

Guidelines for Ordering Urine Testing for Drugs-of-Abuse: Targeted and Screening Tests (CLP013)

Revised March, 2013

1. Purpose

The purpose of this Guideline is to acquaint clinicians with the available laboratory-based urine testing regimens for Drugs-of-Abuse (DOA), the most appropriate use and the limitations of this testing, and the Ontario Health Insurance Plan (OHIP) reimbursement restrictions for these tests.

2. Background

Clinicians screening for an incidental or accidental episode of drug abuse will follow a different protocol than that of clinicians with caseloads that include habitual abusers of multiple drugs, or who are monitoring patients for adherence to a treatment program. In screening for DOA, clinicians should take into account the specific clinical situation being assessed.

3. Scope

This Guideline will only encompass testing for DOA in urine samples. Testing for DOA in saliva, hair, or other biological materials is beyond the scope of this Guideline. Contact the Laboratory Director for drug testing requirements in matrices other than urine.

Observed specimen collection (required for DOA testing for the United States Department of Transportation, Children's Aid Societies, or for medical-legal cases etc.) is not routinely available in licensed Specimen Collection Centres in Ontario. Consult with your laboratory to see if this service can be accommodated.

This guideline will not cover measurement of therapeutic drug levels. Analysis of inhalants and/or volatiles (e.g. toluene, benzene, chloroform, nitrous oxide, methanol, isopropanol, acetone, etc.) is also beyond the scope of this Guideline. However, if detection of inhalants/volatiles is required, a preliminary consultation with the Laboratory Director or toxicologist is mandatory.

4. Specimen Integrity Requirements

Testing for specimen substitution and/or adulteration is performed by most laboratories upon request and may include one or both of the following:

- temperature strips affixed to urine collection containers to monitor the temperature of the collected specimen at the point-of-collection,
- chemical tests for adulteration and dilution (pH, specific gravity, creatinine, oxidants, etc.).

5. A) Target Drug Testing

Analytes in this category are confined to those that can be tested with immunoassays. Clinicians should order testing for the specific (target) drug, or group of drugs e.g. opiates, oxycodone, buprenorphine, benzodiazepines, cocaine, methadone, ethanol, etc. when:

- the patient is known to have taken a specific drug(s) and/or,
- the patient is being monitored for adherence to a drug treatment program.

Requests for individual drugs that cannot be tested with immunoassays will be performed using chromatographic techniques. Order tests for any target drug by writing the name of the specific drug(s) required on the OHIP laboratory requisition in the “Other Tests” section.

B) Drugs-of-Abuse Screens

Clinicians should order a DOA screen when the patient is a known multiple drug user, or is suspected of using specific drugs that are detected by the DOA screen.

DOA screens vary slightly from laboratory to laboratory, but generally include tests for:

- opiates,
- benzodiazepines,
- methadone metabolite (EDDP),
- cocaine metabolite (BEG),
- oxycodone, and
- amphetamines.

Some laboratories choose to include ethanol, delta-9-tetrahydrocannabinol (THC) metabolite, phencyclidine (PCP), and/or barbiturates in their DOA screens.

DOA Screens are limited to those analytes which can be performed using immunoassays.

C) Broad Spectrum Toxicology Screen

Clinicians should order broad spectrum toxicology screens when they wish to:

- determine the specific drug(s) being abused by patients at a point in time,
- occasionally monitor a patient’s adherence to the requirements of their treatment program, i.e. to ascertain if a patient is using any DOA over and above those tested
- identify a possible DOA in a patient who is not known to be abusing drugs,
- identify specific drugs that cannot be detected with automated immunoassays (e.g. hydromorphone and fentanyl) and are therefore not included in the DOA screen.

In the above circumstances, clinicians are advised to request a “broad spectrum toxicology screen”. If a specific drug(s) is/are required (e.g. fentanyl), please specify the drug or drugs in the “Other Tests” section of the OHIP laboratory requisition.

Broad spectrum urine toxicology screens are generally performed using chromatographic separation techniques, followed by identification of the drugs using mass spectrometry. The mass spectrometer is usually set up to detect a limited number of specific drugs, and the test menu is laboratory-specific. **It is important to note that chromatography/mass**

spectrometry will not detect every potential DOA. Clinicians interested in detecting the presence of a specific drug(s) should consult the laboratory to confirm whether that drug(s) is included on the laboratory's broad spectrum toxicology screen menu. If the drug(s) is not detected by their broad spectrum urine toxicology screen, the laboratory will make every effort to detect this drug(s) in another manner.

