabs, trips, white lightning, window panes.

***Source*:** LSD is manufactured from lysergic acid which occurs naturally in the ergot fungus that grows on wheat and rye. It is a Schedule I controlled substance, available in liquid, powder, tablet (microdots), and capsule form. The liquid is often applied to blotter paper squares (frequently with colorful designs), stickers, sugar cubes, candy, or soda crackers. LSD is also available in dropper bottles or in the form of gelatin sheets/shapes (window panes).

***Drug Class*:** Hallucinogen, psychedelic, psychotomimetic.

***Medical and Recreational Uses*:** No medicinal use. Recreationally used as a hallucinogen and for its ability to alter human perception and mood.

***Potency, Purity and Dose*:** The strength of illicit LSD nowadays ranges from 20 to 80 µg per dose, which is considerably less than doses reported during the 1960s and early 1970s, of 100-200 µg or higher per unit. Experienced users typically administer 100-200 µg for a "good high". The potency of liquid LSD in dropper bottles may vary because the liquid is water based.

***Route of Administration*:** Primarily oral administration, but can be inhaled, injected, and transdermally applied.

Pharmacodynamics: LSD is primarily a non-selective 5-HT agonist. LSD may exert its hallucinogenic effect by interacting with 5-HT_{2A} receptors as a partial agonist and modulating the NMDA receptor-mediated sensory, perceptual, affective and cognitive processes. LSD mimics 5-HT at 5-HT_{1A} receptors, producing a marked slowing of the firing rate of serotonergic neurons.

Pharmacokinetics: LSD has a plasma half-life of 2.5-4 hours. Metabolites of LSD include N-desmethyl-LSD, hydroxy-LSD, 2-oxo-LSD, and 2-oxo-3-hydroxy-LSD. These metabolites are all inactive.

***Molecular Interactions / Receptor Chemistry*:** Metabolism via cytochrome P450 isoenzymes has not been described.

***Blood to Plasma Concentration Ratio*:** Data not available.

Interpretation of Blood Concentrations: Threshold toxic dose in humans has been reported with 100-200 µg with associated blood concentrations of 2-30 ng/mL. Intravenous doses of 1-2 µg /kg have been associated with blood concentrations of 1-5

ng/mL LSD. Single oral doses of 160 µg resulted in peak plasma concentrations of up to 9 ng/mL LSD.

Interpretation of Urine Test Results: LSD use can typically be detected in urine for periods of 2-5 days. In a reported case of LSD intoxication, a concentration of 11 ng/mL of LSD was detected in the urine. In subjects receiving 200-400 µg of LSD, concentrations in urine ranged from 1-55 ng/mL.

***Effects*:** Effects are unpredictable and will depend on the dose ingested, the user's personality and mood, expectations and the surroundings.
Psychological: Hallucinations, increased color perception, altered mental state, thought disorders, temporary psychosis, delusions, body image changes, and impaired depth, time and space perceptions. Users may feel several emotions at once or swing rapidly from one emotion to another. "Bad trips" may consist of severe, terrifying thoughts and feelings, fear of losing control, and despair.
Physiological: Tachycardia, hypertension, dilated pupils, sweating, loss of appetite, sleeplessness, dry mouth, tremors, speech difficulties, and piloerection.

***Side Effect Profile*:** Rhabdomyolysis, renal failure, prolonged mania, panic, impairment in color discrimination, and residual visual effects have been described. LSD users may manifest relatively long-lasting psychoses, such as schizophrenia or severe depression.

***Duration of Effects*:** Onset of effects is rapid following intravenous administration (10 minutes). Following oral ingestion, onset of the first effects are experienced in 20-30 minutes, peaking at 2-4 hours and gradually diminishing over 6-8 hours. Residual effects may last longer. Flashbacks may occur suddenly, often without warning, and may occur within a few days or more than a year after use.

***Tolerance, Dependence and Withdrawal Effects*:** Frequent, repeated doses of LSD are unusual and therefore tolerance is not commonly seen. Tolerance does develop to the behavioral effects after 3-4 daily doses, but no withdrawal syndrome has been described. LSD is not considered an addictive drug since it does not produce compulsive drug-seeking behavior.

***Drug Interactions*:** Cross-tolerance with mescaline and psilocybin has been demonstrated in animal models. LSD blocks subjective alcohol effects in many subjects. Possible seizures when concurrently taken with lithium or fluoxetine.

***Performance Effects*:** LSD produces significant psychedelic effects with doses as little as 25-50 µg. LSD impairs reaction time (auditory and visual), choice reaction time, and visual acuity for up to 4 hours. Impaired divided attention, ataxia, and grossly distorted perception have also been reported following LSD use.

***Effects on Driving*:** Epidemiology studies suggest the incidence of LSD in driving under the influence cases is extremely rare. In Denver, Colorado between Jan 1988 to June 1990, 242 drivers detained for driving while impaired were evaluated by drug

recognition examiners; only 1 case of LSD was confirmed following urine toxicology screens.

***DEC Category*:** Hallucinogen.

***DEC Profile*:** Horizontal gaze nystagmus not present; vertical gaze nystagmus not present; lack of convergence not present; pupil size dilated; reaction to light normal; pulse rate elevated; blood pressure elevated; body temperature elevated. Other characteristic indicators may include extreme changes in behavior and mood, trance-like state, sweating, body tremors, piloerection, hallucinations, paranoia, and changes in sense of light, hearing, touch and smell.

***Panel's Assessment of Driving Risks*:** The use of LSD is not compatible with the skills required for driving due to its severe psychomotor, cognitive and residual effects.

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Methadone

Methadone hydrochloride is a white crystalline powder or colorless crystals. Available primarily in tablet or liquid form.

Synonyms: 6-dimethylamino-4.4-diphenyl-3-heptanone; Dolophine® Hydrochloride, Methadose®, Methadone Hydrochloride Intensol™.

Source: Methadone is a synthetic narcotic analgesic and is a schedule II controlled substance. Methadone is available by prescription as oral solutions (1-2 mg/mL strength), tablets (5-10 mg), dispersible tablets (40 mg), or injectable solutions (10 mg/mL).

Drug Class: Narcotic analgesic.

Medical and Recreational Uses: Methadone is an analgesic prescribed for the relief of moderate to severe pain, and is used in detoxification treatment of opioid dependence and maintenance in narcotic addiction. Compared to morphine, methadone has a much longer duration of action, suppressing opiate withdrawal symptoms and remaining efficacious for an extended period of time with repeated administration. Recreationally, methadone is abused for its sedative and analgesic effects.

Potency, Purity and Dose: Available as the racemic mixture, (R)- or *l*-methadone is 8-50 times more potent than the (S)- or *d*-isomer. For relief of severe acute pain the usual adult dose is 2.5-10 mg every 3-4 hours. For methadone maintenance the daily dose is generally 60-80 mg, but can vary from 30-120 mg. For detoxification treatment an initial oral dose of 15-20 mg is administered, with an additional dose if withdrawal symptoms are not suppressed; a stabilizing dose of 40 mg in single or divided dosages is prescribed for 2-3 weeks, then the dose is gradually decreased. Concurrent use of other prescription medication is common.

Route of Administration: Oral ingestion, intravenous, intramuscular or subcutaneous injection.

Pharmacodynamics: Methadone is a long acting μ opioid receptor agonist with potent central analgesic, sedative, and antitussive actions. Methadone inhibits ascending pain pathways, alters perception of and response to pain (dissociative effect), and produces generalized CNS depression. Respiratory depression also occurs due to complete blockade of respiratory centers to pCO_2. (S)-Methadone lacks significant respiratory depressive action and addiction liability.

Pharmacokinetics: When administered orally, methadone is rapidly absorbed from the gastrointestinal tract and can be detected in the blood within 30 minutes. Oral bioavailability varies from 41-99% and plasma protein binding is 60-90%. After repeated administration there is gradual accumulation in tissues. As for most lipid soluble drugs, a large between and within subject variability is observed. The half-life of (R,S)-methadone is 15-60 hours, and 10-40 hours for (R)-methadone. Methadone undergoes extensive biotransformation in the liver primarily to two inactive metabolites,

2-ethylidene-1.5-dimethyl-3.3diphenylpyrrolidine (EDDP) and 2-ethyl-5-methyl-3,3-diphenyl-1-pyrroline (EMDP), through N-demethylation and cyclization. These are eliminated by the kidney and excreted through the bile. In total, nine metabolites have been identified including two minor active metabolites, methadol and normethadol.

Molecular Interactions / Receptor Chemistry: Methadone is metabolized to EDDP via the cytochrome P450 CYP3A4 isoform. Potential inhibitors of this isoform could decrease the rate of methadone elimination if administered concurrently, while potential inducers could increase the rate of elimination. Methadone itself inhibits cytochrome P450 2D6 isoform.

Blood to Plasma Concentration Ratio: 0.75 and 0.77 reported.

Interpretation of Blood Concentrations: Methadone can be detected in plasma within 30 minutes following oral ingestion, reaching a peak concentration at ~4 hours. Mean EDDP concentration are ~15% that of methadone. There is often a large overlap between reported therapeutic (0.03-0.56 mg/L) and fatal concentrations (0.06-3.1 mg/L). Peak serum concentrations following a single oral dose of 15 mg were 0.075 mg/L, 0.86 mg/L for 100 mg, and 0.83 mg/L for 120 mg; all at 4 hours. Chronic oral administration of 100-200 mg to tolerant subjects produced average peak plasma concentrations of 0.83 mg/L at 4 hours, decreasing to 0.46 mg/L at 24 hours. Peak plasma methadone concentrations of 0.034 mg/L were obtained at 50 minutes following intramuscular injection of 10 mg, while intravenous administration of 10 mg produced concentrations of 0.096 mg/L at 34 minutes. Concentrations greater than 0.10 mg/L are required for prevention of opiate withdrawal symptoms. In cancer patients treated for pain relief and sedation, methadone concentrations were 0.35 ± 0.18 mg/L.

Interpretation of Urine Test Results: The percentage of a dose excreted in the urine as unchanged methadone and EDDP will vary with the pH of the urine. Urinary excretion of unchanged parent drug is 5-50% and EDDP 3-25%. It may be possible to use excretion data to monitor individuals' compliance in a methadone program after establishing their intraindividual variation in excretion patterns through long-term monitoring.

Effects:
Psychological: Drowsiness, sedation, dizziness, lightheadedness, mood swings (euphoria to dysphoria), depressed reflexes, altered sensory perception, stupor, and coma.
Physiological: Strong analgesia, headache, dry mouth, facial flushing, nausea, constipation, respiratory depression, muscle flaccidity, pupil constriction, and decreased heart rate.

Duration of Effects: Onset of analgesia occurs 10-20 minutes following parenteral administration and 30-60 minutes after oral administration. Oral administration results in a delay in onset, lower peak concentration and longer duration of action. Following single oral doses effects may last 6-8 hours, increasing to 22-48 hours in cases of chronic administration.

Side Effect Profile: Sedation, alteration in cognitive and sensory efficiency, respiratory depression, nausea, vomiting, headache, constipation, urinary retention, sweating, sleep disorders, and concentration disorders. Infrequent side effects include urticaria, hypersensitivity reaction, shock, and pulmonary edema. Overdose can include slow, shallow breathing, respiratory depression, clammy skin, convulsions, extreme somnolence, apnea, circulatory collapse, cardiac arrest, coma, and possible death.

Tolerance, Dependence and Withdrawal Effects: Upon repeated administration, tolerance may develop to the nauseant, miotic, sedative, respiratory depressant, and cardiovascular effects of methadone. Tolerance develops more slowly to methadone than to morphine in some patients. Methadone can produce physiological and psychological drug dependence of the morphine type, and has the potential for being abused. Withdrawal symptoms are similar to those of other opioids but are less severe, slower in onset, and last longer. Symptoms include watery eyes, runny nose, nausea, loss of appetite, diarrhea, cramps, muscle aches, dysphoria, restlessness, irritability, anxiety, pupillary dilation, piloerection, tremors, chills, sweating, increased sensitivity to pain, insomnia, and tachycardia.

Drug Interactions: There is additive CNS depressive effects with concurrent use of sedatives, hypnotics, tranquilizers, other narcotic analgesics, tricyclic antidepressants, alcohol and other CNS depressant drugs, resulting in exaggerated respiratory depression and sedation. Methadone can potentiate the deleterious effects of alcohol. Pentazocine, nalbuphine, butorphanol and buprenorphine are partial agonists and will behave as antagonists in the presence of methadone, resulting in the precipitation of withdrawal symptoms. Rifampin reduces blood concentrations of methadone and may lead to withdrawal. Blood levels of desipramine have increased with concurrent methadone therapy.

Performance Effects: In general, laboratory studies have shown that non-tolerant individuals receiving single doses of methadone have produced dose-dependent reductions in reaction time, visual acuity, information processing, and sedation. Significant psychomotor impairments are seldom evident when tolerant subjects have been tested, including performance deficits in reaction time, attention, and peripheral vision. In the majority of experimental clinical trials, psychophysical performance tests have yielded the same results for methadone substitution patients as for control groups. However, variable results have been observed. Attention and perception tasks have been impaired in methadone maintenance patients, but sociodemographic factors may have played a role. In patients receiving 35-85 mg methadone daily, significant impairment was measured on attention, perception and learning tasks but there was no reaction time deficit. In patients receiving a daily average of 63 mg methadone, significant impairment in distance perception, attention span and time perception was observed. No significant adverse effects were measured with addicts stabilized for at least 1 year on daily oral doses of methadone.

Effects on Driving: The drug manufacturer cautions that methadone may impair the mental and/or physical abilities required for the performance of potentially hazardous

tasks, and that the sedative effects of the drug may be enhanced by concurrent use of other CNS depressants, including alcohol. In healthy, non-methadone using volunteers, single doses of methadone will impair driving ability. Numerous European studies of long-term methadone maintenance patients have shown that appropriately administered methadone does not cause significant psychomotor or cognitive impairment when administered regularly and when the subject abstains from all other drugs. However, in the majority of cases, patients did not exhibit stable abstinence from drug use and had an increased occurrence of simultaneous psychiatric/neurotic disorders or personality disturbances which, by themselves, could be a reason to doubt their driving ability. In Germany, the Joint Advisory Council for Traffic Medicine at the Federal Ministry of Transport, Building and Housing and the Federal Ministry for Health issued the following recommendation: Heroin addicts treated with methadone are generally not fit to drive; however, these patients may be considered fit to drive if they show a period of methadone substitution for more than a year; stable psychosocial integration; no evidence of the consumption of additional psychotropic substances; evidence of a subject's readiness to feel responsible for himself/herself; therapy compliance; and no evidence of serious personality defects.

DEC Category: Narcotic Analgesic.

DEC Profile: Horizontal gaze nystagmus not present; vertical gaze nystagmus not present; lack of convergence not present; pupil size constricted; little to no reaction to light; pulse rate down; blood pressure down; body temperature down. Other characteristic indicators may include muscle tone flaccidity, droopy eyelids, drowsiness, depressed reflexes, and dry mouth.

Panel's Assessment of Driving Risks: Moderate to severely impairing in naïve or non-tolerant individuals, causing dose-dependent reductions in reaction time, visual acuity and information processing. Significant psychomotor impairment is not expected in tolerant individuals. Driving ability and driving fitness are nevertheless often limited because of consumption of additional psychotropic substances and psychopathological findings.

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Methamphetamine (and Amphetamine)

Methamphetamine hydrochloride is a white to light brown crystalline powder, or clear chunky crystals resembling ice. Methamphetamine base is a liquid.

Synonyms: *Methamphetamine*: chalk, chrissy, crank, crystal, glass, go, hydro, ice, meth, rock candy, speed, whiz; Desoxyn®; *Amphetamine*: dextroamphetamine; Dexedrine®, Adderall®, Benzedrine®, DextroStat®, Biphetamine®, Gradumet®.

Source: The majority of street methamphetamine is produced in clandestine laboratories (e.g. reduction of *l*-ephedrine or *d*-pseudoephedrine over red phosphorus with hydroiodic acid, or reduction with sodium or lithium in condensed liquid ammonia). Methamphetamine remains concentrated in western U. S. states and some rural areas elsewhere. *d*-Methamphetamine is a schedule II controlled substance (Desoxyn®) available in 5 mg white, 10 mg pink, and 15 mg yellow strength tablets. Amphetamine is also a Schedule II controlled substance and is usually supplied as the sulfate salt of the *d*-isomer (Dexedrine®), or as the racemic mixture (Benzedrine®), or a mixture of the two (Adderall®). Dexedrine® is available in 5, 10, and 15 mg strength, orange/black capsules, or 5 mg tablets. Adderall® is available in 5, 7.5, 10, 12.5, 20, and 30 mg strength, blue or orange tablets.

Drug Class: CNS stimulant, sympathomimetic, appetite suppressant.

Medical and Recreational Uses: Medicinally, methamphetamine is used in the treatment of narcolepsy, attention deficit disorder (ADD), and attention deficit hyperactivity disorder (ADHD). Typical doses are 10 mg/day or up to 40 mg daily, and a course of greater than six weeks is not recommended. Methamphetamine is infrequently used in the treatment of obesity, overeating disorders, and weight loss due to its abuse potential. Amphetamine is also used in ADD, narcolepsy, and weight control. Recreationally, methamphetamine is abused to increase alertness, relieve fatigue, control weight, treat mild depression, and for its intense euphoric effects.

Potency, Purity and Dose: Purity of methamphetamine is currently very high, at 60-90%, and is predominantly *d*-methamphetamine which has greater CNS potency than the *l*-isomer or the racemic mixture. Common abused doses are 100-1000 mg/day, and up to 5000 mg/day in chronic binge use. Therapeutic doses of Desoxyn® are 2.5-10 mg daily, with dosing not exceed 60 mg/day. To treat narcolepsy, 5-60 mg/day of amphetamine is ingested in divided doses; and in ADD and ADHD doses of 2.5-10 mg/day is administered, depending on age.

Route of Administration: Methamphetamine users often begin with intranasal or oral use and progress to intravenous use, and occasionally smoking. In contrast to cocaine, the hydrochloride salt of methamphetamine can itself be smoked. Methamphetamine is used sometimes with alcohol or marijuana, particularly during the withdrawal phase.

Pharmacodynamics: Methamphetamine increases synaptic levels of the neurotransmitters dopamine, serotonin (5-HT) and norepinephrine, and has α and β

adrenergic agonist effects. Norepinephrine is responsible for methamphetamine's alerting, anorectic, locomotor and sympathomimetic effects; dopamine stimulates locomotor effects, psychosis, and perception disturbances; and 5HT is responsible for delusions and psychosis. Methamphetamine's effects are similar to cocaine but its onset is slower and the duration is longer. Racemic amphetamine and d-amphetamine have similar chemical properties and actions to methamphetamine but are less potent.

Pharmacokinetics: Following oral administration, peak methamphetamine concentrations are seen in 2.6-3.6 hours and the mean elimination half-life is 10.1 hours (range 6.4-15 hours). The amphetamine metabolite peaks at 12 hours. Following intravenous injection, the mean elimination half-life is slightly longer (12.2 hours). Methamphetamine is metabolized to amphetamine (active), p-OH-amphetamine and norephedrine (both inactive). Several other drugs are metabolized to amphetamine and methamphetamine and include benzphetamine, selegeline, and famprofazone.

Molecular Interactions / Receptor Chemistry: Methamphetamine is metabolized to amphetamine via cytochrome P450 2D6. Potential inhibitors of the 2D6 isoenzyme could decrease the rate of methamphetamine elimination if administered concurrently, while potential inducers could increase the rate of elimination.

Blood to Plasma Concentration Ratio: 0.65 (N=1).

Interpretation of Blood Concentrations: Blood concentrations can generally be used to distinguish therapeutic use from abuse. Concentrations of 0.02-0.05 mg/L are typical for therapeutic use, and up to 0.2 mg/L have been documented. Concentrations greater than this represent abuse. Concentrations do not disclose phase of use. Normal concentrations in recreational use are 0.01 to 2.5 mg/L (median 0.6 mg/L). Concentrations above this range will likely be associated with severe, possibly life threatening, toxicity. There is no evidence for improved performance in any task or test following use of doses greater than 40 mg (or concentrations greater than 0.2 mg/L).

Peak blood methamphetamine concentrations occur shortly after injection, a few minutes after smoking, and around 3 hours after oral dosing. Peak plasma amphetamine concentrations occur around 10 hours after methamphetamine use.

Interpretation of Urine Test Results: Positive results generally indicate use within 1-4 days but could be up to a week following heavy chronic use. Rate of excretion into the urine is heavily influenced by urinary pH. Between 30-54% of an oral dose is excreted in urine as unchanged methamphetamine and 10-23% as unchanged amphetamine. Following an intravenous dose, 45% is excreted as unchanged parent drug and 7% amphetamine.

Effects: Methamphetamine effects are less intense after oral ingestion than following smoked or intravenous use.
Early phase – Psychological: Euphoria, excitation, exhilaration, rapid flight of ideas, increased libido, rapid speech, motor restlessness, hallucinations, delusions, psychosis, insomnia, reduced fatigue or drowsiness, increased alertness, heightened sense of well

being, stereotypes behavior, feelings of increased physical strength, and poor impulse control.
Early phase – Physiological: Increased heart rate, increased blood pressure, increased respiration rate, elevated temperature, palpitations, irregular heartbeat, dry mouth, abdominal cramps, appetite suppressed, twitching, pallor, dilated pupils, HGN at high doses, faster reaction time, increased strength, and more efficient glucose utilization.
Late phase – Psychological: Dysphoria, residual stimulation, restlessness, agitation, nervousness, paranoia, violence, aggression, lack of coordination, pseudo-hallucinations, delusions, psychosis, and drug craving.
Late phase – Physiological: Fatigue, sleepiness with sudden starts, itching/picking/scratching, normal heart rate, and normal to small pupils which are reactive to light.

Binge use of methamphetamine can be broken down into the following phases: Rush – (5 minutes) intense euphoria, rapid flight of ideas, sexual stimulation, high energy, obsessive/compulsive activity, thought blending, dilated pupils; Shoulder – (1 hour) less intense euphoria, hyperactivity, rapid flight of ideas, obsessive/compulsive activity, thought blending, dilated pupils; Binge use – (1-5 days) the drug is frequently readministered in an attempt to regain or maintain euphoria; Tweaking – (4-24 hours) dysphoria, scattered and disorganized thought, intense craving, paranoia, anxiety and irritability, hypervigilance, auditory and tactile hallucinations, delusions, and normal pupils; Crash – (1-3 days) intense fatigue, uncontrollable sleepiness and catnapping, continuing stimulation, drug craving; Normal – (2-7 days) apparent return to "normalcy" although drug craving may appear; Withdrawal – anergia, anhedonia, waves of intense craving, depression, hypersomnolence, exhaustion, extreme fatigue.

Side Effect Profile: Light sensitivity, irritability, insomnia, nervousness, headache, tremors, anxiety, suspiciousness, paranoia, aggressiveness, delusions, hallucinations, irrational behavior, and violence. In overdose, symptoms may include hyperthermia, tachycardia, severe hypertension, convulsions, chest pains, stroke, cardiovascular collapse, and possible death. Other common side effects following abuse of amphetamines include viral hepatitis, Sexually Transmitted Diseases (STDs), HIV, septicemia, abscesses, collapsed blood vessels, and malnutrition. Chronic abuse generally produces a psychosis that resembles schizophrenia and is characterized by paranoia, picking at the skin, preoccupation with one's own thoughts, and auditory and visual hallucinations. Violent and erratic behavior is frequently seen among chronic abusers. Over time, methamphetamine appears to cause reduced levels of dopamine, which can result in symptoms like those of Parkinson's disease.

Duration of Effects: Onset of effects is rapid following intravenous use and smoking, while effects onset more slowly following oral use. Overall effects typically last 4-8 hours; residual effects can last up to 12 hours.

Tolerance, Dependence and Withdrawal Effect: Methamphetamine has a high potential for abuse and dependence. Tolerance may develop and users may quickly become addicted and use it with increasing frequency and in increasing doses. Abrupt

discontinuation of use can produce extreme fatigue, mental depression, apathy, long periods of sleep, irritability, and disorientation.

Drug Interactions: Phenobarbital, propoxyphene, phenytoin and MAOI's slow the metabolism of amphetamines and increases their effect on the release of norepinephrine and other monoamines from adrenergic nerve endings. Amphetamines may counteract sedative effects of antihistamines. Methamphetamine may restore ethanol induced impairment in simple repetitive tasks of short duration, however, there is no restoration of ethanol-induced deficits of balance and steadiness. In general, high doses of amphetamines are likely to increase the impairing effects of alcohol. Chlorpromazine and haloperidol block dopamine and norepinephrine reuptake, thus inhibiting the central stimulant effects of amphetamines. Amphetamine potentiates the analgesic effect of meperidine.

Performance Effects: Laboratory studies have been limited to much lower doses than those used by methamphetamine abusers. Doses of 10-30 mg methamphetamine have shown to improve reaction time, relief fatigue, improve cognitive function testing, increase subjective feelings of alertness, increase time estimation, and increase euphoria. However, subjects were willing to make more high-risk choices. The majority of laboratory tests were administered 1 hour post dose. Expected performance effects following higher doses may include agitation, inability to focus attention on divided attention tasks, inattention, restlessness, motor excitation, increased reaction time, and time distortion, depressed reflexes, poor balance and coordination, and inability to follow directions.

***Effects on Driving*:** The drug manufacturer states that patients should be informed that methamphetamine and amphetamine may impair the ability to engage in potentially hazardous activities such as driving a motor vehicle. In epidemiology studies drive-off-the-road type accidents, high speed, failing to stop, diminished divided attention, inattentive driving, impatience, and high risk driving have been reported. Significant impairment of driving performance would also be expected during drug withdrawal. In a recent review of 101 driving under the influence cases, where methamphetamine was the only drug detected, blood concentrations ranged from <0.05-2.36 mg/L (mean 0.35 mg/L, median 0.23 mg/L). Driving and driver behaviors included speeding, lane travel, erratic driving, accidents, nervousness, rapid and non-stop speech, unintelligible speech, disorientation, agitation, staggering and awkward movements, irrational or violent behavior, and unconsciousness. Impairment was attributed to distraction, disorientation, motor excitation, hyperactive reflexes, general cognitive impairment, or withdrawal, fatigue and hypersomnolence.

DEC Category: CNS stimulant.

DEC Profile: Horizontal gaze nystagmus not present; vertical gaze nystagmus not present; lack of convergence not present; pupil size dilated; reaction to light slow; pulse rate elevated; blood pressure elevated; body temperature normal to down. Other

characteristic indicators may include restlessness, body tremors, talkativeness, exaggerated reflexes, anxiety, and track marks or recent injection sites.

Panel's Assessment of Driving Risks: At lower dose, amphetamines have few effects on cognitive functioning and may result in an enhancement of some psychomotor tasks, but risk-taking increases at higher doses and responses become inappropriate. Drug withdrawal could also lead to the impairment of psychomotor skills required for safe driving.

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Methylenedioxymethamphetamine (MDMA, Ecstasy)

MDMA is a white, tan or brown powder. Available primarily in tablet form.

Synonyms: 3,4-methylenedioxymethamphetamine; ecstasy, ADAM, candy canes, disco biscuit, doves, E, eckie, essence, hug drug, love drug, M&M, rolls, white doves, X, XTC.

Source: MDMA is the methylenedioxy derivative of methamphetamine. Starting materials in its illicit manufacture include isosafrole (Leuckart reaction) and safrole (Merck patent). MDMA is most commonly found in tablet forms of various colors, carrying distinctive markings on one side such as a dove, E, yin/yang symbol, Mitsubishi symbol, etc. MDMA is a Schedule I controlled substance.

Drug Class: Mild CNS stimulant, empathogen, entactogen, mild hallucinogen and psychedelic, appetite suppressant.

Medical and Recreational Uses: Originally patented as an appetite suppressant and used as a possible adjunct to psychotherapy, there is currently no legitimate medical use in the U. S. MDMA is recreationally used as a party, rave or dance drug for its stimulant, mild hallucinogenic, and empathogenic properties.

Potency, Purity and Dose: MDMA exists as a racemic mixture, with the S-(+)-enantiomer having greater CNS potency compared to the R-(-)-enantiomer. Potency of street samples is highly variable, and tablets sold as 'ecstasy' may in fact contain little or no MDMA, but may contain caffeine, ephedrine, phenylpropanolamine, paramethoxyamphetamine (PMA), methylenedioxyamphetamine (MDA), dextromethorphan, amphetamine, methamphetamine, and ketamine. Some tablets have been reported to contain LSD or heroin. Typical doses in a series of pills can range between 10–150 mg of MDMA. User surveys report a range of doses between 50-700 mg in a session, with an average of 120 mg. Most common pattern of use is binge consumption at all night rave or dance parties. MDMA is frequently taken with other recreational drugs such as ethanol, marijuana, cocaine, methamphetamine, nitrous oxide, and GHB.

Route of Administration: Primarily oral administration, although MDMA could conceivably be dissolved and injected, or crushed and snorted.

Pharmacodynamics: MDMA is a phenylethylamine that has stimulant as well as psychedelic effects. MDMA is related in structure and effects to methamphetamine, however, it has significantly less CNS stimulant properties than methamphetamine. MDMA has a high affinity for 5-HT_2 receptors. Both S- and R- enantiomers of MDMA cause acute depletion of presynaptic serotonin (5-HT), depression of 5-HT synthesis by tryptophan hydroxylase, and retrograde destruction of 5-HT neurons following high doses. MDMA also increases levels of norepinephrine and dopamine. The MDMA metabolite, S-(+)- MDA, elicits more stereotypic behavior and is an even more potent

neurotoxin than the parent drug. MDA destroys serotonin-producing neurons which play a direct role in regulating aggression, mood, sexual activity, sleep, and sensitivity to pain.

Pharmacokinetics: MDMA is rapidly absorbed and the half-life of MDMA is ~ 7 hours, although non-linear pharmacokinetics have been observed due to stereoselective pharmacokinetics of the enantiomers. MDMA is metabolized to MDA which is the only metabolite reported in blood and plasma. S-(+)- MDA accumulates in blood due to stereoselective metabolism of S-(+)-MDMA. MDA is further metabolized to its 3-hydroxy-4-methoxy and 3,4-dihydroxy derivatives (HMA and HHA). Additional MDMA metabolites include 3-hydroxy-4-methoxymethamphetamine (HMMA) and 3,4-dihydroxymethamphetamine (HHMA). These polar hydroxylated metabolites are conjugated prior to their excretion in urine.

Molecular Interaction / Receptor Chemistry: The majority of MDMA N-demethylation to MDA is via the cytochrome P450 2D6 isoenzyme, with minor contributions by the 1A2 isoform. Potential inhibitors of these isoenzymes could decrease the rate of MDMA elimination if administered concurrently, while potential inducers could increase the rate of elimination. Both extensive and poor MDMA metabolizers have been identified.

Blood to Plasma Concentration Ratio: Data not available.

Interpretation of Blood Concentrations: No clear correlation exists between MDMA blood concentrations and effects. MDMA and MDA are the analytes detected in blood, with MDA concentrations typically only 5-10% of the corresponding MDMA concentrations. Higher MDA:MDMA ratios may indicate co-administration of MDA. Plasma concentrations following single oral doses of 50, 75, 100, 125 and 150 mg of MDMA were 0.02-0.08 mg/L, 0.13 mg/L, 0.19-0.21 mg/L, 0.24 mg/L, and 0.44 mg/L, respectively. Peak concentrations of MDMA and MDA are observed at 1.5-2 hours and 4 hours, respectively.

Interpretation of Urine Test Results: MDMA, MDA, HMMA, HHMA, HMA and HHA are typically found in urine following their hydrolysis. MDA and HMMA concentrations in urine are typically 10-15% of the corresponding MDMA concentrations.

Effects:
Psychological: Low to moderate doses (50-200 mg) produce mild intoxication, relaxation, euphoria, an excited calm or peace, feelings of well-being, increase in physical and emotional energy, increased sociability and closeness, heightened sensitivity, increased responsiveness to touch, changes in perception, and empathy. At higher doses, agitation, panic attacks, and illusory or hallucinatory experiences may occur.
Physiological: Low to moderate doses (50-200 mg) produce mild visual disturbances (blurred or double vision, increased light sensitivity), dilated pupils, dry mouth, sweating, ataxia, muscle tension, and involuntary jaw clenching.

Side Effect Profile: Impairment of cognitive, perception, and mental associations. Psychological difficulties include confusion, depression, sleep problems, drug craving, severe anxiety, and paranoia. Subjects may experience fatigue, uncoordinated gait, decreased fine motor skills, attentional dysfunction (difficulty to maintain attention during complex tasks), preoccupation, hyperthermia, tachycardia, hyperthermia, hyponatremia, convulsions, and catatonic stupor. Prolonged cognitive and behavioral effects may occur including poor memory recall, flashbacks, panic attacks, psychosis, and depersonalization due to serotonergic neuron damage and decreased serotonin production as a result of long-term use.

Duration of Effects: Following oral administration, effects onset in 20-30 minutes and desired effects may last only an hour or more, depending on dose. Other general effects last for approximately 2-3 hours. LSD is sometimes used in combination with MDMA to increase its duration of effects. Residual and unwanted effects are generally gone within 24 hours although confusion, depression and anxiety may last several weeks.

Tolerance, Dependence and Withdrawal Effect: Drug stacking refers to the ingestion of single doses consecutively as effects begin to wane, similar to cocaine or methamphetamine binges. Such extensive or binge use usually occurs over weekends, and can result in exhaustion, apathy, depression, irritability, insomnia and muscle tension early the next week (often referred to as "terrible Tuesdays"). Tolerance does develop, however, the occurrence of physical and/or psychological dependence is unknown. Persistent neurological deficits may occur, including serotonergic neuron damage which leads to less production of serotonin.

Drug Interactions: The dopamine D_2 receptor antagonist, haloperidol, attenuates psychological effects of MDMA but has no effect on physiological effects.

Performance Effects: MDMA can enhance impulsivity and make it difficult for a person to maintain attention during complex tasks (selective attention, divided and sustained attention, and complex attention tasks). Laboratory studies have demonstrated changes in cognitive, perception and mental associations, instability, uncoordinated gait, and poor memory recall. Distortion of perception, thinking, and memory, impaired tracking ability, disorientation to time and place, and slow reactions are also known performance effects. Single oral doses of MDMA causes subjective excitability, anxiety, perceptual changes, and thought disorders 1-3 hours post dose.

Effects on Driving: In an advanced driving simulator study, subjects were given a mean single dose of 56 mg MDMA. Compared to a sober state, moderate effects on vehicle control, acceptance of higher levels of risk, acute changes in cognitive performance, and impaired information processing ability were observed. In six subjects arrested for driving under the influence, MDMA was the only drug detected at blood concentrations ranging from <0.05-0.58 mg/L. The subjects were cooperative and laid back, and experienced muscle twitching, body tremors, perspiring, dilated pupils, slow reaction to light, and poor performance on field sobriety tests. The following concentrations of MDMA have also been measured in other retrospective studies; serum

MDMA concentrations ranging from 0.001-0.514 mg/L (mean 0.076 mg/L) in 18 cases of driving impairment; blood MDMA concentrations ranging from 0.04-0.38 mg/L (mean 0.18±0.14 mg/L; median 0.19 mg/L) in 9 impaired driving cases; blood MDMA concentrations of 0.12, 0.08, and 0.14 mg/L in 3 impaired driving cases; and a blood MDMA concentration of 2.14 mg/L and urine 118.8 mg/L in one driving fatality case. Another study reported the occurrence of speeding, jumping red lights, hallucinations/delusions, and a sense of detachment in five impaired driving cases, however, no MDMA concentrations were mentioned.

DEC Category: Hallucinogen; (with many characteristics similar to a CNS stimulant)

DEC Profile: Horizontal gaze nystagmus not present; vertical gaze nystagmus not present; lack of convergence not present; pupil size dilated; reaction to light slow; pulse rate elevated; blood pressure normal to elevated; body temperature normal to elevated. Other characteristic indicators may include profuse sweating, muscle twitching, body tremors, and poor performance in field sobriety tests. Subjects are usually described as very cooperative and "laid-back". Note that elevated blood pressure and body temperature are not always observed.

Panel's Assessment of Driving Risks: Low to moderate single doses of MDMA can cause acute changes in cognitive performance and impair information processing, which in turn would impair driving ability. Basic vehicle control is only moderately affected, however, subjects may accept higher levels of risk.

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Morphine (and Heroin)

Morphine and heroin are white, crystalline powders. Illicit heroin may vary in color from white to dark brown due to impurities, or may appear as a black tar-like material.

