# Testing for Impairing Substances in Health Care Professionals

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## Executive Summary

This report provides guidance to AHPRA over the type of impairing substances that should be tested in health care professionals, and to the extent that information is available, the likely prevalence of such substances in the cohorts registered by health profession National Boards, and how they should be tested.

Most of the pharmaceutical opioids (e.g. fentanyl, hydromorphone, oxycodone, methadone, pethidine, tramadol) and many of the other higher risk impairing substances (such as ketamine, midazolam, propofol, zolpidem) are not covered by the list of drugs in the Australian/NZ standard for urine testing of drugs of abuse (AS/NZS 4308:2008). New illicit substances such as most of the designer stimulants and all of the synthetic cannabinoids are also not detectable by laboratories applying this standard. As such it is recommended that analytical testing in the future will need to cover a much broader range of substances if impaired practitioners are likely to be detected, particularly if they are using drugs accessed from their workplace.

While urine is still regarded as the most useful single specimen and will cover most of the needs of AHPRA, there will be occasions when a blood or hair test is desirable, and potentially even testing for drugs in oral fluid if a suspected impaired practitioner can be tested while at a workplace, such as is already possible for breath testing for alcohol. Testing for drugs in the workplace using preliminary testing devices is limited to common illicit drugs, although a full range of drugs can be tested in a laboratory, ideally using chromatographic screening with mass spectrometry. This can give the largest range of substances and low detection limits. Hair testing is primarily useful when a history of use is required and results contribute to other information on substance use.

The broader range of testing required will impact on the availability of suitable laboratories, the cost of a test (or series of tests), and may also impact on the turn-around time for the report, although this will depend on the laboratory and local arrangements. The frequency and duration of testing will depend on the substance abused and the individual circumstances, and of course will be dependent on the practitioner's progress.

It is recommended to develop a central review process using the services of an officer who has the appropriate qualifications and necessary training to understand what laboratories can do and how to best interpret a laboratory report. This is likely to improve the decision making process in cases reported to AHPRA.

Ultimately there will be no fool proof method to detect any suspected substance abuse in health professionals, both in terms of ensuring all substances can be screened and ensuring the frequency of testing has a 24/7 coverage. Cost and logistics will be key factors to consider and the individual risk of re-offending. Each case will need to have a risk assessment conducted and an appropriate testing regimen implemented.

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## Introduction and Scope

The Australian Health Practitioner Regulation Agency (AHPRA) and the respective National Boards are responsible for the implementation of the National Registration and Accreditation Scheme across Australia and work with 14 National Health Practitioner Boards in implementing this scheme.

Part of this responsibility is to protect the community by assessment and management of health practitioners who are impaired by substance abuse. AHPRA ensure that any policies and procedures:

- Are consistent with the objectives and guiding principles in law;
- Aim to keep health practitioners practising where safe and appropriate; and
- Are informed by international research and published best practice.

The Boards' involvement in health practitioners who are impaired is limited to their regulatory assessment and management but the Boards have no role in the treatment of health practitioners who are impaired.

AHPRA is seeking information that will allow it to have nationally consistent policies, while also ensuring that decision making is consistent, fair and robust and that these policies are evidence based.

The purpose of this report is to assist in the establishment of nationally consistent, evidence-based approaches for the assessment and management of health practitioners who are impaired, by:

1. An evidence-based approach for assessing, testing and managing (regulatory management) health practitioners who may be impaired, consistent with the National Law. Management includes monitoring, such as biological testing;
2. Indications for when and how to use a range of monitoring modalities, primarily chemical testing.

The report is divided into two sections:

**Section 1** provides information on the fundamentals of drug use and drug detection of relevance to health professionals with appropriate citations of published literature, and;

**Section 2** provides more specific information to guide the development of appropriate national policies and procedures relating to the monitoring of substance-impaired health professionals.

The report also contains appendices:

Appendix 1 provides monographs for a number of selected drugs;
Appendix 2 provides three illustrative case reports;
Appendix 3 provides a simplified guide to pharmacokinetics for information; and
Appendix 4 provides the terms of reference for the production of this report.

# Section 1 – Fundamentals of Drug Use and Drug Detection

## 1.1 Introduction

For the purposes of this report the word drug refers to any substance that has been subject to abuse, or can be abused for the purpose of being mind-altering or affecting perception, cognitive or psychomotor functions in a human being. These substances may be illicit, in that there is no legal use permitted or known in Australia, or they may be legally available (such as from a prescription) but are not being used for an intended therapeutic purpose or are either being been misused or abused.

This section reviews the world literature on the type of drugs of relevance to detecting possible impaired health care professionals with particular reference to medical practitioners, dentists, nurses and pharmacists. This section also includes a review of drug detection methods, appropriate specimens that can be used for drug detection and their respective strengths and weaknesses.