Examples of drugs that are most commonly detected on broad spectrum (urine) toxicology screens are provided in the table below:

Drugs	Examples
Antihistamines	diphenhydramine, pseudoephedrine
Opiates	natural (morphine), semi-synthetic (hydromorphone, oxycodone) and synthetics (fentanyl)
Sedatives/hypnotics	diazepam, alprazolam
Opiate Agonists	methadone/methadone metabolite, buprenorphine
Anti-psychotics	clozapine, risperidone
Anti-depressants	amitriptyline, venlafaxine, sertraline
Anti-epileptics	gabapentin, carbamazepine
Stimulants/hallucinogens/depressants	amphetamine, ecstasy, ketamine, phencyclidine, THC, Ritalin, cocaine
Cardioactive drugs	lidocaine, verapamil

Notable drugs that might be expected to be identified on a broad spectrum toxicology screen (urine), but which are NOT generally detected and/or reported include:

- Lysergic acid diethylamide (LSD)
- Gamma hydroxybutyrate (GHB)
- Mephedrone and other substituted cathinones (e.g. bath salts)
- Synthetic cannabinoids (e.g. K2, Spice)
- Flunitrazepam (Rohypnol)
- Cotinine
- Acetaminophen

6. Results Reporting

Laboratory reports will provide a qualitative interpretation for the laboratory's specific panel of DOA, based on the testing laboratory's established cut-off concentrations. These cut-offs (usually given in ng/mL or µg/L) may or may not be listed on the laboratory report, but are readily available from the laboratory performing the testing. Qualitative results (positive/negative) will be reported for each requested drug.

Some laboratories may provide semi-quantitative results for these drugs and may report the drugs' concentrations in ng/ml.

7. Interpretations of DOA Test Results

Interpretation of results for DOA testing is often complex, requiring a consultation with a toxicologist. Patient-specific factors, such as weight, dose, level of hydration, time lag between drug ingestion and urine voiding, can influence the amount of drug excreted in the urine. Pharmacokinetic properties, such as the half-life of the substance being detected and the individual rate at which the substance is metabolized by the patient, will also affect the ability of the tests to detect the drug(s) in question.

When interpreting DOA test results, clinicians need to consider:

- the level/concentration at which an individual drug is detected by the testing system (the cut-off concentration),
- the drugs that are detected by the testing system and more importantly those that are not detected and,
- substances that may give false-positive results (in immunoassays).

It is vital for clinicians ordering tests for DOA to understand that the limitations of the analysis are method and laboratory-specific. The test results themselves are of reduced value without a thorough understanding of the test limitations. Positive results for drugs that are not in fact present, as well as negative results for those that are present, can lead to conflict between clinicians and patients. This can result in loss of trust, suspicion of diversion, and/or non-adherence to the treatment plan, creating a sub-optimal treatment environment for both patients and clinicians.

A consultation with the laboratory's toxicologist can provide valuable advice for clinicians in selecting appropriate DOA tests to order and in interpreting their results.

False Positives

A false-positive result occurs when test results indicate that a drug is present when in fact it is not present. False-positive results most often occur when an interfering drug(s) or substance(s) is present in the sample and it is detected by the assay system thus generating a positive result.

Immunoassays may be subject to false positives, as antibodies used in some assays will detect substances/medications not considered to be DOA. Examples of this include:

- Structurally related (e.g. ephedrine) as well as structurally unrelated (e.g. ranitidine) compounds have been reported to interfere with some amphetamine/methamphetamine assays.
- Ibuprofen and dextromethorphan are known to cause false-positive results in certain phencyclidine (PCP) immunoassays.
- Diphenhydramine cross-reacts with the anti-methadone antibody in some immunoassays, causing a false-positive result.
- Quinolones and rifampin can cause false-positive results in some opiates immunoassays
- Promethazine can cause false-positive results in some amphetamines immunoassays
- Quetiapine and verapamil can cause false-positive results in some methadone immunoassays
- Sertraline can cause false-positive results in some benzodiazepines immunoassays

Chromatographic analysis will assist in ruling out suspected false positives in immunoassays, if they are caused by cross-reactivity of a substance that is not a DOA (or the metabolite of a DOA) with the antibody of the immunoassay (e.g. in some PCP immunoassays the antibody cross-reacts with ibuprofen).