Synonyms: *Morphine*: Astramorph®, Duramorph®, Infumorph®, Kadian®, Morphine Sulfate®, MSIR®, MS-Contin®, Oramorph SR®, Roxanol®. *Heroin*: diacetylmorphine, diamorphine; Mexican brown or Mexican black tar heroin; bags, blue-steel, China white, H, horse, junk, no-name, silk, skag, smack. Scramble (cut heroin), bone (uncut heroin for smoking), chippers (occasional users).

Source: Morphine is a naturally occurring substance extracted from the seedpod of the poppy plant, *Papavar somniferum*. The milky resin that seeps from incisions made in the unripe seedpod is dried and powdered to make opium, which contains a number of alkaloids including morphine. Morphine concentration in opium can range from 4-21%. An alternate method of harvesting morphine is by the industrial poppy straw process of extracting alkaloids from the mature dried plant, which produces a fine brownish powder. Morphine is a schedule II controlled substance and is available in a variety of prescription forms: injectables (0.5-25 mg/mL strength); oral solutions (2-20 mg/mL); immediate and controlled release tablets and capsules (15-200 mg); and suppositories (5-30 mg). Heroin is a schedule I controlled substance and is produced from morphine by acetylation at the 3 and 6 positions. The majority of heroin sold in the U. S. originates from Southeast Asia, South America (Columbia) and Mexico. Low purity Mexican black tar heroin is most common on the West coast, while high purity Columbian heroin dominates in the East and most mid-western states.

Drug Class: Narcotic analgesic.

Medical and Recreational Uses: Morphine is used medicinally for the relief of moderate to severe pain in both acute and chronic management. It can also be used to sedate a patient pre-operatively and to facilitate the induction of anesthesia. Heroin has no currently accepted medical uses in the U.S., however, it is an analgesic and antitussive.

Potency, Purity and Dose: The dosage of morphine is patient-dependent. A usual adult oral dose of morphine is 60-120 mg daily in divided doses, or up to 400 mg daily in opioid tolerant patients. Recreationally, daily heroin doses of 5-1500 mg have been reported, with an average daily dose of 300-500 mg. Addicts may inject heroin 2-4 times per day. Depending on the demographic region, the street purity of heroin can range from 11-72% (average U.S. purity is ~38%). Heroin may be cut with inert or toxic adulterants such as sugars, starch, powdered milk, quinine, and ketamine. Heroin is often mixed with methamphetamine or cocaine (“speedball”) and injected; or co-administered with alprazolam, MDMA (Ecstasy), crack cocaine, or diphenhydramine.

Route of Administration: *Morphine*: oral, intramuscular, intravenous, rectal, epidural, and intrathecal administration. Morphine tablets may be crushed and injected, while opium can be smoked. *Heroin*: smoked, snorted, intravenous (“mainlining”), and

subcutaneous ("skin popping") administration. Black tar heroin is typically dissolved, diluted and injected, while higher purity heroin is often snorted or smoked.

Pharmacodynamics: Morphine produces its major effects on the CNS primarily through μ-receptors, and also at κ- and δ-receptors. μ_1-receptors are involved in pain modulation, analgesia, respiratory depression, miosis, euphoria, and decreased gastrointestinal activity; μ_2-receptors are involved in respiratory depression, drowsiness, nausea, and mental clouding; κ-receptors are involved in analgesia, diuresis, sedation, dysphoria, mild respiratory depression, and miosis; and δ-receptors are involved in analgesia, dysphoria, delusions, and hallucinations. Heroin has little affinity for opiate receptors and most of its pharmacology resides in its metabolism to active metabolites, namely 6-acetylmorphine, morphine, and morphine-6-glucuronide.

Pharmacokinetics: The oral bioavailability of morphine is 20-40%, and 35% is bound in plasma. Morphine has a short half-life of 1.5 - 7 hours and is primarily glucuroconjugated at positions 3 and 6, to morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), respectively. A small amount (5%) is demethylated to normorphine. M6G is an active metabolite with a higher potency than morphine, and can accumulate following chronic administration or in renally impaired individuals. The half-life of M6G is 4 +/- 1.5 hours. Close to 90% of a single morphine dose is eliminated in the 72 hours urine, with 75% present as M3G and less than 10% as unchanged morphine. Heroin has an extremely rapid half-life of 2-6 minutes, and is metabolized to 6-acetylmorphine and morphine. The half-life of 6-acetylmorphine is 6-25 minutes. Both heroin and 6-acetylmorphine are more lipid soluble than morphine and enter the brain more readily.

Molecular Interactions / Receptor Chemistry: The uridine 5'-diphosphate-glucuronosyltransferase (UGT) 2B7 isoform is primarily involved in the metabolism of morphine. Potential inhibitors of this UGT isoform could decrease the rate of morphine elimination if administered concurrently, while potential inducers could increase the rate of elimination.

Blood to Plasma Concentration Ratio: Morphine 1.02; M6G 0.57; M3G 0.59

Interpretation of Blood Concentrations: Tolerance makes interpretation of blood or plasma morphine concentrations extremely difficult. Peak plasma morphine concentrations occur within an hour of oral administration, and within 5 minutes following intravenous injection. Average plasma concentrations of 0.065 mg/L are necessary for adequate therapeutic analgesia in ambulatory patients. Anesthetic concentrations can reach beyond 2 mg/L in surgical patients. Following oral doses of 10-80 mg, corresponding peak morphine concentrations in serum were 0.05-0.26 mg/L. Following an intravenous dose of 8.75g/70 kg, a peak serum concentration of 0.44 mg/L was reached. In 10 intravenous drug fatalities, where morphine was the only drug detected, postmortem whole blood morphine concentrations averaged 0.70 mg/L (range 0.20-2.3 mg/L). Following a single 12 mg intravenous mg dose of heroin, a peak heroin concentration of 0.141 mg/L was obtained at 2 minutes, while the 6-acetylmorphine and

morphine concentrations were 0.151 and 0.044, respectively. A single 5 mg intravenous dose of heroin produced a peak plasma morphine concentration of 0.035 mg/L at 25 minutes, while intravenous doses of 150-200 mg have produced plasma morphine concentrations of up to 0.3 mg/L. Intranasal administration of 12 mg heroin in 6 subjects produced average peak concentrations of 0.016 mg/L heroin in plasma within 5 minutes; 0.014 mg/L of 6-acetylmorphine at 0.08-0.17 hours; and 0.019 mg/L of morphine at 0.08-1.5 hours.

Interpretation of Urine Test Results: Positive morphine urine results generally indicate use within the last two to three days, or longer after prolonged use. Detection of 6-acetylmorphine in the urine is indicative of heroin use. High concentrations may indicate chronic use of the drug. It is important to hydrolyze urine specimens to assess a urine morphine concentration.

Effects: Depends heavily on the dose of morphine or heroin, the route of administration, and previous exposure. Following an intravenous dose of heroin, the user generally feels an intense surge of euphoria ("rush") accompanied by a warm flushing of the skin, dry mouth, and heavy extremities. The user then alternates between a wakeful and drowsy state ("on the nod").
Psychological: Euphoria, feeling of well-being, relaxation, drowsiness, sedation, lethargy, disconnectedness, self-absorption, mental clouding, and delirium.
Physiological: Analgesia, depressed heart rate, respiratory depression, CNS depression, nausea and vomiting, reduced gastrointestinal motility, constipation, flushing of face and neck due to dilatation of subcutaneous blood vessels, cramping, sweating, pupils fixed and constricted, diminished reflexes, and depressed consciousness.

Side Effect Profile: Drowsiness, inability to concentrate, apathy, lessened physical activity, constipation, urinary retention, nausea, vomiting, tremors, itching, bradycardia, severe respiratory depression, and pulmonary complications such as pneumonia. Medical complications among abusers arise primarily from adulterants found in street drugs and in non-sterile injecting practices, and may include skin, lung and brain abscesses, collapsed veins, endocarditis, hepatitis and HIV/AIDS. Overdose can include slow, shallow breathing, clammy skin, convulsions, extreme somnolence, severe respiratory depression, apnea, circulatory collapse, cardiac arrest, coma, and death.

Duration of Effects: Depending on the morphine dose and the route of administration, onset of effects is within 15-60 minutes and effects may last 4-6 hours. The duration of analgesia increases progressively with age although the degree of analgesia remains unchanged. Following heroin use, the intense euphoria lasts from 45 seconds to several minutes, peak effects last 1-2 hours, and the overall effects wear off in 3-5 hours, depending on dose.

Tolerance, Dependence and Withdrawal Effects: Both morphine and heroin have high physical and psychological dependence. With regular use, tolerance develops early to the duration and intensity of euphoria and analgesia. Withdrawal symptoms may occur if use is abruptly stopped or reduced. Withdrawal can begin within 6-12 hours after the last

dose and may last 5-10 days. Early symptoms include watery eyes, runny nose, yawning and sweating. Major withdrawal symptoms peak between 48-72 hours after the last dose and include drug craving, restlessness, irritability, dysphoria, loss of appetite, tremors, severe sneezing, diarrhea, nausea and vomiting, elevated heart rate and blood pressure, chills alternating with flushing and excessive sweating, goose-flesh, abdominal cramps, body aches, muscle and bone pain, muscle spasms, insomnia, and severe depression.

Drug Interactions: Alcohol increases the CNS effects of morphine such as sedation, drowsiness, and decreased motor skills. There is a higher risk of respiratory depression, hypotension and profound sedation or coma with concurrent treatment or use of other CNS depressant drugs such as barbiturates, benzodiazepines, hypnotics, tricyclic antidepressants, general anesthetics, MAO inhibitors, and antihistamines. Morphine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression. Small doses of amphetamine substantially increase the analgesia and euphoriant effects of morphine and may decrease its sedative effects. Antidepressants may enhance morphine's analgesia. Partial agonists such as buprenorphine, nalbuphine, butorphanol, and pentazocine will precipitate morphine withdrawal.

Performance Effects: Laboratory studies have shown that morphine may cause sedation and significant psychomotor impairment for up to 4 hours following a single dose in normal individuals. Early effects may include slowed reaction time, depressed consciousness, sleepiness, and poor performance on divided attention and psychomotor tasks. Late effects may include inattentiveness, slowed reaction time, greater error rate in tests, poor concentration, distractibility, fatigue, and poor performance in psychomotor tests. Subjective feelings of sedation, sluggishness, fatigue, intoxication, and body sway have also been reported. Significant tolerance may develop making effects less pronounced in long-term users for the same dose. In a laboratory setting, heroin produced subjective feelings of sedation for up to 5-6 hours and slowed reaction times up to 4 hours, in former narcotic addicts. Euphoria and elation could also play a role on perception of risks and alteration of behaviors.

Effects on Driving: The drug manufacturer states that morphine may impair the mental and/or physical abilities needed to perform potentially hazardous activities such as driving a car, and patients must be cautioned accordingly. Driving ability in cancer patients receiving long-term morphine analgesia (mean 209 mg daily) was considered not to be impaired by the sedative effects of morphine to an extent that accidents might occur. There were no significant differences between the morphine treated cancer patients and a control group in vigilance, concentration, motor reactions, or divided attention. A small but significant slowing of reaction time was observed at 3 hours. In several driving under the influence case reports, where the subjects tested positive for morphine and/or 6-acetylmorphine, observations included slow driving, weaving, poor vehicle control, poor coordination, slow response to stimuli, delayed reactions, difficultly in following instructions, and falling asleep at the wheel.

DEC Category: Narcotic Analgesic.

DEC Profile: Horizontal gaze nystagmus not present; vertical gaze nystagmus not present; lack of convergence not present; pupil size constricted; little or no reaction to light; pulse rate down; blood pressure down; body temperature down. Other characteristic indicators may include presence of fresh injection marks, track marks, flaccid muscle tone, droopy eyelids, drowsiness or "on-the-nod", and low raspy slow speech.

Panel's Assessment of Driving Risks: Classification of risk depends on tolerance, dose, time of exposure, acute or chronic use, presence or absence of underlying pain, physiological status of individual, and the presence of other drugs. Moderately to severely impairing in non-tolerant individuals. Mild to moderately impairing if morphine is used as medication on a regular basis for chronic pain. Severely impairing in acute situations if used orally, or as an intravenous medication, or if either drug is taken illicitly.

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Phencyclidine (PCP)

PCP is a white, crystalline powder (contaminants may cause tan to brown color), or a clear, yellowish liquid.

***Synonyms*:** 1-phenylcyclohexylpiperidine; amp, angel dust, animal tranquilizer, dips, dust, elephant, embalming fluid, formaldehyde, fry, hog, ozone, peace pill, rocket fuel, Sernyl, Sernylan, super kools, TicTac, tranq, water, wet.

***Source*:** Synthetic chemical made in clandestine laboratories, or diverted from veterinary sources. PCP is currently a Schedule II controlled substance. In illicit synthesis, piperidine is reacted with cyanide and cyclohexanone to make piperidinocyclohexanecarbonitrile (PCC), which is then reacted with phenylmagnesium bromide to make PCP. PCP can be mixed with dyes and sold in a variety of tablets, capsules and colored powders. PCP is also sold as a liquid in small shaker bottles. PCP analogs are also available: cyclohexamine (PCE), phenylcyclohexylpyrrolidine (PHP), phenylcyclopentylpiperidine (PCPP), and thienylcyclohexylpiperidine (TCP).

***Drug Class*:** Hallucinogen, dissociative anesthetic, psychotomimetic, sedative-hypnotic.

***Medical and Recreational Uses*:** Formerly used as a surgical anesthetic, however, there is no current legitimate medical use in humans. Used as a veterinary anesthetic or tranquilizer. Recreationally used as a psychedelic and hallucinogen.

***Potency, Purity and Dose*:** A light dose typically consists of 3-5 mg; a common dose is 5-10 mg; while a strong dose is greater than 10 mg. Lighter doses are usually smoked, intravenously or intranasally administered, while heavier doses are commonly ingested orally. The liquid can be sprinkled on tobacco or marijuana then smoked, or the cigarettes or joints themselves can be dipped in PCP solution; the resulting PCP dose can therefore vary widely. Due to difficulty of synthesis, street preparations have highly variable concentrations of PCP and byproducts. PCC, the PCP precursor, is found in approximately 20% of illicit samples and is more toxic than PCP as it releases cyanide. Abuse of PCP precursors or analog chemicals leads to similar or more devastating pharmacological effects than PCP. PCP is often administered or mixed with other drugs such as crack cocaine (“beam me up”), cocaine hydrochloride (“lovelies”), and marijuana (“crystal supergrass”, “donk”, “killer joints”, “sherms”, “wacky weed”, “wicky stick”).

***Route of Administration*:** Smoked, intravenous injection, snorted, added as eye drops, oral ingestion, and transdermal absorption.

Pharmacodynamics: Dopaminergic, anticholinergic and opiate-like activities exist. PCP is a non-competitive NMDA-receptor antagonist, and blocks dopamine reuptake and elevates synaptic dopamine levels. It has high affinity to sites in the cortex and limbic structures.

Pharmacokinetics: Well absorbed following all routes of administration, although ~ 50% of PCP in cigarette smoke is converted to an inactive thermal degradation product.

PCP is highly lipid soluble and is stored in fat and brain tissue. The plasma binding of PCP is 65% and its half-life ranges from 7-46 hours (average 21 hours). PCP is extensively metabolized to inactive metabolites by a variety of metabolic routes.

***Molecular Interaction / Receptor Chemistry*:** The cytochrome P450 3A isoenzyme plays a major role in PCP biotransformation. Potential inhibitors of this isoenzyme could decrease the rate of PCP elimination if administered concurrently, while potential inducers could increase the rate of elimination. PCP itself may inhibit 2B1 and 2C11 isoforms.

***Blood to Plasma Concentration Ratio*:** 0.94 and 1.0 reported.

***Interpretation of Blood Concentrations*:** There is no direct correlation between PCP concentration and behavioral or physical findings. Blood levels peak 1-4 hours after ingestion. Average peak plasma concentrations of 2.7 and 2.9 ng/mL were achieved after a 1 mg oral and intravenous dose, respectively. PCP concentrations ranged from 0.3 to 143 ng/mL in 63 patients presenting at a psychiatric hospital emergency room and were associated with a wide variety of psychotic clinical pictures resembling mania, depression or schizophrenia. All these patients had at least one manifestation of toxic psychosis and/or acute delirium, in addition to other symptoms. Similarly, plasma PCP concentrations ranged up to 812 ng/mL in 22 patients with nonfatal PCP intoxication. The most common physical findings were combativeness-agitation (64%), depressed level of consciousness (50%), hypertension (43%), miosis (43%) and tachycardia (43%). Blood PCP concentrations ranged from 12 to 118 ng/mL in 26 individuals arrested for public intoxication.

***Interpretation of Urine Test Results*:** Elimination of PCP in 72 hours urine ranges from 4 to 19% for unchanged drug and 25 to 30% for conjugated metabolites. Approximately 97% of a dose is excreted in 10 days, and PCP use can be detected in urine by immunoassay up to a week following a high dose. Urine PCP concentrations ranged from 0.4-340 mg/L in 19 intoxicated patients.

***Effects*:**
Psychological: Effects are usually dose dependent, and include euphoria, calmness, feelings of strength and invulnerability, lethargy, disorientation, loss of coordination, distinct changes in body awareness, distorted sensory perceptions, impaired concentration, disordered thinking, illusions and hallucinations, agitation, combativeness or violence, memory loss, bizarre behavior, sedation, and stupor.
Physiological: Rise in blood pressure and heart rate, flushing, profuse sweating, generalized numbness of extremities, blurred vision, grimacing facial expression, speech difficulties, ataxia, muscular incoordination, marked analgesia, nystagmus, and anesthesia. In the anesthetized state, the patient remains conscious with a staring gaze and rigid muscles.

***Side Effect Profile*:** Excessive salivation, nausea, vomiting, amnesia, combativeness, severe anxiety, paranoia, flashbacks, seizures, coma, and death. PCP can simulate

schizophrenic-like symptomatology such as flattened affect, dissociative thought disorder, depersonalization and catatonic states. Long periods of use may lead to memory loss, difficulties with speech and thinking, depression, weight loss, liver function abnormalities, and rhabdomyolysis.

Duration of Effects: Onset of effects is very rapid when smoked or injected (1-5 minutes) and are delayed when snorted or orally ingested (30 minutes), with a gradual decline of major effects over 4-6 hours. A return to 'normal' may take up to 24 hours. Consciousness is regained within 10-60 minutes following intravenous administration, with a prolonged recovery period of 3-18 hours. Long-term psychological effects are possible and PCP may precipitate a psychotic reaction lasting a month or more that clinically appears like schizophrenia.

Tolerance, Dependence and Withdrawal Effects: Most PCP users administer the drug intermittently, although daily use has been reported and tolerance may develop. There is evidence of tolerance to behavioral effects of PCP in animals. PCP can be addicting and use can lead to psychological dependence, craving and drug seeking behavior. There has been no demonstration of physical dependency in humans. Upon abrupt discontinuation, physical distress, lack of energy, and depression are reported. Long periods of use may lead to memory loss, difficulties with speech and thinking, depression, and weight loss. These can last up to a year after cessation of use.

Drug Interactions: Benzodiazepines can decrease hypertensive effects and reverse seizure activity of PCP. Chlorpromazine and PCP use can cause severe hypotension. PCP may enhance effects of other CNS depressants like barbiturates and alcohol.

***Performance Effects*:** Laboratory studies have shown that PCP causes disorientation, drowsiness, dizziness, ataxia, double or blurred vision, body image changes, disorganization of thoughts, combativeness, impairment of eye-hand coordination, memory impairment, paresthesia, slowed reaction time, distorted perceptions of space. Effects generally occur within 1 hour post dose. Subjective sensation of intoxication has been reported up to 8 hours and slowed reaction time up to 14 hours.

***Effects on Driving*:** Fifty-six (56) subjects were arrested for erratic driving and were evaluated by a drug recognition examiner. All subjects were judged to be driving under the influence of PCP, and blood PCP concentrations ranged from 12 to 188 ng/mL (mean 51 ng/mL). Similarly, blood PCP concentrations ranged from 10 to 180 ng/mL (mean 73 ng/mL) in 50 subjects arrested for driving under the influence of PCP.

***DEC Category*:** Phencyclidine.

***DEC Profile*:** Horizontal gaze nystagmus present; vertical gaze nystagmus present; lack of convergence present; pupil size normal; reaction to light normal; pulse rate elevated; blood pressure elevated; body temperature elevated. Other characteristic indicators may include rigid muscles, cyclic behavior, sudden turn to violence, lack of response to

painful stimuli, trance-like state or blank stare, sweating, incomplete or delayed verbal responses.

***Panel's Assessment of Driving Risks*:** The use of PCP is not compatible with skills required for safe driving. Severe impairment of mental and physical abilities can occur following single doses.

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Toluene

Toluene is a colorless, flammable liquid with a sweet pungent odor.

***Synonyms*:** Toluol, methylbenzene, methyl benzol, and phenylmethane.

***Source*:** Toluene is an aromatic hydrocarbon, occurring naturally in crude oil and in the tolu tree. It is produced during the process of making gasoline and other fuels from crude oil, in making coke from coal, and as a by-product in the manufacture of styrene. Toluene has numerous commercial and industrial applications and is a solvent in paints, lacquers, thinners, glues, correction fluid and nail polish remover, and is used in the printing and leather tanning processes. Due to its easy accessibility, low cost and ease of concealment, some U.S. states have placed restrictions on the sale of these products to minors.

***Drug Class*:** Volatile solvent, CNS depressant.

***Medical and Recreational Uses*:** No approved medical use of toluene. It is frequently abused for its intoxicating effects. Recreational use is most common among younger adolescents primarily because it is readily available, inexpensive and legal.

***Potency, Purity and Dose*:** Solvents in many commercial and industrial products are often mixed and the solvent "sniffer" is often exposed to other solvents in addition to toluene. Acute and chronic accidental exposure to toluene can also occur, particularly in work environments. Regulatory Limits: OSHA recommends a maximum of 200 ppm toluene in workplace air for an 8-hour work day, 40-hour work week; NIOSH recommends an exposure limit of 100 ppm toluene in workplace air; and ACGIH recommends an exposure limit of 50 ppm in workplace air.

***Route of Administration*:** Inhalation of vapor. May be sniffed directly from on open container, or "huffed" from a rag soaked in the substance and held to the face. Alternatively, the open container or soaked rag can be placed in a bag where the vapors can concentrate before being inhaled. Exposure can also occur by ingesting the liquid or via skin contact.

***Pharmacodynamics*:** Solvents have three proposed mechanisms of action: they may alter the structure of membrane phospholipid bi-layers, impairing various ion channels; they may alternatively alter membrane bound enzymes or receptor-site specificity for endogenous substrates; or they may produce toxic metabolites modifying the hepatic microsomal system and possibly adducting RNA and DNA molecules. Toluene depresses neuronal activity and reversibly enhances $GABA_A$ receptor-mediated synaptic currents and α_1-glycine receptor-activated ion channel function. Toluene also inhibits glutamatergic neurotransmission via NMDA receptors and alters dopaminergic transmission.

***Pharmacokinetics*:** Toluene is well-absorbed following oral ingestion and rapidly absorbed following inhalation. Toluene is detectable in the arterial blood within

10 seconds of inhalation exposure. It is highly lipid soluble and accumulates in adipose tissue, tissues with high fat content, and highly vascularized tissues. Highest concentrations are found in the liver, kidney, brain and blood. The initial half-life in whole blood averages 4.5 hours, (range of 3-6 hours), with a terminal phase half-life of 72 hours. The half-life in adipose tissue ranges from 0.5-2.7 days, increasing with amounts of body fat. Approximately 80% of a dose is metabolized in the liver. Side-chain hydroxylation to benzyl alcohol is followed by oxidation to benzaldehyde by alcohol dehydrogenase, oxidation to benzoic acid by aldehyde dehydrogenase and conjugation with glycine to hippuric acid or reaction with glucuronic acid to form benzoyl glucuronide. Ring hydroxylation to o- and p-cresol is a minor (~1%) metabolic pathway. 4%-20% is excreted unchanged by the lungs and <0.1% is excreted unchanged in the urine. 60%-70% is excreted in urine as hippuric acid (glycine conjugate), and 10%-20% as benzoic acid glucuronide conjugate.

Molecular Interactions / Receptor Chemistry: Toluene is metabolized to benzyl alcohol via the cytochrome P450 2E1 isoform, and to a lesser extent to benzyl alcohol, o-cresol, and p-cresol by 2B6, 2C8, 1A2 and 1A1 isoforms. Potential inhibitors of these isoenzymes could decrease the rate of toluene elimination if administered concurrently, while potential inducers could increase the rate of elimination.

Blood to Breath Concentration Ratio: Ranges from 7 to 15

***Interpretation of Blood Concentrations*:** In non-exposed individuals, average toluene concentrations have been measured at 0.47 µg/L (non-smokers) and 1.14 µg/L (smokers). Toluene is detectable in arterial blood within 10 seconds of inhalation exposure. Exposure to 38 ppm for 8 hours resulted in blood toluene concentrations of 0.59 mg/L. Similarly, exposure to 34 ppm for 8 hours resulted in blood toluene concentrations of 0.457 mg/L, decreasing to 0.038 mg/L after 16 hours. Exposure to 100 ppm for 30 minutes produced 0.4 mg/L of blood toluene in resting individuals and 1.2 mg/L after exercise. In 136 toluene abusers hospitalized or arrested while intoxicated, blood toluene concentrations ranged from 0.3-30 mg/L. Three fatalities from acute toluene inhalation had blood concentrations of 50, 60, and 79 mg/L. In 8 fatal cases of accidental or intentional acute exposure of toluene, blood concentrations ranged from 10-48 mg/L (mean 22 mg/L).

In 53 toluene abusers, blood concentrations of less than 1.0 mg/L corresponded to an odor of "chemical" on the subject's breath; some signs of impairment were observed at concentrations of 1.0-2.5 mg/L; 50% of subjects with concentrations of 2.5-10 mg/L were hospitalized with marked intoxication including hallucinations; and unconsciousness or death were reported at concentrations of 10 mg/L or greater. In 6 subjects with blood toluene concentrations ranging from 9.8-31 mg/L, slurred speech, slow movements, and an inability to concentrate were observed within minutes of cessation of use.

***Interpretation of Urine Test Results*:** In 136 toluene abusers hospitalized or arrested while intoxicated, urine toluene concentrations ranged from 0-5 mg/L. In 120 glue sniffers, concentrations of toluene in the urine ranged from 0.1-40.3 mg/L. Urinary o-

cresol and hippuric acid concentrations may have a high correlation with blood toluene concentrations. Hippuric acid excretion increases during the first 4 hours of exposure to up to 4 times the background level, then decreases rapidly to background levels within 6 hours. O-cresol excretion peaks during the last hour of chronic exposure or in the period immediately after acute exposure. Exercise increases the rate of both hippuric acid and o-cresol excretion. Hippuric acid concentrations (not corrected for creatinine) in non-exposed persons averaged 800 mg/L (range 400-1400); daily exposure to 50 ppm averaged 1920 mg/L (range 1260-2930); 100 ppm ranged from 2800-3500 mg/L; and 200 ppm averaged 5970 mg/L (range 4120-8650). O-cresol is not normally detected in the urine of non-exposed persons, while exposure to 200 ppm results in concentrations of 1-3 mg/L.

***Effects*:**
Psychological: Dizziness, euphoria, grandiosity, floating sensation, drowsiness, reduced ability to concentrate, slowed reaction time, distorted perception of time and distance, confusion, weakness, fatigue, memory loss, delusions, and hallucinations.
Physiological: Irritation to the nose, throat, and eyes, headache, nystagmus, slurred speech, ataxia, staggering, impaired color vision, vigilance, nausea, vomiting, respiratory depression, convulsions, severe organ damage, coma, and death.
Mild exposure (100-1500 ppm) dose-dependently results in euphoria, dizziness, reduced inhibitions, feelings of inebriation similar to alcohol intoxication, headache, nausea, lethargy, slow thought and speech, impairment of coordination, loss of memory, slowed reaction time, fatigue, sedation, confusion, impaired cognition function, impaired visual perception, staggering gait, muscular fatigue, and insomnia. More severe intoxication (10,000-30,000 ppm) will lead to tremors, arrhythmias, paralysis, unconsciousness, coma, and death. Chronic exposure may result in paranoid psychosis, temporal lobe epilepsy, mental retardation, and visual impairment.

***Side Effect Profile*:** Toluene can cause brain, liver and kidney damage, hearing loss, memory impairment, and attention deficits. Death can result from heart failure, asphyxiation or aspiration. Toluene also owes its pharmacology to a mucosal irritant effect from an exothermic reaction with water. This results in vomiting, lacrimation and ocular burning, cough, chest pain, wheezing and possible interstitial edema, and kidney toxicity with tubular acidosis. Toluene exposure is also associated with a transient liver injury.

Duration of Effects: Once inhaled, the extensive capillary surface of the lungs allows rapid absorption of toluene and blood levels peak rapidly. Entry into the brain is extremely fast and onset of effects is almost immediate. Toluene effects generally last several hours.

Tolerance, Dependence and Withdrawal Effects: Tolerance to the effects of toluene has been shown in rats. Toluene has the potential to produce physical and psychological dependence, and its abuse liability is significant. Signs of physical dependence are observed on withdrawal.

Drug Interactions: There is a likely synergy or potentiation of effects with other solvents and CNS depressants. Acute consumption of ethanol inhibits toluene elimination resulting in increased blood toluene concentrations and tissue exposure. This is probably due to competition for alcohol dehydrogenase.

Performance Effects: Most analyses on performance have been on subjects exposed to 50-200 ppm over a 6-8 hour work period. Marked impairment in neurological and neuropsychological test performance have been observed, including impaired working memory and executive cognitive functions, impairment of visual-vigilance tasks, loss in color vision and visual perception, inability to concentrate, slow movements, and decreased response time to simple brief tests.

***Effects on Driving*:** No driving or simulator studies exist for toluene. Blood toluene concentrations were above ~1.0 mg/L in 114 drivers arrested on suspicion of driving while intoxicated in Norway between 1983-1987. In 29 of these cases toluene was the only detected drug, with mean blood concentrations of 10 mg/L (range 1-29.3 mg/L). The authors stated there was no simple relation between blood toluene concentrations and degree of impairment, however, almost all drivers with blood toluene concentrations greater than 9.2 mg/L were considered impaired or highly probably impaired. No driving observations were documented.

DEC Category: Inhalant

DEC Profile: Horizontal gaze nystagmus present in high doses; vertical gaze nystagmus present in high doses; lack of convergence present; pupil size normal; reaction to light slow; pulse rate elevated; blood pressure elevated; body temperature normal. Other characteristic indicators may include strong odor of solvent or chemical on breath or clothes, residue of substance around nose, mouth or hands, slurred speech, and general intoxication.

Panel's Assessment of Driving Risks: Acute and chronic exposure to toluene can result in severe impairment.

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Zolpidem (and Zaleplon, Zopiclone)

Zolpidem is a white to off-white crystalline powder.

Synonyms: N,N, 6-trimethyl-2-p-tolyl imidazo[1,2-a]pyridine-3-acetamide L-(+)-tartrate; zolpidem tartrate; Ambien®.

Source: Zolpidem is available by prescription and is a Schedule IV controlled substance. Ambien® is available in strengths of 5 mg and 10 mg (white and pink oval tablets, respectively). Sonata® contains zaleplon. Imovane® contains zopiclone.

Drug Class: Non-benzodiazepine sedative-hypnotic, CNS depressant, sleep aid.

Medical and Recreational Uses: Zolpidem is a non-benzodiazepine hypnotic used in short-term treatment (up to 4 weeks) of insomnia. Zaleplon and zopiclone also are indicated for the treatment of insomnia.

Potency, Purity and Dose: Recommended zolpidem dose is 10 mg immediately before bedtime (5 mg in the elderly). Recommended nighttime zaleplon and zopiclone doses are 5-20 mg and 7.5 mg, respectively. Patients treated with zolpidem often concurrently use other medications such as antidepressants, narcotic analgesics, and muscle relaxants

Route of Administration: Oral.

Pharmacodynamics: While zolpidem has a chemical structure unrelated to benzodiazepines, it is a $GABA_A$ receptor agonist and shares some of the pharmacological properties of benzodiazepines. Zolpidem preferentially binds to receptors containing an $\alpha 1$ subunit (also known as BZ1- or $\omega 1$-receptor subtypes). Zolpidem shortens sleep latency and prolongs total sleep time in patients with insomnia, but has little effect on the stages of sleep in normal subjects. It also has weak anticonvulsant properties. Zaleplon binds preferentially to BZ-1, but also to BZ-2 and BZ-3; while zopiclone binds equally to BZ-1 and BZ-2.

Pharmacokinetics: Zolpidem is absorbed readily from the gastrointestinal tract. First-pass hepatic metabolism results in an oral bioavailability of 67%, and 92% is bound in plasma. Zolpidem has a short elimination half-life (2.2 + 0.4 hours), which is reduced in children (~ 1.4 hours) and increased in the elderly (~ 2.8 hours) and patients with hepatic cirrhosis (~ 9.9 hours). Peak plasma concentrations are detected at 1.5-2.5 hours. Peak concentrations are decreased with food and increased in patients with hepatic insufficiency. Zaleplon has a bioavailability of 30% and has a shorter half-life (1.1 hours) compared to zolpidem.

Molecular Interactions / Receptor Chemistry: Zolpidem is converted to hydroxylated metabolites principally by cytochrome P450 3A4 isoenzymes, with minor contributions by 1A2 and 2C9 isoforms. Potential inhibitors of these isoenzymes could decrease the

rate of zolpidem elimination if administered concurrently, while potential inducers could increase the rate of elimination

***Blood to Plasma Concentration Ratio*:** Data not available.

Interpretation of Blood Concentrations: Single doses of 5 mg zolpidem resulted in average peak concentrations of 0.06 mg/L at 1.6 hours; 10 mg produced 0.12 mg/L at 1.6 hours; 15 mg produced 0.20 mg/L at 1.5 hours; and 20 mg produced 0.23 mg/L at 2.1 hours.

Interpretation of Urine Test Results: Urinary excretion of unchanged zolpidem is less than 1%.

Effects:
Psychological: Sleep induction, drowsiness, dizziness, lightheadedness, amnesia, confusion, concentration difficulties, and memory impairment.
Physiological: Nausea, ataxia, slow and slurred speech, slow reflexes, and difficulty with coordination.

Side Effect Profile: Somnolence, lightheadedness, vertigo, headache, nausea, fatigue, cognitive deficits, and impairment of consciousness ranging from somnolence to light coma. Infrequently reported side effects include agitation, depressive syndrome, detachment, nightmares, hallucination, leg cramp, paresthesia, speech disorder, double vision, dry mouth, and diarrhea. Hangover effects are unlikely with zolpidem, although morning-after anterograde amnesia may occur. In overdose, patients mainly suffer somnolence and drowsiness, pinpoint pupils, respiratory depression, and in extreme cases, coma and respiratory failure.

Duration of Effects: Following 10-20 mg oral doses of zolpidem, effects can last up to 4-5 hours (dose-dependent). There are generally no residual effects the morning after a nighttime dose of zolpidem. Sedation may extend for 8-16 hours following intoxication. Zaleplon has a more rapid onset and shorter duration of effects compared to zolpidem, while zopiclone has longer duration of effects.

Tolerance, Dependence and Withdrawal Effects: Tolerance and dependency are not typically detected after 4 weeks of therapeutic use; however, tolerance may develop with chronic use. There is some evidence of tolerance and physical dependency observed with chronic administration of zolpidem in animal models. Withdrawal following abrupt discontinuation may include mild dysphoria and insomnia, abdominal and muscle cramps, vomiting, sweating, tremors, convulsions, fatigue, flushing, lightheadedness, nervousness, and panic attacks.

Drug Interactions: Imipramine has an additive effect of decreased alertness; chlorpromazine has an additive effect of decreased alertness and decreased psychomotor performance; ritonavir decreases clearance though inhibiting CYP3A hydroxylation; ketoconazol also decreases clearance; and flumazenil is an effective and therapeutic

pharmacodynamic antagonist. Alcohol increases the sedation and decreases psychomotor performance produced by zolpidem. Other CNS depressant drugs may potentiate the effects of zolpidem. Zopiclone has additional performance decrements when concurrently taken with alcohol, carbamazepine, and diazepam.