## 1.2 Prevalence of Drugs

The usage of illicit drugs in Australia in the general community is high when compared to most other developed economies. Household surveys conducted by the Australian Institute for Health and Welfare (AIHW) and the United Nations office on Drugs and Crime (UNODC) (World Drug Report 2012) illustrate the prevalence of these drugs quite clearly [1, 2]. In a recent published systematic review the use in Australia in the previous year and life-time of methamphetamine/amphetamine was 2.7 and 6.3% respectively. Similarly, the prevalence for cannabis was 9.1% & 33.5%), cocaine (1.6%, 5.9%) and opiates (0.2%, 1.6%) [3].

There is a host of data available in other worker groups. For example, transport workers and petroleum industries in Italy have shown a positive rate of 2%, made up of cannabis, cocaine, methadone, opiates, buprenorphine, ecstasy and other derivatives and amphetamines in decreasing prevalence [4]. Many of these positive cases occurred around weekends presumably since they most often used recreationally.

There is some data on drug use in the four professions that this report focuses on.

When alcohol is excluded the incidence of drug dependency in health care professionals has been estimated at between 1 to 2%. This data is largely drawn from overseas studies with many of the studies conducted several years ago.

An American survey of self-reported use by almost 10,000 physicians found that 18% reported use of minor opiates (codeine, propoxyphene) in the past year of which 4.5%

reported use in the past month. For major opiates (pethidine, fentanyl etc) these percentages were 1.1% and 0.3%, respectively. Cannabis (4.6, 2.1)[1], benzodiazepines (11.4, 5.3), cocaine (1.1, 0.3), inhalants (0.5, 0.3) and other psychedelics (0.4, 0.2) were also reported to be used [5]. Their use of minor opiates and benzodiazepines were largely for self-treatment. 9.3% of the survey respondents reported the consumption of more than 5 alcoholic drinks per day in the past month (of which 0.6% were daily).

This reported use may not necessarily represent use by Australian medical practitioners, however there is no local data available publically that the author is able to locate.

Anaesthetists are often recognised as being over-represented in the medical community as doctors most likely to abuse drugs. For example, in the USA 13% of physicians treated for substance abuse were anaesthetists, who only represented 3% of the registered medical practitioners [6]. While anaesthetists were among the most prevalent in a survey of over 5000 physicians from 12 specialities, emergency physicians had the highest use of cocaine (2.5%), major opiates (2.3%), and cannabis (10.5%). Physicians involved in family practice and psychiatry were also over-represented [7].

In Australia, the most common drugs used by 79 doctors who had their ability to possess, supply, prescribe or administer opioids withdrawn by the NSW Department of Health was pethidine (84%) followed by morphine, mixed opioids, barbiturates, ketamine and benzodiazepines over the period 1985-1994 [8]. The study concluded that the outcome for these doctors was poor and includes the death of 13% in the study period from various causes including three suicides and one drug overdose.

Medical practitioners have been reported as being more likely to commit suicide than the general population and other university graduates [9, 10]. This applied particularly to female practitioners.

For other health care professionals there is much less data available. Access to drugs at pharmacies has the potential for a significant risk for pharmacists. A survey of 697 dentists, nurses, pharmacists and physicians registered in north-eastern USA identified risks factors for alcohol and drug use in these professions [11]. Nearly 40% of pharmacists reported using potentially addictive substances with 20% reporting repeated use and almost 6% identified themselves as being drug abusers at some point during their pharmacy careers.

Lifetime use of drugs by pharmacy students in a college in the North East of the USA has been reported as 8% for opioids with 5% using in the last year, primarily hydrocodone, oxycodone and codeine, while amphetamine was also used to a similar extent in this cohort [12].

Self-reported rates of opioid and anxiolytic use in the past month are considerably higher among pharmacists than members of the general public, and lifetime opioid misuse is higher among pharmacists than other health professionals [13]. In those treated for their addiction

[1] Reported use in the past year and past month, respectively

opioid use was highest followed by sedative/hypnotics [14]. A substantial proportion of pharmacists started experimenting with drug use as students although generally limited in amount with 35% of the students who ever used a drug either became dependent or were at risk of drug abuse [15].

Nurses are also known to suffer from drug addiction, particularly those with access to drugs at their workplace. A survey of 12 nurses admitted to a clinical research unit designed to study addiction in the early 1970s were found to use drugs obtained at the workplace; largely opioids (58%, mainly pethidine) and barbiturate-like drugs (33%) [16]. Alcohol was also abused by 42%.

Alcohol abuse in health care professionals appears to be less than the general population, although in one study dentists had the highest prevalence of alcoholism in the four health care professions [17]. Alcohol use tended to correlate with use of drugs in these health care professionals and drug use tended to occur in their younger years [18].