However, if the immunoassay is positive because the patient ingested a non-DOA substance (e.g. selegiline), which metabolized in vivo to a DOA (amphetamine), chromatographic analysis will only confirm the presence of the DOA (amphetamine).

False Negatives

A false-negative result will occur when a drug is present, but is not recognized by the assay that is supposed to detect it (e.g. fentanyl and oxycodone both of which have “opiate” activity will not be detected at typical abuse levels by the “opiates” immunoassay).

False negatives can occur when:

- interfering substances are present in the specimen,
- the absolute quantity of the drug in the specimen is below the limit of detection,
- the specimen has been treated with a “blocking agent” such as bleach or nitrite.

Procedure Limitations

Many DOA are metabolized to water-soluble compounds to some degree prior to elimination in urine (creating metabolites and/or conjugates). Laboratories may choose to hydrolyze urine samples prior to chromatographic analysis to maximize the concentration of unconjugated drug or drug metabolite, thereby improving the chance of detecting these drugs with the laboratory’s testing systems. Please check with your laboratory to see if hydrolysis is routinely performed. Without a hydrolysis step in the testing protocol, some drugs that are in fact present in the urine may not be detected.

Gas Chromatography-Mass Spectrometry (GC-MS) and Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) Limitations

Clinicians are reminded that not every drug that is present in a urine sample will be detected by every analytical system. The menu of drugs detected on a (urine) broad spectrum toxicology screen is laboratory-specific. In general, urine toxicology screens detect more than 40 of the most commonly abused drugs and some testing systems detect many more.

New DOA are constantly being designed and introduced into the community. Your laboratory may not yet be looking for these new drugs. Please speak to the Laboratory Director/toxicologist to determine if the specific drug of interest is detected by the laboratory’s analytical systems or for requests to detect a drug that is not on the menu of drugs normally detected.

Certain drugs may be detected by the analytical system used in the laboratory, but only when the concentration of those drugs is very high. Consequently, although present in the urine in small quantities, these drugs often go undetected unless the laboratory is specifically requested to look for them. Examples include drugs such as hydrocodone, hydromorphone, and even buprenorphine. When there is interest in a specific drug, identify the name of the drug on the laboratory requisition in the “Other Tests” area.

Opiate Assays

The immunoassays currently in use in Ontario laboratories for “target drug testing” or for “DOA” screens are generally very specific for a single drug and/or for the metabolite(s) of that drug. However, some immunoassays test for categories of drugs, (e.g. opiates, amphetamines, and

benzodiazepines) instead of one specific drug or drug metabolite. For example, urine “opiates” assays will detect drugs in the opiate category, albeit not all drugs that have “opioid” pharmacological activity.

In addition, the detection limit for each drug analyzed by the immunoassay is specific to a laboratory and may vary from laboratory to laboratory.

The following are some salient features of opiate assays that need to be considered when interpreting results:

- The cut-off for the “opiates” immunoassay is usually set at 300 µg/L, although a 2,000 µg/L cut-off is available from some laboratories. The 2,000 µg/L cut-off is used to reduce the incidence of clinically false positive opiate test results in patients who are not abusing opiate drugs, but who have eaten foods containing poppy seeds.
- Certain semi-synthetic and/or synthetic opiates will not be detected with currently available “opiates” immunoassays and possibly even with some chromatographic techniques.
- “Opiates” assays are generally calibrated against morphine or codeine. If the assay cut-off for a positive reading is 300 µg/L, the assay will be interpreted as positive when the concentration of morphine (or codeine) exceeds 300 µg/L. However, the assay will NOT necessarily be positive if the sample contains more than 300 µg/L of another opioid (e.g. hydromorphone), due to reduced reactivity with the detecting antibody used in the opiate immunoassay.
- The degree with which substances other than morphine are detected by the “opiates” assay depends on the affinity of the substance for the particular antibody used in the assay.
- “Opiates” assays used in various Ontario medical laboratories are not identical.