Performance Effects: Unsteady gait, confusion, disorientation, and significant cognitive and psychomotor impairment can be observed within 1-5 hours following zolpidem doses of 10-20 mg. Memory impairment (learning, recall and recognition of words, pictures, and numbers) psychomotor slowing (digit symbol substitution task, circular light tasks), reduced attentional capacity (impaired divided and sustained attention), impaired balance (ataxia, dizziness), visual disturbances (double vision), and impaired time estimation have been recorded. Psychomotor impairment can be found up to 5 hours after a single 15 mg oral dose and up to 8.25 hours after a 20 mg dose. Memory and learning impairment can be found up to 8.25 hours following a 10-20 mg dose. There has been no significant residual effect on memory or actual driving when subjects have been tested the morning after a single 10 mg dose.

Following a single 10-20 mg dose of zaleplon, studies have shown no residual effects on actual driving (5-10 hours) or on body sway, reasoning, retrieval and spatial memory (4-9 hours); however, significant impairment has been reported within 1-3 hours of dosing. Minor impairment of delayed free recall has occurred 4 hours after 20 mg dose of zaleplon. For zopiclone, a single 7.5 mg dose can cause severe residual effects on actual driving at 5 and 10 hours, severe residual effects on body sway and memory at 4 hours, and minor impairment of delayed free recall 9 hours after dosing.

Effects on Driving: The drug manufacturer states that patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination such as driving a motor vehicle. Within the first 4-5 hours, zolpidem can produce significantly impaired coordinative, reactive and cognitive skills following single oral doses of 10-20 mg. However, no significant adverse effects were observed during a 1.5 hour driving test on a rural road, 10-12 hours after drug administration. In five reported cases of driving impairment in which zolpidem was the only drug detected, blood concentrations of zolpidem ranged from 0.08 to 1.4 mg/L (mean 0.65 mg/L). Symptoms and observed behavior included erratic driving (weaving, lane travel), slow and slurred speech, slow reflexes, dazed appearance, disorientation, confusion, loss of balance and coordination, loss of short-term memory, blacking out, somnolence, dilated pupils, double vision, poor performance on field sobriety tests, poor attention, and an inability to stand or walk unassisted. In another six reported cases of driving under the influence of zolpidem, blood concentrations ranged from 0.1 to 0.73 mg/L (mean 0.31 mg/L). The subjects were involved in automobile accidents or were seen to drive erratically, and symptoms included slow and slurred speech, ataxia, unsteady gait, confusion and disorientation.

DEC Category: CNS depressant

DEC Profile: Horizontal gaze nystagmus present; vertical gaze nystagmus present for high doses; lack of convergence present; pupil size normal; reaction to light slow; pulse

rate down; blood pressure down; body temperature normal. Other characteristic indicators may include slow and slurred speech, somnolence, and poor performance on field sobriety tests.

Panel's Assessment of Driving Risks: Zolpidem causes significant effects when driving within 5 hours of use (10 mg dose). Zaleplon causes significant impairment within 3 hours of use (10 mg), but no significant impairment after 4 hours (10 mg) and 5 hours (20 mg). Zolpidem and zaleplon are relatively free of residual morning-after effects. Zopiclone causes severe impairment 1-5 hours after dosing (7.5 mg), with residual hangover effects up to 10-11 hours.

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Biographical Sketches of Lead Authors and Main Contributors

Lead Authors

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Dr. Fiona J. Couper received her B.Sc. (Honors) degree in Pharmacology/Toxicology and her Ph.D. degree in Forensic Medicine/Toxicology from Monash University, Melbourne, Australia. During this period, Dr. Couper also worked as a forensic toxicologist at the Victorian Institute of Forensic Medicine (VIFM) in Melbourne. From 1997-1998, Dr. Couper held a postdoctoral fellowship position at the National Institute of Forensic Sciences and the VIFM, and in late 1998 became a senior research fellow at the University of Washington and the Washington State Toxicology Laboratory, in Seattle, U.S.A. Dr. Couper is now the Chief Toxicologist at the Office of the Chief Medical Examiner, Washington D.C. Dr. Couper's research has focused on the effects of prescription and illicit drugs on driving impairment, the use of drugs to facilitate sexual assaults, GHB and drug overdoses in the emergency room, and the prevalence of drug use in various community groups. Dr. Couper is also an active member of the Society of Forensic Toxicologists (SOFT), the American Academy of Forensic Sciences (AAFS), and the International Association of Forensic Toxicologists. Additionally, she is the chair of the Joint AAFS/SOFT Drugs and Driving Committee.

Barry Logan, Ph.D.

Dr. Barry K. Logan was born in Bearsden, Scotland, and earned his bachelor's degree in chemistry and Ph.D. in forensic toxicology from the University of Glasgow. In 1986 he accepted a research position in the Department of Toxicology and Chemical Pathology at the University of Tennessee in Memphis. In 1990 he joined the faculty of the University of Washington (UW) in the Department of Laboratory Medicine and was appointed Washington State Toxicologist. In 1999 the Washington State Toxicology Laboratory merged with the Washington State Patrol, and Dr. Logan was named Director of the newly created Forensic Laboratory Services Bureau. In addition to his duties as State Toxicologist and Clinical Assistant Professor at UW, he oversees operations of the State Patrol Crime Laboratories, Breath Test Section, and Implied Consent Section. Dr. Logan has more than 70 publications in the field of forensic toxicology and drug analysis, and is Board Certified by the American Board of Forensic Toxicology. He has been elected to the National Safety Council's Committee on Alcohol and Other Drugs and to the International Council on Alcohol, Drugs, and Traffic Safety, and has served as a consultant to the National Institute of Justice, the United Nations Drug Control Program, and numerous state agencies. He is a Fellow of the American Academy of Forensic Sciences, an active member of the Society of Forensic Toxicologists, and serves on the editorial boards of the Journal of Forensic Sciences and the Journal of Analytical Toxicology. His current research interests include stimulant use and driving impairment, drug interactions and postmortem toxicology, and drug facilitated sexual assault.

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Dr. Michael R. Corbett received his B.Sc., M.Sc. and Ph.D. degrees in chemistry from the University of Toronto, the last being conferred in 1989. He is also the coordinator, and an instructor, in the forensic science courses offered through the School of Continuing Studies at the University of Toronto, and has supervised undergraduate students in research projects at the Department of Pharmacology. Dr. Corbett received the prestigious "Excellence in Teaching Award" for overall cumulative achievement in 2001. Dr. Michael Corbett is currently a senior forensic toxicologist in the Province of Ontario in Canada. In the area of alcohol, other drugs, and the operation of motor vehicles, Dr. Corbett has been directly involved in over 2500 cases. He is a designated analyst pursuant to the Criminal Code of Canada. He has provided educational programs on alcohol screening devices and instruments, including human subject testing, to police, lawyers, judges, media, and university students. Dr. Corbett serves as a member of the editorial board of the Journal of Analytical Toxicology. He belongs to numerous professional peer organizations including the AAFS, SOFT and The International Association of Forensic Toxicologists (TIAFT). He also participates in committees including the Committee on Alcohol and Other Drugs of the Highway Traffic Safety Division of the National Safety Council and the Joint AAFS/SOFT Drugs and Driving Committee. Dr. Corbett is certified as a Diplomat in Forensic Toxicology by the American Board of Forensic Toxicology (D-ABFT).

Laurel Farrell, M.S.

Ms. Laurel J. Farrell received her B.A. in Chemistry from the University of Northern Colorado in 1979. Ms. Farrell then worked for the Colorado Department of Public Health and Environment for over twenty-one years serving in a variety of capacities in the drug and alcohol analytical laboratories. For the last half of her employment she served as the staff authority in the toxicology laboratory routinely providing expert testimony in Colorado courts and in US District Court on the effects of alcohol and other drugs on human performance. For the last two and half years, Ms. Farrell has been assigned to the Colorado Bureau of Investigation's Denver Laboratory. She is a member of several professional organizations. As an active member of the Society of Forensic Toxicologists, she has just finished seven years as an officer/director serving as President in 2002. She is a Fellow of the American Academy of Forensic Sciences and served as Chair of the Joint AAFS/SOFT Drugs and Driving Committee from 2000-2002 and as a member on this committee from 1995 to the present. Over that time period, Ms. Farrell has assisted in coordinating a number of continuing education workshops in the area of drug impaired driving and has recently served a guest editor for two volumes of Forensic Science Review focusing on the Effects of Drugs on Human Performance and Behavior. She is also an elected member of the National Safety Council's Committee on Alcohol and Other Drugs and the International Council on Alcohol, Drugs, and Traffic Safety.

Marilyn Huestis, Ph.D.

Dr. Marilyn A. Huestis is the Acting Chief, Chemistry and Drug Metabolism Section (CDM), Clinical Pharmacology and Therapeutics Research Branch, Intramural Research Program (IRP), National Institute on Drug Abuse (NIDA), NIH. Dr. Huestis conducts controlled drug administration studies and directs the core chemistry laboratory of the IRP, NIDA. She has worked in the fields of clinical and emergency toxicology, therapeutic drug monitoring, urine drug testing, and forensic toxicology, which have provided a unique background and the knowledge and experience necessary for drug abuse research. Her research focuses on the pharmacodynamics and pharmacokinetics of drugs of abuse. Special areas of interest include cannabinoids, alternate matrices for drug analysis, correlations of blood levels of drugs with performance effects, medication development projects including the buprenorphine as a pharmacotherapeutic agent in opioid dependence, and in utero drug exposure. Pregnant opiate addicts receiving buprenorphine or methadone as part of their treatment program have provided a unique opportunity to study the disposition of drugs in the mother and fetus, and the relationship between drug concentrations in a wide variety of biological specimens and maternal and neonatal outcome measures. Dr. Huestis hopes to develop a better understanding of drug abuse in women and the consequent drug exposure of neonates and children. Dr. Huestis is the principal investigator of several phase I clinical studies evaluating the effects of the cannabinoid receptor antagonist, SR 141716 in cannabis users. Dr. Huestis received a bachelor's degree in biochemistry from Mount Holyoke, a master's degree in clinical chemistry from the University of New Mexico, and a doctoral degree in toxicology from the University of Maryland in Baltimore. Dr. Huestis has been working in the fields of forensic and analytical toxicology, and clinical chemistry for more than thirty years and is recognized nationally and internationally for her contributions to the field. She has published extensively in these fields and serves on the Editorial Board of the Journal of Analytical Toxicology. She is an Adjunct Associate Professor in the Toxicology program of the University of Maryland at Baltimore and directs graduate and post-graduate student research. Dr. Huestis is currently President of the International Association of Forensic Toxicologists, past president of the Society of Forensic Toxicologists (SOFT) and past Chair of the Toxicology Section of the American Academy of Forensic Sciences. Dr. Huestis is also a member of the International Cannabinoid Research Society, American Association for Clinical Chemistry, the International Association of Therapeutic Drug Monitoring and Clinical Toxicology, the California Association of Toxicologists, Society of Hair Testing, and the United States Anti-Doping Agency Research Advisory Board.

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Mr. Wayne K. Jeffery received his B.Sc (Pharmacy) degree in 1968 and M.Sc. (Pharmaceutical Chemistry) degree in 1971, from the University of Alberta, Edmonton, Alberta, Canada. He has been the Toxicology Section Head, Royal Canadian Mounted Police, Forensic Laboratory, Vancouver, since 1976. Mr. Jeffery is a member of 7 professional associations, including the Alberta Pharmaceutical Association and the Canadian Pharmaceutical Association. He has been a member of the Canadian Society of

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Jan Raemakers, Ph.D.

Dr Jan Ramaekers obtained his Ph.D. in psychopharmacology from Maastricht University, on behavioral toxicity of medicinal drugs. Dr Ramaekers spent 8 years of research at the Institute for Human Psychopharmacology at Maastricht University. During these years he conducted a large number of experimental studies on the effects of medicinal drugs, such as antidepressants, antipsychotics, anxiolytics, anticonvulsants and antihistamines on cognition, psychomotor function and actual driving performance of healthy volunteers and patients. In 1995, the Institute for Human Psychopharmacology received the Widmark Award (International Counsel of Alcohol, Drugs and Traffic Safety), “for numerous contributions to the advancement of the cause of alcohol, drugs and traffic safety and sustained contributions to the support in this field”. In 1998, Dr Ramaekers accepted a position as Assistant Professor at the Faculty of Psychology at Maastricht University. He has been a co-organizer of courses in the field of Human Psychopharmacology, Biological Psychology and Traffic & Aviation Psychology. Dr Ramaekers is currently involved in research on the effects of illicit drugs, i.e. marijuana and MDMA, on driving. He is a member of the British Association of Psychopharmacology (BAP), the Collegium Internationale Neuro-Psychopharmacologicum (CINP) and the International Counsel of Alcohol, Drugs and Traffic Safety (ICADTS).

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Appropriate Use of Drug Testing in Clinical Addiction Medicine

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Disclosure information for the **ASAM Expert Panel Members and Quality Improvement Council** is available in **Appendix 6**.

INTRODUCTION

Purpose

The purpose of the *Appropriate Use of Drug Testing in Clinical Addiction Medicine* is to provide guidance about the effective use of drug testing in the identification, diagnosis, treatment, and promotion of recovery for patients with, or at risk for, addiction. This document draws on existing empirical evidence and clinical judgment on drug testing with the goal of improving the quality of care that people with addiction receive.

By focusing on the identification, diagnosis, treatment, and promotion of recovery for patients with, or at risk of, addiction, the appropriateness document:

- Identifies current clinical practice and disagreement regarding the use of drug testing.
- Utilizes the Research and Development/University of California Los Angeles (RAND/UCLA) Appropriateness Method, which combines existing empirical evidence and clinical expertise to develop recommendations for appropriate practice.
- Compiles recommendations in a comprehensive document for use by a variety of providers who utilize drug testing.

Background

Drug testing uses a biological sample to detect the presence or absence of a specific drug (or drugs) as well as drug metabolites within a specific window of time. No universal standard exists today in clinical drug testing for addiction identification, diagnosis, treatment, medication monitoring, or recovery.

The American Society of Addiction Medicine (ASAM) recognizes that the absence of guidance creates a vacuum. Even in the context of limited research about how to approach a given clinical practice, providers and payers make decisions about what kind of care patients should and do receive. This appropriateness document is intended to guide provider decisions about drug testing to improve the quality of care that patients with addiction receive.

It is ASAM policy that the elements of drug testing (eg, matrix, drug panel, testing technology) be determined by the provider based on patient-specific needs, not by arbitrary limits from insurance providers [1]. However, most physicians and other providers employing drug testing in addiction care have operated without authoritative guidance about how this therapeutic tool should be utilized effectively in treatment.

ASAM has produced 2 key documents related to drug testing: ''Public Policy Statement on Drug Testing as a

• Adopted by the ASAM Board of Directors April 5, 2017
Endorsed by the American College of Medical Toxicology.

Component of Addiction Treatment and Monitoring Programs and in other Clinical Settings'' and ''Drug Testing: A White Paper of the American Society of Addiction Medicine'' [1,2]. Neither document provides specific guidance and neither was developed using a rigorous methodology to develop practice recommendations.

In its 2010 policy statement, ASAM recognized drug testing as part of medical care for people being treated for addiction. The Statement expressed ASAM policy that drug testing should not face undue restrictions; decisions about the types and frequency of testing should be made by the ordering physician; and arbitrary limits on reimbursement by payers interfere with the physician's judgment and violate federal parity laws. The Statement provided a brief review of drug testing purposes, practices, and procedures that are recommended by ASAM.

The White Paper provided extensive background regarding the science and current practices of drug testing in various contexts, as well as broad suggestions for ways to improve drug testing in clinical practice. However, the White Paper acknowledged that more specific clinical guidance was needed and would be forthcoming from ASAM.

In the White Paper, ASAM advocates for the use of ''smarter'' drug testing as follows:

> Smarter drug testing means the increased use of random testing rather than the more common scheduled testing, and it means testing not only urine but also other matrices such as blood, oral fluid (saliva), hair, nails, sweat and breath when those matrices match the intended assessment process. In addition, smarter testing means testing based upon clinical indication for a broad and rotating panel of drugs rather than only testing for the traditional five-drug panel that was designed not by practicing physicians or researchers, but by the federal government for government-mandated testing such as that required of commercial drivers. Smarter testing means improved sample collection and detection technologies to decrease sample adulteration and substitution. Designing appropriate steps to respond to the efforts of individuals trying to subvert the testing process must be considered when evaluating the costs/benefit ratio of different testing matrices, recognizing that such countermeasures may have a dramatic impact on the usefulness of testing. Smarter drug testing means careful consideration of the financial costs of testing in relationship to the value and in many cases, medical necessity, of the test results. It means considering the advantages and limitations of the many testing technologies available today. [2]

This appropriateness document is designed to guide providers toward ''smarter'' drug testing.

Addiction treatment is increasingly delivered in primary care offices, with the proliferation of addiction medications such as buprenorphine and naltrexone. Drug-testing technology using matrices such as oral fluid (saliva), sweat, and hair is becoming increasingly sophisticated. Although urine is still by far the most common matrix, an evidence base is building for alternatives. And finally, the availability of synthetic drugs (some designed specifically to evade detection by drug testing) has grown dramatically and will continue to do so. According to ASAM's White Paper, the dramatic proliferation of potentially addictive drugs is one of the most challenging problems facing drug testing today [2]. Consistent with the ''smarter'' drug testing paradigm, the ASAM White Paper states, ''The most important challenge in drug testing today is not the identification of every drug we are technologically capable of detecting, but to do medically necessary and accurate testing for those drugs that are most likely to impact clinical outcomes.''

Cost Considerations

This document is designed to convey statements about drug testing as part of appropriate clinical care. It is not an analysis of the cost benefits of drug testing using various technologies or under various circumstances. However, ASAM is acutely aware that this document will be released in a context where a lack of clarity about the appropriate use of drug testing has led not only to inconsistent clinical practice, but also unethical and/or fraudulent activities.

The inappropriate use of drug testing can have extraordinary costs to third-party payers, taxpayers, and at times the patients who are receiving care. Though non-monetary, this has also cost the addiction treatment field because of loss of credibility. Examples of inappropriate and often-costly drug-testing practices are (1) the routine use of large, arbitrary test panels, (2) unnecessarily frequent drug testing without consideration for the drug's window of detection, and (3) the confirmation and quantification of all presumptive positive and negative test results [3,4].

It is ASAM's position that these and other inappropriate drug-testing practices are harmful not only because they waste valuable resources but because they do not fit the standards of appropriate clinical care. Providers have an obligation to ensure the highest possible quality of treatment for all patients, which includes the appropriate use of clinical drug testing. One of the purposes of this document is to clarify appropriate clinical use of drug testing and, in so doing, shine a light on drug-testing practices that are clearly outside of these boundaries. The delineation of appropriate treatment practices will confer multiple benefits; most importantly, it will improve patient care. At the same time, it will reduce waste and fraud.

How to Use This Document

Unlike clinical guidelines that typically focus on either more generalized or disease-specific recommendations, this appropriateness document determines when, where, and how often a drug test should be performed for the identification, diagnosis, treatment, and recovery of patients with, or at risk for, addiction.

Providers

This document contains practical information to guide the appropriate use of drug testing to help identify, diagnose, treat, and support recovery for patients with or at risk of addiction. Providers are encouraged to utilize this appropriateness document to improve their quality of care, recognizing that it will be necessary to seek supplemental information when questions arise that this document does not comprehensively address. For example, providers seeking specific guidance for interpreting drug test results should consider

consulting with a laboratory or a physician with Medical Review Officer (MRO) certification.

Payers

The primary audience for this document are providers who utilize drug testing in clinical settings. It is not designed as a template for payer policies. For example, it would be inappropriate to translate the statement that ''during the initial phase of treatment, drug testing should be at least weekly'' into a payer policy that will not reimburse drug tests that are more frequent than weekly.

Administrators

Healthcare administrators in residential, outpatient, and other settings should reference this document as a guide for appropriate practice related to drug testing. This document may inform policy decisions related to establishing or improving a drug-testing program in a variety of clinical settings.

Scope of Project

This document focuses on clinical drug testing for identification, diagnosis, treatment, and recovery of patients with, or at risk for, addiction. ASAM recognizes that drug testing is used in other contexts (eg, criminal justice, workplace, and pain management settings). ASAM's intent with this document, however, is to focus primarily on patients in addiction treatment and recovery, where drug testing is used to assess the patient for indicators of a substance use disorder (SUD), monitor the effectiveness of the treatment plan, and support recovery, and to also focus on selected special populations at risk for addiction. Although ASAM acknowledges that these recommendations may be applied to other settings where drug testing is utilized, note that the materials reviewed and methodology used were restricted to the populations and settings described.

Included and Excluded Settings

Inasmuch as the scope of the project includes the recognition of addiction, which often occurs in general healthcare settings, these settings are included briefly in this context. This document excludes recommendations for federally mandated workplace forensic testing, which are regulated by Substance Abuse and Mental Health Services Administration (SAMHSA). Drug testing in the contexts of criminal justice and pain management is also outside the scope of this document.

Types of Tests

This document will address considerations involved in the timing and selection of presumptive and definitive drug testing. Also, while urine drug testing (UDT) is the most common type of test utilized in the identification, diagnosis, treatment, and monitoring of patients with addiction, ASAM recognizes that drug test technology utilizing biological matrices such as oral fluid, hair, and sweat is becoming increasingly advanced and widespread.

Settings

This document includes recommendations about the frequency and duration of drug testing according to ASAM levels of care (eg, Outpatient and Residential) and includes a section on considerations for Opioid Treatment Services (OTS), including Opioid Treatment Programs (OTP) as well as Office-Based Opioid Treatment (OBOT). Also, while not an ASAM level of care, the document also includes recommendations for patients in recovery residences. In cases where no specific guidance was recommended for a particular level of care, the reader is directed back to the general principles section regarding appropriate clinical practice.

Special Populations

This document includes considerations for the following special populations: adolescents, pregnant women, people in recovery, and health and other professionals. For adolescents, the focus is in general healthcare settings and not in addiction treatment settings because there are unique considerations for drug testing adolescents in general healthcare settings. For pregnant women, the focus is also primarily in general healthcare settings for pregnant and postpartum women.

Intended Audience

This appropriateness document is intended for addiction specialists and for all providers utilizing drug testing in the context of the identification, diagnosis, treatment, and monitoring of patients with, or at risk for, addiction. This document will also be useful for physicians and other providers concerned about the possibility of addiction in their patient population.

Qualifying Statement

This document is intended to aid providers in their clinical decision-making and patient management. The document strives to identify and define clinical decision-making junctures that meet the needs of most patients in most circumstances. Recommendations in this document are not intended to substitute for independent clinical judgment based on the particular facts and circumstances presented by individual patients. Clinical decision-making should involve consideration of the quality and availability of expertise and services in the community wherein care is provided. In circumstances in which the document is being used as the basis for regulatory or payer decisions, improvement in quality of care should be the goal. Because lack of patient understanding and adherence may adversely affect outcomes, providers should make every effort to promote the patient's understanding of, and adherence to, prescribed and recommended pharmacological and psychosocial treatments and any associated testing. Patients should be informed of the risks, benefits, and alternatives to a particular treatment or test, and should be an active party to shared decision-making whenever feasible. Recommendations in this document do not supersede any federal or state regulation.

Terminology and Key Terms

Below are brief definitions of select key terms and explanations of how they are used in this document. For example, the term ''provider'' is used throughout this document to refer to any individual or organization who may utilize clinical drug testing for identification, diagnosis, treatment, and recovery of patients with, or at risk for, addiction.

This includes addiction treatment clinicians, addiction treatment programs, drug treatment programs and primary or general healthcare physicians. Please refer *Appendix 2: Glossary and Terms* to clarify the use of other specific terms. *Appendix 1: Abbreviations and Acronyms* provides further clarification.

Analyte: The component of a biological sample that is identified and measured. In drug testing, both parent drugs and the products of drug metabolism are targeted. Their presence indicates exposure to a substance or family of substances.

Definitive testing: In contrast to presumptive testing, testing performed using a method with high sensitivity and specificity that is able to identify specific drugs, their metabolites, and/or drug quantities. Definitive testing is likely to take place in a laboratory and each individual test can be expensive. Gas or liquid chromatography combined with mass spectrometry is the gold standard method in definitive drug testing.

Expected test results: In the context of addiction treatment that includes medication (eg, buprenorphine) an expected test result is positive for prescribed medication and negative for other addictive substances.

Matrix (plural matrices): The biological material used for analysis in a drug test. Examples include blood, urine, oral fluid (spit/saliva), hair, nails, sweat, and breath.

Negative test result: The result reported by a test that fails to detect the presence of a target substance in a sample. This can indicate either a complete lack of the drug or drug metabolite or a level too low to be detected by the test. In this document, a ''negative test result'' refers to a test result showing no use of non-prescribed addictive substances. However, in the context of addiction treatment that includes medication, the terms positive and negative have been replaced with ''unexpected'' and ''expected.''

Patient: Anyone who receives care for an addiction in a specialty addiction treatment center or other healthcare setting.

Point of collection test/point of care test (POCT): A drug test performed at the site where the sample is collected using either an instrumented or non-instrumented commercial device (eg animmunoassay test strip or dipstick or a machine-based immunoanalyzer with optical reader).

Positive test result: The result reported by a test that detects the presence of a target substance in a sample. In this document, a ''positive test result'' refers to a test result showing the use of non-prescribed addictive substances. However, in the context of addiction treatment that includes medication, the terms positive and negative have been replaced with ''unexpected'' and ''expected.''

Presumptive testing: In contrast to definitive testing, testing performed using a method with lower sensitivity and/or specificity, which establishes preliminary evidence regarding the absence or presence of drugs or metabolites in a sample.

Provider: Used throughout the appropriateness document, this term is intentionally broad. It encompasses anyone (an individual or organization) who participates in providing care to patients with addiction, including staff at specialty addiction treatment centers or other healthcare settings that provide addiction treatment.

Unexpected test results: In the context of addiction treatment that includes medication (eg, buprenorphine), an unexpected test result could be (a) negative for prescribed medication, (b) positive for other addictive substance, or (c) both.

Window of detection: The range of time that a substance can be detected in a sample. It refers both to the time to detection (time to be absorbed and distributed to sample material) and time to clearance (time to be metabolized/eliminated/excreted). Each matrix and analyte has a different window of detection, ranging from minutes to months.

PART 1: PRINCIPLES OF DRUG TESTING IN ADDICTION TREATMENT

Clinical Value of Drug Testing

Principles of Biological Detection of Substance Use

Drug tests are tools that provide information about an individual's substance use. Any practitioner involved with the care of patients with addiction should understand what information drug testing can and cannot convey. Drug testing has been referred to as ''the technology of addiction treatment'' [5], but like any technology, its value depends on whether it is utilized correctly. Drug testing is an effective technology when the right test is selected for the right person at the right time.

Drug tests are designed to detect whether a substance has been used within a particular window of time. The test involves collecting a biological sample, also called a specimen, which is tested for the presence or absence of a specific substance or substances. While it can be a powerful tool, a drug test is designed to answer a rather narrow question: is substance X detected in sample Y? The answer is limited to the substance or substances that are targeted by the test, the individual sample which was tested (representing the patient's biological state at the time of collection), and the detection method used by the test. If the answer is yes, the result is labeled ''positive'' and if no, the result is labeled ''negative.''

A positive drug test result indicates that the patient providing the sample had a detectable amount of the targeted substance(s) in his or her system when the sample was collected. The timing of sample collection is important. Substances have a constant rate of elimination from the body, but the rate varies across biological sample type, or matrix. Some drug tests may be better or worse at detecting a substance in a particular matrix, which means it is important for a provider to understand the test's sensitivity and specificity to gauge the possibility of false negatives or positives. But even the most effective test under ideal circumstances can only measure the presence of a substance within the window of time it remains detectable in the body, also called the window of detection.

A positive drug test is not sufficient evidence for a diagnosis of an SUD. It does not explain whether a patient's symptoms are caused by the presence of a substance. In most cases, a drug test does not measure impairment and in most cases a drug test does not measure patterns of use over time.

It is important not to over-interpret a negative test result. A negative result does not mean that a patient has not used substances; it merely means that the patient has not used the substance(s) targeted by the test within the window of detection or used an amount less than the test is capable of detecting. Not only does an accurate negative test result not rule out substance use, it also does not rule out SUD, which can be present without recent substance use.

Drug Testing and Self-Reported Substance Use

If the appropriate interpretation of a drug test result is so narrow, why test at all? Drug testing provides another source of information to complement self-report, collateral report, and provider assessment. Having an additional, alternative means of assessing a patient's recent substance use is important to treatment planning and ongoing treatment adjustment.

Because individuals with addiction pathologically pursue reward and/or relief by substance use, some patients will give inaccurate or incomplete histories. Therefore, it behooves providers to verify self-report with biological testing. In contrast to a patient's self-report, biological test results are considered ''objective'' in that they are not subject to limitations caused by memory, social acceptability, or missing information. For example, a patient might not accurately remember his or her substance use history, may try to minimize or overstate his or her past use, and may not be aware of the composition of the substances he or she has consumed, especially as synthetic drugs increase in prevalence.

Patients facing potential negative consequences if substance use is detected, such as increased sanctions or legal action, may be less likely to self-report accurately. For example, a multisite trial of patients with prescription drug use disorders concluded that ''self-reports of substance use are most likely to be valid when participants believe that they will not suffer negative consequences'' as a result of their report [6]. In situations where substance use may result in these consequences, the combination of self-reported use and drug test results may lead to a more accurate picture of recent substance use.

Due to its inherent limitations, drug testing should not be relied upon as the sole measure of a patient's substance use. All drug testing should be accompanied by a discussion with the patient about his or her substance use. A patient's self-report provides additional clinically relevant information that drug testing cannot. In the event that a patient's self-reported substance use differs from the results of a drug test, the provider should use the discrepancy as a springboard for therapeutic discussions.

Drug Testing and Patient Outcomes

The decision to use any tool in health care should be grounded in the principles of improved patient care and outcomes. Although evidence is limited that the use of drug testing in addiction treatment improves patient outcomes, the expert panel cited extensive clinical experience supporting the use of drug testing to improve patient outcomes.

Moreover, two 2014 studies illuminated the currently unrealized role of drug tests in addiction treatment. Blum et al [7] looked at whether drug test results are useful indicators of patients' progress in treatment and concluded that testing for both prescribed addiction medications and illicit drug use can improve a provider's ability to determine the effectiveness of the current treatment approach. However, a systematic review of patient charts concluded that drug testing does not appear to change the way patients are managed by their treatment providers, although it was unclear whether these results were due to provider behavior or actual lack of effect of drug testing on management or outcome of patients in addiction treatment [8]. Together, these results suggest that drug testing has the potential to improve patient outcomes if used correctly and consistently to monitor and adjust treatment plans. Drug testing should be used widely in addiction treatment settings and its use should be integrated into the process of making treatment decisions.

Drug Testing and Evidence-Based Therapy

Although drug testing in addiction treatment settings is common, providers have heretofore received very limited guidance on how drug testing should be integrated with evidence-based addiction treatment.

The most extensively researched behavioral therapy used in conjunction with drug testing is contingency management. Contingency management can involve tying behavioral incentives to the result of a drug test and has been shown to be an effective approach to addiction treatment [9]. It is clear that the contingency management model fits well with drug testing [10] and the expert panel recommends combining the 2. When using drug testing as part of contingency management, providers should also seek self-reported information from patients about substance use.

Clinical Use of Drug Testing

Therapeutic Tool

Drug testing should be used as a tool for supporting recovery rather than exacting punishment. Every effort should be made to persuade patients that drug testing is a therapeutic, rather than punitive, component of treatment. This process may require time and multiple conversations. If drug testing is used in such a way that it creates an ''us versus them'' mentality, it is at odds with the therapeutic alliance. In fact, drug testing can be thought of as a tool to improve the therapeutic alliance in that it transfers the role of detector from the provider to the test.

Using drug testing as a therapeutic tool means addressing test results as a part of therapy. Drug testing should be used to explore denial, motivation, and actual substance use behaviors. Test results that do not align with a patient's self-report should generate therapeutic discussion with the patient. If a patient refuses to undergo a drug test, that refusal should be an area of focus for the patient's treatment plan. Some of the value of using drug test results as a topic of therapeutic discussion has been demonstrated by 2 qualitative studies that showed favorable responses to drug test discussions among some patients in treatment [11,12].

In addition to measuring treatment efficacy, drug testing may also serve as a source of motivation and reinforcement for abstinence [13]. Providers should use negative test results as a source of encouragement.

Assessment

Drug testing should be a key component of assessment for SUD and should be used to assist in treatment planning.

Test results should always be combined with patient history, psychosocial assessment, and a physical examination during an assessment. According to ASAM's *Principles of Addiction Treatment*, ''Laboratory testing in the clinical setting is intended to guide diagnosis and treatment planning...the provider must combine the findings from the history and physical examination with that of the laboratory testing for accurate interpretation and management'' [14]. The results of the medical and psychosocial assessment generate valuable information (eg, types of substances used) that should inform the provider's decision about drug testing (see *Choosing a Test*, p. 7).

It is recommended that treatment providers include drug testing at intake. Drug test results at intake have been determined to be a useful predictor of treatment outcomes [15,16]. Patients who submit a positive drug test at intake may benefit from different approaches to treatment than patients who submit a negative test [17].

Drug testing as part of an initial assessment provides additional benefits. For example, test results can help illuminate any links between substance use and psychiatric or medical symptoms a patient is experiencing. For a patient presenting with altered mental status, a negative drug test result may support differentiation between intoxication and/or presence of an underlying psychiatric and/or medical condition that should be addressed in treatment planning. Drug testing can also verify a patient's substance use history or demonstrate a discrepancy between self-reported use and test results. Finally, drug tests may be used to help determine optimal placement in a level of care using *The ASAM Criteria*, particularly in assessing Dimension 1 (Acute Intoxication and/or Withdrawal Potential), Dimension 4 (Readiness to Change), and Dimension 5 (Relapse, Continued Use, or Continued Problem Potential).

Drug testing may also assist providers in re-assessing patient needs while the patient is receiving treatment. For example, it is appropriate to conduct drug tests when patients display a change in clinical status, such as apparent sedation/ataxia/agitation or other behavior change that might indicate recent drug exposure.

Monitoring

Drug testing should be used to monitor the effectiveness of a patient's treatment plan. If a goal of treatment is to reduce or eliminate substance use, drug testing can be thought of as an ongoing measure of treatment performance. A pattern of tests that are positive for expected prescribed medications and negative for other unexpected substance use, in combination with other indicators, suggest a patient's treatment plan is effective. In contrasts, tests that are positive for unexpected substance use (and/or negative for expected prescribed substances) suggest that the treatment plan should be adjusted. If a provider is making treatment adjustments, test results can be helpful in determining optimal placement in a level of care. Providers should note that immediate cessation of substance use early in treatment may not be a realistic treatment goal. The section on *Responding to Test Results* provides more detail on the appropriate response to test results.

Drug testing is only one measure of one treatment goal and it should not be the only method of detecting substance use or monitoring treatment outcomes; results should be interpreted in the context of collateral and self-report and other indicators.

Summary of Recommendations

Clinical Value of Drug Testing

Principles of Biological Detection of Substance Use

- Providers should understand that drug tests are designed to measure whether a substance has been used within a particular window of time.

Drug Testing and Self-Reported Substance Use

- Drug testing should be used in combination with a patient's self-reported information about substance use.
- Drug testing is an important supplement to self-report because patients may be unaware of the composition of the substances(s) they have used.
- Drug testing is particularly appropriate for patients facing negative consequences if substance use is detected, who are therefore less likely to provide accurate self-reported substance use information.
- Discrepancy between self-report and drug tests results can be a point of engagement for the provider.

Drug Testing and Patient Outcomes

- Because evidence suggests that drug testing assists with monitoring adherence and abstinence in treatment and can improve patient outcomes, drug testing should be used widely in addiction treatment settings.

Drug Testing and Evidence-Based Therapy

- Contingency management is most extensively researched behavioral therapy used in conjunction with drug testing. When utilizing contingency management therapy to encourage abstinence, providers should consider incorporating drug testing.

Clinical Use of Drug Testing

Therapeutic Tool

- Drug testing is recommended as a therapeutic tool as part of evidence-based addiction treatment.
- Providers should utilize drug testing to explore denial, motivation, and actual substance use behaviors with patients.
- If drug-testing results contradict self-reports of use, therapeutic discussions should take place.
- Providers should present drug testing to patients as a way of providing motivation and reinforcement for abstinence.
- Providers should educate patients as to the therapeutic purpose of drug testing. To the extent possible, persuade patients that drug testing is therapeutic rather than punitive to avoid an ''us versus them'' mentality.