Illicit drug use in dentists (in the USA) over one year was estimated at 9.8% compared to 6.7% in physicians and 6.5% in the general population [17]. In dentists drugs used were predominately cannabis (8.8%) followed by minor opiates, anxiolytics, minor and major opioids. In physicians less used cannabis (3.8%), but 1.7% used hallucinogens, 1% used cocaine followed by anxiolytics and major opioids.

While these data cannot necessarily be extrapolated to current health care professionals in Australia, the data serves to illustrate that the prevalence of substance abuse in these professionals are likely to be not that different to the general community.

## 1.3 Common Drugs of Abuse

There are potentially hundreds of drugs that can be used and abused, including the numerous legally-available drugs in Australia and the many hundreds of other drugs many of which are illegal or are likely to become illegal as their availability and use permeates our society [19, 20].

The latter phrase refers in particular to new drugs flooding into the world that are designed to overcome various laws at least for a brief period for the consumer to have a “legal high” [21]. These new drugs are discussed later.

When health care professionals abuse drugs they are likely to fall into two main groups in terms of the drugs they use without a valid medical need or prescription:

a) Use of illicit drugs as for many drug users in the community, predominately amphetamines, cocaine, heroin and cannabis; and/or
b) Substances available at their workplace, largely through diversion.

At this point in time opioids are regarded as the one of most likely abused drugs among many of the health care professionals, particularly fentanyl, followed by anxiolytics and hypnotics

(particularly benzodiazepines), cocaine, propofol, ketamine and anaesthetic gases such as halothane [6].

The table below summarises the more common abused drugs that are likely to be abused by health care professionals.

**Table 1. Most Common Substances Likely to be Abused by Health Care Professionals**

| |
|---|
| Opioids including opioid-based anaesthetics<br>Fentanyl<br>Heroin (diacetylmorphine)<br>Hydromorphone<br>Methadone<br>Morphine<br>Oxycodone<br>Pethidine (also known as meperidine)<br>Tramadol (and possibly tapentadol in future)<br>Other opioids including those used as anaesthetics e.g. alfentanil, remifentanil, sufentanil |
| Benzodiazepines and related anxiolytics/hypnotics<br>Alprazolam<br>Diazepam<br>Midazolam<br>Zolpidem/zopiclone<br>All other benzodiazepines may be subject to misuse and/or abuse such as bromazepam, clobazam, clonazepam, flunitrazepam, lorazepam, nitrazepam, oxazepam, temazepam, triazolam etc |
| Other anaesthetics<br>Nitrous oxide<br>Ketamine<br>Halothane<br>Propofol |
| Other drugs<br>Amphetamines such as ecstasy (MDMA) and methamphetamine, and new designer stimulants<br>Cannabis (marijuana) and other drugs that mimic THC (synthetic cannabinoids)<br>Cocaine<br>Heroin (diacetylmorphine) |

Notes. Some drugs can be classified in more than one group, i.e. midazolam is both a benzodiazepine and used in anaesthesia. These are listed only once against their main pharmacological class. THC = $\Delta^9$-tetrahydrocannabinol, MDMA = 3,4-dimethylenedioxymethamphetamine.

This list is by no means complete but serves to indicate the most common drug or drug class known to be abused by health care professionals and also indicates some of the diversity of drugs (and other substances) used recreationally [19]. Most of these drugs have a legal use in Australia and could be available to one or more of the health care professionals.

For example, anaesthetic drugs are used daily by anaesthetists, and not surprisingly are sometimes diverted for their personal use. Narcotic analgesics and the benzodiazepines also have a much wider availability to health care professionals.

In contrast, while cocaine has a limited medical use it is more readily obtainable from illicit sources. Dexamphetamine is used in the treatment of attention deficit hyperactivity disorder

(ADHD) but illicit meth(yl)amphetamine is by far the most common strong stimulant used and is readily available in Australia from illicit suppliers. THC ($\Delta^9$-tetrahydrocannabinol) is now available in Australia as a mouth spray in combination with cannabidiol (Sativex) for the treatment of multiple sclerosis sufferers with muscle spasticity. More likely, however, users of cannabis would obtain the drug through illicit sources including synthetic derivatives such as Spice, K2 etc [20].

## 1.4 New Drugs of Abuse

Of particular concern in recent years is the increasing availability of the so-called new drugs designed to bypass existing legislation on illicit drugs. Predominately, these belong to three drug-types;

- Stimulants,
- Synthetic cannabinoids, and
- Hallucinogens

Their availability and subsequent use places a substantial burden on analytical laboratories to detect these compounds, many of which are more potent than the drug they replace and many of which are not available as reference material for use by laboratories to develop analytical assays. Consequently only a few laboratories in Australia have the capability to detect these drugs, and even then, their capability is restricted to only some of the emerging drugs.