Ethyl Alcohol (Ethanol)

Depending on the amount of ethanol consumed and the individual’s rate of ethanol metabolism, urine tests for ethanol will usually be negative at 6-12 hours post ingestion. Generally speaking, the specimen of choice for ethanol analysis is blood (grey-top tube, fluoride/oxalate) rather than urine.

Caution: Urine from patients with diabetes can produce a false-positive result for alcohol due to in-vitro bacterial conversion of glucose to alcohol.

9. Confirmation Requests

Chromatographic/mass spectrometric confirmation of the presence of DOA is required by the legal system to rule out the possibility of a false-positive result (chain-of-custody will most likely be required as well). While mass spectrometric confirmatory testing is available to clinicians, there is generally little need to “confirm” the presence of DOA detected in immunoassay-based screening assays performed in Ontario-accredited laboratories. Exceptions might include robust denial of a positive drug test by a patient in a drug treatment program. Consultation with the laboratory/toxicologist in such cases is highly recommended.

In cases where a chromatographic confirmation (by GC/MS or LC/MS/MS) is deemed necessary, please request the confirmation of the specific drug of interest. This request must be written on the laboratory requisition, e.g. “Confirm for cocaine”. Confirmation of a DOA that is required for diagnosis and/or treatment is an OHIP-insured procedure.

10. Chain-of-Custody Collections

Chain-of-custody is defined as “the control of the movement and location of physical evidence from the time it is obtained until the time it is presented in court”. Under certain circumstances, usually when the testing results could become the subject of a medical-legal case, specimens may need to be collected under chain-of-custody protocols. This involves the use of special forms and procedures not routinely available in specimen collection centres. Consultation with the Laboratory Director or toxicologist in these circumstances is advised.

11. Billing/Reimbursement Restrictions

- i. Chain-of-custody collection is not an OHIP-insured service.
- ii. While confirmation/quantitation testing for medical necessity is OHIP-insured, confirmation/quantitation for any other reason is not (e.g. determining the concentration of methadone in a Tang-diluted methadone dose). Orders for non-medically necessary drug confirmation/quantitation will be billed back to the ordering physician.
- iii. While saliva and hair testing may be available from your laboratory, tests (both screening and confirmatory) on these materials are not currently insured by OHIP.

iv. Point-of-Care DOA Testing:

Toxicology screens ordered for the purpose of “checking/quality control of an in-office testing system” or “to confirm the results of a point-of-care test” are services that are not insured by OHIP. They may be ordered from a laboratory as an uninsured service and the cost of the testing will be billed to the ordering physician.

The number of tests performed in a physician’s office for which OHIP will pay is subject to certain limitations.

v. Secondary Testing

There is an OHIP reimbursement restriction on “secondary testing” for specimens already tested in a physician’s office. Secondary testing refers to performing additional tests (albeit different tests than those initially performed) on a different day on a specimen that was already used for testing in the office.

vi. Multiple Urine Samples from the Same Patient

OHIP will not reimburse laboratories for multiple urine samples from the same patient (albeit collected on different days), if they are delivered to the lab on the same day. OHIP considers the date the specimen arrives in the laboratory to be the service date, and will not pay for

DOA testing on more than one specimen from the same patient on the same service date. Please submit urine specimens to the laboratory on the day that they are collected. Do not submit several urine samples from the same patient on the same day.

vii. **Payment Responsibility**

OAML member laboratories are committed to using their best efforts to ensure the provision of laboratory services, while at the same time supporting the expectation that member laboratories should be compensated privately for providing uninsured services. Payment for laboratory tests not reimbursed by OHIP will continue to be the responsibility of the clinician who ordered the test.

The following references were used in the preparation of this guideline:

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This Guideline was prepared to assist clinicians who order tests from community laboratories. Users must ensure that their own practices comply with all specific government policies and specific legislative and accreditation requirements that apply to their organizations. The Guideline is not meant to be construed as legal advice or be all inclusive on this topic. Given the complexity of legal requirements, users are reminded that whenever there is uncertainty regarding whether some aspect of a Guideline is appropriate for their practice or organization, further direction should be obtained from the Laboratory Director, their own professional association, college and/or legal counsel or appropriate government ministry.