- If a patient refuses a drug test, the refusal itself should be an area of focus in the patient's treatment plan.

Assessment

- Treatment providers should include drug testing at intake to assist in a patient's initial assessment and treatment planning.
- Results of a medical and psychosocial assessment should guide the process of choosing the type of drug test and matrix to use for assessment purposes.
- Drug test results should not be used as the sole determinant in assessment for SUD. They should always be combined with patient history, psychosocial assessment, and a physical examination.
- Drug testing may be used to help determine optimal placement in a level of care.
- Drug testing can serve as an objective means of verifying a patient's substance use history.
- Drug testing can demonstrate a discrepancy between a patient's self-report of substance use and the substances detected in testing.
- For a patient presenting with altered mental status, a negative drug test result may support differentiation between intoxication and/or presence of an underlying psychiatric and/or medical condition that should be addressed in treatment planning.
- Drug testing can be helpful if a provider is required to document a patient's current substance use.

Monitoring

- Drug testing should be used to monitor recent substance use in all addiction treatment settings.
- Drug testing should be only one of several methods of detecting substance use or monitoring treatment; test results should be interpreted in the context of collateral and self-report and other indicators.

PART 2: PROCESS OF DRUG TESTING IN ADDICTION TREATMENT

Choosing a Test

When choosing a test, providers will make decisions about the following factors:

- The information they wish to gain from testing
- The substance or substance(s) targeted
- Matrix sample collected
- The reliability/usefulness of the result
- Cost

"Smarter" drug testing means that providers actively address these factors in the process of choosing a drug test, rather than defaulting to perceived organizational or industry norms [2].

Clinical Necessity and Value

Tests should be chosen based on the information they are expected to reveal. All tests are designed to answer certain questions and all tests have limitations. Providers should first determine the purpose of the test—what question it needs to answer—and choose the test best able to provide that answer.

Test selection should be individualized based on a patient's clinical needs and their self-reported substance use (see *Drug testing and self-reported substance use*, p. 5). When possible, it is recommended that providers conduct a drug test after obtaining a patient's self-report. Admitted use and knowledge of preferred substances can guide the provider's process of choosing a drug test.

Individualization of testing does not mean that every patient will get a different test, but that he or she *can* if the circumstances warrant it. The expert panel concluded that the use of a routine test panel is generally acceptable practice. However, this should not block the ability of providers to use alternative matrices and tests, individualized to the patient's needs.

Identifying Substance(s) of Interest

The substances targeted in a patient's routine drug test should be adjusted based on the patient's drug of choice, prescribed medications, and drugs commonly used in the patient's geographic location and peer group.

It is generally useful for addiction treatment programs/providers to establish a routine panel based on the most commonly used substances in their treatment population with consideration for regional patterns of use.

Substance use trends vary considerably by region. Providers should be aware of which drugs tend to be prevalent in their region and attentive to new substance use trends and emerging drugs (many of them synthetic) that may become available to their patient population for the first time. Note that an important area for future research is when and how to identify novel synthetic drugs, such as cannabinoids and cathinones, for various patient populations.

Because emerging drugs will continue to proliferate, providers will always be playing catch-up when trying to detect substance use. Test panels should be updated regularly to address local substance use trends. A testing laboratory can be a valuable resource regarding information related to changes in substance use at the local level. Medical toxicologists can also provide information on regional variations in drug use or on local trends.

Providers should not rely on a 5-panel screen known as the NIDA-5 (or SAMHSA-5) as a routine drug panel. This panel is intended for workplace drug testing; the substances targeted and their associated cutoff levels are not appropriate for the clinical care of patients with addiction.

Providers should be aware that some drugs share common metabolites. For example, codeine and heroin are both metabolized to morphine. The detection of morphine indicates that an individual has been exposed to one of these opioids, but that result by itself cannot determine if the drug that was consumed was morphine, codeine or heroin. Detecting which opioid requires a test for either a parent drug (eg, heroin) or an analyte specific to that substance (eg, 6-monoacetylmorphine [6-MAM]).

Matrix Advantages and Disadvantages

Urine, blood, exhaled breath, oral fluid (saliva), sweat, and hair are some biological samples (known as matrices) that

are used in drug testing. As defined by ASAM, ''smarter'' drug testing means using the matrix best able to answer the clinical question at hand. Although urine is the best established matrix in addiction treatment settings, other matrices provide different levels of sensitivity and specificity over different windows of detection. For example, heroin is rapidly converted to 6-MAM and subsequently to morphine. Heroin or 6-MAM must be detected to specifically confirm heroin rather than general opiate use. While 6-MAM remains present at detectable concentrations in oral fluid for longer than urine, the subsequent metabolic products remain detectable in urine for longer than oral fluid.

A main consideration in matrix choice is also its varying susceptibility to sample tampering. Rotating matrices can reduce the potential for tampering with samples. However, providers should understand the advantages and disadvantages of each matrix before considering such strategies.

The use of an alternative matrix is also appropriate if a particular sample type cannot be collected (eg, patients on dialysis, who are bald or have dry mouth or shy bladder) or when a sample collection technique is too invasive (such as direct observed urine testing for a patient with sexual trauma). If a given sample is likely to be prone to confounds, providers should choose an alternative matrix. For example, heavily chemically treated hair is not appropriate for drug testing.

Clinical considerations that pertain to matrices are covered more fully in *Part 4: Biological Matrices.*

Presumptive and Definitive Tests

Drug testing can be divided into 2 classes: presumptive and definitive. Presumptive tests generally have lower sensitivity and/or specificity compared to definitive tests.

The primary benefit of presumptive testing methods is a much faster turnaround time to receive results, which allows for a more rapid therapeutic response that can more meaningfully link substance use and behavior. Therefore, presumptive tests should be used when it is a priority to have more immediate (although potentially less accurate) results. If a patient disputes the results of a presumptive test, the test should be confirmed using a definitive method. If a patient confirms that he or she used a substance detected by a presumptive test, it is not necessary to perform a definitive test to confirm the result. Presumptive testing should be a routine part of initial and ongoing assessment of a patient's use of substances.

Definitive testing should be used whenever a patient disputes the findings of a presumptive test, when a provider wants to detect a specific substance not adequately identified by presumptive methods (eg, heroin rather than opiates) or when the results will inform a decision with major clinical or non-clinical implications for the patient (eg, treatment transition, changes in medication therapies, changes in legal status).

If a provider expects the result of a presumptive test to be positive (eg, a patient reports recent use), and information regarding specific substance and/or quantity is desired, it may be appropriate to skip the presumptive test in favor of a definitive test. When ordering a definitive test, providers should advise the testing laboratory of suspected or expected substance(s) in the specimen. Providers should be aware that many laboratories do not automatically perform definitive testing on positive presumptive results (known as ''reflex testing'') and may require an additional order for such testing to occur.

Use of Specific Terms

Presumptive and definitive tests are often referred to using terminology, which actually describe differences in analytical method (eg, immunoassay vs. chromatography/mass-spectrometry), test setting (eg, the point of care or in a laboratory) or underlying purpose (eg, screening or confirmation). While some of these differences may have fallen neatly within the category of presumptive and definitive testing in the past, advances in technology have made these generalizations increasingly inaccurate. Table 1 illustrates a number of terms often used interchangeably to refer to presumptive and definitive tests.

In this document, the terms ''presumptive'' and ''definitive'' are used, except when referring to a specific aspect of a test (eg, Point of Care Tests).

Immunoassay Versus Chromatography/Mass Spectrometry

For the most part, presumptive testing uses immunoassay technology and definitive testing uses a combination of various chromatography and mass spectrometry techniques. However, there are some immunoassays, which can be used as definitive tests (eg, Immunoassays for cocaine metabolites are quite specific).

Immunoassays use antibodies designed to bind with a specific drug (eg, methadone), metabolite (eg, 6-MAM) or class of compounds (eg, opiates, which detects morphine) in a sample. If no drug compounds are present in a sample, the antibodies will instead bind with a conjugate compound and register as a colored line in the test readout area. Immunoassays have varying degrees of sensitivity and specificity depending on the particular antibodies and the cutoff value used. A cutoff value is the amount of substance that needs to be detected in a sample for it to be considered positive. Test results are positive if there is enough drug or metabolite present in a sample to react with a predetermined threshold of antibodies in the assay.

TABLE 1. Terms Often Used Imprecisely to Refer to Presumptive and Definitive Tests

Presumptive	Definitive
Qualitative	Quantitative
Preliminary	Confirmatory
Immunoassay	Chromatography/mass-spectrometry
Point of care/in-office/lab-based	In-office/lab-based
Screen	Confirmation
Semi-quantitative/quasi-quantitative	Absolute level/creatinine-corrected
Simple (cup/strip/dipstick/cassette)	Complex
Class or category test	Specific drug identification

Reference 146.

Gas or liquid chromatography combined with mass spectrometry are the gold standard methods of drug testing. Chromatography is used to separate a specimen into its component parts and mass spectrometry to identify those parts. These methods are both highly sensitive and highly specific. This testing is likely to take place in a laboratory and each individual test can be expensive.

Screening Versus Confirmation

The terms ''screening'' and ''confirmation'' refer to the purpose of the test. A common practice in testing is to first screen samples using an inexpensive test to rule out likely negative samples and then confirm potential positive results using a highly specific test. Often, immunoassay methods are used to screen samples and positively screened samples are confirmed using a chromatography/mass-spectrometry method or an immunoassay using a lower cutoff value and/or one targeting specific substances within a class.

When using a cutoff, a negative result does not exclude the presence of a drug or metabolite in a sample, but reflects it was not a sufficient amount to cross the cutoff limit. Screening tests often use cutoffs chosen to minimize the incidence of false positives. This, consequently, increases the incidence of false negatives. Many laboratories and point of care tests (POCTs) use screening cutoff levels calibrated for workplace or law enforcement drug testing. These cutoffs may be set very high to identify individuals which use large amounts of a substance and minimizes false positives from accidental environmental exposure (eg, from second-hand marijuana smoke); therefore, they may not be appropriate for clinical use. Providers should know the cutoff concentration used for immunoassay when interpreting a presumptive or definitive test result of ''no drug present.''

Class or Category Test Versus Specific Substance Test

A drug ''screen'' can also refer to an immunoassay, which reacts to the presence of a class of drugs. The specific substance is then ''confirmed'' using a test method, which can identify a specific substance or metabolite. It is often only possible to test for specific substance using chromatography/mass-spectrometry, but immunoassays are also available that are highly targeted and specific to individual substances.

The degree of an immunoassay's specificity depends on the extent to which antibodies will bind specifically with a target compound while excluding structurally related compounds, also known as cross-reactivity. The less specific an immunoassay is for a single substance, the higher the cross-reactivity is for other substances. For example, standard opiate immunoassays target morphine-like molecules and best detect morphine and codeine. They show moderate cross-reactivity with the morphine-derived semi-synthetics hydrocodone and hydromorphone, and poor cross-reactivity with thebaine-derived semi-synthetics oxycodone and oxymorphone. Fentanyl, meperidine, methadone, and buprenorphine have negligible to no cross-reactivity with a standard opiate immunoassay. Semi-synthetic opioids less structurally similar to morphine and fully synthetic opioids are better detected with immunoassays that use different antibodies that are specific to these analytes.

Qualitative Versus Quantitative

A qualitative test is one that detects the presence or absence of a particular compound in a sample. A quantitative test is one that measures the quantity of a particular compound in a sample. Immunoassays are qualitative tests. Most chromatography/mass-spectrometry techniques are quantitative. Quantitative results are reported as the concentration within a sample. The concentrated amount should be used cautiously when interpreting the dose or timing of substance use because of individual differences in metabolism.

POCT Versus Laboratory

While definitive testing used to be the performed exclusively in the lab, the line is becoming increasingly blurry due to enhancements in the quality and availability of point of care testing (POCT). Although simple POCTs, such as urine dipstick technologies, are prone to lower accuracy and precision, newer POCT analyzers have significantly greater quality control and rival central laboratory analysis in terms of their sensitivity and specificity. For routine clinical use, POCT (including newer urine dipstick testing) is more efficient and economical and provides reliable results. For high stakes testing (eg, testing that will inform an irreversible clinical decision), formal laboratory analysis remains the ''gold standard'' testing methodology (Table 2).

Cost

Providers should always consider cost both to patients and insurers when choosing drug tests. Smarter drug testing means careful consideration of the financial costs of testing in

TABLE 2. Definitions of Sensitivity and Specificity

	Sensitivity	Specificity
Definition	The likelihood that a given test is able to detect the presence of a drug or metabolite that is actually in the specimen	The likelihood that a given test is able to identify the specific drug or metabolite of interest in the specimen and not to erroneously label other drugs or metabolites
Determined by	Ability to avoid false negatives, where the presence of a drug is missed in a positive sample	Ability to avoid false positives, when an analyte is misidentified as the target in a negative sample
Calculated by	Number of false negatives/number of positive samples	Number of false positives/Number of Negative samples
Utility	A negative result in a test with high sensitivity is useful for ruling out substance use, since positive samples are rarely missed	A positive result in a test with high specificity is useful for ruling in substance use, since negative samples are rarely mislabeled

Adapted from American Society of Addiction Medicine [2].

relationship to the value and in many cases, medical necessity, of the test results [2].

Responding to Test Results

According to the ASAM White Paper, ''All physicians (and others) involved in drug testing should determine the questions the test are intended to answer before the testing is administered and should have a plan for what to do with the results'' [2]. It is important for providers to attach a meaningful response to test results, both positive and negative, and deliver it as quickly as possible. Although negative and positive test results can provide valuable information about recent substance use, providers should be aware that a positive drug test does not diagnose a SUD and a negative test result does not rule out a SUD (see *Clinical Value of Drug Testing*, p. 4).

Drug testing should function as a therapeutic tool (see *Clinical Use of Drug Testing*, p. 5), so a provider's response to test results should not be confrontational. This approach can perpetuate an ''us versus them'' mentality that reduces the effectiveness of drug testing to support recovery.

Providers may also be compelled to make significant, sometimes irreversible, clinical decisions on the basis of drug test results. For example, a provider may consider whether a patient should be transferred to a higher level of care after multiple positive test results. Providers are encouraged to consider all relevant factors when making a significant clinical decision, rather than drug test results exclusively, keeping in mind that immediate abstinence may not be a realistic goal for patients in the early stages of treatment.

Providers should also be aware that all tests have some rate of false-positive and false-negative outcomes (Table 3). False positives occur when a negative sample is incorrectly labeled as positive. This can occur if the target analyte is present in the sample, but for reasons other than a patient knowingly consuming an addictive substance. Perhaps the most infamous example of false positives of this kind comes from consuming poppy seeds, which produce a detectable amount of morphine in the body. The amount produced, however, results in a much lower body tissue concentration of morphine than that resulting from typical recreational or medicinal opioid use. Samples can also become contaminated through handling collection containers after the use of alcohol-containing hygiene products or hand sanitizers. The use of a detection threshold, or cutoff limit, is meant to reduce false-positive results from unintentional, incidental contact with a substance by effectively decreasing the sensitivity of a test.

Of greater concern are false positives resulting from the misidentification of a similar substance for the target. The list of potential sources of false positives is too extensive to list here, but a few noted examples include; cough suppressants resulting in positive opioid results, ephedrine in cold medicine resulting in positive result for amphetamines, and antidepressants resulting in positive opioid results. Comprehensive reviews of sources of false positives have been published for UDT [18,19], but providers should be aware that new examples of false positives are continuously detected for various tests, and tests are continuously updated and refined to address these limitations. Providers without formal toxicology training can participate in available courses, and/or should collaborate with a medical toxicologist, a toxicologist from the testing laboratory, or a physician certified as an MRO. Providers could consider MRO training and/or certification through organizations including the American Association of MROs and/or the Medical Review Office Certification Council.

False negatives occur when a positive sample is incorrectly labeled as negative. Sometimes this is the result of the use of a cutoff limit. In this case, a negative result does not exclude the presence of a drug or metabolite, but reflects it was not a sufficient amount to cross the cutoff limit.

Unclear Test Results

When test results are unclear, providers should communicate with the testing laboratory to properly interpret them. It is important that the relationship between an addiction treatment provider and a testing laboratory be collaborative (see *Choosing a laboratory*, p. 14) to enable proper interpretation of test results. Providers may also consider consulting with a medical toxicologist or MRO for assistance in interpreting unclear test results. Sometimes test results are unclear because of tampering (dilution, substitution, or adulteration). When a provider suspects tampering may have occurred, he or she may have the option to retain the sample for additional testing (including specimen validity testing), use a different matrix, or change/add to the test panel. The original sample should not be discarded; instead, it should be retained to help investigate whether and how tampering occurred. Note that urine is the matrix most prone to sample tampering; see *Urine*, p. 17, for more detail on avoiding and responding to tampering with urine samples.

Presumptive Test Results

There are 2 possible outcomes to a presumptive test: positive and negative.

Positive presumptive test results should be referred to as ''presumptive positive'' results until confirmed by a definitive test, although it is not always necessary to perform a definitive test on a presumptive positive sample (see *Presumptive and definitive tests*, p. 12). An appropriate response to a

TABLE 3. Possible Test Outcomes

	Positive sample	Negative sample
Positive test result	True positive Test correctly identified the presence of target analyte.	False positive Test misidentified an analyte as target analyte.
Negative test result	False negative Test missed the presence of target analyte.	True negative Test correctly did not identify any target analyte.

presumptive positive test result includes speaking with the patient, discussing possible cross-reactivity related to medications or food, and ordering a definitive test if the patient's self-report is not consistent with the presumptive test result. Providers may also want to consult with their testing laboratory for assistance interpreting the presumptive positive result.

Presumptive tests are often called ''qualitative tests'' because they are designed to measure the presence or absence of the target drug/analyte, rather than the amount. Because presumptive tests use cutoff values and are designed to have high sensitivity and lower specificity, providers should use caution when interpreting and responding to presumptive test results.

Particularly in the case of presumptive tests, providers should remember that a negative test result does not rule out substance use (which could have occurred outside the window of detection, below the cutoff value or been excluded from the test panel) or SUD (which is a clinical diagnosis). If presumptive test results are negative, but the patient exhibits signs of use (eg, through signs of intoxication or withdrawal), it is appropriate to confirm using a definitive test with greater sensitivity. Providers may also want to expand the drug panel to include previously untargeted substances.

Definitive Test Results

The results of a definitive test can be taken as conclusive. In the event of a positive definitive test, providers should consider adjusting the patient's treatment plan. The patient may benefit from intensified treatment or the addition of an adjunctive treatment element.

Even if the result of a definitive test is quantitative, providers should use caution when using test results to draw conclusions about the amount or pattern of a patient's substance use. There are some tests and methods that are better at correlating the quantity of drug measured in a sample with amount used. For example, a blood or breath test for ethanol or hair test for the metabolite ethyl glucuronide (EtG) can indicate point-in-time or average-over-time alcohol use. The concentration of ethanol or EtG in urine, however, is dependent on additional factors such as hydration and metabolic health (see *Comparing Matrices*, p. 35). For questions about interpreting a positive test result, providers should consult with their testing laboratory.

In the event of a negative definitive test, providers should be mindful of the limitations of drug testing (see *Clinical Value of Drug Testing*, p. 4) and not over-interpret its significance. A patient whose definitive test results are negative may still have engaged in substance use (outside of the window of detection of the test) or have an SUD (which is a clinical diagnosis).

Test Scheduling

Test schedule is an area of interest for providers and payers. There is very little guidance about clinically appropriate test schedules, which has led to both an over- and under-utilization of drug testing, and generally, an approach to test scheduling that does not meet the standards of ''smarter'' testing.

Test Frequency

For patients in addiction treatment, frequency of testing should be dictated by patient acuity and level of care. For recommendations related to specific level of care, see *Part 5: Settings*.

There is no magic formula for determining the test frequency a patient should receive. The expert panel strongly disagreed with statements about specific numerical limitations on drug test frequency. For example, the panel agreed that the following statement is inappropriate: ''Drug testing should be scheduled no more than 24 times per year.''

In accordance with the principle of ''smarter'' drug testing, the provider's therapeutic questions should dictate the frequency of drug testing. In formulating questions, providers should be aware that there is currently insufficient evidence that more frequent testing leads to decreased substance use. Based on these questions, providers should look to the tests' detection capabilities and windows of detection to help determine the frequency of testing. (*See Appendix 4: Windows of Detection Table* for a chart describing matrices and windows of detection for various target analysis.)

As a general principle, drug testing should be scheduled more frequently at the beginning of treatment. The Expert Panel recommends that a patient in early recovery be tested at least weekly. As the patient becomes more stable in recovery, the frequency of drug testing should be decreased, but performed at least on a monthly basis. Individual consideration may be given for less frequent testing if a patient is in stable recovery.

If the patient returns to substance use after a period of abstinence, the provider should resume the early recovery testing schedule, possibly in conjunction with an adapted or intensified treatment plan.

Random Testing

Whatever the frequency, clinical consensus favors unannounced drug testing over scheduled drug testing and random testing schedules to fixed testing schedules [2,13,20]. A fixed schedule (eg, every Monday) offers patients increased opportunity to engage in sample tampering. Even if the frequency is within a test's normal window of detection (eg, a urine immunoassay screen for amphetamines every Monday and Thursday) it is possible for a patient to engage in substance use on Thursday night and not produce a positive result on Monday morning. Although not always possible to implement, a random testing schedule can eliminate such strategic workarounds by making patients unaware of when exactly they will be tested.

Providers should note that the way randomization is applied to scheduling in a clinical setting can make it more or less effective. The purest form of randomization is to have a set probability (eg, 15%) that a patient could be tested on any given day. This is akin to rolling a die every day and testing whenever a 6 appears. While this eliminates known safe periods, the length of time a patient may go between testing can be quite long.

To avoid unknown testing intervals, many addiction treatment providers randomly select a day from a fixed interval [21]. Once the day is selected, however, no testing

will occur until the start of the next interval, leaving the problem of known non-testing periods if the selected day occurs early within the interval (eg, Monday from a weekly interval). Instead, providers can randomly select the interval from a set of allowable days between testing (eg, 2, 3, . . . 6, 7 days). This limits both the maximum interval between tests and known non-testing periods.

Summary of Recommendations

Choosing a Test

Clinical Necessity and Value

- Before choosing the type of test and matrix, providers should determine the questions they are seeking to answer and familiarize themselves with the benefits and limitations of each test and matrix.
- Test selections should be individualized based on specific patients and clinical scenarios.
- Patients' self-reported substance use can help guide test selection.

Identifying Substance(s) of Interest

- Drug-testing panels should be based on the patient's drug of choice, prescribed medications, and drugs commonly used in the patient's geographic location and peer group.
- Addiction treatment programs/providers should establish a routine immunoassay panel.
- Providers should not rely on the NIDA 5 (also known as the SAMHSA 5) as a routine drug panel.
- Test panels should be regularly updated based on changes in local and national substance use trends. Providers should collaborate with the testing laboratory when determining the preferred test selections to obtain information about local and demographic trends in substance use.

Matrix Advantages and Disadvantages

- Providers should understand the advantages and disadvantages of each matrix before considering rotational strategies.
- If a particular specimen cannot be collected (eg, due to baldness, dry mouth, shy bladder), providers should consider collecting an alternative specimen.
- If a given sample is likely to be prone to confounds, providers should choose an alternative matrix. For example, heavily chemically treated hair is not appropriate for drug testing.

Presumptive and Definitive Tests

- Presumptive testing should be a routine part of initial and ongoing patient assessment.
- Presumptive testing should be used when it is a priority to have more immediate (although less accurate) results.
- Providers should know the cutoff threshold concentrations that their laboratory uses when interpreting a report of "no drug present."
- Federal cutoff threshold concentrations used for occupational testing are not appropriate for clinical use.
- Definitive testing techniques should be used whenever a provider wants to detect specific substances not identified by presumptive methods, quantify levels of the substance present, and refine the accuracy of the results.
- Definitive testing should be used when the results inform clinical decisions with major clinical or non-clinical implications for the patient (eg, treatment transition, changes in medication therapies, changes in legal status).
- If a patient disputes the findings of a presumptive test, a definitive test should be done.
- When ordering a definitive test, providers should advise the testing laboratory if the presence of any particular substance or group of substances is suspected or expected.
- Because not all laboratories automatically perform a definitive test of positive presumptive results (the common term for this is "reflex" testing), providers should be aware that laboratories may require a specific order for definitive testing.

Cost

- Providers should always consider cost both to patients and insurers when utilizing drug testing.

Responding to Test Results

- Providers should attach a meaningful therapeutic response to test results, both positive and negative, and deliver it to patients as quickly as possible.
- Providers should not take a confrontational approach to discussing positive test results with patients.
- Providers should be aware that immediate abstinence may not be a realistic goal for patients early in treatment.
- When making patient care decisions, providers should consider all relevant factors surrounding a case rather than make a decision based solely on the results of a drug test. Considering all relevant factors is particularly important when using drug test results to help make irreversible patient care decisions.

Unclear Test Results

- Providers should contact the testing laboratory if they have any questions about interpreting a test result or to request information about the laboratory procedures that were used.
- Providers may consult with a medical toxicologist or a certified MRO for assistance in interpreting drug test results.
- If the provider suspects the test results are inaccurate, he or she should consider repeating the test, changing the test method, changing/adding to the test panel, adding specimen validity testing, or using a different matrix.
- If tampering is suspected, samples should not be discarded. Rather, further testing should be performed to help identify whether and how tampering occurred.
- Providers should consider samples that have been tampered with to be presumptive positive.

Presumptive Test Results

- Positive presumptive test results should be viewed as "presumptive positive" results until confirmed by an independent chemical technique such as gas chromatography mass spectrometry (GC-MS) or liquid chromatography-mass spectrometry (LC-MS).

- An appropriate response to positive presumptive test results includes speaking with the patient.
  - Providers should seek definitive testing if the patient denies substance use.
  - Providers should review all medications, herbal products, foods, and other potential causes of positive results with the patient.
- An appropriate response to positive presumptive test results may include speaking with the laboratory for assistance in interpreting the test results.
- Because presumptive tests may use cutoff values, a negative presumptive test result should not be over-interpreted. It does not rule out substance use or SUD, as the latter is a clinical diagnosis.
- It is appropriate to consider ordering a definitive test if presumptive test results are negative, but the patient exhibits signs of relapse.

Definitive Test Results

- In the event of a positive definitive test result, consider intensifying treatment or adding adjunctive treatments.
- An appropriate response to positive definitive test results may include speaking with the laboratory for assistance in interpretation.
- Providers should use caution when using drug test results to interpret a patient's amount or frequency of substance use. Individual metabolism and variability in absorption should be considered.
- Providers should not over-interpret a negative definitive test result. It does not rule out substance use or SUD, as the latter is a clinical diagnosis.

Test Scheduling

Test Frequency

- For people in addiction treatment, frequency of testing should be dictated by patient acuity and level of care.
- Providers should look to tests' detection capabilities and windows of detection to determine the frequency of testing.
- Providers should understand that increasing the frequency of testing increases the likelihood of detection of substance use, but there is insufficient evidence that increasing the frequency of drug testing has an effect on substance use itself.
- Drug testing should be scheduled more frequently at the beginning of treatment; test frequency should be decreased as recovery progresses.
- During the initial phase of treatment, drug testing should be done at least weekly. When possible, testing should occur on a random schedule.
- When a patient is stable in treatment, drug testing should be done at least monthly. Individual consideration may be given for less frequent testing if a patient is in stable recovery. When possible, testing should occur on a random schedule.

Random Testing

- Random unannounced drug tests are preferred to scheduled drug tests.
- A random-interval schedule is preferable to a fixed-interval schedule because it eliminates known non-testing periods (eg, if Monday is randomly selected from a week interval, the patient knows they will not be tested Tuesday-Saturday) and it is preferable to a truly random schedule because it limits the maximum number of days between tests.

PART 3: ADDITIONAL CONSIDERATIONS FOR DRUG TESTING IN ADDICTION TREATMENT

Documentation and Confidentiality

Addiction treatment providers and programs should have testing procedures in writing and share these with patients. One way to do this is to incorporate information about drug testing into patients' treatment agreements. Providers should also carefully document drug-testing procedures and rationale for individual patients. Documentation should include:

- Rationale for drug test types
- Rationale for drug-testing decisions
- Potential sources of cross-reactivity, including various foods and current medications
- Particular characteristics of the sample with potential to lead to problems with interpretation (eg, hair that has been chemically treated)
- Test results

Sometimes providers are asked to share test results with outside entities, such as social services agencies or the criminal justice system. The expert panel suggests that providers keep test results confidential to the extent permitted by law and use caution when sharing test results with outside entities. Providers should ensure that the patient has given informed consent for sharing test results; however, even when patients have authorized the release of test results, providers should be mindful that the aims and methods of employment-related drug testing and forensic drug testing are different from the aims and methods of clinical drug testing. Optimally, test results should be confirmed with a definitive test, although it may be appropriate to share presumptive results when they are negative. When sharing presumptive test results, ensure that they are clearly labeled "presumptive." Providers are responsible for providing patient education about confidentiality, consent, and sharing test results with outside entities.

Practitioner Education and Expertise

Knowledge and Proficiency

The accuracy of any drug test is predicated on the use of valid testing procedures, which include sample collection, analysis, and interpretation of results. Inadequate provider proficiency can result in inaccurate test results. The outcomes of a drug test can have serious consequences for patients; therefore, providers have a responsibility to ensure that they and their staff have the knowledge and proficiency necessary to carry out their roles in the drug-testing protocol.

A provider's necessary level of knowledge and proficiency about drug testing depends on his or her role in the

testing process. Providers who order tests should primarily be aware of the limitations of testing, common sources of false-positive and false-negative results, and tradeoffs between testing methods. They should:

- Be familiar with the limitations of presumptive testing
- Be familiar with the potential for cross-reactivity in drug testing (see *Responding to Test Results*, p. 10)
- Be familiar with the potential for sample tampering to obscure test results (see *Urine sample integrity*, p. 17)
- Understand the benefits of alternative matrices to urine (eg, oral fluid, hair, etc)
- Be aware of the costs of different test methods

Interpretation of drug test results is usually not extensively covered in medical school. Individuals who interpret test results should have some knowledge of toxicology and other issues related to proper interpretation. Providers without formal toxicology training can participate in available courses, and/or should collaborate with a medical toxicologist, a toxicologist from their laboratory, or a physician certified as a MRO. Providers could consider MRO training and/or certification through organizations including the American Association of MROs and/or the Medical Review Office Certification Council.

Language and Attitude

Successfully sending the message that drug testing is a therapeutic tool rather than a punitive measure will depend on providers and programs using therapeutic language and a proactive attitude towards testing and test results. Providers should use neutral terminology that does not further stigmatize addiction and its symptoms. Test results should be referred to using the terms ''positive'' or ''negative'' as opposed to ''clean'' or ''dirty.'' These terms are consistent with a growing body of research literature and clinical guidance about non-stigmatizing language [22,23].

Furthermore, staff attitudes toward drug testing and drug test results should remain consistent throughout the organization. If some members of the treatment team convey the message that drug testing is an important part of proactively addressing continued symptomatology while other members are dismissive, patients will benefit less from drug testing as a therapeutic tool.

Test Facilities and Devices

Addiction treatment providers can choose to conduct their own testing on-site, send samples to a qualified laboratory, or both. These choices involve tradeoffs in quality, turnaround time for results, availability of test technology, and cost.

Point of Care Tests

Some addiction treatment providers perform on-site drug testing using Point of Care Tests (POCTs). There are advantages and disadvantages to POCTs. The most significant advantage of POCTs is the short turnaround time for results, which can be available within minutes. This allows providers to respond to a patient's use of substances quickly and meaningfully (see *Responding to Test Results*, p. 10).

However, it is important to recognize that many POCTs use immunoassay technology, which (varying by the substances being detected and the matrix being used), can have drawbacks. POCTs may be vulnerable to cross-reactivity, detect classes of drugs rather than specific drugs, and require confirmation by a definitive test. Another major disadvantage of POCTs is that despite internal quality control measures, improper sample handling can result in inaccurate results. It has been said that ''the single most important quality issue surrounding POCT devices is the initial and ongoing training of the individual(s) performing the testing to maintain competency'' [24].

Ongoing staff training and quality control are essential. Individuals who collect, store, and interpret POCTs should be educated about the devices' sensitivity, the spectrum of analytes detected, the potential for cross-reactivity, cutoff values, and the nomenclature of the device being used. Users of POCTs should refer to the POC package insert or the manufacturer to determine the device's capabilities.

To ensure POCTs are being used effectively, providers should conduct individual- and organization-level evaluations of staff proficiency by comparing POCT results to the results of a qualified laboratory. POC testing can be implemented comprehensively or on a more limited basis. For example, one provider may use POCTs to conduct all presumptive testing while another uses POCTs only to confirm self-reported substance use that could be detected by the test's panel. Depending on the extent of POCT use, cost should be a consideration when deciding whether to use a POCT protocol. There are costs associated with the extra staff time and space as well as the equipment and supplies necessary to perform the test, staff training, quality assurance procedures, and documentation of POC testing.

Office based testing is most practically done utilizing Clinical Laboratory Improvement Amendments (CLIA)-waived tests. CLIA-waived tests are POCTs defined by the FDA as ''simple'' and having an ''insignificant risk for an erroneous result.'' More information from the FDA can be found on the website: https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm124105.htm. Additional resources, including online training and recommendations for the use of CLIA-waived tests can be found on the CMS website: https://www.cms.gov/regulations-and-guidance/legislation/clia/downloads/waivetbl.pdf. When considering a CLIA waiver, providers should keep in mind that some states have regulations that differ from the federal guidelines pertaining to waivers to perform this type of POCT procedure.

Choosing a Laboratory

Regardless of whether a provider uses POCTs, the selection of an appropriate laboratory is an important component of an effective drug-testing protocol. It is important to choose carefully. Providers should contact the director or a medical toxicologist at the prospective laboratory directly to discuss panels, types of drug tests, testing procedures, and technical assistance. Some laboratories are geared toward workplace testing; this is not ideal for an addiction treatment setting. It is more appropriate to work with a laboratory that

has experience working with addiction treatment settings. Also look for a laboratory that allows providers to order specific tests for each patient because drug testing in addiction treatment should be individualized.

The ability to consult with laboratory staff when needed is an important consideration in choosing a laboratory. The relationship between the testing laboratory and the addiction treatment center should be collaborative. Providers should be able to communicate with the testing laboratory about test panels, detecting sample tampering, test result interpretation, and regional drug use trends.

Certification requirements should be reviewed. Laboratories that perform forensic drug testing for federal agencies and federally regulated industries are required to maintain a national certification overseen by the Department of Health and Human Services (HHS). Typically, it is not necessary for a laboratory working with an addiction treatment provider to have an HHS certification. However, it is important to confirm that the laboratory follows established federal and state regulations. The CLIA of 1967 and of 1988 set forth conditions that all laboratories must meet to be certified to perform testing on biological specimens. Additionally, state clinical laboratory programs operate under individual state laws; these state programs are usually authorized through the Centers for Medicare & Medicaid Services. Providers should investigate whether state law requires a specific certification for a testing laboratory working with an addiction treatment provider. A list of state CLIA contacts is available on the Centers for Medicare and Medicaid Services website (https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA).

Summary of Recommendations

Documentation and Confidentiality

- Addiction treatment programs should provide written drug-testing procedures to patients. Procedures should be reviewed with the patient at the start of his or her treatment.
- Providers should document the rationale for the drug tests they order and the clinical decisions that are based upon drug test results.
- Providers should ask patients about and document potential sources of cross-reactivity, including various foods and current medications.
- Particular characteristics of a sample with the potential to lead to problems with interpretation (eg, hair that has been chemically treated) should be documented at the time of collection.
- Test results should be documented.
- Test results should be kept confidential to the extent permitted by law. Providers should thoroughly explain to patients all rules regarding confidentiality, consent, and sharing test results with outside entities.
- In general, providers should use caution when sharing test results with outside entities such as justice settings or employers. When sharing test results with outside entities, it is optimal that positive results be verified with a definitive test.

Practitioner Education and Expertise

Knowledge and Proficiency

- Providers responsible for ordering tests should be familiar with the limitations of presumptive and definitive testing.
- Providers responsible for ordering tests should be familiar with the potential for cross-reactivity in drug testing.
- Providers responsible for ordering tests should consider the possible impact of tampering on test results. Providers should note that tampering is more likely in settings where consequences for substance use are severe, such as discharge from treatment.
- Providers responsible for ordering tests should understand the potential benefits of alternative matrices to urine (eg, oral fluid, hair, etc).
- Providers responsible for ordering tests should be aware of the costs of different test methods.
- If the provider responsible for making clinical decisions based on test results does not have training in toxicology, he or she should collaborate with a medical toxicologist, a toxicologist from the testing laboratory, or an individual with MRO certification, as needed.

Language and Attitude

- Providers should communicate with patients about drug testing using non-stigmatizing language. For example, results should be discussed as ''positive'' or ''negative'' as opposed to ''clean'' or ''dirty.''
- Providers should exhibit a consistent and positive attitude toward drug testing. Ambivalent attitudes toward drug testing among staff can be a barrier to its effective use.

Test Facilities and Devices

Point of Care Tests

- Staff training and demonstrated proficiency is particularly important for organizations that use point of care tests (POCTs).
- Providers performing POCTs should be evaluated for their proficiency. POCTs should be performed only by providers who demonstrate adequate proficiency with the drug test in question. Facilities using POCTs should periodically evaluate the accuracy of their system in comparison to a qualified laboratory.
- Users of POCT devices need to be educated about the tests.
  - They need to understand the statistical and analytical sensitivity of the device.
  - They need to understand the spectrum of analytes (drugs and metabolites) detected by the device.
  - They need to understand any known interferences from drugs or metabolites that could affect interpretation of results.
  - They need to understand the nomenclature of the device.
- Users of POCTs should refer to the POC package insert and/or the manufacturer to determine the device's capabilities.
- Cost issues should be considered when deciding to initiate a POCT protocol. These include costs associated with additional staff time and training, space to perform testing,

quality assurance procedures, and documentation of POCT results.

Choosing a Laboratory

- Providers should seek to work with a laboratory that has expertise in drug testing in addiction treatment settings.
- When selecting a laboratory, providers should investigate whether state law requires a specific certification.
- It is important to work with a laboratory qualified to perform accurate tests and assist in the interpretation of results.
- Providers should work to create a collaborative relationship with the laboratory; important areas for collaboration are test panel selection, detecting sample tampering, interpreting test results, and regional drug use trends.
- When selecting a laboratory, providers should contact the toxicology director or a medical toxicologist at the laboratory to discuss panels, types of drug tests, testing procedures, and technical assistance.
- Because drug testing should be individualized, laboratories should allow providers to order specific tests for each patient.

PART 4: BIOLOGICAL MATRICES

Comparing Matrices

Urine, blood, exhaled breath, oral fluid (saliva), sweat and hair are some biological samples that are used in drug testing. Smarter testing involves choosing the matrix best capable of detecting the substance of interest within the desired window of detection, and this often involves making tradeoffs in terms of test capabilities. See Table 4 for information about relative advantages and disadvantages of available matrices. *Appendix 4: Windows of Detection Table* contains detection windows for specific parent drugs and metabolites in urine, blood and oral fluid.

Biological drug testing detects the presence or absence of parent drug compounds and/or their metabolites, which remain in the body for longer periods of time, in a biological sample. Drugs and their metabolites become present in the body primarily by being absorbed into the bloodstream and then distributed to other matrices via mechanisms such as passive diffusion and ultrafiltration. Specific mechanisms will be discussed in the section for each matrix addressed in this document.

The physiological distribution of drugs implies a varying relationship between the concentration a drug or metabolite has in different matrices depending on properties such as lipid solubility, acid dissociation (pK_a) and protein binding tendency. For example, drugs that are more acidic (eg, benzodiazepines) will have higher concentrations in fluids with higher pH (eg, plasma/blood) while more basic drugs (eg, amphetamines and opiates) will have higher concentrations in fluids with lower pH (eg, saliva/oral fluid).

The relationship between concentration and matrix depends on (a) the pharmacokinetic profile of the drug; (b) the consumer's underlying health functioning; and (c) the pattern, dose and route of drug administration. These factors influence the absorption, distribution, and elimination of the

TABLE 4. Comparing Testing Characteristics Across Matrices

	Blood	Breath	Oral Fluid	Urine	Sweat	Hair
General detection period	<24 hours [2] 1–8 hours [25] 1–48 hours [26]	~1 hr per standard drink	<24 hours [2] 12–24 hours [27] 1–36 hours [28] 5–48 hours [29] 12–48 hours [25]	1.5–4 days [29] 1–3 days [25,26,30]	Continuous, usually 1–4 weeks [2,26]	7–90 days [2] 7–100 days [26]
POCT/On-site immunoassay available	Yes, primarily used for alcohol	For alcohol	Yes	Yes	No	No
Primarily detects	Parent drug compound; blood alcohol concentration	Parent drug compound; blood alcohol concentration	Parent drug compound	Drug metabolite	Parent drug compound	Parent drug compound
Best use in treatment setting	Determination of acute impairment or intoxication for alcohol	Determination of acute impairment or intoxication for alcohol	Short-term detection in ongoing treatment	Intermediate-term detection in ongoing treatment	Medium-term prospective monitoring	Long-term monitoring; 3-month drug use history
Ease of collection	Requires staff trained in phlebotomy	Easily collected	Easily collected	Requires specialized collection facility (restroom)	Easily collected	Easily collected
Intrusiveness of collection	High for intravenous access	Low	Low	High	Low	Low
Resistance to tampering	High	High	High, but some uncertainty	Low	High, but some uncertainty	High when chemically untreated
Retesting same sample	Difficult	Generally not possible	Difficult	Possible	Possible depending on patch used	Easy

TABLE 5. General Windows of Detection Across Matrices

	Minutes	Hours	Days	Weeks	Months
Blood	■	■			
Breath	■	■			
Oral Fluid	■	■	■		
Urine		■	■		
Sweat		■	■	■	
Hair				■	■

Adapted from Substance Abuse and Mental Health Services Administration [53].

drug and ultimately determine their window of detection. For example, tetrahydrocannabinol (THC), the primary compound in cannabis, is highly lipid soluble and binds to fat cells in the body. A person who uses cannabis once may only test positive for 24 hours, while a person who has used chronically may test positive for a month or longer after cessation as stored THC continues to be eliminated from the body [31] (Table 5).

In general, the longest windows of detection occur in hair, followed by sweat, urine, oral fluid and blood [29]. But maximum detection time is not the only important criteria for choosing a test. Other factors to consider include:

- Time to detection
- Time to obtain results (availability of POCT)
- Ease of collection (need for trained personnel, collection facilities)
- Invasiveness/unpleasantness of collection
- Availability of the sample (eg, renal health, shy bladder, baldness, dry mouth)
- Susceptibility of the sample to tampering

The accuracy of any drug test is predicated on obtaining a valid specimen. The nature of addiction may lead some patients to try to mask continued substance use or relapse. The pressure to do so may depend on the severity of the consequences they will face if detected, such as increased sanctions, or legal action. (see *Drug testing and self-reported substance use*, p. 5).

Urine

Basics of Urine Drug Testing

As the kidneys filter the bloodstream, waste and other by-products including metabolites are extracted and eliminated along with water from the body as urine. It takes approximately 2 hours after use for a substance to be detected in urine, a longer time to detection than for other bodily fluids such as saliva and breath [32]. The window of detection for most substances of interest is 1–3 days and up to 4 days in some cases and is dependent on factors such as fluid intake and urinary pH. The concentration of a drug or its metabolites in urine represents the amount, which has accumulated in the bladder since the last void.

See Table 4 for more information about the advantages and disadvantages of UDT in comparison to alternative matrices.

Use of Urine Drug Testing in Addiction Treatment

At this time, urine is the most well-established and well-supported biological matrix for presumptive detection of substance use in addiction treatment settings. Urine is the most commonly used biological specimen for drug and alcohol testing in clinical settings [33]. Urine is also the best established matrix in POC testing. UDT represents a mature technology; because of its popularity, the drug-testing industry has focused development on producing more rapid and less expensive technologies for testing urine. This means there are many testing options available, generally at lower cost compared to other matrices.

Disadvantages of Urine Drug Testing

There are 2 major drawbacks to UDT: (1) the ease of sample tampering through substitution, dilution, and adulteration, and (2) the invasiveness and resource intensity of witnessed sample collection, the primary means of countering sample tampering.

If appropriate measures to reduce urine sample tampering are not able to be taken and tampering is of high concern, providers should consider testing an alternative specimen. The use of alternative matrices to complement UDT could take place in a number of ways, including on a clinic-wide basis by rotating the collection of specimen types (see *Matrix advantages and disadvantages*, p. 7) or on an individual collection-by-collection basis.

Urine Sample Integrity

Urine is the specimen most prone to sample tampering. UDT can be circumvented through sample substitution, dilution and adulteration by ingesting something prior to a test (in vivo) or adding something to a sample (ex vivo) with the purpose of obscuring the test results. A substituted sample is one that replaces the patient's urine with another sample, either urine or some other liquid. Diluting a urine sample makes it less likely that a drug or its metabolite(s) can be detected above the cutoff threshold of an immunoassay test. Adulteration involves the use of a masking agent that destroys the presence of drugs in urine or interferes with the enzymatic reactivity of an immunoassay test.

There are measures that can be taken to mitigate the risk of urine sample tampering and ensure sample integrity, described in the following sections. Providers should choose a urine sample collection method that will protect patients' dignity and privacy while minimizing opportunities for tampering. Each clinic should have clear specimen tampering and diversion control strategies in place and these should be discussed with patients. In order for sample tampering policies to have their intended effect, providers should be trained appropriately in these measures.

Observed Urine Sample Collection

The primary method used to prevent urine sample tampering is direct observation of urination by a staff member of the same gender during collection. Observation prevents several common ex vivo methods of substitution, dilution and adulteration at the time of collection. For example, substitution generally requires a patient to carry the replacement sample in a container with them to the bathroom. A patient can dilute a sample by adding liquids such as water or colored fluids (apple juice, lemonade) to the sample container. Adulterants that are added to a sample container include many household chemicals. The most commonly used chemicals include table salt (sodium chloride), vinegar, Drano, dish soap, hand soap, liquid laundry bleach, denture cleansing tablets, lemon juice, ascorbic acid, hydrogen peroxide, and rubbing alcohol (isopropyl alcohol) [34].

If there are concerns about urine sample tampering, or if a provider suspects sample tampering has occurred, sample collection should be observed. (See *Signs of urine sample tampering* for a discussion of what constitutes reasonable concern or suspicion regarding tampering). If collection was previously unobserved, this change should be explained to the patient and described as being undertaken in their best interest. This may provide an opportunity for therapeutic discussion about the patient's health and well-being, which underlie the decision to change collection procedure.

Limitations of Observed Urine Sample Collection

There are a few problems with singular reliance on observed sample collection as a tampering mitigation strategy. First, observed urine collection does not completely prevent sample tampering. Supervised collection addresses ex vivo, but not in vivo methods of sample tampering. For example, urine can be made dilute by rapidly consuming large amounts of fluid approximately 1 to 2 hours prior to the test (water loading) or taking diuretics. Adulterants taken prior to providing a sample include oxidizing agents such as nitrites or agents, which affect urine pH such as soda crackers.

Routine observed collection may not be feasible, even when tampering is suspected, due to staffing issues. Same-sex staff might not be available to supervise patients or a patient/staff member's gender identity may not fit into the traditional male/female dyad, which can complicate the issue of same-sex observation. Direct observation of urination is potentially embarrassing and uncomfortable for both the patient and person supervising collection. Staff may avoid very close observation and miss the use of commercially available sample substitution devices.

Direct observation of urination can be seen by patients as a perceived violation of trust and respect and patients frequently indicate they would prefer an alternative specimen be collected if available [35]. Consider the use of unobtrusive sample collection method for patients with a history of psychological trauma, particularly sexual trauma. Observed urination may be distressing for these patients.

Given these limitations, providers should utilize other strategies—either in addition to or instead of—observed collection to mitigate urine sample tampering.

Unobserved Urine Sample Collection

Having a well set up bathroom collection area can remove some opportunities for sample tampering during unobserved collection. Although all of the following may not be possible in all facilities, providers should employ appropriate measures to decrease the likelihood of urine sample tampering during unobserved collection. Do not allow patients to carry personal items with them into the collection area. Ensure that potential adulterants, such as soap, ammonia, or bleach are not readily available in the collection area. Place blue dye in the toilet and turn off the water source to the collection area during collection. Provide an alternative hand cleansing option to patients as they exit the bathroom.

Specimen Validity Testing

Urine sample integrity can be verified through specimen validity testing. Specimen validity testing indicates that a sample has been tampered with by detecting the presence of adulterants or the absence of biological indicators of normal human urine. Specimen validity testing can detect both in vitro and in vivo methods of tampering. However, not all adulterants can be detected in standard adulterant test, including Visine eye drops and newer adulterants such as Urine Luck, UrinAid, Klear, and Whizzies [34].

Definitive testing should always include specimen validity testing which measures creatinine concentration, pH level and specific gravity. At the presumptive testing stage, not all samples need to be tested for specimen validity. However, some POCT devices include specimen validity tests for specific gravity and pH.

If a sample is suspected of having been tampered with then it should be tested for specimen validity, including creatinine concentration, pH level, specific gravity and adulterants. (See *Signs of urine sample tampering*, p. 18 for a discussion of what constitutes reasonable concern or suspicion regarding tampering.)

Signs of Urine Sample Tampering

There are differing opinions on what criteria best indicate that urine sample tampering may have occurred. SAMHSA's guidelines for urine sample verification in federal workplace testing programs are a useful reference point [20]. With regard to sample integrity, most of the SAMHSA guidelines are considered appropriate in the addiction treatment context with the exception of universal presumptive specimen validity testing. This would be difficult to undertake given the cost and currently available technology.

Unusual Specimen Characteristics

All urine samples should be inspected for unusual characteristics that indicate that tampering may have occurred. Characteristics include:

- Unexpected temperature
- Unusual color
- Unusual smell
- Soapy appearance, cloudiness or particles floating in the liquid

A recently provided sample should be within expected body temperature range, approximately 90 to 100 degrees within 4 minutes of production. This can be evaluated using a heat sensitive strip on the outside of a collection cup. A sample that is too cold suggests that a substitute sample or cold liquid was added to the sample. A sample that is too hot suggests that a chemical heat pack like a hand warmer was used to try to mask the addition of a cold liquid.

A visual inspection can indicate that a sample may be dilute or adulterated. Dilute urine is lighter in color than normal urine, which ranges from light/pale yellow to dark/deep amber. Nitrites also tend to make the color of urine dark. Urine that has been diluted with liquids such as vinegar, ascorbic acid and rubbing alcohol can sometimes be detected by their distinct smell. Table salt (sodium chloride) and denture tablets may be visible as undissolved granules. Dish and hand soap will give the sample a soapy appearance.

If the sample exhibits unusual specimen characteristics, perform specimen validity testing. Sample inspection should not be relied upon solely as evidence of sample tampering, but as an indication of the need for further testing [36,37]. Abnormal urine appearance can also be the result of a urinary tract infection, kidney stones, yeast infection, diet (eg, beets, asparagus) and the use of over-the-counter vitamins and medications (eg, ex-lax, Vitamin B) [38].

Requiring a minimum volume sample can help to increase the reliability of temperature readings and visual inspection as well as ensure there will be enough specimen available for testing.

Unusual Behavior

The expert panel advised broad use of clinical judgment in identifying behavioral signs that a patient may have tampered with a urine sample.

If a patient's behavior suggests that he or she has recently used an illicit substance, but continues to produce negative urine test results, sample collection should be observed and specimen validity testing conducted. A patient may also continue to produce negative urine test results for reasons that are related to the testing procedure including the use of a substance not targeted in the test or is using an amount below the threshold of detection for the cutoff used by the test. The provider could adjust the test panel or order a more sensitive test (see *Choosing a Test*, p. 7) (Table 6).

Responding to Specimen Validity Test Results

Samples are considered substituted or invalid if they fail some aspect of specimen validity testing. It is appropriate for practitioners to consider samples that have been tampered with to be presumptive positive. Providers should respond as they would to a presumptive positive drug test result and rapidly involve the patient in therapeutic discussion (see *Responding to Test Results*, p. 10).

If a specimen is invalid, most labs will stop the testing process on the assumption that the concentration of a drug or metabolite as measured in the sample will be uninterpretable.

TABLE 6. Components of Urine Specimen Validity Testing

Characteristic	Description
Creatinine	Creatinine is the product of muscle metabolism and is produced at a fairly constant rate by the body. Creatinine is used clinically as an indicator of renal health, with very high or very lowconcentrations indicating abnormal kidney function as in Diabetes Insipidus. Creatinine will be very low if an individual has over-hydrated, and very high concentrations can result from the use of some adulterants. SAMHSA has set criteria for normal creatinine concentrations in urine, with <20 mg/dL indicating a dilute sample. This limit is meant to screen out probable instances of attempted tampering among the general workplace population. Creatinine concentrations can be used to normalize drug concentrations if practitioners want to continue with definitive testing of a dilute sample.
Specific gravity	Specific gravity is a measure of the concentration of dissolved particles in a liquid by comparing its density to the density of water. The specific gravity of normal human urine is between 1.003 and 1.030. While a urine specific gravity of 1.000 is essentially water and suggest dilution, higher specific gravity values can indicate that an adulterant has been added to a sample. For example, the amount of table salt needed to produce a false-positive results in specific gravity over 1.035 [34]. Most sources recommend that specific gravity need only be checked if creatinine is <20 mg/dL.
pH	pH is a measure of acid-base and ranges between 4.5 and 8.0 in urine. It greatly affects the concentration and stability of some drug and drug metabolites in urine and therefore the likelihood that they will be detected. The pH of the sample may influence the enzymatic action and performance of immunoassay screens. Abnormal pH can indicate that a sample is dilute or adulterated. Bleach, acid, soap, detergent and vinegar all alter pH to outside the normal human range [34]. Abnormal pH can also be the result of a kidney or urinary tract infection as well as diets extremely high in protein or low in carbohydrates.
Immunoglobulin (IgG)	IgG is the most common antibody in the bloodstream. Concentrations <0.5 μg/ml suggest that a sample was substituted with synthetic or animal urine. While IgG is discussed in the literature and is available as part of a specimen validity test at many lab facilities, the expert panel had mixed opinions regarding the appropriateness of its inclusion in specimen validity testing, with some commenting that it was not commonly used in their practice.
Adulterants	Testing for the presence of adulterants such as glutaraldehyde, pyridium chlorochromate and nitrites can be done on-site or in a laboratory [39]. However, not all adulterants can be detected in standard adulterant test, including Visine eye drops and newer adulterants such as Urine Luck, UrinAid, Klear, and Whizzies [34].

Adapted from Kirsh KL, Christo PJ, Heit H, et al. [154].

In the case of dilute urine, however, the creatinine concentration of the sample can be used to normalize drug concentrations.

Dilute Urine Samples

Dilution is the most common cause of an invalid sample. A combination of low creatinine (below 20 mg/dL) and specific gravity is used to indicate that a sample is dilute. Expert panel members commented that dilution is usually the result of deliberate water loading. Practitioners can employ a number of solutions to decrease the likelihood of collecting a dilute sample. For patients with a history of dilute urine samples, providers should:

- Advise the patient to decrease water intake prior to sample collection
- Collect samples first thing in the morning
- Collect samples before work or on days off (if a patient's occupation involves the need to hydrate heavily)
- Consider the use of an alternative matrix

There are some health conditions, primarily kidney ailments and diabetes, which can lead to unusually high or low specific gravity and low creatinine levels [40]. However, a dilute urine sample resulting from an underlying health condition, such as Diabetes Insipidus, is very rare. Providers should first advise patients with a dilute sample about apparent tampering and evaluate for an underlying etiology only if the trend continues.

Urine Testing for Specific Substances

Urine is the most well-established and well-supported biologic matrix when conducting drug testing for patients with addiction, but its utility depends on the substance of interest and the information the provider needs. Providers should consider the questions they are seeking to answer when conducting a urine test for a substance of interest and be aware of known detection issues. For example, THC is detectable in urine, but it is difficult to distinguish when the substance was used. See *Appendix 4: Windows of Detection Table* for window of detection for specific substances in urine as compared to oral fluid and blood.

Alcohol

Alcohol use can be detected through the direct measurement of ethyl alcohol (EtOH) or one of its metabolites. EtOH has a very short detection window of approximately 10–12 hours and varies considerably by consumption pattern, hydration level and individual metabolism. If providers are interested in detecting such recent alcohol consumption, a breath test may be more convenient than urine EtOH.

Instead of EtOH, providers are encouraged to use tests of ethyl metabolites, which are detectable in urine for longer periods of time. The expert panel primarily encouraged the use of direct alcohol metabolites EtG and/or ethyl sulfate (EtS), detectable in urine for up to 1 to 2 days and widely available in testing. The expert panel also briefly reviewed the use of phosphatidyl ethanol (PEth) and found its extended window of detection to have promising clinical applications; however, most panel members expressed that they were not yet familiar with this technology and it is not yet widely available. No existing recommendations were found regarding testing of fatty acid ethyl ester (FAEE) in urine. FAEEs are formed by the reaction of ethanol with free fatty acids and their amount does not correlated with the amount of alcohol consumed [41]. EtG, EtS, PEth, and FAEEs are considered direct biomarkers of alcohol use because there are present only when alcohol has been consumed. Indirect markers including carbohydrate-deficient transferrin and gamma glutamyl transferase are used primarily to evaluate chronic excessive alcohol consumption, rather than the clinical determination of recent alcohol consumption, and were not reviewed by the panel.

Although rare, it is possible for exposure to ethanol-containing products such as hand sanitizer to result in a positive EtG or EtS test [42]. Patients should be advised to avoid the use of ethanol-containing products before an EtG or EtS test.

Amphetamines

Urine testing is helpful when assessing a patient's amphetamine use. However, there are known limitations to urine immunoassays for amphetamines and providers should be cautious when interpreting their results. Standard amphetamine immunoassays target amphetamine, which is also a direct metabolite of methamphetamine. Amphetamine immunoassays are also subject to many false-positives compared to other drug class assays. For example, Adderall and Benzedrine contain amphetamine, Vicks Inhalers contain methamphetamine, and Bupropion is known to result in positive methylenedioxymethamphetamine (MDMA) test results. Providers should know the sensitivity and specificity of the test being used for each of the amphetamine variants. The testing laboratory will have this information.

Benzodiazepines

Urine testing is helpful when assessing a patient's benzodiazepine use. There are known limitations to urine immunoassays for benzodiazepines and providers should be cautious when interpreting their results. Most general benzodiazepine assays have very low sensitivity to clonazepam and lorazepam. Some assay tests perform better than others, however, and depend on the antibodies used by the manufacturer. Providers should know the sensitivity and specificity of the test being used for each of the benzodiazepine variants. The provider's laboratory will have this information.

Immunoassays are generally not sensitive to therapeutic doses of benzodiazepines. Providers should know the cutoff limits of the test being used. If a patient's benzodiazepine immunoassay is negative, but the patient states that he or she is taking their medication as prescribed, providers can request a definitive test if they wish to confirm use.

Opiate/Opioids

Urine testing is helpful when assessing a patient's opioid use. There are known limitations to urine immunoassays for opiate use and providers should be cautious when interpreting their results. Providers should carefully review the testing report produced by the laboratory to ensure they

understand which opiates and opioids a test is capable of detecting. Semi-synthetic and synthetic opioids may not be included in a test for opiates using immunoassay technology.

A standard opiate immunoassay will detect the use of morphine, codeine (which is metabolized to morphine) and heroin (which is metabolized to 6-MAM and subsequently to morphine) and return a positive opiate result. Metabolites specific to codeine must be detected to confirm codeine use. Heroin or 6-MAM must be detected to confirm heroin use. Hydrocodone and hydromorphone (a metabolite of hydrocodone) are also detected in most standard opiate immunoassays.

Oxycodoneand oxymorphone (a metabolite of oxycodone) are detected in a few but not most standard opiate immunoassays depending on the antibodies used by the manufacturer. One author listed the cross-reactivity of standard opiate immunoassays with oxycodone as ranging between 1% and 10% in 2012 [34]. Providers should be aware of the cross-reactivity of the assay they are using.

Meperidine, methadone, buprenorphine, and fentanyl will not be detected in a standard opiate immunoassay and require their own test.

Although rare, the consumption of poppy seeds can result in a positive opiate immunoassay test result and patients should be instructed to avoid the consumption of poppy seeds. The cutoff designated by SAMHSA for use in the Federal Workplace Guidelines is designed to eliminate positive opiate results from poppy seed consumption. Providers who use a lower cutoff for their clinical population may have an increased risk of positives from this type of exposure (see *Presumptive and definitive tests*, p. 8).

Cocaine

Cocaine use can be detected in urine. Urine testing targets the cocaine metabolite benzoylecgonine (BZE) as cocaine itself has a very short half-life. Compared with opiate, benzodiazepine, and amphetamine tests, presumptive tests for cocaine are more sensitive and specific because they target a specific analyte.

Cannabis

Cannabis use can be detected in urine. Urine testing targets THC metabolite THC-9-carboxylic acid (THC-COOH).

Blood

Basics of Blood Testing

Blood is mainly composed of plasma, serum, white blood cells and red blood cells. Although whole blood samples are sometimes analyzed, more often they are filtered and only plasma or serum is analyzed. Blood testing allows for the precise measurement of drug concentration levels and can be used to interpret dose or timing, which can be very useful in emergency situations.

See Table 4 for more information about the advantages and disadvantages of blood testing in comparison to other matrices.

See *Appendix 4: Windows of Detection Table* for windows of detection for various substances in blood as compared to urine and oral fluid.

Use of Blood Testing in Addiction Treatment

The relevance of blood testing is limited mostly to emergency situations where there is a need to assess impairment and degree of intoxication, and is primarily used to assess alcohol use. Drawbacks to blood testing include the need for staff to be trained in phlebotomy, the invasiveness of drawing blood, and the fact that collected blood samples are hazardous to handle.

Breath

Basics of Breath Testing

Drugs are detected in exhaled breath as aerosolized particles formed from the fluid lining of the lungs. In the context of alcohol testing, a breath test represents the amount of alcohol present in exhaled breath, which is diffused into the air held in the lungs from pulmonary capillary blood. Breath alcohol concentration (BrAC) can then be used to estimate blood alcohol concentration (BAC).

See Table 4 for more information about the advantages and disadvantages of breath testing in comparison to other matrices.

Use of Breath Testing in Addiction Treatment

Breath testing has primarily been directed at the detection of recent alcohol use and impairment; it currently represents the most used matrix for POC alcohol testing. Such devices have largely been developed for roadside and other forensic testing environments. This means that while such devices will be relatively simple to use and provide rapid results, cutoff levels may be optimized to identify degree of intoxication or use above a legal limit and may be of less value when applied to a clinical population or setting. Similarly, remote breath monitoring for alcohol use, while a promising technology, was outside the scope of the current project and was not considered.

Two known drawbacks of breath testing are sample contamination from food or oral hygiene products, which contain alcohol and insufficient breath volume [34]. Some devices require larger sample volumes than others and getting a sufficient breath volume is necessary for devices to work properly.

Researchers have begun to expand the substances detected in breath beyond alcohol. In a recent study, testing patients in an outpatient addiction treatment program for amphetamine, benzodiazepine, cannabis, cocaine, buprenorphine, methadone and opioid use, using definitive breath testing was determined to be viable and preferred by patients over urine testing [43].

Oral Fluid

Basics of Oral Fluid Testing

Drugs are present in oral fluid primarily through passive diffusion from the bloodstream to salivary glands and through absorption and excretion by mucous membranes in the oral cavity during ingestion or inhalation. Because oral fluid testing is primarily blood-based, oral fluid drug concentrations generally correlate with plasma concentrations and

provide a good indication of parent drug presence and impairment [44]. However, if a substance is consumed orally, it will often be present at very high concentrations due to direct contact with mouth surfaces, which make it difficult to correlate concentration and intoxication for a period of about 2 hours after dosing.

See Table 4 for more information about the advantages and disadvantages of oral fluid testing in comparison to other matrices.

See *Appendix 4: Windows of Detection Table* for more information about oral fluid's window of detection for various substances in comparison to urine and blood.

Use of Oral Fluid Testing in Addiction Treatment

Oral fluid testing is appropriate for presumptive detection of substance use in addiction treatment settings. Oral fluid has gained attention as a possible replacement for urine as the matrix of choice in drug testing [45]. The expert panel did not prefer its use over UDT at this time, but suggested that oral fluid may have certain advantages which can be capitalized on in clinical practice.

Although oral fluid offers a shorter window of detection than urine (12–48 hours for most substances), it is unobtrusively collected, does not require the same staff and bathroom facility resources, and so far, does not suffer from the same sample tampering problems that urine has. Oral fluid is also more likely to contain detectable concentrations of parent drug compounds, making it possible to identify the drug consumed, while urine typically targets metabolites, which may be shared across drug class. For example, 6-MAM, a direct marker for heroin, is present in oral fluid at high concentrations but quickly degrades in urine.

Like breath testing, oral fluid has been primarily developed and evaluated for use in roadside and other forensic settings, although it is being increasingly studied in clinical applications [44]. Oral fluid has also been the focus of a great deal of POCT device development.

Drawbacks to oral fluid testing include difficulty with sample collection due to dry mouth, sample contamination from smoking and eating, and oral cavity contamination from recently consumed drugs. Also, while a 2008 study found that commercially available adulterants designed to mask positive results are less effective than those found for urine testing, adulteration methods for oral fluid may become more sophisticated as the technology becomes more widely used [44].

Collection of Oral Fluid Samples

One benefit of oral fluid testing is that sample collection is observed, but is unobtrusive. Oral fluid is collected with a device such as an absorbent pad that is held in the mouth for 30 to 60 seconds before placing the pad into a container. Oral fluid collection with a device such as a pad is preferable to direct expectoration into a container. The pad serves to filter contaminants such as food particles, making them a more precise measurement tool than expectoration [46]. The pad can also help stimulate saliva production, although this may affect pH level and skew analyte concentrations. Dry mouth is a common side effect of the use of many illicit drugs such as cannabis and amphetamines as well as prescription medications. Small oral fluid sample volumes mean there may not be enough specimen available for analysis and prevents retesting of the same sample for validity or subsequent definitive testing [47].

Contamination from food particles can interfere with test results. Providers should encourage patients to abstain from eating for 15 to 60 minutes prior to sample collection. Contamination of the oral cavity from recently consumed drugs can skew quantitative results. If a patient recently took a drug by mouth (ingestion or inhalation), it is recommended that practitioners wait at least 2 hours before collecting an oral fluid sample. Qualitative detection of recent use, however, will still be valid [28].

Sweat

Basics of Sweat Testing

The mechanism by which drugs are incorporated into sweat is not fully understood and several potential mechanisms have been proposed, including diffusion from blood vessels passing by sweat glands or through sebaceous glands also present on the surface of the skin, which primarily excrete lipids [32].

Sweat is collected continuously by an absorbent pad or "sweat patch" that is held close to the skin with an adhesive area, similar to a Band-Aid. Drug concentrations represent an individual's accumulated use of substances over the period the patch was worn, usually 1 to 2 weeks, but can be up to 4 weeks. Drawbacks to this method include possible external contamination and the loss of patch adhesion over time, which can result in the sweat patch falling off for some patients [24,48].

See Table 4 for more information about the advantages and disadvantages of sweat testing in comparison to other matrices.

Use of Sweat Testing in Addiction Treatment

As a new technology, little research exists regarding the use of sweat testing in addiction treatment settings. At this time, there is insufficient evidence to support the routine use of sweat testing in addiction treatment. More research is needed before sweat testing can be recommended over urine testing in clinical settings.

An overview of sweat testing literature considers the practice to be promising [32]. A wide detection window that captures any substance use may be advantageous for some patients, although that window comes with the tradeoff of delay between use and therapeutic response. Sweat testing is also a form of prospective detection, that is, the device is applied prior to the activity that it is supposed to detect. For patients who view testing as having a helpful deterrent effect, prospective testing methods may be additionally beneficial (see *Clinical Use of Drug Testing*, p. 5). The sweat patch also offers a passive collection technique that does not require intensive staff training.

Hair

Basics of Hair Testing

Hair can be thought as a continuous collection device which absorbs compounds as blood passes through the hair

follicle and as sweat gathers and is absorbed around the base of a growing hair shaft. Scalp hair is the most commonly tested sample, but pubic, armpit and facial hair can be also be used. Head hair provides a window of detection of approximately 3 months; body hair, which grows much more slowly, can be used to detect use up to 12 months [49,50]. Hair testing does not detect recent use or impairment. Hair takes approximately 8 days to grow from the follicle to above the scalp, making it possible to collect. Drug and metabolite compounds in hair also begin to degrade over time, limiting interpretation to segments of hair grown in the prior 3 months. Chemical treatments such as dyeing, bleaching, perming, and straightening can alter the structure of hair and degrade drug compounds that may be present [51].

The literature on hair testing shows variability in drug absorption based on hair's characteristics, including pigmentation, texture and porosity, which may lead to incidental racial discrimination [42,52]. Drug compounds are incorporated into dark and thick hair at greater concentrations compared to lighter or thinner hair, although large sample studies suggest these differences do not lead to a significant race effect.

Hair testing appears to be useful for detecting amphetamines, cocaine, opioids, phencyclidine, and MDMA, but less so for marijuana [53].

See Table 4 for more information about the advantages and disadvantages of hair testing in comparison to other matrices.

Use of Hair Testing in Addiction Treatment

The routine use of hair testing is not appropriate for most addiction treatment settings. While the primary advantage of hair testing is the wide window of detection, hair testing is costly, and interpretation of hair test results is potentially discriminatory and can be confounded by passive external contamination.

The window of detection for hair testing is clinically relevant in a few situations. Practitioners may want to know about a patient's past 3-month substance use when assessing a patient and creating a treatment plan. Hair testing may also be useful during long-term monitoring. The cost may be prohibitive, however, if repeated tests are needed over a long period of time.

Collection of Hair Samples

If hair is collected, patients should be asked about their use of chemical hair treatments (eg, dying, bleaching, perming, and relaxers) at the time of sample collection. Use of chemical hair treatments should be recorded and non-head hair (ie, pubic, arm, beard) or an alternative specimen should be collected if possible.

Summary of Recommendations

Urine

Use of Urine Drug Testing in Addiction Treatment

- Urine should be considered the most well-established and well-supported biological matrix for presumptive detection of substance use in a clinical setting.
- Urine should be considered the best established matrix for POCTs.
- If tampering is of high concern or appropriate measures to reduce the likelihood of tampering cannot be taken, providers should consider using an alternative specimen type.

Urine Sample Integrity

- Urine should be considered the matrix most prone to sample tampering through dilution, adulteration and substitution.
- Providers should choose collection methods that protect patients' dignity and privacy while minimizing opportunities for tampering.
- Observed sample collection can deter urine sample tampering; if there are concerns about tampering, collection should be observed by a same-gender staff member.
- Observed urine sample collection does not completely prevent sample tampering; providers should consider other strategies to mitigate urine sample tampering.
- Providers should consider the use of an unobtrusive sample collection method for patients with a history of psychological trauma, especially sexual trauma.
- Providers should employ appropriate measures in the facility where patients provide specimens to decrease the likelihood of urine sample tampering during unobserved collection.
  - Do not allow personal items in the collection area.
  - Ensure that potential adulterants, such as soap, ammonia, or bleach are not readily available in the collection area.
  - Consider placing blue dye in the toilet and turn off the water source to the collection area during collection.
- If a provider suspects that a patient has engaged in substance use but continues to produce negative urine test results, sample collection should be observed and specimen validity testing should be conducted.
- If a sample is suspected of having been tampered with, it should be tested for specimen validity including creatinine concentration, pH level, specific gravity and adulterants.
- All samples undergoing definitive testing should be tested for creatinine concentration, pH level and specific gravity (if creatinine is low).

Signs of Urine Sample Tampering

- All urine samples should be checked for unusual specimen characteristics. Characteristics include:
  - Temperature outside expected range of 90–100 degrees within 4 minutes of production (This can be checked using a heat sensitive strip).
  - Unusual color or smell, soapy appearance, cloudiness or particles floating in the liquid.
- If a urine sample exhibits unusual specimen characteristics, the sample should undergo specimen validity testing to help identify whether and how tampering occurred.

Responding to Specimen Validity Test Results

- Providers should consider samples that have been tampered with to be presumptive positive.

- For patients with past incidences of dilute urine samples, it is advisable to collect samples in the morning or request that patients decrease water intake prior to sample collection.
- For patients with past incidences of dilute urine samples, use creative solutions, such as collecting before work, on days off, or use an alternative matrix.

Urine Testing for Specific Substances

- Urine testing for the use of alcohol is appropriate with current clinical tools. EtG is an appropriate target metabolite when monitoring a patient for complete alcohol abstinence.
  - Ethanol-containing products, including hand sanitizers and mouthwash, should be avoided before an EtG test.
- Urine testing is helpful when assessing amphetamine use. Particular caution should be paid to the interpretation of amphetamine immunoassays due to known limitations in specificity.
- Urine testing is helpful when assessing benzodiazepine use.
  - Particular caution should be paid to the interpretation of benzodiazepine immunoassays due to known limitations in specificity.
  - Immunoassay results should be used cautiously when monitoring a patient's adherence to prescribed benzodiazepines. If a patient reports that he or she is taking the drug but a urine drug screen is negative, further analysis using definitive testing should be considered.
- Urine testing is helpful when assessing opioid use.
  - Particular caution should be paid to the interpretation of opiate immunoassays due to known limitations in specificity.
  - Patients should be instructed to avoid the consumption of food items that contain poppy seeds because they can result in a positive opiate test.
- Urine testing is helpful when assessing cannabis use, although it is difficult to determine the timing or cessation of consumption in chronic users due to extended windows of detection for THC.

Blood

- The relevance of blood testing in addiction treatment is limited mostly to emergency situations where there is a need to assess intoxication or impairment.

Breath

No statements about the appropriateness of breath testing were endorsed by the Expert Panel.

Oral Fluid

- Oral fluid testing is appropriate for presumptive detection of substance use in addiction treatment settings.
- Oral fluid collection with a device that facilitates saliva collection is preferable to expectoration.
- The creation of a sample for oral fluid testing should be observed.
- It is recommended that patients abstain from eating for 15–60 minutes prior to oral fluid sample collection.
- If a patient recently took a drug by mouth (ingestion or inhalation), it is recommended to wait at least 2 hours before collecting an oral fluid sample.

Sweat

- There is insufficient evidence to support the use of sweat testing in addiction treatment. More research is needed before sweat testing can be recommended over urine testing in clinical settings.

Hair

- Hair testing in addiction treatment can detect long-term patterns of use. Routine use of hair testing is not appropriate for addiction treatment.

PART 5: SETTINGS

Although the Principles of Drug Testing (Part 1) apply broadly to addiction treatment settings, some settings and levels of care warrant specific guidance. The ASAM Criteriais a widely accepted standard model for describing the continuum of addiction care [54]. Within *The ASAM Criteria* are 5 broad levels of care (ranging from 0 to 4) that reflect a continuum of service intensity with sublevels within each.

- 0.5: Early Intervention
- 1.0: Outpatient Services
- 2.0: Intensive Outpatient/Partial Hospitalization Services
- 3.0: Residential/Inpatient Care
- 4.0: Medically Managed Intensive Inpatient Services
- OTS: Opioid Treatment Services

Very little research has examined optimal drug-testing practices specific to ASAM levels of care. As a result, this document groups recommended practices into two level-of-care categories: 1) Outpatient and Intensive Outpatient Services (Levels 1 and 2), and 2) Residential/Inpatient and Medically-Managed Intensive Inpatient Services (Levels 3 and 4). This document also examines drug-testing practices in OTS, with special consideration for OTPs and OBOT. Drug testing in OTS will differ from other levels of care because patients are on prescribed opioid agonist and/or antagonist medications. While this complicates the interpretation of opioid drug test results, the use of drug testing can assist in monitoring patients' response to different medication doses, monitoring adherence and in monitoring for possible medication diversion. Finally, this document considers drug testing in sober living environments known as recovery residences, which are not included in *The ASAM Criteria*, but often serve as an important component of the continuum of care for patients with addiction.

This document points specifically to the importance of maintaining a therapeutic drug-free environment in settings where patients are being treated—that is, in Level 3 and 4 facilities as well as recovery residences. Because these are structured settings, drug testing is an important tool because it helps ensure a safe, recovery-oriented environment.

The following recommendations are designed to provide additional guidance to providers working with addiction patients in specific settings.

Outpatient Services (1.0) and Intensive Outpatient/Partial Hospitalization Services (2.0)

The ASAM Criteria defines Level 1 Care as ''organized outpatient treatment services'' that are ''tailored to each patient's level of clinical severity and function and are designed to help the patient achieve changes in his or her substance use.'' Level 2 care includes intensive outpatient programs (9–19 hours of structured programming per week for adults) and partial hospitalization services (20 or more hours of clinically intensive programming per week, typically with direct access to psychiatric, medical, and laboratory services).

Because the opportunity for substance use is greater in outpatient treatment than in more intensive levels of care, drug testing has a particularly important role in monitoring substance use.

Whenever possible, the schedule of drug testing should be random and unannounced (see *Test Scheduling*, p. 11).

In outpatient care, drug testing should be scheduled on days following weekends, holidays and paydays whenever feasible. Providers should communicate with patients about plans for these additional tests to avoid the ''us against them'' mentality and nurture the therapeutic alliance. Additional drug testing should be considered if a patient is experiencing stressful psychological events.

Residential/Inpatient Services (3.0) and Medically Managed Intensive Inpatient Services (4.0)

Residential/Inpatient Services (Level 3.0) are defined by The ASAM Criteria as ''organized treatment services in a 24-hour residential setting'' and Medically Managed Intensive Inpatient Services (Level 4.0) are defined as ''an organized service delivered in an inpatient setting'' usually requiring ongoing nursing/medical care in addition to addiction treatment.

Drug testing plays an important role in both assessment and in maintaining a drug-free therapeutic environment in residential treatment and can alert providers when the therapeutic and treatment environment has been compromised by smuggled drugs [2]. Drug testing can also be used to support recovery when patients leave the addiction treatment facility on passes. When residents are off-site for a period of time, they should be asked to provide a sample for drug testing shortly following their return. Providers should communicate with patients about plans for these additional tests to avoid the ''us against them'' mentality.

To the extent that residential programs are predicated on the goal of abstinence, drug testing is useful in assessing whether patients are having difficulty accomplishing this goal.

Drug testing can be used to support recovery in residential treatment.

Opioid Treatment Services (OTS)

The ASAM Criteria defines OTS as ''a collection of pharmacological and nonpharmacological treatment.'' Pharmacological treatments for opioid use disorders include agonist (methadone, buprenorphine) and antagonist (naltrexone) medications [2]. Two specific services in this category are OTPs and OBOT (including buprenorphine and naltrexone). Considerations relevant to OTPs and OBOT are discussed below.

The primary purposes of drug testing in the context of OTS are: a) detecting substance use that could complicate treatment response and patient management; b) monitoringadherence with the prescribed medication; and c) monitoring possible diversion. Providers should note that drug tests play a particularly important role in patient safety in the context of OTS because they can identify potentially lethal drug combinations, such as benzodiazepines with opioid agonists.

Drug testing has potential application across all stages of OTS, including pre-induction assessment and treatment planning, active treatment, and during maintenance and recovery. Consistent with the Principles of Drug Testing (Part 1), OTS providers should utilize drug testing during the assessment phase and throughout treatment. Furthermore, drug testing in OTS may be paired with the contingency management, a research-supported practice that offers incentives for predefined behaviors.

A final important consideration for OTS is provider education about the use of drug tests to detect opiates, semisynthetic opioids, and synthetic opioids. There is considerable nuance to distinguishing specific opioids using drug tests, which is important for OTS providers who need to distinguish between opioid agonists prescribed to support recovery and opiate/opioid use that is inconsistent with the treatment plan. As with benzodiazepines, the use of illicit opiates or opioids could be lethal in combination with prescribed opioid agonists.

A Note on Language

In OTS, an ''expected'' drug test result is positive for the patient's prescribed medication, but negative for all other unexpected substances. An ''unexpected'' drug test result could be negative for the prescribed medication, positive for unexpected substance(s), or both.

Testing Schedule

The frequency and duration of drug testing in OTS should be individualized, depending upon the stage of treatment as well as other patient factors. There is no ''magic number'' or appropriate frequency of testing that can be applied to every patient, although providers should note that federal regulations set annual minimum numbers in OTPs. In OTS, testing should be more frequent during the induction and stabilization phase of treatment and less frequent during the maintenance stage. Testing may be more frequent during the induction stage to ensure that the patient has stabilized on the initial dose. The expert panel found drug testing during and after tapering from medications to be an important way to support a patient's recovery, and suggested that providers may want to consider increasing drug-testing frequency during and after tapering from medications.

Responding to Test Results

In OTS, a common incentive for an expected drug test is to offer take-home doses. Providers should respond to

expected drug test results with positive feedback and consider the use of take-home medication as an incentive.

Providers should be aware that one of the purposes of drug testing in OTS is detecting possible diversion. For example, the presence of a prescribed medication's metabolites indicates that it was consumed and metabolized. High concentrations of a parent drug in the absence of its metabolites are observed when small amounts of medication are added to the sample during collection. If this pattern is observed, providers should assess the patient for potential diversion. However, a test that is negative for prescribed medication should not be interpreted on its own as diversion; it could indicate a more rapid metabolism and the need for a higher dose.

Consistent with the Principles of Drug Testing, it is not appropriate to respond punitively to unexpected drug test results in OTS treatment. Rather, unexpected results could indicate a need for a higher level of care, a higher dose of medication, a different testing schedule (eg, unannounced, with greater frequency), and/or increased patient education.

Considerations for Opioid Treatment Program Settings

While OTPs can utilize methadone, buprenorphine, and naltrexone, the most common medication used in OTPs is methadone.

With regard to testing frequency in OTPs, the 8 times per year currently required by SAMHSA's *Federal Guidelines for Opioid Treatment Programs* should be viewed as a minimum [55]. Many patients will require more frequent testing, and determinations about optimal frequency are best made on an individualized basis. In OTPs, the expert panel concluded that unexpected drug test results could lead to a number of responses including discontinuation of take-home doses, a more frequent or more random drug-testing schedule, increased counseling and peer group sessions tailored to individuals with unexpected drug test results in OTPs. Providers should communicate to patients that these responses are not designed to be punitive, but as increased support for the patient in the context of his or her treatment plan.

Considerations for Office-Based Opioid Treatment Settings

OBOT comprises the use of buprenorphine and/or naltrexone. There are several formulations of both buprenorphine and naltrexone, but this document does not address specific considerations for different formulations. No research was located that distinguished between, for example, drug-testing practices for sublingual buprenorphine as opposed to the subdermal buprenorphine implant.

In order to provide OBOT, providers should have access to a drug-testing laboratory. The test panel should always include the therapeutic drug and/or its metabolites to indicate that medication was consumed; this helps providers monitor medication adherence and also evaluate for possible diversion. However, drug testing should not be the only strategy for reducing or preventing diversion: providers should also use other measures, such as increased office visits, Prescription Monitoring Programs, observed dosing, and medication counts. With regard to frequency, the expert panel recommended that buprenorphine patients receive drug testing at least monthly, unless otherwise clinically indicated. Patients who are stable in their recovery may require less frequent testing.

Before beginning naltrexone, it is critical that a patient be withdrawn from opioids. Therefore, a negative drug test result should be obtained before beginning treatment with naltrexone. Drug testing also is indicated throughout treatment using naltrexone. With regard to frequency, the expert panel recommended that naltrexone patients receive drug testing at least monthly, unless otherwise clinically indicated.

Recovery Residences

According to the National Association for Recovery Residences, ''Recovery Residence (RR) is a broad term describing a sober, safe, and healthy living environment that promotes recovery from alcohol and other drug use and associated problems. At a minimum, RRs offer peer-to-peer recovery support with some providing professionally delivered clinical services all aimed at promoting abstinence-based, long-term recovery'' [56]. Drug testing is particularly important in an environment where abstinence is a therapeutic social norm, and recovery residences fit this criterion. Because the integrity of the group relies on each participant's ongoing sobriety, weekly drug testing (or more frequent if there is suspicion of substance use) is appropriate in a recovery residence; participants may be expelled from the facility if a drug test result indicates substance use. Weekly testing can use presumptive methods; weekly definitive test panels in recovery residences are a potential opportunity for fraud (for a discussion, see *Cost Considerations*, p. 2). However, as in any setting, a drug test result used as input to a major decision such as program expulsion should use a definitive testing method. Expulsion should not interfere with an individual's continued therapeutic relationship with his or her outpatient addiction treatment provider.

Summary of Recommendations

Outpatient Services (1.0) and Intensive Outpatient/Partial Hospitalization Services (2.0)

- Because the opportunity for substance use is greater in outpatient treatment than in more intensive levels of care, drug testing has a particularly important role in monitoring substance use.
- Providers should implement a random unannounced schedule of testing in outpatient services whenever possible, because the patient's opportunity for substance use is greater relative to residential treatment.
- Drug testing should be scheduled on days following weekends, holidays and paydays when feasible. Providers should communicate with patients about plans for additional drug tests around events/special occasions.
- Additional drug testing should be considered if a patient is experiencing stressful psychological events.

Residential/Inpatient Services (3.0) and Medically Managed Intensive Inpatient Services (4.0)

- Drug testing plays an important role in maintaining a drug-free therapeutic environment in residential treatment.

- When residents leave the treatment program on passes, they should be asked to provide a sample for drug testing shortly after their return. Providers should communicate with patients about plans for additional drug testing following their return.

Opioid Treatment Services

- The primary purposes of drug testing in the context of OTS are (a) detecting substance use that could complicate treatment response and patient management; (b) monitoring adherence with the prescribed medication; and (c) monitoring possible diversion.
- Drug testing can be an important tool for detecting the use of substances that can be lethal in combination with a prescribed opioid agonist medication (eg, benzodiazepines).
- Drug testing has potential application across all stages of OTS including pre-induction assessment and treatment planning, active treatment, and during maintenance and recovery. Providers should utilize drug testing during the assessment phase and throughout treatment.
- Providers should utilize drug testing as an aspect of contingency management in OTS.
- Provider education should include knowledge of the metabolic pathways of commonly prescribed opioids.

Testing Schedule

- Drug-testing frequency is determined by stage of treatment as well as other patient factors and should be individualized.
- Testing should be more frequent during the stabilization period, and less frequent during the maintenance period.
- Drug testing during and after tapering from methadone or buprenorphine continues to be an important way to support a patient's recovery; providers may want to consider increasing drug-testing frequency during tapering and in the period after tapering.

Responding to Test Results

- Expected drug test results (ie, positive for prescribed medication and negative for unexpected substances) should be praised and responded to with tangible contingencies such as take-home doses of medication.
- High concentration of a parent drug in the absence of its metabolites is consistent with sample tampering in the form of post-collection addition of the drug to the sample and potential diversion. In this case, a follow-up assessment should be conducted with the patient.
- A test that is negative for the prescribed medication (eg, negative for buprenorphine in a patient prescribed buprenorphine) should not be used on its own to determine that diversion is occurring.
- Unexpected drug test results could indicate the need for 1 or more of the following responses: (1) a higher level of care; (2) a higher dose of medication;(3)a different schedule of testing, such as random rather than scheduled and/or more frequent; and/or (4) increased education for the patient.

Considerations for Opioid Treatment Program Settings

- For patients in OTP settings, the federally mandated ''eight tests per year'' should be seen as a minimum, and it is often appropriate to perform testing more frequently than 8 times per year; determinations about testing frequency and duration should be made with consideration of individual patients, as noted above.
- For patients in OTP settings, provider response to unexpected test results can include discontinuation or reduction of take home doses of medication, more frequent or random schedule of drug testing, and increased counseling and peer group sessions.

Considerations for Office-Based Opioid Treatment Settings

- For patients in OBOT settings, the drug test panel should include the therapeutic drug and/or its metabolites.
- In addition to drug testing, diversion can be reduced or prevented by frequent office visits, Prescription Monitoring Programs, observed dosing, and medication counts.
- In order to provide buprenorphine or naltrexone treatment, providers must have access to drug-testing laboratories.
- Frequency of drug testing in buprenorphine treatment should be at least monthly, unless otherwise clinically indicated (eg, patients who have become stable in recovery may require less frequent testing).
- Drug testing (and negative test result for opioids) is indicated before starting treatment of opioid use disorder using naltrexone. Drug testing also is indicated throughout treatment using naltrexone.
- Frequency of drug testing in treatment of opioid use disorder using naltrexone should be at least monthly, unless otherwise clinically indicated.

Recovery Residences

- Weekly random drug testing is appropriate in a recovery residence.
- Any patient expelled from a recovery residence should be able to continue an ongoing therapeutic relationship with his or her outpatient addiction treatment provider.

PART 6: SPECIAL POPULATIONS

Adolescents

Healthcare for adolescents and adults bears many similarities. Many of the general principles of drug testing for adults remain unchanged for adolescents. However, there are some important factors with this population, which deserve unique consideration before deciding when and how to drug test an adolescent.

Unlike the majority of this appropriateness document, this guidance for adolescents is not to be applied to patients in addiction treatment. Rather, the following recommendations address care for adolescents in general healthcare settings.

When to Test Adolescents

Adolescent drug testing is only to be used in some scenarios. It is not appropriate or necessary to conduct a drug

test for all adolescents in general healthcare settings. The American Academy of Pediatrics (AAP) suggests drug testing as an aspect of adolescents' recovery programs, or as a component of assessment for substance use as suspected by a parent or other adult [36,57]. High-risk populations may benefit from use of drug testing to assist in early identification of substance use, a group including but not limited to those with known past substance use, those in treatment for mental health disorders, those with a history of past trauma, and those with declining academic performance.

When an adult observes symptoms characteristic of substance use in an adolescent, providers should use drug testing as part of an assessment for a possible SUD. However, as with adults, drug testing of adolescents should not be used in isolation. ASAM and SAMHSA recommend that drug testing be used in primary care settings in combination with the results of standardized screening questionnaires [2].

Adolescents in long-term recovery from an addiction can benefit from drug testing in general healthcare settings. Monitoring adolescents using drug testing can facilitate therapeutic conversations about recurrent substance use and drug testing can give the patient extrinsic motivation to follow their treatment plan and help the provider make adjustments, as needed.

A primary care physician (PCP) may be called upon to administer a drug test. A PCP should be an informed practitioner if he or she chooses to use this tool. As long as he or she is familiar with the general principles of drug testing, the PCP may order a test. If he or she does not have proficiency in drug testing, the physician ought to refer the patient to a specialist for treatment or consult with a medical toxicologist or MRO about conducting drug tests or interpreting their results.

Adolescents and Self-Reported Substance Use

Though an adolescent reports substance use and/or substance use history, drug testing may still provide additional value. Although commonly assumed to be the case, research is mixed with regard to whether adolescents are less likely than adults to self-report accurately. For example, 1 study found low correlations between self-report and drug test results among adolescents in a ''high-risk urban setting'' [58], whereas concordance between the 2 were found to be relatively high among teens in addiction treatment [59]. These results suggest that setting might be a factor in the accuracy of self-report. Moreover, perception of negative consequences if substance use is detected seems to contribute to lower likelihood of accurate self-report (see *Drug testing and self-reported substance use*, p. 5).

As with adults, there is also the concern that illicitly acquired substances may contain compounds different from those the person using them believes to be present. This is of particular relevance to adolescents as they are more likely to obtain substances through friends without knowing their origin and have less practical knowledge about the substances they use.

Adolescents and Home Testing Kits

Many pharmacies sell home drug testing kits over the counter. Providers should not encourage the use of home drug testing on adolescents. The results of a drug test require careful interpretation and knowledge that untrained persons do not possess. The general population lacks training. Administering tests or properly interpreting results requires knowledge in light of the sensitivity and specificity of the test. In addition, parental drug testing could damage the parent-child relationship [36]. Encourage parents who wish to test their child to instead work with a medical professional who can evaluate whether it is appropriate to conduct a test. Note that primary care professionals do not always have training in drug test interpretation.

Adolescent Consent

ASAM, AAP, and ACOG all discourage performing drug testing on adolescents who have not had the opportunity to give informed consent [36,45,60].

Exceptions exist where it is appropriate to waive the need for consent. Situations where the patient's safety could be compromised should be handled on a case-by-case basis. For example, an adolescent patient experiencing a seizure or other medical emergency may be drug tested in the absence of his or her consent. A patient who is under medical supervision following a suicide attempt is included in this emergency designation.

If an adolescent refuses to consent to a drug test in a non-emergency situation, respect his or her autonomy. In the meantime, continue the evaluation through alternative methods including verbal screening and reports from family members. Alternatively, providers can refer the adolescent to a specialist with additional mental health or substance use expertise. If drug testing continues to be warranted and the patient continues to be treated by the PCP, he or she can suggest drug testing again after the patient has grown more comfortable with the provider.

Providers should explain drug-testing protocols in full before initiating the process. This helps the adolescent make an informed decision. It also encourages trust in the patient-provider relationship.

Adolescent Confidentiality

An open flow of information between guardians and children should typically be encouraged. Before beginning the drug testing process, ask the adolescent for permission to share the results with parents/guardians and discuss confidentiality with parents/guardians in order to encourage parental involvement. Adolescents often feel strongly about confidentiality and providers can encourage young patients to share test results with their parents by explaining how this could benefit their health and help create an environment of familial trust and respect.

Providers should respect the patient's decision if he or she asks to keep test results private. Even if the adolescent does not share his or her results with guardians, providers are still in a position to make decisions based on those results.

Providers should also talk to the parents or guardians of adolescent patients about their confidentiality policy. This can help guardians understand what they will or will not be told, and encourage their communication and involvement. It also sets shared expectations.

Note that there are legal and ethical caveats that prevent providers from promising unconditional confidentiality to adolescent patients. If a medical professional suspects that an adolescent patient's drug use puts him or her in imminent danger of acute physical harm to themselves or others, the provider may be obligated to tell an adult authority. Providers should know relevant federal and state laws and consider where this line should be drawn, given that risk of harm is a spectrum and not simple to quantify.

Choosing a Test Panel for Adolescent Patients

Drug test panels for adolescents should include the substances most used by the demographic. Providers should be aware of demographic trends in substance use among adolescents, which may differ from trends among adults. Youth often have access to fewer options than adults, making their choices based on availability more than personal preference. Provides are advised to consult with their testing laboratory about local drug trends, particularly those affecting adolescents.

Patterns of use for adolescents are known to differ from those of adults. Access to preferred substances may be sporadic, and as such, a patient may rotate through a variety of substances based on availability. This can make targeting a test panel challenging and increases the importance of self-report and knowledge of patient history and local trends.

Responding to Positive Test Results

If a true positive drug test result indicates that an adolescent is engaging in high-risk substance use, the provider should assist the patient and his or her parent or guardian in developing a plan for monitoring and treatment. Both the patient and his or her parents or guardians should be actively involved in the development of a plan of action, if possible. Mere awareness of an adolescent's substance use is not a satisfactory end result of a positive drug test.

Pregnant Women

Many principles of drug testing for a general population apply to pregnant patients. However, there are some important factors with this population that deserve unique consideration before deciding when and how to utilize drug testing for a pregnant patient.

Note that this section does not refer specifically to patients who are receiving addiction treatment. Rather, these recommendations primarily apply to pregnant and postpartum women in general healthcare or prenatal care settings. Additional guidance on addressing substance use among pregnant patients from the perspectives of screening and treatment as well as regulatory and law enforcement considerations is available in the ASAM Policy Statement ''Substance Use, Misuse, and Use Disorders During and Following Pregnancy, with an Emphasis on Opioids'' [61], which was published after this project was well underway, and could therefore not be included in the full process.

Consequences and Confidentiality

Providers have an obligation to be aware that there are serious legal and social consequences of detecting and monitoring substance use among pregnant women. In some cases, state reporting requirements may conflict with 42 Code of Federal Regulation (CFR) Part 2, which is federal law. 42 CFR Part 2 is a federal regulation that protects the confidentiality of patient addiction treatment records.

According to SAMHSA, 42 CFR Part 2 does not protect patient information in states where maternal substance use is considered child abuse or neglect and requires reporting to state or local authorities [62]. In 23 states plus the District of Columbia, laws designate substance use during pregnancy to be child abuse. (As of 2017, these states included Alabama, Arizona, Arkansas, Colorado, the District of Columbia, Florida, Illinois, Indiana, Iowa, Louisiana, Maryland, Minnesota, Missouri, Nevada, North Dakota, Oklahoma, Rhode Island, South Carolina, South Dakota, Texas, Utah, Virginia, Washington, and Wisconsin.) [63]. ASAM opposes policies that define substance use by pregnant women as ''child abuse or maltreatment'' and carry penalties, rather than providing these women with effective health care [61].

However, given that many pregnant women do face consequences if substance use is detected, providers who treat pregnant patients should be knowledgeable about federal- and state-level laws pertaining to confidentiality and reporting requirements. ASAM recommends that, with the exception of emergency situations, pregnant women should provide explicit written consent for drug testing including during labor and delivery [61]. This informed consent should include an understanding of the possible consequences of test results.

Providers should refer to SAMHSA's TIP 51 ''Substance Abuse Treatment: Addressing the Specific Needs of Women'' for information on ethical and legal issues in substance-using pregnant women and their children [64]. If questions arise during specific cases, providers can consult with an attorney or their state medical society about balancing their responsibility to uphold 42 CFR Part 2 and state reporting requirements.

Patient confidentiality should be maintained to the full extent permitted by state and federal law. This includes the results of drug tests and any associated diagnoses. The role of the provider is to help his or her patients improve and maintain their health. Though the provider is obligated to follow reporting mandates, fulfilling this duty is not his or her primary function. The expert panel recommends that providers have honest and straightforward discussions with pregnant patients about confidentiality. Providers should assure pregnant patients that in general, private medical information will not be shared with any third parties, and then clearly communicate the exceptions.

Screening, Assessment, and Monitoring

A review of recommendations for clinical management of substance use in pregnancy encouraged screening for all women of childbearing age. These procedures could be followed by drug testing only if the screening questions indicated substance use [65]. ACOG recommends that pregnant women be screened at the first prenatal visit about past and present use of alcohol, tobacco, and other drugs using validated screening questions [45]. The expert panel recommends that comprehensive substance use assessment, which

may include drug testing with the patient's consent, be considered part of obstetrical practice. Providers working with this population should learn about and appropriately use clinical laboratory testing (see *Practitioner Education and Expertise*, p. 13). Providers should be aware that there are serious consequences that transcend health associated with drug testing in this population, and know that there are other ways to assess for substance use. Furthermore, for a pregnant patient with a history of addiction, the postpartum period is a time of increased vulnerability. Relapse assessment, which may include drug testing, should be part of the postpartum visit. Postpartum is a period of increased stressors, which can be a barrier to recovery. Again, providers have an obligation to keep in mind the serious potential consequences associated with drug testing in postpartum as well as pregnant patients.

For providers who do not specialize in the treatment of addiction, the ability to refer patients to appropriate care is essential. Providers should create links to a variety of addiction treatment settings in their communities that serve pregnant women, so that pregnant patients with SUDs can access appropriate care.

Patient-Provider Relationship

A woman who perceives mistreatment or experiences discrimination from her healthcare provider may avoid prenatal care to the detriment of her own health and that of her future child [65,66]. During any appointment where drug testing is discussed or performed, providers should emphasize the therapeutic reasons for the practice. Both the provider and patient should be aware that drug testing is intended to help both the woman and her family and does not serve a punitive purpose (see *Clinical Use of Drug Testing*, p. 5).

Test Considerations

The hormonal chemistry of pregnancy does not affect the results of the urine drug test. Therefore, urine is an appropriate matrix for drug testing of pregnant women. Providers can rotate matrices based on clinical judgment (see *Comparing Matrices*, p. 16).

The American College of Obstetricians and Gynecologists and ASAM jointly recommend that all pregnant women should be asked about alcohol use using a validated instrument and receive a brief intervention, if necessary [2,45]. Providers should inform patients that there is no known safe level of drinking during pregnancy. If the provider suspects Alcohol Use Disorder or the patient displays known risk factors, a laboratory test for alcohol use is warranted. More information about detecting alcohol in urine and alternative matrices is available in *Appendix 4: Windows of Detection Table*.

There is some evidence that pregnant women are less willing to disclose use of opioids and benzodiazepines than other substances [67]. These substances can have repercussions for maternal and fetal health. Including them in the test panel can provide important information that impacts clinical decision making. For example, if a provider learns that a pregnant patient is using opioids, and an assessment shows the patient has an opioid use disorder, opioid agonist medication (either methadone or buprenorphine) is the standard of care [61].

Test Results

It is important to respond proactively to test results that indicate a pregnant woman is using substances. Most general principles about responding to test results still apply (see *Responding to Test Results*, p. 10).

As a follow-up to a presumptive positive test, use definitive testing to clearly identify individual drugs. Because of the limitations of presumptive testing (see *Presumptive and definitive tests*, p. 8) and the known social and legal consequences of detecting substance use during pregnancy, definitive test should be conducted to confirm presumptive positive test results.

In keeping with the principles of Screening, Brief Intervention and Referral to Treatment (SBIRT), providers can respond to a positive drug test by conducting a brief intervention that contains preventive education, offering a referral to treatment, or (if the provider offers addiction care such as buprenorphine) creating a treatment plan for the patient. It is important that providers be familiar with local treatment resources and programs for pregnant women. Any referrals to nearby programs can thus take into consideration factors that could impact the patient's success, such as transportation access, financial impact, childcare options, and co-occurring medical needs.

If the patient is already receiving addiction treatment, ASAM recommends that the presence of a positive result on a urine drug test be used to increase the intensity of the treatment plan [61]. According to ASAM, ''It should not be used as a basis for termination of treatment services or as the basis for arrest, incarceration, or as a prima faciae basis for reflexive revocation of probation or parole, particularly in this vulnerable population.'' [61]

People in Recovery

Continuing Care

Many have argued that most patients receive an inadequate ''dose'' of addiction treatment and little support in the form of continuing care [53]. The appropriate duration of treatment and continuing care depends on the type and degree of substance use.

The expert panel agreed that 5 years of monitoring with a drug-testing component is appropriate for most patients in stable recovery, although this rarely occurs in practice. As with addiction treatment, there is evidence that any approach to drug testing people in recovery should be individualized based on the severity and chronicity of the addiction.

The Recovery Management Checkup (RMC) model [68] is a promising approach to ongoing intervention and treatment re-engagement, as needed. An RMC consists of periodic interviews with patients after leaving a formal treatment setting, an assessment of individual's recovery needs, discussion of desired behavior change using a Motivational Interviewing approach, and referral to additional services as needed. Drug testing is not a central component of the RMC model; typically, RMCs rely on self-report using a standardized interview instrument. However, when the RMC has utilized urine testing as adjunct to self-report, it has improved the accuracy of self-reported substance use [69]. This suggests

TABLE 7. Physician's Health Programs [10,71]

Scope
Most PHPs work with other healthcare professionals (dentists, veterinarians, pharmacists, etc)
Approach
PHPs expect each physician participant to maintain lifelong abstinence from alcohol and drugs. Relapses are seen as temporary setbacks or learning experiences
The elements in PHP care management are part of an integrated long-sustained program. The level of cohesion and coordination that comes from such integration may contribute to the PHP's high long-term recovery rates
Monitoring
The minimum period of monitoring for addiction is 5 years
The minimum period of monitoring for harmful substance use is 1 year and a maximum of 2 years assuming no additional concerns are raised during the monitoring period
A contractual component between PHPs and participants should include an agreement for abstinence and the requirement to immediately report any use of alcohol or mood altering chemicals
A contractual component between PHPs and participants should include an agreement to submit to biological specimen monitoring without question
The monitoring function involves periodic interviews as well as random urine and hair testing
The average PHP participant receives weekly random drug testing for the first 6 to 12 months followed by once or twice per month for the remainder of the agreement. Testing is random, meaning that typically every day of the work week the physician participants call a phone number to see if that day they need to submit a sample for testing. If they had been tested the day before, they could be tested next
If problems emerge, frequency of random testing is substantially increased
Failing to attend required treatment and support groups may result in heightened testing frequency
Many physicians in recovery cite continued urine testing as a powerful deterrent to drug use, which greatly increases their motivation to remain abstinent
Drug Testing Protocol
Commonly marketed drug panels such as "NIDA-5" and "CSAT-7" are not adequate for testing in this population
Most PHP programs routinely use ethyl glucuronide testing to better detect alcohol use
The panel most often performed is a 20+ drug health professional drug panel
Witnessed collection is the gold standard: deviation from this collection protocol for a specimen must be approved by the PHP
A forensic laboratory facility qualified to perform and confirm a state of the art healthcare testing profile must be used
Level of detection testing rather than using predetermined cut-off should be employed in analysis and reporting
A toxicologist must be available for consultation in test interpretation
Adulteration testing must include at a minimum specific gravity and creatinine and other tests for adulterants as recommended by the laboratory
Responding to a Positive Result
Adjustment of treatment/continuing care/monitoring is undertaken based upon on-going evaluation of the monitored health condition
Detailed relapse statistics for chemically addicted individuals will facilitate an analysis of monitoring efficacy. Information should be recorded about the relapse (ie, relapse severity, substance type, content/setting, temporal relationship to patient care, whether impairment was suspected, etc)
All positive screening results must be confirmed prior to reporting.
Alcohol positive results should be reflexed to test for glucose and yeast
Voluntary withdrawal from practice pending evaluation and/or treatment is usually indicated when inappropriate toxicology results are received
Each relapse should be evaluated clinically with a graduated response tailoring treatment intensification to relapse severity

that it is feasible to integrate drug testing into RMCs and that such an addition could improve the effectiveness of the intervention.

The most well-known use of drug testing as a part of continuing care is within Physicians Health Programs (PHPs). Although PHPs are overseen by states (and therefore vary), Table 7 illustrates consistent elements of PHPs. This model has been highly effective among physicians and other healthcare professionals [70]. Drug testing is a consistent element of PHPs and generally occurs periodically for 5 years after a physician leaves a formal treatment setting. A positive definitive test result triggers an immediate re-evaluation of the patient to consider the benefits of a different treatment approach or a more intensive level of care. This model, including regular drug testing, may have applications for other populations who would benefit from continuing care [10].

Health and Other Professionals

Because of the exceptional outcomes that PHPs produce, their use should continue among physicians and expanded to include other health professionals and for other safety sensitive professionals. Drug testing is an important component of PHPs and is especially helpful because health professionals have increased access to psychoactive substances. Professionals in recovery who have significant occupational exposure to addictive substances should receive more frequent drug testing.

Summary of Recommendations

Adolescents

When to Test Adolescents

- Use drug testing to assist in early identification of substance use in high-risk populations of adolescents including but not limited to those with known past substance use and those in treatment for mental health disorders.
- Drug testing to monitor adolescents in addiction treatment or recovery from an SUD can be performed by providers in primary care.
- When an adult observes symptoms characteristic of substance use in an adolescent, providers should use drug testing as part of an assessment for a possible addiction.

Adolescents and Self-Reported Substance Use
- Even if an adolescent reports substance use, providers should consider drug testing for additional information because adolescents are less likely to self-report accurately.

Adolescents and Home Testing Kits
- Because of a variety of limitations with home drug testing process and interpretation, providers should not encourage the use of home drug testing for adolescents.

Adolescent Consent
- Before beginning the drug testing process with an adolescent, providers should explain drug-testing protocols in full.
- Drug testing an adolescent without his or her consent is not appropriate, except in emergency situations (eg, accidents, suicide attempts, and seizures).
- Providers should acquire consent before drug testing an adolescent with symptoms such as school failure, fatigue, or excessive moodiness. Because these are not emergency situations, they are not hazardous enough to warrant skipping this step.
- If an adolescent refuses to consent to a drug test, the provider should clearly document refusal and continue to evaluate the possibility of SUD through other methods and refer the patient to a specialist with additional mental health or substance use expertise.

Adolescent Confidentiality
- Before beginning the drug testing process, providers should ask the adolescent for permission to share the results with parents/guardians and discuss confidentiality with parents/guardians in order to encourage parental involvement.
- If an adolescent declines to share drug test results, the provider should not share them unless there is an acute risk of harm to the patient or others.

Choosing a Test Panel for Adolescent Patients
- Drug test panels for adolescents should include the substances most used by the demographic.

Responding to Positive Test Results
- If a positive definitive drug test result indicates that an adolescent is engaging in high-risk substance use, the provider should assist the patient and his or her parent or guardian in developing a plan for monitoring and treatment.

Pregnant Patients

Consequences and Confidentiality
- Providers should be aware of the adverse legal and social consequences of detecting substance use among pregnant women. They should familiarize themselves with local and state reporting requirements before conducting a drug test and relay this information to their patient before conducting a drug test.

Screening, Assessment, and Monitoring
- Comprehensive substance use assessment, which may include drug testing, is part of obstetrical best practices. Providers working with this population should learn about and appropriately use clinical laboratory tests.
- For a pregnant patient with a history of addiction, providers should be aware that the postpartum period is a time of increased vulnerability. Therefore, assessment for relapse, which may include drug testing, should be part of the postpartum visit.
- Providers should keep drug test results and associated diagnoses confidential to the extent permitted by law.

Patient-Provider Relationship
- When speaking with patients, providers should emphasize the therapeutic reasons for drug testing to avoid stigmatization.

Test Considerations
- In a prenatal care setting, routine Screening and Brief Intervention for alcohol use should be conducted. Laboratory testing for alcohol use is not recommended except in cases of suspected or known risk factors for Alcohol Use Disorder.
- As pregnant women who use substances are less willing to disclose use of opioids and benzodiazepines than other substances, testing for opioids and benzodiazepines helps identify an often underreported behavior.
- Urine is an appropriate matrix for drug testing women who are pregnant.

Test Results
- As a follow up to a presumptive positive test result, providers should use definitive tests to clearly identify individual drugs.
- Responses to positive drug test results can include: patient education, referral to treatment, and the creation of a treatment plan.
- Providers should be familiar with local treatment resources and programs for pregnant women.

People in Recovery
- It is appropriate to conduct drug testing for a minimum of 5 years in healthcare settings for most patients in stable recovery. The frequency of drug testing for patients in stable recovery should depend on the severity and chronicity of the patient's addiction.
- It is appropriate for patients in stable recovery to receive periodic RMCs that include a drug-testing component.
- Immediate evaluation for treatment or treatment intensification as a response to a positive drug test result is appropriate for most patients in stable recovery.

Health and Other Professionals
- Drug testing is especially useful in supporting recovery of individuals who have increased access to psychoactive substances, including healthcare professionals and professionals in safety sensitive positions. Additional testing should be considered for those in recovery who have significant occupational exposure to addictive substances.

AREAS FOR FURTHER RESEARCH

Part 1: Principles of Drug Testing in Addiction Treatment

- Further research is needed on whether and how drug testing can be used to determine efficacy of and adjustments to treatment plans.
- Additional research is needed on the relationship between drug testing and functional status and other addiction treatment outcomes. Further research should include mediators and moderators of the relationship.
- More research is needed on the utility of clinical drug testing in populations where SUD is often identified, including primary care, emergency room, and pain management patients.

Part 2: Process of Drug Testing in Addiction Treatment

- Significantly more research is needed on optimal testing frequency as well as the relationship between specific frequency and duration of drug testing and treatment monitoring and outcomes.
- Additional research is needed on how to utilize drug testing to detect novel and synthetic drugs (eg, cannabinoids, cathinones).
- While evidence suggests that random testing schedules are more effective than testing on a predictable timeline, further study is needed to determine whether there are situations where non-random testing is sufficient.
- Further and ongoing research is needed on which drugs should be included in drug test panels.
- Further research is needed on determinations of when a definitive test as follow up or in place of a presumptive test should occur.
- Additionally, more research is needed on the benefits of forgoing presumptive testing and beginning with definitive testing, and on discerning the roles of different kinds of definitive testing.

Part 3: Additional Considerations for Drug Testing in Addiction Treatment

- More research on effective personnel training to increase the reliability of drug testing conducted at the point of care is needed.
- The development of appropriate cutoffs for POCT needs more research. Though manufacturer recommended cutoffs are generally more appropriate for workplace rather than clinical drug testing, producing guidelines for a clinical setting requires more information.
- Further research is needed on the effects of conducting onsite testing and interpretation versus routinely sending tests to a laboratory for results.
- Further research on the impact of insurer regulations and restrictions on drug testing, addiction treatment, and overall healthcare costs would be useful.

Part 4: Biological Matrices

- Further research is needed to develop a protocol for evaluating sample tampering in UDT. Further research is also needed to clarify what methods should be employed to verify specimen validity in alternative matrices.
- Additional study is required to determine the detectability of cannabis use in multiple matrices, namely oral fluid and hair.
- Research is lacking on what substances' metabolites can be helpfully detected through hair testing. More information on false positives, environmental adulterants, and detection windows would be beneficial.
- More research is needed on whether hair and nail testing is clinically useful in ascertaining substance use patterns and history.
- More research is needed on the utility of sweat testing in addiction treatment settings.
- Additional research is needed on oral fluid, including which specific drugs/metabolites oral fluid testing might best detect.
- Further research on tobacco testing in the context of addiction treatment would be useful.

Part 5: Settings

- Further research is needed on the role of drug testing for identification of potential issues in primary care or other settings outside of addiction treatment such as mental health settings.
- Before making any specific recommendations of frequency or duration specific to level of care, further research should occur.
- Further research will be required to offer complete information regarding appropriate drug testing panels in OTS. The same applies to the role of drug testing in determining optimal dosing in the context of OTS.
- In the context of OTS, further research is needed on frequency of drug testing and on response to drug testing results.
- Further research is needed to determine whether testing frequency should vary between full agonists, partial agonists, and antagonists when treating addiction involving opioid use.

Part 6: Special Populations

- While it is agreed that instances exist where an adolescent ought to be drug tested regardless of their own desires, the exact circumstances would benefit from further refinement.
- Further research is needed to determine what, if any, clinical benefit there is to routinely utilizing drug testing with pregnant women.
- Additional research is needed on what methods might be utilized to test for identification of alcohol use during pregnancy.
- Further research is needed on how widely the drug testing standards developed for PHPs could be applied to other addiction treatment programs.

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Appendix 1: Abbreviations and Acronyms

6-MAM	6-Monoacetylmorphine
AAP	American Academy of Pediatrics
AGOC	American Congress of Obstetricians and Gynecologists
ASAM	American Society of Addiction Medicine
CLIA	Clinical Laboratory Improvement Amendments
EtOH	Ethyl alcohol or ethanol
EtG	Ethyl glucuronide
EtS	Ethyl sulfate
MRO	Medical Review Officer
NIDA	National Institutes of Drug Abuse
OBOT	Office-Based Opioid Treatment
OTP	Opioid Treatment Program
OTS	Opioid Treatment Services
PCP	Primary Care Physician
PHP	Physician Health Program
POCT	Point of Care Testing
RAM	RAND/UCLA Appropriateness Method
SAMHSA	Substance Abuse and Mental Health Services Administration
SBI	Screening and Brief Intervention
SBIRT	Screening, Brief Intervention, and Referral to Treatment
SUD	Substance Use Disorder
UDT	Urine drug testing

Appendix 2: Glossary and Terms

Below are terms that are used throughout the appropriateness document. Note that some terms listed below are used to convey a specific meaning for the purposes of this appropriateness document (eg, ''provider'').

Terms and Definitions

Abstinence: Intentional and consistent restraint from the pathological pursuit of reward and/or relief that involves the use of substances and other behaviors. These behaviors may involve, but are not necessarily limited to, gambling, video gaming, spending, compulsive eating, compulsive exercise, or compulsive sexual behaviors. Note that patients in opioid agonist therapy may be considered abstinent if they are not pathologically pursuing the use of substances and other behaviors.

Adherence: Adherence is a term that health professionals have been using increasingly to replace the term ''compliance.'' Refers to how closely patients cooperate with, follow, and take personal responsibility for the implementation of their treatment plans. Often used with the more narrow sense of how well patients accomplish the goal of persistently taking medications, and also refer more broadly to all components of treatment. Assessment of patients' efforts to accomplish the goals of a treatment plan is essential to treatment success. These efforts occur along a complex spectrum from independent proactive commitment, to mentored collaboration, to passive cooperation, to reluctant partial agreement, to active resistance, and to full refusal. Attempts to understand factors that promote or inhibit adherence/compliance must take into account behaviors, attitudes, willingness, and varying degrees of capacity and autonomy.

Adolescence: The American Academy of Pediatrics categorizes adolescence as the totality of 3 developmental stages—puberty to adulthood—which occur generally between 11 and 21 years of age.

Addiction: A primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits, caused by prior repeated drug use, leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors. Addiction is characterized by inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death.

Analyte: The component of a biological sample that is identified and measured. In drug testing, both parent drugs and the products of drug metabolism are targeted. Their presence indicates exposure to a substance or family of substances.

ASAM Criteria dimensions: The *ASAM Criteria* use 6 dimensions to create a holistic biopsychosocial assessment of an individual to be used for service planning and treatment. Dimension 1 is acute intoxication or withdrawal potential. Dimension 2 is biomedical conditions and conditions. Dimension 3 is emotional, behavioral, or cognitive conditions or complications. Dimension 4 is readiness for change. Dimension 5 is continued use or continued problem potential. Dimension 6 is recovery/living environment.

Collateral report: Information delivered by a third party, commonly a family member or partner, about a patient's substance use or signs of substance use.

Confounds: Any variable present in a drug testing process that prevents the accuracy of results. For example, eating a food that produces a false-positive result. The influence of a confound may be applied accidentally, as when a patient cannot produce a urine sample due to a shy bladder, or with intent, as when a patient dilutes a urine sample.

Conjugate: A compound produced by the chemical joining of at least 2 other compounds.

Contingency management: An evidence-based psychosocial intervention in which patients are given tangible rewards to reinforce positive behaviors such as abstinence. Also referred to as motivational incentives.

Continuing care: After completion of a formal addiction treatment program, aftercare is a stage of continued assistance to a person in recovery. Although intensity of care is reduced in this stage, the patient still has a support system and often may retain contact with a professional. Aftercare includes the development and use of skills and strategies for life in recovery.

Cross-reactivity: Immunoassays suffer from a lack of specificity, in that they will react to compounds with similar chemical structures. This is known as cross-reactivity. They target compounds present in the body for reasons other than the consumption of illicit substances. For example,

consuming poppy seeds and drugs derived from the poppy plant will both metabolize to detectable amounts of morphine in the body.

Definitive testing: In contrast to presumptive testing, testing performed using a method with high sensitivity and specificity that is able to identify specific drugs, their metabolites, and/or drug quantities. Definitive testing is likely to take place in a laboratory and each individual test can be expensive. Gas or liquid chromatography combined with mass spectrometry is the gold standard method in definitive drug testing.

Drug testing: The process of analyzing a biological specimen to check for the presence of chemicals that indicate exposure to selected substances.

Expected test results: In the context of addiction treatment that includes medication (eg, buprenorphine) an expected test result is positive for prescribed medication and negative for other substance use.

False negative: The analytical failure to detect the presence of a drug or drug metabolite that is present in the specimen. A false negative on a screening immunoassay test can be discovered by confirmation testing using GC-MS or LC-MS/MS testing when these tests are used on samples that have been screened as negative.

False positive: The reporting of a positive drug or drug metabolite that is not present in the specimen. A false positive on a screening immunoassay test is often discovered by confirmation testing using GC-MS or LC-MS/MS testing.

- *Clinical false positive*—Apositive test result caused by incidental or extraneous exposure to a substance.
- *Analytical false positive*—Apositive test result caused by changes in the sample, which may be related to physical disease or conditions of the donor or improper or delayed storage, and others.

Federal cutoff concentrations: SAMHSA issues recommended drug test cutoff levels for the substances and substance metabolites tested during the standard workplace drug testing analysis. The standard focuses on the ''SAMHSA Five,'' the substances for which workplaces typically screen (amphetamines, cannabinoids, cocaine, opiates, and phencyclidine). This standard is not appropriate to apply to drug testing in the context of addiction treatment.

Fixed testing schedule: *(See also: Random testing schedule)* A predictable time when drug testing will occur, such as every Monday or every 10 days. This is discouraged as patients can use knowledge of the routine to strategically use substances on days when the detection risk is smallest.

General healthcare setting: A widely defined term in this document indicating a setting where healthcare is provided that is not primarily an addiction treatment service.

Induction (office and home): The phase of opioid treatment during which maintenance medication dosage levels are adjusted until a patient attains stabilization. Buprenorphine induction may take place in an office-based setting or home-based setting. Methadone induction must take place in an OTP.

Level of care: Section 4 of the appropriateness document addresses the use of drug testing across the ASAM Levels of Care, which are listed below. In addition to the 5 broad Levels of Care, the section addresses drug testing in OTS, and when medications are used to treat addiction involving opioid use in primary care settings.

- 0.5—Early Interventions
- 1.0—Outpatient Services
- 2.0—Intensive Outpatient/Partial Hospitalization Services
- 3.0—Residential/Inpatient Services
- 4.0—Medically Managed Intensive Inpatient Services
- Opioid Treatment Service

Maintenance: Pharmacotherapy on a consistent schedule for persons with an addiction, usually with an agonist or partial agonist, which mitigates cravings and withdrawal symptoms. Maintenance treatments are also designed to mitigate against the risk of overdose. Depending on the individual, these treatment plans can be time-limited or remain in place lifelong. Methadone, buprenorphine, and naltrexone are among medications prescribed.

Matrix (matrices): The biological material used for analysis in a drug test. Examples include blood, urine, oral fluid (spit/saliva), hair, nails, sweat, and breath.

Medical Review Officer (MRO): A physician trained and certified to interpret drug test results and to validate the testing process. To become a certified MRO, physicians must take an in-person training course. Their training includes collection procedures for urine specimens; chain of custody, reporting, and record keeping; and interpretation of drug and validity tests results. Re-certification must be undergone every 5 years. This is a federally defined role.

Medical Toxicologist: A physician trained in this formal medical subspecialty has focused training in the diagnosis, management and prevention of adverse health effects due to medications, occupational and environmental toxins, biological agents, and clinical evaluation of patients.

Metabolite: A product of the metabolism or metabolic process. Urine drug tests typically identify the presence of 1 or more metabolites that can originate in a potentially addictive substance.

Negative Test Result (*See also: Positive test result)*: The result reported by a test that fails to detect the presence of a target substance in a sample. This can indicate either a complete lack of the drug or drug metabolite or a level too low to be detected by the test. In this document, a ''negative test result'' refers to a test result showing no use of non-prescribed addictive substances. However, in the context of addiction treatment that includes medication, the terms positive and negative have been replaced with ''unexpected'' and ''expected.''

Office-Based Opioid Treatment (OBOT): Physicians in private practices (and Nurse Practitioners and Physician Assistants who have recently been given the authority to prescribe under the 2016 Comprehensive Addiction and Recovery Act) or a number of types of public sector clinics can be authorized to prescribe outpatient supplies of the partial opioid agonist buprenorphine. There is no regulation per se of the clinic site itself, but of the individual physician who prescribes buprenorphine.

Opioid Treatment Program (OTP): A program certified by the United States, Substance Abuse and Mental Health Services Administration (SAMHSA), usually comprising a facility, staff, administration, patients, and services, that engages in supervised assessment and treatment, using methadone, buprenorphine, or naltrexone, of individuals who are addicted to opioids. An OTP can exist in a number of settings including, but not limited to, intensive outpatient, residential, and hospital settings. Services may include medically supervised withdrawal and/or maintenance treatment, along with various levels of medical, psychiatric, psychosocial, and other types of supportive care.

Opioid Treatment Services (OTS): An umbrella term that encompasses a variety of pharmacological and nonpharmacological treatment modalities. This term broadens understanding of opioid treatments to include all medications used to treat opioid use disorders and the psychosocial treatment that is offered concurrently with these pharmacotherapies. Pharmacological agents include opioid agonist medications such as methadone and buprenorphine, and opioid antagonist medications such as naltrexone.

Patient: Used throughout the appropriateness document, this term is intentionally broad. It encompasses anyone who receives care for an addiction in a specialty addiction treatment center or other healthcare setting.

Point of Collection Tests/Point of Care Tests (POCT): A drug test performed at the site where the sample is collected using either an instrumented or non-instrumented commercial device (eg, a, immunoassay test strip or dipstick or machine-based immunoanalyzer); in distinction to a laboratory-developed test. (A POC test is often referred to as an ''instant test''; ''home drug test'' kits purchasable by laypersons are also POC tests).

Positive Test Result: The result reported by a test that detects the presence of a target substance in a sample. In this document, a ''positive test result'' refers to a test result showing the use of non-prescribed addictive substances. However, in the context of addiction treatment that includes medication, the terms positive and negative have been replaced with ''unexpected'' and ''expected.''

Presumptive Testing: In contrast to definitive testing, testing performed using a method with lower sensitivity and/or specificity which establishes preliminary evidence regarding the absence or presence of drugs or metabolites in a sample. The results of presumptive tests are qualitative in that they detect the presence or absence of particular compound, but not their quantity. Immunoassays are good at identifying true negative samples (high sensitivity) and are therefore well suited for use as a screen to eliminate cases from further analysis.

Provider: Used throughout the appropriateness document, this term is intentionally broad. It encompasses anyone who participates in providing care to patients with addiction, including staff at specialty addiction treatment centers or other healthcare settings that provide addiction treatment.

Random Testing Schedule: (*See also: Fixed testing schedule*) A recurring drug testing plan with varying amounts of days between testing that cannot be predicted. Clinical consensus favors random testing schedules to fixed testing schedules. A random schedule can eliminate ''safe'' periods where a patient might choose to use without detection.

Recovery: The process of sustained action that addresses the biological, psychological, social, and spiritual disturbances inherent in addiction. This effort is in the direction of a consistent pursuit of abstinence, addressing impairment in behavioral control, dealing with cravings, recognizing problems in one's behaviors and interpersonal relationships, and dealing more effectively with emotional responses. Recovery actions lead to reversal of negative, self-defeating internal processes and behaviors, allowing healing of relationships with self and others. The concepts of humility, acceptance, and surrender are useful in this process.

Recovery residence (RR): Recovery residence is a broad term describing a sober, safe, and healthy living environment that promotes recovery from alcohol and other drug use and associated problems. At a minimum, RRs offer peer-to-peer recovery support with some providing professionally delivered clinical services all aimed at promoting abstinence-based, long-term recovery

Reflex testing: A practice where a laboratory automatically performs definitive testing on positive presumptive results for the purposes of refining the information the sample can provide. If a laboratory does not practice ''reflex testing,'' this action requires an additional order from the provider.

Relapse: A process in which an individual who has established abstinence or sobriety experiences recurrence of signs and symptoms of active addiction, often including resumption of the pathological pursuit of reward and/or relief through the use of substances and other behaviors. When in relapse, there is often disengagement from recovery activities. Relapse can be triggered by exposure to rewarding substances and behaviors, by exposure to environmental cues to use, and by exposure to emotional stressors that trigger heightened activity in brain stress circuits. The event of using or acting out is the latter part of the process, which can be prevented by early intervention.

Sample/specimen: The biological substrate that is submitted to be tested. A ''sample'' refers to the part collected from a patient for testing (part of a whole). A ''specimen'' refers to what is analyzed (the sample becomes its own entity).

Sample tampering: This term refers to any deliberate attempt to falsify drug test results. Examples of tampering would include dilution of the sample, adulteration through addition of various substances to the sample, or substitution with a sample from another person.

Sensitivity: Also called the ''true positive rate'' or the ''recall rate'' in some fields, sensitivity measures the proportion of actual positives which are correctly identified as such (eg, the percentage of sick people who are correctly identified as having the condition). Sensitivity refers to the likelihood that a given test is able to detect the presence of a drug or metabolite that is actually in the specimen.

Specificity: Measures the proportion of negatives that are correctly identified as such (eg, the percentage of healthy people who are correctly identified as not having the condition, sometimes called the ''true negative rate''). Specificity refers to the likelihood that a given test is able to identify the specific drug or metabolite of interest in the

specimen and not to erroneously label other drugs or metabolites falsely.

Stabilization: Includes the medical and psychosocial processes of assisting the patient through acute intoxication and withdrawal to the attainment of a medically stable, fully supported, substance-free state. This often is done with the assistance of medications, though in some approaches to detoxification, no medication is used.

Substance use: Used instead of ''drug use'' or ''drug and alcohol use,'' this term refers to the use of psychoactive drugs, which may include illegal drugs, medications, or alcohol. This does not refer to nicotine.

Substance use disorder (also substance-related disorder) (SUD): This term is used as defined in the Diagnostic and Statistical Manual 5 (DSM-5). It is abbreviated here as ''SUD.''

Substitution: when a previously collected biological specimen is used in place of a specimen collected at the time of the drug test. For example, if a donor provides previously collected urine (from herself or someone else, or even non-human urine) in place of their own urine at the time of the test.

Toxicology screening: Also called ''toxicology testing,'' this term refers to the process of testing for the presence of toxins or poisons. Clinical drug testing in addiction treatment settings has different aims than does toxicology screening in emergency medical settings or intensive care settings, and thus should not be referred to as ''toxicology screening'' or ''toxicology testing.''

Treatment plan: A therapeutic strategy that may incorporate patient education, drug therapy, and the participation of health professionals. Treatment plans are especially important in the optimal management of complex or chronic illnesses such as addiction.

Unexpected test results: In the context of addiction treatment that includes medication (eg, buprenorphine), an unexpected test result could be a) negative for prescribed medication, b) positive for other substance use or c) both.

Validity testing: A test used to determine if a specimen is adulterated, diluted, substituted, or otherwise invalid.

Window of detection: The range of time that a substance can be detected in a biological sample given the cutoff values for the test being performed. It refers both to the time to detection (time to be absorbed and distributed to sample material) and time to clearance (time to be metabolized/eliminated/excreted). A test conducted before the substance or its metabolites have adequately entered the biological sample reads as negative. Each matrix and analyte has a different window of detection, ranging from minutes to months.

Appendix 3: Methodology

Appropriateness Document Versus Clinical Guideline

In March 2016, ASAM contracted with the Institute for Research, Education, and Training in Addiction (IRETA) to develop an appropriateness document addressing drug testing in the context of addiction treatment using the RAND/UCLA Appropriateness Method (RAM). The RAM is ideal for the identification of under use or overuse of specific clinical procedures or tests, as well as in situations where rigorous clinical trials are lacking.

The purpose of this appropriateness document is to determine when, where or how often a drug test should be performed for the identification, diagnosis, treatment, and recovery of patients with, or at risk for, addiction. The document takes into account:

- Available scientific evidence;
- Individual patient characteristics;
- Risk/benefit of testing;
- Available healthcare resources.

Clinical guidelines, on the other hand, typically focus on either more generalized or disease-specific recommendations—such as ASAM's National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use.

Overview of Approach

The RAND/UCLA Appropriateness Method provides a specific process for combining the best available scientific evidence with the collective clinical judgment of field experts to arrive at recommended practices. The RAND/UCLA Appropriateness Method is ideal for the identification of under use or overuse of specific clinical procedures or tests, as well as in situations where rigorous clinical trials are lacking. This use of the RAND/UCLA method will produce a set of appropriateness statements regarding the use of drug testing in the identification, diagnosis, treatment and promotion of recovery for patients with, or at risk for, addiction.

ASAM's Quality Improvement Council (QIC) was the oversight committee for the development of the appropriateness document. The QIC appointed a 11-member expert panel to participate throughout the development process, rate treatment scenarios, and review the draft document. In selecting the panel members, the QIC made every effort to avoid actual, potential, or perceived conflicts of interest that may arise as a result of relationships with industry and other entities among members of the expert panel. All QIC members, expert panel members, and external reviewers of the document were required to disclose all current related relationships, which are presented in Appendices 6 and 7.

The expert panel was comprised of experts and researchers from multiple disciplines, medical specialties, and subspecialties, including academic research, internal medicine, adolescent medicine, pain medicine, emergency medicine, medical toxicology, anesthesiology, psychiatry, and obstetrics/gynecology. Physicians with both allopathic and osteopathic training were represented. Furthermore, the panel members represented a range of practice settings including OTPs, physician health programs, private practice, and academic medical centers. The expert panel was assisted by a technical team from IRETA. The moderator and medical advisor was selected by the IRETA project team and approved by the QIC.

Task 1: Collecting Existing Research and Guidelines and Policies

Review of Existing Clinical Guidelines

Existing clinical guidelines were located primarily via a structured internet search with the keywords ''drug testing,'' ''guidelines,'' and ''insurance.'' Treatment Improvement Protocols (TIPs) and Technical Assistance Publications (TAP) published by the Substance Abuse and Mental Health Services Administration (SAMHSA) were utilized. Publications by authoritative professional societies, including the American Society of Addiction Medicine (ASAM), the American Academy of Pediatrics (AAP), and the American College of Obstetrics and Gynecologists (ACOG) were also consulted. References from these existing guidelines were consulted to locate additional resources (see Appendix 5 for a complete list of clinical guidelines reviewed).

Overall, the review of existing guidelines revealed that numerous consensus panels and expert groups have offered guidance on the use drug testing for patients with addiction. However, with the notable exceptions of SAMHSA's TIP 40 and TIP 43, very few of these guidelines address specific levels of care.

Review of Existing Payer Policies

Although not typically evidence-based, a representative sample of payer policies was consulted, to provide information about the patient populations, and types and frequency of drug testing currently being reimbursed in clinical care. ASAM provided suggestions of payer policies to review. Overall, the review of selected payer policies demonstrated that there is a wide range of drug-testing services that are considered medically necessary or reimbursable by insurance plans. Statements from representative payer policies were selected and incorporated into the draft appropriateness statements.

Review of Research Literature

A review of empirical evidence regarding drug testing in clinical contexts for people with addiction was conducted. Relevant research was identified in the PubMed database using the MeSH search terms Substance-Related Disorders and Substance Abuse Detection. To capture the most up-to-date findings for the field's rapidly evolving detection capabilities, the search was limited to articles published in the previous 10 years. Earlier papers important to the field were identified through reverse citation search and included in the development of statements, but not the literature review. In order to have a complete picture of relevant research on this topic, this review was not limited to randomized controlled trials or similarly rigorous methodologies; it included cohort studies and case studies [72]. Of the 866 articles identified, 113 were retained following a title and abstract review for relevance to the topic of biological detection of addictive substances in an appropriate population or setting.

The literature review sought to evaluate the state of the research literature on drug testing in the identification, diagnosis, treatment, and monitoring of patients with, or at risk for, addiction. Overall, the literature review revealed that drug testing has rarely been examined for its value as a clinical intervention. Many research studies include drug testing as an outcome measure of treatment adherence or progress, but few examined whether and how drug testing itself works to improve outcomes for patients with addiction (Fig. 1).

Task 2: Development of Statements

To develop the appropriateness statements, a 1-day meeting was held with the project team and Medical Advisor. During this meeting, the team discussed the reviews of existing clinical guidelines, payer policies and research literature. Statements in these existing publications pertaining to the appropriate use of drug testing in the identification, diagnosis, treatment, and monitoring of patients with, or at risk for, addiction were identified and discussed.

Each appropriateness statement was rated by the project team on quality of clinical consensus and empirical evidence. A high clinical evidence rating was reserved for statements supported by multiple sources. A high empirical evidence rating was reserved for statements emerging from multiple studies using rigorous study methodology (eg, randomized control trials).

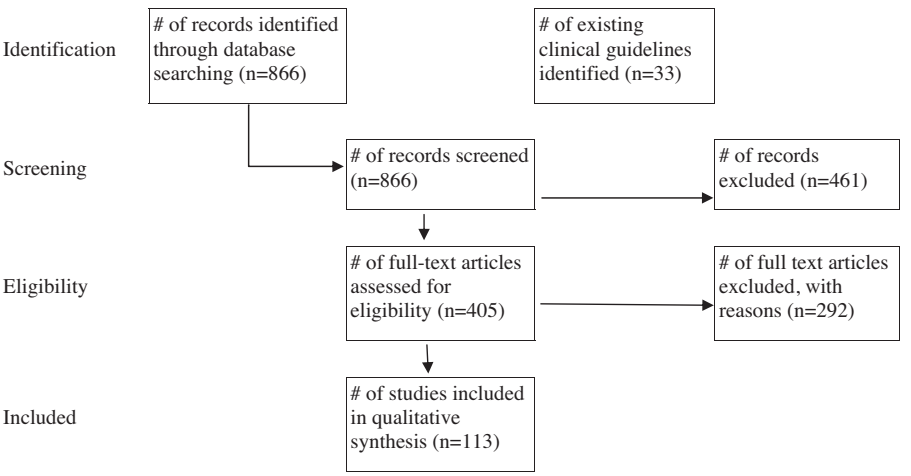

FIGURE 1. Study selection process.

There were some clinical areas relevant to addiction treatment settings where adequate empirical evidence or existing clinical recommendations were not found (eg, certain levels of care). In these situations, appropriateness statements were generated in conjunction with the Medical Advisor and the lack of the existing evidence was clearly documented.

The statements and supporting evidence ratings were organized in an appropriateness statement document.

Task 3: Development of the Background Paper

A background paper was developed as a companion piece to the appropriateness statement document. It was organized in direct parallel to the statement document, with each statement or set of statements in the appropriateness statement document corresponding to a description of the statement's source and the strength of evidence.

Task 4: Expert Rating, First Round

Each expert rated the appropriateness of each statement on a 1 to 9 Likert scale, where 1 = the statement is extremely inappropriate, 5 = uncertainty or neutrality about the appropriateness of the statement and 9 = the statement is extremely appropriate. Appropriateness refers to whether the expected benefit of following the statement outweighs any anticipated risks by a sufficiently wide margin that it is worth following the statement [72]. The experts were asked to use their own best clinical judgment (rather than perception of what other experts might say) considering an average patient presenting to an average provider who performs drug testing in an average setting that provides care for patients with addiction. Some sections pertained specifically to special populations or settings; the experts were made aware of appropriateness statements intended for specific populations or settings.

Panel members were encouraged to refer to the background paper for a discussion of each appropriateness statement and the clinical or empirical evidence supporting it. Panel members were also encouraged to make comments and suggest changes that could be made to improve each statement and identify gaps in the statements.

Each statement was classified by Appropriateness (''inappropriate,'' ''uncertain,'' or ''appropriate'') in accordance with the panel's median score and by Agreement (''agree'' or ''disagree'') in accordance with the distribution of panel's scores. Statements with median scores in the 1 to 3 range were classified as inappropriate, those in the 4 to 6 range as uncertain, and those in the 7 to 9 range as appropriate. Statements with no more than 2 panelist ratings outside of the Appropriateness category were classified as with agreement and those with 3 or more panelist ratings outside the Appropriateness category as with disagreement. The ''three or more'' cutoff for disagreement is commonly used for panel sizes of 8 to 10 members. It indicates that at least one-third of the panelists view a statement differently than (at least) another one-third of the panelists.

Task 5: Expert Panel Meeting

The 11-member expert panel came together for a 2-day meeting to discuss their ratings, focusing on statements about which they disagreed. The goal of the discussion was to discern whether discrepant ratings were due to real clinical disagreement or to fatigue or misunderstanding (''artifactual'' disagreement). The expert panel was encouraged to modify statements and suggest additional statements during the discussion.

Task 6: Expert Rating, Second Round

After the expert panel meeting, each expert rated the appropriateness of the subset of previously disagreed upon or uncertain statements, as well as the new statements that were constructed, on a 1 to 9 Likert scale, where 1 = the statement is extremely inappropriate, 5 = uncertainty or neutrality about the appropriateness of the statement and 9 = the statement is extremely appropriate. A summary of the statements, their final ratings and associated evidence is included in the evidence table, which is a separate supplemental document.

The RAND/UCLA Method provides for a third round of rating for necessity. Necessity refers to practices that *must* be offered to patients fitting a particular clinical description, in that it would be considered improper care *not* to offer them. Hence, necessity is a more stringent criterion than appropriateness, and was premature to address in the context of drug testing for addiction treatment.

There is an urgent need for further research in several aspects of drug testing in addiction treatment. A section entitled Areas for Further Research was developed based upon the literature review, areas yielding little agreement among the expert panel, and input from all stakeholders.

Task 7: Compilation of the Appropriateness Document

The first draft of the appropriateness document was created and sent to the expert panel and ASAM staff. During a subsequent teleconference held in January 2017, ASAM shared feedback with the project team regarding the document, and a revised version was provided.

Task 8: External Review

ASAM directed an external review of the appropriateness document. Input was solicited from ASAM members; stakeholders including experts from the addiction treatment community, professional societies and others. The document was also available on the ASAM website for the public at large to review and submit comments. The external review period was conducted from February 3, 2017 to February 28, 2017.

ASAM Policy on Document Updates

Board approved clinical documents will be considered for reaffirmation, update, or sunset at least every 5 years based on a review of published literature since the document was published; FDA decisions (eg, new product approvals or labeling changes); or other significant practice or policy developments. Based on the QIC's review, it will determine if the revisions require a full update. Clinical documents should go through a full update when new evidence suggests the need to modify clinically important

recommendations. This would be particularly true if new evidence shows that a recommended intervention causes previously unknown substantial harm, or that a new intervention is significantly superior to a previously recommended intervention, or that a recommendation can be applied to new populations. Final Board approval will be required for all document modifications.

The QIC will consider focused updates for guidelines every 2 years when advancements in addiction research and practice warrant. This will include a review of the literature and inclusion of any new drug formulations or information in medical research or practice that requires a focused update. The QIC may, at its discretion, choose to consider a focused update sooner, if important changes have taken place that affect selected recommendations and clinical practice would benefit from selected updates when a complete update may not be necessary. More specifically, the following scenarios can be used to determine the type of focused updates needed:

- Scenario 1: No new evidence. Insert box at top of guideline that summarizes literature search including dates and number of abstracts reviewed, and indicates no new evidence identified and thus no changes to recommendations. Approval by QIC and Guideline Committee chair. To Executive Committee of Board of Directors for final approval.
- Scenario 2: New evidence/no change to recommendations. Summary of search and review, plus include a list of relevant references identified. Approval by QIC and Guideline Committee chair. To Executive Committee of Board of Directors for final approval.
- Scenario 3: New evidence/recommendations change. Current review and approval process for substantive updates and publication in print and online versions of journal. For recommendations that require input from the Guideline Committee, they will go through a similar process that was used to develop the original recommendations. All changes need to be reviewed and approved by chairs of the QIC and Guideline Committee. To Executive Committee of Board of Directors for final approval.
- Scenario 4: Ad hoc, rapid update. New evidence or treatment practice/change to recommendations. Publish a focused update with notice in journal with summary of key new evidence. Would allow for more rapid change to a guideline without a formal, comprehensive literature search and review. Change would be made to selected recommendations based on relevant published high-impact evidence or regulatory decisions. All changes need to be reviewed and approved by chairs of the QIC and Guideline Committee. If warranted, they may also need to go to the Guideline Committee for review. To Executive Committee of Board of Directors for final approval.

If the recommendations have changed, all changes to the full guideline will be made online using a different font or italics. The associated resources, including the pocket guide, phone app, and slide deck will also be updated.

Appendix 4: Windows of Detection Table

Drug Target Analyte	Detection Time in Urine [Cutoff (ng/mL) Initial; Confirm]	Reference	Detection Time in Oral Fluid [Cutoff (ng/mL) Initial; Confirm]	Reference	Detection Time in Blood [Cutoff (ng/mL)]	Reference
Alcohol						
EtOH	10–12 hours [NS[1]]	[53,73,74]	24 hours [NS]	[74]		
EtG	1–2 days [500] (1 drink)	[40,74,75]				
EtS	1–2 days [100](1 drink)	[40,76]				
PEth					1–2 weeks [NS] (heavy use)	[76]
Cocaine						
Cocaine	24 hours [50]	[77]	5–12 hours [1] (single use) 8–48 hours [1] (chronic use)	[29,78] [78]	12 hours [10]	[29]
BZE	2–3 days [300; 150] (single use)	[78–80]	12–24 hours [1] (single use)	[29,78]	2 days [10]	[29]
	1–3 days [300; 150] (infrequent use)	[81,82]	1.5–3 days [1] (chronic use)	[78]		
	4 days [300; 150] (prolonged use)	[79]	1–2 days [5]	[83]		
	12 days [300; 150 (chronic use)	[82]				
	1–3 days [150; 300]	[82]				
Amphetamine						
Amphetamine	1–2 days [100] (single/ infrequent use)	[79,80,84]	1–2 days [100]	[83]	2 days [4]	[29]
	7–10 days [100] (prolonged use)	[79]	20–50 hours [10]	[29,78]		
	2–4 days [NS] (frequent use)	[84]				
	2–4 days [1000; 500]	[81,82]				
	2–4 days [500; 250]	[74]				

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Appendix 4 (*Continued*)

Drug Target Analyte	Detection Time in Urine [Cutoff (ng/mL) Initial; Confirm]	Reference	Detection Time in Oral Fluid [Cutoff (ng/mL) Initial; Confirm]	Reference	Detection Time in Blood [Cutoff (ng/mL)]	Reference
Methamphetamine						
Analyte not specified	1–2 days [100] (single/ infrequent use)	[79,80,84]	6–76 hours [2.5] (single use)	[78]		
	7–10 days [100] (prolonged use)	[79]	1–2 days [40]	[83]		
	2–4 days [NS] (frequent use)	[84]				
	2–5 days [500; 250]	[74]				
Amphetamine	2–4 days [1000; 200]	[81,82]	24 hours [50; 2.5]	[78]		
Methamphetamine	2–4 days [1000; 500]	[81,82]	24 hours [2.5]	[29]	2 days [3]	[29,83]
	1.5–6 days [2.5]	[29]				
MDMA (Ecstasy)						
Analyte not specified	2 days [25]	[77]				
	1–3 days [NS]	[80,85]				
MDMA	2 days [20]	[29]	24 hours [125]	[29]	24 hours [20]	[29]
Morphine						
Analyte not specified	2–5 days [300]	[74]	12–24 hours [1]	[29]		
	3 days [25]	[77]	24 hours [0.6]	[78]		
	1–3 days [NS]	[73,85]	1–36 hours [NS]	[74]		
Codeine						
Analyte not specified	1–3 days [300; 300]	[81]	7 hours [40]	[29]		
	1–2 days [300; 300]	[53]	7–21 hours [2.5]	[29,78]		
	3 days [25]	[77]	1–36 hours [NS]	[44,74]		
	2–4 days [300]	[74]				
Morphine	1–3 days [300; 300]	[81,82]				
Oxymorphone						
Formulation not specified						
Analyte not specified	3 days [25]	[77]				
Immediate-release						
Analyte Not Specified	36–60 hours [100]	[53]				
Extended-release						
Analyte not specified	1–4 days [100]	[53]				
Oxycodone						
Formulation not specified						
Analyte not specified	3 days [25]	[77]				
	1–3 days [100]	[79]				
	2–4 days [NS]	[73]				
Immediate-release						
Analyte not specified	1–1.5 days [100]	[53]				
Extended-release						
Analyte not specified	1.5–3 days [100]	[53]				
Hydromorphone						
Analyte not specified	1–2 days [300]	[53,79]	6 hours [1] (single use)	[78]		
	3 days [25]	[77]				
	2–4 days [NS]	[73]				
Hydrocodone						
Analyte not specified	1–2 days [100]	[53,79]				
	3 days [25]	[77]				
Fentanyl						
Analyte not specified	1–2 days [5]	[79]				
	3 days [0.2]	[77]				
Heroin						
6-MAM	1–3 days [300;10]	[53,78]	0.5–8 hours [1]	[29,78]		

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Appendix 4 (*Continued*)

Drug Target Analyte	Detection Time in Urine [Cutoff (ng/mL) Initial; Confirm]	Reference	Detection Time in Oral Fluid [Cutoff (ng/mL) Initial; Confirm]	Reference	Detection Time in Blood [Cutoff (ng/mL)]	Reference
	2–3 days [300;10]	[74]				
	1–2 days [150]	[79]				
Morphine	1–3 days [300; 300]	[81,82]	12–24 hours [1]	[83]	20 hours [1]	[29]
	1–2 days [2000]	[79]	2–12 hours [1]	[78]		
Heroin	2–24 hours [1]	[78]				
Methadone						
Analyte not specified	3–11 days [300] (maintenance does)	[53]	1–3 days [5] (occasional use)	[83]		
			3–5 days [5] (chronic use)	[83]		
Methadone	2–4 days [300; 300]	[81,82]	24 hours [20]	[78]		
	7 days [100]	[77]				
EDDP	7 days [100]	[77]				
Buprenorphine						
Analyte not specified	4 days [0.5]	[53]				
Buprenorphine	7 days [0.5]	[77]	5 days [1]	[78]		
Norbuprenorphine	7 days [0.5]	[77]				
Benzodiazepines						
Short acting						
Analyte not specified	24 hours [300]	[53]				
	2 days [100]	[77]				
Intermediate acting						
Analyte not specified	1–12.5 days [300]	[53]				
	5 days [100]	[77]				
Long Acting						
Analyte not specified	30 days [200; 200]	[81,82]				
Diazepam						
Analyte not specified	2–7 days [500]	[78]	1–3 days [NS]	[85]		
	5–8 days [300]	[53]	5–50 hours [NS]	[78]		
	10 days [100]	[77]				
	7–21 days [NS]	[85]				
Nordiazepam	6–24 days [300]	[53]				
	10 days [100]	[77]				
Barbiturates						
Formulation Not Specified						
Analyte not specified			1–2 days [20]	[83]		
Short acting						
Analyte not specified	2–4 days [200; 200]	[81,82]				
	4–6 days [300]	[53]				
	24 hours [NS]	[73]				
Pentobarbital, Secobarbital						
Analyte not specified	3 days [100]	[77]				
Intermediate Acting						
Analyte not specified	3–8 days [300]	[53]				
Amobarbital						
Analyte not specified	3 days [100]	[77]				
Butalbital						
Analyte not specified	7 days [100]	[77]				
Long Acting						
Analyte not specified	30 days [200; 200]	[81,82]				
	10–30 days [300]	[53]				
Phenobaribital						
Analyte not specified	15 days [100]	[77]				

(*Continued on next page*)

Appendix 4 (*Continued*)

Drug Target Analyte	Detection Time in Urine [Cutoff (ng/mL) Initial; Confirm]	Reference	Detection Time in Oral Fluid [Cutoff (ng/mL) Initial; Confirm]	Reference	Detection Time in Blood [Cutoff (ng/mL)]	Reference
Cannabis						
THC	1–3 days [100,50,20;15] (casual use)	[81,82]	2–24 hours [1] (single use)	[78]	5 hours [10]	[29]
	3 days [NS] (single use)	[44]	4–14 hours [NS] (single use)	[44]		
	30 days [100,50,20;15] (chronic use)	[81,82]	22.5 hours [0.5] (occasional use)	[86]		
	36 days [NS] (chronic heavy use)	[44]	30+ hours [0.5] (frequent use)	[86]		
			4–30 hours [NS] (chronic heavy use)	[44]		
			34 hours	[29]		
			1–2 [1] days	[83]		
THCCOOH	3–4 days [50] (single use)	[31]	8 hours [15] (occasional use)	[86]	36 hours [10]	[29]
	7 days [20] (single use)	[31]	30+ hours [15] (frequent use)	[86]		
	1–5 days [50] (infrequent use)	[80]				
	10 days [50] (heavy use)	[31]				
	21 days [20] (heavy use)	[31]				
	36 hours [15] (single use 1.75% THC)	[29]				
	3.5 days [15] (single use 3.55% THC)	[29]				
	1–5 days [20] (regular use 1.75% THC)	[87]				
	3–6 days [20] (regular use 3.55% THC)	[87]				
	3 days [NS] (single use)	[53,73]				
	4–7 days [NS] (moderate use)	[53,73]				
	10–15 days [NS] (heavy use)	[53,73]				
	30–60 days [NS] (chronic heavy use)	[53,73]				
Phencyclidine						
Analyte not specified	2–7 days [25; 25] (casual use)	[81,82]	1–2 days [1]	[83]		
	7–8 days [25] (single use)	[77,79]				
	2–4 weeks [25] (prolonged use)	[79]				
	30 days [25; 25] (chronic use)	[81,82]				
	5–6 days [25; 25]	[74]				
	1.5–10 days [NS] (casual use)	[53]				
	Several weeks [NS] (chronic use)	[53]				
LSD						
Analyte not specified	36 hours [0.2]	[29]				
LSD	24 hours [0.5]	[77]				
O-H-LSD	5 days [5]	[77]				
GHB						
Analyte not specified	12 hours [10,000]	[29]	5 hours [4,000]	[29]	5 hours [4,000]	[29]

1, cutoff not stated; EtOH, ethyl alcohol or ethanol; EtG, ethyl glucuronide; EtS, ethyl sulfate; PEth, phosphatidyl ethanol; BZE, benzoylecgonine; 6-MAM, 6-monoacetylmorphine; EDDP, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine; THC, tetrahydrocannabinol; THCCOOH, 11-nor-9-carboxy-THC; O-H-LSD, 2-oxo-3-hydroxy-LSD.

Appendix 5: Clinical References

Resource	Year	Description
Addiction Treatment		
Principles of Addiction Medicine, 5th edition	2014	Chapter 112 ''The Science and Clinical Uses of Drug Testing'' summarizes the science and clinical practice of drug testing in addiction medicine
Public Policy Statement On Drug Testing as a Component of Addiction Treatment and Monitoring Programs and in other Clinical Settings by ASAM	2010	Policy statement supporting the unrestricted use of urine drug testing in addiction diagnosis, treatment and monitoring. Recommends the use of drug testing in clinical diagnostic and treatment settings
The Role of Biomarkers in the Treatment of Alcohol Use Disorders	Rev. 2012	Comprehensive summary of alcohol biomarkers for use in alcohol use disorders treatment. Published by SAMHSA
TIP 42: Substance Abuse Treatment for Persons with Co-Occurring Disorders	2008	SAMHSA TIP on substance abuse treatment with individuals with co-occurring disorders
VA/DOD Management of Substance Use Disorders	2009	VA published practice guideline includes brief mention of drug testing
Specific Levels of Care		
ASAM Criteria	2013	Addresses drug testing in the context of some of the levels of care
ASAM National Practice Guideline on the use of Medications in the Treatment of Addiction Involving Opioid Use	2015	Recent practice guideline includes a section on drug testing in medication assisted treatment
TIP 40: Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Use Disorders	2004	SAMHSA TIP on the use of buprenorphine
TIP 43: Medication-Assisted Treatment for Opioid Addiction in OTPs	2008	SAMHSA TIP on medication-assisted treatment
TIP 45: Detoxification and Substance Abuse Treatment	Updated 2015	SAMHSA TIP on detoxification
TIP 47: Clinical Issues in Intensive Outpatient Treatment	2006	SAMHSA TIP focused on intensive outpatient treatment
General Health Care Settings		
AMA Drug Screening and Mandatory Drug Testing Policy Statement	2006	AMA policy statement advocating that physicians be familiar with strengths and limitations of drug testing
ASAM White Paper	2013	Reviews science of drug testing for primary prevention, addiction diagnosis, and treatment monitoring
Tap 32: Clinical Drug Testing in Primary Care	2012	SAMHSA TAP addressing clinical drug testing in primary care
Other Potentially Relevant Settings		
A Clinical Guide to Urine Drug Testing: Augmenting Pain Management and Enhancing Patient Care	2008	Written CME monograph targeted to physicians who treat chronic pain
California NORML Guide to Drug Testing	2012	Guide to interpretation of drug testing for THC
Evidence-based practice for point-of-care testing—Chapter 7, Drugs and Ethanol	2006	Includes clinical and non-clinical settings
Procedures for Transportation Workplace Drug and Alcohol Testing Programs	Updated 2015	Workplace drug and alcohol testing for the Federally regulated transportation industry
TIP 30: Continuity of Offender Treatment for Substance Use Disorders from Institution to Community	2008	SAMHSA TIP addressing substance use in the criminal justice context
TIP 54: Managing Chronic Pain in Adults with or in recovery from SUDs	2011	SAMHSA TIP focused on managing chronic pain and substance use disorders
Urine Drug Testing in Clinical Practice, 5th ed	2012	Written CME module targeted to physicians who treat chronic pain
Women and Pregnancy		
ACOG Committee Opinion No. 633: Alcohol Abuse and Other Substance Use Disorders: Ethical Issues in Obstetric and Gynecologic Practice	2015	Discusses the complex ethical issues inherent in screening and treating alcohol and other substance use disorders in OB/GYN settings
ASAM Public Policy Statement on Substance Use, Misuse, and Use Disorders During and Following Pregnancy, with an Emphasis on Opioids*	2017	Policy statement focused on opioid use in pregnant women. Includes Screening/Prevention, Treatment, Education, and Regulatory/Law Enforcement
TIP 51: Substance Abuse Treatment: Addressing the Specific Needs of women	2015	SAMHSA TIP on addressing specific needs of women in substance use disorder treatment
WHO guidelines for the identification and management of SUDs in pregnancy	2014	WHO guidelines on identification and management of substance use disorders in pregnancy
Adolescents		
American Academy of Pediatrics: Testing for Drugs of Abuse in Children and Adolescents	2014	AAP clinical report to provide guidance to pediatricians on efficacy and efficient use of drug testing in children and adolescents
American Probation & Parole Assn's Drug Testing Guidelines and Practices for Juvenile Probation and Parole Agencies	1992	Guideline for the use of drug testing in the context of juvenile justice
Physician Health Programs		
Physician Health Program Guidelines	2005	Physician Health Program Guidelines including drug testing.
Payer Policies		
Auditor's Report of MassHealth, State Medicaid Program	2013	All Medicaid claims, mainly in treatment settings.
Drug Testing or Screening in the Context of Substance Abuse and Chronic Pain Guideline by Anthem Blue Cross Blue Shield	2015	Specific to Outpatient Treatment.
Florida True Blue Policy on Drug Testing in Addiction Treatment	2013	Specific to Addiction Treatment.
Moda Health Clinical Drug Screening And/Or Drug Testing	2016	Not specific to any healthcare setting.
Palmetto Guidelines on Controlled Substance Monitoring and Drugs of Abuse Coding	2015	Not specific to any healthcare setting.
United Healthcare Medical Policy on Drug Testing	2015	Not specific to any healthcare setting.

*The ASAM Public Policy Statement on Pregnancy was published after the appropriateness statements had been generated and rated; however recommendations from this document are cited in the text of the *Pregnant Women* section.

Appendix 6: ASAM Expert Panel and Quality Improvement Council Disclosures

Expert Panel Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational or other financial benefit	Salary	Expert Witness	Other
Louis E. Baxter, MD, DFASAM (Secondary Internal Medicine and Addiction Medicine)	Professional Assistance Program of NJ, Inc.	Behavioral Health of the Palm Beaches	None	None	None	None	Behavioral Health of the Palm Beaches	None	None
Lawrence S. Brown, MD, MPH, DFASAM (Internal Medicine and Addiction Medicine)	START Treatment & Recovery Centers	None	None	None	None	None	None	None	None
Matthew Owen Hurford, MD (Behavioral Health and Addiction Medicine)	Community Care Behavioral Health Organization	None	None	None	None	None	Community Care Behavioral Health Organization	None	None
Kurt Kleinschmidt, MD (Emergency Medicine, Medical Toxicology, and Addiction Medicine)	University of Texas Southwestern Medical Center	None	None	None	None	None	None	None	None
Marla D. Kushner, DO, FACOFP, DFASAM, FSAHM (Family Medicine, Addiction Medicine and Adolescent Medicine)	Marla D. Kushner, DO, SC	Medical Director, New Hope Recovery Center Medical Director, Insight Behavioral Health Arch program	Alkermes Kaleo	None	None	None	None	None	None
William S. Jacobs, MD (Addiction Medicine, Pain Medicine and Anesthesiology)	Medical College of Georgia	Associate Professor	None	None	None	None	None	None	None
Lewis S. Nelson, MD (Emergency Medicine, Medical Toxicology, and Addiction Medicine)	New York University School of Medicine	None	None	None		None	None	2015: Gordon vs Niederhoffer (Arsenic poisoning) Defense 2015: Barnette vs Springill (opioid death) Plaintiff 2015: Tirpack v 125 North10 LLC (Alcohol intox and fell) Defense 2016: Suarez vs NYC (alcohol intox and injured) Defense	Core Expert Group: CDC's Opioid Prescribing Guidelines CDC Expert Panel on Suicide and Prescription Drug Overdoses
Michael Sprintz, DO, FASAM (Pain Medicine, Addiction Medicine and Anesthesiology)	Sprintz Center for Pain and Dependency	Leigance Consulting FDA (Anesthetic and Analgesic Drug Products Advisory Committee) Collegium Pharmaceuticals	Burrell Behavioral Health	Sprintz Center for Pain and Dependency iLumHealth, LLC	None	None	Sprintz Center for Pain and Dependency	None	None
Mishka Terplan, MD, MPH, FASAM (OB/GYN and Addiction Medicine)	Behavioral Health System Baltimore	On the SAMHSA Expert Panel for the Development of a Guide to the Management of Opioid-Dependent Pregnant and Parenting Women and Their Children Consultant for National Center for Substance Abuse and Child Welfare	None	None	Grant from Gilead focused on linking methadone clients with HCV to community providers so that they can be evaluated for receipt of medication	None	None	Submitted 3 affidavits and provided expert testimony in 1 court case–all related to issues of drug use in pregnancy (one involved child reunification) and involved drug testing and test result interpretation. This work has been in collaboration with National Advocates for Pregnant Women. One for the defense and one upcoming for the plaintiff, both representing the mother.	None
Elizabeth A. Warner, MD (Psychiatry and Addiction Medicine)	Tampa General Hospital	None	None	None	None	None	None	None	None

Appendix 6 (*Continued*)

Expert Panel Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational or other financial benefit	Salary	Expert Witness	Other
Timothy J. Wiegand, MD, DABAM, FACMT, FAACT (Internal Medicine, Medical Toxicology, Clinical Pharmacology, and Addiction Medicine)	University of Rochester Medical Center	None	None	None	None	None	None	None	None

The above table presents the relationships of the **ASAM Appropriate Use of Drug Testing in Clinical Addiction Medicine** during the past 12 months with industry and other entities that were determined to be relevant to this document. These relationships are current as of the completion of this document and may not necessarily reflect relationships at the time of this document's publication. A person is deemed to have a *significant* interest in a business if the interest represents ownership of 5% or more of the voting stock or share of the business entity, or ownership of $10,000 or more of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. A relationship is considered to be *modest* if it is less than *significant* under the preceding definition. *No financial relationship* pertains to relationships for which there is no monetary reimbursement. **Indicates significant relationship.

QIC Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/Principal	Personal Research	Institutional, Organizational or other financial benefit	Salary	Expert Witness	Other
John Femino, MD, DFASAM	None	None	Dominion Diagnostics	None	None	None	None	None	None
Kenneth Freedman, MD, MS, MBA, DFASAM	Massachusetts Department of Public Health- *ASAM Board Member*	None	None	None	None	None	None	None	None
Barbara Herbert, MD, FASAM	Commonwealth Care Alliance	None	None	None	None	None	None	None	None
Margaret A. Jarvis, MD, DFASAM	Geisinger Health System- *ASAM Board Member*	None	None	U.S. Preventive Health, Inc.	None	None	None	Examined Records for FBI Investigation of Sober Houses in Florida	Royalties from Up-to-Date
Margaret Kotz, DO, DFASAM	University Hospitals Medical Group	None	None	None	None	None	None	None	None
David Pating, MD, FASAM	Kaiser Permanente	None	None	None	None	None	None	None	None
Sandrine Pirard, MD, PhD, MPH, FAPA, FASAM	None	None	None	None	None	None	None	None	None
Robert J. Roose, MD, MPH, FASAM	Mercy Medical Center	None	None	None	None	None	None	None	None

The above table presents the relationships of the **ASAM Quality Improvement Council (Oversight Committee)** during the past 12 months with industry and other entities that were determined to be relevant to this document. These relationships are current as of the completion of this document and may not necessarily reflect relationships at the time of this document's publication. A person is deemed to have a *significant* interest in a business if the interest represents ownership of 5% or more of the voting stock or share of the business entity, or ownership of $10,000 or more of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. A relationship is considered to be *modest* if it is less than *significant* under the preceding definition. *No financial relationship* pertains to relationships for which there is no monetary reimbursement. **Indicates significant relationship.

Appendix 7: External Reviewer Relationships With Industries and Other Entities

External Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Salary	Institutional, organizational or other financial benefit	Expert Witness	Other
Anthony Albanese, MD, FACP, DFASAM	Individual Reviewer-*ASAM Board Member*	VA Office of Academic Affiliations	None	AbbVie Pharmaceuticals Gilead Sciences Merck Pharmaceuticals**	None	None	Department of Veterans Affairs**	UC David School of Medicine California Society of Addiction Medicine American Society of Addiction Medicine Agape Network	None	None
Terry L. Alley, MD, DABAM, DFASAM	Individual Reviewer—*ASAM Board Member*	Vista Taos Renewal Center	None	None	None	None	None	None	None	None
Anika Alvanzo, MD, MS, FASAM, FACP	Individual Reviewer	Johns Hopkins University School of Medicine	Indivior, Inc.	None	None	None	None	None	None	None
Gavin Bart, MD, PhD, FACP, DFASAM	Individual Reviewer—*ASAM Board Member*	Hennepin County Medical Center	None	None	None	None	None	None	None	None
Andrea Barthwell, MD, DFASAM	Individual Reviewer	Encounter Medical Group	Bræburn Pharmaceuticals Encounter Medical Group, P.C.** The Manor Millennium Health Treatment Partners LLC** Two Dreams U. S. DOJ**	None	None	None	None	None	None	None
B. Steven Bentsen, MD, MBA, DFAPA	Individual Reviewer	Beacon Health Options	None	None	None	None	None	None	None	None
David Bergland	Individual Reviewer	Forensic Fluids Laboratories	None	None	None	None	None	None	None	None
Patrick Bohan	Individual Reviewer	Truetox Laboratories, LLC	None	None	None	None	None	None	None	None
George Braucht, LPC & CPCS	National Alliance for Recovery Residences	Brauchtworks Consulting	Georgia Association of Recovery Residences** Georgia Council on Substance Abuse** Georgia Department of Community Supervision** -Georgia State Board of Pardons and Paroles** Face sand Voices of Recovery** National Alliance for Recovery Residences**	None	None	None	Georgia Department of Community Supervision** Georgia State Board of Pardons and Paroles**	None	None	None
Martha E. Brown, MD	Federation of Physicians Health Programs	University of Florida College of Medicine	None	None	None	None	None	None	None	None
Amy B. Cadwallader, PhD	Individual Reviewer	American Medical Association	None	None	None	None	Aegis Sciences Corporation	None	None	None
Melinda Campopiano, MD	Substance Abuse and Mental Health Services Administration	Substance Abuse and Mental Health Services Administration	None	None	None	None	None	None	None	None
Paul L. Cary	National Association of Drug Court Professionals	Retired	None	None	None	None	None	None	None	None
Margaret Chaplin, MD, FASAM	Individual Reviewer	N/A	None	None	None	None	None	None	None	None
Darwyn Chern, MD, FAPA, FASAM	Individual Reviewer	Partners in Recovery	None	None	None	My Data Choices Evaluation of Effective Consent Strategies for Patients with Behavioral Health Conditions R01 MH108992- 01A1 National Institute of Mental Health	None	None	None	None
Kelly J. Clark, MD, MBA, DFAPA, DFASAM	Individual Reviewer—*ASAM Board Member*	CleanSlate Centers	Braeburn** -Indivior**	None	None	None	CleanSlate Centers**	None	None	None

Appendix 7 (*Continued*)

External Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Salary	Institutional, organizational or other financial benefit	Expert Witness	Other
Edward Cone, PhD, F-ABFT	Individual Reviewer	ConeChem Research, LLC	Consultant to SAMHSA** Research Triangle Institute International** CDM** -OraSure on drug testing procedures and products**	None	None	None	None	None	None	None
Nancy Deming, MSW, LCSW, MAC, AADC-S	Association for Addiction Professionals	Valley HealthCare System	None	None	None	None	None	None	None	None
Paul H. Earley, MD, DFASAM	Individual Reviewer—*ASAM Board Member*	Georgia Professionals Health Program, Inc.	Principal Earley Consultancy, LLC VP of Medical Affairs, DynamiCare, Inc.**	Speaker, Alkermes, Inc.**	Stockholder, DynamiCare, Inc.**	None	Georgia Professionals Health Program, Inc.**	None	Occasional Expert Witness usually related to Addiction among Health Professionals	
Greg Elam, MD	Individual Reviewer	National Toxicology Specialists, Inc.	None	Airline Pilot Association** Guest speaker at HIMS conferences** Cornerstone of Recovery**	National Toxicology Specialists, Inc.**	None	National Toxicology Specialists, Inc.**	None	Local attorney in divorce case, testified about positive cocaine hair test Local attorney in civil case regarding school expulsion, researched positive drug test, no testimony	None
J. Ramsay Farah, MD, MPH, FAAP, FACPM, DFASAM, CMRO, CPE	Individual Reviewer-*ASAM Board Member*	Phoenix Health Center	None	Orexo	Phoenix Health Center**	PROOVE	None	Maryland State Medical Association Maryland Society of Addiction Medicine American Society of Addiction Medicine	None	None
James Ferguson, DO, DFASAM, C-MRO	Individual Reviewer	FirstLab	SAMHSA CSAP DWP Drug Testing Advisory Board (DTAB)	American Osteopathic College of Occupational and Preventive Medicine Honorarium	None	None	FirstLab (aka FirstSource Solutions)**	None	California State Medical Board California Board of Registered Nursing California State Board of Veterinary Medicine Ohio State Medical Board All 2016 All representing plaintiff Boards All issues of probation and licensing All related to Peth results	None
Ron Flegel	Substance Abuse and Mental Health Services Administration	Department of Health and Human Services/CSAP	None	None	None	None	None	None	None	None
Alistair James Reid Finlayson, MD, FRCP(C), DABPN, DABAM, FASAM, DLFAPA	Individual Reviewer	Vanderbilt University Medical Center	None	None	None	None	None	None	None	None
Eric F. Foster, Am, CADC	National Council for Behavioral Health	Illinois Association for Behavioral Health	None	None	None	None	None	None	None	None
Mark Friedlander, MD	Individual Reviewer	Aetna	None	None	None	None	None	None	None	None

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Appendix 7 (*Continued*)

External Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Salary	Institutional, organizational or other financial benefit	Expert Witness	Other
Dean Fritch, PhD, DABFT, DABCC-TC	Individual Reviewer	OraSure Technologies, Inc.	None	None	None	None	OraSure Technologies, Inc.**	None	None	None
Benjamin Gerson, MD	Individual Reviewer	OMEGA Laboratories	OMEGA Laboratories**	None	None	None	None	None	None	None
Mark Gold	Individual Reviewer	Retired	None	None	None	None	None	None	None	None
R. Jeffrey Goldsmith, MD, DLFAPA, DFASAM	Individual Reviewer—*ASAM President*	University of Cincinnati College of Medicine	None	None	None	None	Cincinnati VAMC	None	None	None
P. Bradley Hall, MD	West Virginia Society of Addiction Medicine—*ASAM West Virginia Chapter President*	WV Medical Professionals Health Program	None	None	None	None	None	None	None	None
William F. Haning III, MD, DFASAM, DFAPA	Individual Reviewer—*ASAM Board Member*	University of Hawaii School of Medicine	None	None	None	None	None	None	None	None
Curtis L. Hamre, LADC	Individual Reviewer	Riverview Recovery Centers	None	None	None	None	None	None	None	None
Harry Haus, MD	Individual Reviewer	Harry Haus MD	None	None	None	None	None	None	None	None
Mary P. Hauser, MA	Individual Reviewer	Dominion Diagnostics, LLC	None	None	Dominion Diagnostics, LLC**	None	Dominion Diagnostics, LLC**	None	None	None
Michael Holland, MD	American College of Medical Toxicology	Center for Toxicology and Environmental Health	None	None	None	None	None	None	None	None
Keith Isenberg, MD	Individual Reviewer	Anthem, Inc.	PCORI project OPTIMUM stakeholder Consortium on Drug Treatment of Alcohol Dependence	None	Anthem**	None	Anthem**	None	None	None
Sandra Jacobson	American Psychiatric Association	University of Arizona College of Medicine- Phoenix	None	None	None	None	None	None	None	None
Frank James, MD, JD	Individual Reviewer	Optum	None	None	None	None	None	None	None	None
Jeff Johnson, BSMT	National Association of Psychiatric Health Systems	Addiction Labs of America	None	None	None	None	None	None	None	None
David Kan, MD, DFASAM	Individual Reviewer	University of California, San Francisco	None	None	None	None	None	None	None	None
Geoffrey Kane, MD, MPH, DFASAM	National Council on Alcoholism and Drug Dependence	Brattleboro Retreat	None	None	None	None	None	None	None	None
Jason Kay, PharmD, MS	Individual Reviewer	Blue Cross Blue Shield Association	None	None	None	None	None	None	None	None
Bobby Kearney, MD, FASAM	Individual Reviewer	Addiction Recovery Medical Services	None	None	None	None	None	None	None	None
Brad Keays	Individual Reviewer	Soberlink Healthcare, LLC	Soberlink**	None	Soberlink**	None	Soberlink**	None	None	None
Lorenzo Leggio, MD, PhD, MSc	Individual Reviewer	National Institute on Alcohol Abuse and Alcoholism	None	None	None	None	None	None	None	None
Anna Lembke, MD, FASAM	Individual Reviewer	Stanford University School of Medicine	None	None	None	None	None	None	None	None
Ilse R. Levin, DO	Individual Reviewer—*ASAM Board Member*	Mid Atlantic Permanente Medical Group	None	None	None	None	None	None	None	None
Petros Levounis, MD, MA, DFASAM	Individual Reviewer—*ASAM Board Member*	Rutgers New Jersey Medical School	None	None	None	None	None	None	None	None
Bridget Lorenz Lemberg	Individual Reviewer	Forensic Fluids Laboratories	None	None	Forensic Fluid Laboratories Inc.**	None	None	None	None	None
Ronald Lim, MD, DFASAM	Individual Reviewer—*ASAM Board Member*	University of Calgary	None	None	None	None	None	None	None	None
Michelle Lofwall, MD, DFASAM	Individual Reviewer	University of Kentucky Center on Drug and Alcohol Research	Consultant to Inidivior on 1 occasion	None	None	Braeburn Pharmaceuticals**	None	AAAP SAMHSA PCM Scientific	None	None
Robert Lovinger, MD	Individual Reviewer	Treasure Coast Recovery	None	None	None	None	None	None	None	None

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External Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Salary	Institutional, organizational or other financial benefit	Expert Witness	Other
Maria Mascola, MD, MPH	American Congress of Obstetricians and Gynecologists	Marshfield Clinic	None	None	None	None	None	None	None	None
Matt McCarty, MD	Individual Reviewer	Genotox Labs	Own 50% of Genotox/Wife owns the other 50%** Own 50% of Balcones Pain Consultants**	Genotox Labs** Balcones Pain Consultants**	Own 50% of ToxProtect/ Wife owns the other 50%	None	None	None	None	None
Perry Meadows, MD, JD, MBA, FAAFp	Individual Reviewer	Geisinger Health Plan	None	None	None	None	None	None	None	None
Michael M. Miller, MD, DFASAM	Individual Reviewer	Rogers Memorial Hospital	Addiction Advisory Board, Purdue PHARMA** Advisory Board, BDSI Pharmaceuticals Advisory Board, Braeburn Pharmaceuticals Consultant, WPS Health Solutions Consultant, UW Hospitals and Clinics	Alkermes BDSI	None	None	None	None	None	None
Christina Mikosz, MD, MPH	Individual Reviewer	Centers for Disease Control and Prevention	None	None	None	None	None	None	None	None
Robert G. Newman, MD, MPH	Individual Reviewer	Beth Israel Medical Center	None	None	None	None	None	None	None	None
David O'Gurek, MD	American Academy of Family Physicians	Temple University Health System	None	None	None	None	None	None	None	None
Yngvild K. Olsen, MD, MPH, FASAM	Individual Reviewer—*ASAM Board Member*	Institutes for Behavior Resources Inc.	None	None	None	None	None	None	None	None
Mitchel Osman	Individual Reviewer	N/A	None	None	None	None	None	None	None	None
Parag Patel, MD	Individual Reviewer	Brightview LLC	None	None	None	None	None	None	None	None
Joseph Pergolizzi, Jr., MD	Individual Reviewer	NEMA Research, Inc.	None	None	None	None	None	None	None	None
Michael Rizzi	American Association for the Treatment of Opioid Dependence	Retired	None	None	None	None	None	None	None	None
Terry R. Rogers, MD	National Association of Addiction Treatment Providers	Lakeside Milam Recovery Centers	None	None	None	None	None	None	None	None
A. Kenison Roy, III, MD, DLFAPA, DFASAM	Individual Reviewer	Addiction Recovery Resources	None	Dominion Diagnostics Speaker Alkermes Advisory Board Indivior Consultant Orexo	Biobehavioral Medicine Company, LLC** CLIA**	None	Biobehavioral Medicine Company, LLC**	None	None	None
Sheryl Ryan, MD	American Academy of Pediatrics	Yale University School of Medicine	None	None	None	None	None	Chair of the American Academy of Pediatrics Committee on Substance Use and Prevention	None	None
Andrew J. Saxon, MD, FASAM	Veterans Healthcare Administration	VA Puget Sound Health Care System	Neurocrine Biosciences	None	None	Medicasafe, Inc.**	None	None	Garrett vs. Martin Tidd vs. Overlake McKown vs. Simon Stredwick vs. Early and Quinn	UpToDate**
Arthur J. Schut, MA	National Council for Behavioral Health	Arthur Schut Consulting LLC	National Council for Behavioral Health National Advisory Council Center for Substance Abuse Treatment SAMHSA NIATx Foundation Behavioral Healthcare Inc.	None	Arthur Schut Consulting LLC**	None	None	None	None	None
Evan Schwarz, MD	Individual Reviewer	Washington University	None	None	None	None	None	None	None	None

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Appendix 7 (*Continued*)

External Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Salary	Institutional, organizational or other financial benefit	Expert Witness	Other
Carl M. Selavka, PhD, D-ABC	Individual Reviewer	Atlantic Diagnostic Laboratories, LLC	None	None	None	None	Atlantic Diagnostic Laboratories, LLC**	None	Atlantic Diagnostic Laboratories, LLC	None
Peter Selby, MBBS, FCFP, DABAM, DFASAM	Individual Reviewer	Centre for Addiction and Mental Health, University of Toronto	None	None	None	None	None	None	None	None
Jeffrey Selzer, MD, DFASAM	Individual Reviewer—*ASAM Board Member*	Committee for Physicians Health	None	None	None	None	None	None	None	None
Linda Shaffer	Individual Reviewer	Foothills Consulting, Inc.	None	None	None	None	None	None	None	None
Michael Shore, MD, DLFAPA, DFASAM	Individual Reviewer	Michael Shore MD	None	None	None	None	None	None	None	None
Karl G. Sieg, MD, FAPA, MRO	Individual Reviewer	Cigna	None	None	None	None	None	None	None	None
Janet Stieg, RN, MS, CPHQ	Individual Reviewer	The J Morris Group	None	None	None	None	None	None	None	None
David W. Streem, MD	Individual Reviewer	Cleveland Clinic	None	None	None	None	None	None	None	None
Stephen Strobbe, PhD, Rn, PMHCNS-BC, CARN-AP, FIAAN	International Nurses Society on Addiction	University of Michigan	None	None	None	None	None	None	None	None
Ronald Suprenant, MD, MBA, FAAFP, DABAM	Individual Reviewer	MED2ORDER, Ltd.	None	None	None	None	None	None	None	None
Donald Taylor	Individual Reviewer	Comprehensive Pain Care, PC	None	None	None	None	None	None	None	None
Douglas E. Tucker, MD, FASAM	California Society of Addiction Medicine	University of California Department of Psychiatry	None	None	None	None	None	None	None	None
Margaret Villalonga	Individual Reviewer	American College of Obstetricians and Gynecologists	None	None	None	None	None	None	None	None
Corey Waller, MD, MS, DFASAM	Individual Reviewer	Camden Coalition of Healthcare Providers	None	None	None	None	None	None	None	None
Laurence M. Westreich, MD, FASAM	American Academy of Addiction Psychiatry	New York University School of Medicine	None	None	None	None	None	None	None	None
Howard Wetsman	Individual Reviewer—*ASAM Board Member*	Townsend	None	None	AAC stock**	None	AAC**	None	None	None
Norman Wetterau, MD, DFASAM	Individual Reviewer—*ASAM Board Member*	Tricounty Family Medicine	None	None	None	None	None	None	None	None
Tricia Wright, MD, MS, FACOG, FASAM	American College of Obstetricians and Gynecologists	University of Hawaii	None	None	None	None	None	None	None	None
Chess Yellott, MD	Individual Reviewer	Renovo Center	None	None	None	None	None	None	None	None
Terry Zobeck, PhD	Individual Reviewer	Office of National Drug Control Policy	None	None	None	None	None	None	None	None

The above table presents the relationships of the **external reviewers** during the past 12 months with industry and other entities that were determined to be relevant to this document. These relationships are current as of the completion of this document and may not necessarily reflect relationships at the time of this document's publication. A person is deemed to have a *significant* interest in a business if the interest represents ownership of 5% or more of the voting stock or share of the business entity, or ownership of $10,000 or more of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. A relationship is considered to be *modest* if it is less than *significant* under the preceding definition. *No financial relationship* pertains to relationships for which there is no monetary reimbursement. **Indicates significant relationship.