### 1.4.1 Designer Stimulants

The most common stimulants belong to the cathinones analogs. These are essentially analogues of amphetamines with a beta-keto group adjacent to the benzene ring on the alkyl chain containing the nitrogen atom.

They form a large family of compounds produced by substitutions at various locations around this basic structure including what are termed beta-keto forms of common amphetamines, such as methamphetamine and MDMA (ecstasy). Over 30 variations are now known.

These analogs have central nervous system stimulant properties very much like methamphetamine and/or MDMA. Like synthetic cannabinoids, these substances are being produced and sold on the streets to overcome bans on the more traditional illicit stimulants.

The main routes of administration of designer cathinones are by nasal insufflation (snorting), inhalation or oral ingestion. When absorbed in the nasal mucosa and/or lungs the absorption is quite rapid leading to effects within minutes, whereas some delay is experienced after oral absorption (approximately 15-45 min).

The effects of the substances depend on the substance used and dose, however typically psychological and physiological effects may last from a few to several hours. Repeated use (such as binge consumption) will lead to a more intense response and a longer duration of effect.

Common responses to these substances include aggression, anxiety, euphoria, empathy, enhancement of mood, sensory changes, mild sexual stimulation, and hallucinations. The consequences of interfering with these neurotransmitters long term leads to dependence and tolerance, and when these drugs are stopped, an abstinence syndrome occurs, much like methamphetamine and other amphetamines.

In Australia in 2011-2012, cathinone-type substances accounted for approximately 47% of analysed seizures containing novel substances [22].

The most common members known in Australia are mephedrone, 3,4-methylenedioxy-pyrovalerone (MDPV), 3,4-methylenedioxymethcathinone (methylone) and 3,4-dimethylmethcathinone (DMMC) as well as the piperazine analogue 1-benzyl-piperazine (BZP).

The European monitoring centre for drugs and drug addiction (EMCDDA) is a useful source of information on the emerging drugs in Europe[2].

None of these analogs cross-react with amphetamine or methamphetamine based immunoassay screening systems (or very little) and require chromatographic identification using mass spectrometry [23].

### 1.4.2 Synthetic Cannabinoids

Synthetic cannabinoids (cannabinomimetics) are compounds that mimic the effects of THC. While some synthetic cannabinoids have a similar chemical structure to THC, most have no obvious structural similarity to THC but probably act at or near the THC receptor.

The cannabinoid receptors belong to a family of receptors known as G-protein coupled receptors in which their activation inhibits the enzyme adenylate cyclase that then produces an intracellular mediator. THC and the known psychoactive cannabinoids inhibit this enzyme and it is believed that this mediates most of the effects of cannabis. This receptor also affects movement of calcium through ion channels. There are two types of cannabinoid receptor; $CB_1$ found mainly in the brain, $CB_2$ found mainly in the periphery. $CB_1$ sites include hippocampus and cortex for cognitive effects (memory and learning), basal ganglia and cerebellum that control balance and coordination, while $CB_2$ receptors play a role in modulating immune response and inflammation.

[2] http://www.emcdda.europa.eu

Synthetic cannabinoids have broadly similar effects to that of cannabis and are usually presented by spraying small amounts of the active substance onto plant materials so as to look like cannabis green vegetable matter. Synthetic cannabis is best known by the brand names Kaos, K2, Kronic, Mango, Northern Lights, Spice and Voodoo.

Synthetic cannabinomimetics can cause cognitive deficits including loss of memory. They also cause anxiety, fatigue, headaches, disorientation, hallucinations, high blood pressure, tachycardia, paranoia, agitation, restlessness, panic attacks, and depression. Heavy and regular use may cause hallucinations, confusion, depression, paranoia, psychosis and heart palpitations.

Thousands of admissions to emergency centres are recorded in the USA each year with symptoms such as tachycardia, extreme agitation, hallucinations, syncope as well as supraventricular tachycardia and generalized seizures have also been reported in cases of severe toxicity, and even severe psychosis.

The long-term health effects of these drugs are unknown and will almost certainly be compounded by other ingredients in the product, such as green plant material.

There are well over 100 substances (and quite possibility over 500) that could be classified as synthetic cannabinoids, or substances that appear to mimic one or more of the effects normally attributed to THC.

The most common drugs include the following, all of which have been banned by the Australian government: AM-694, JWH-018, JWH-073, JWH-122, JWH-200, JWH-250, CP-47,497, CP47,497-C8, CP-50,5561 (levonandradol), WIN-55,212-2, and various analogs of 2-(3-hydroxycyclohexyl)phenols, 1H-indol-3-yl-(1-napthyl)methane, 3-(1-naphthoyl)indoles, 3-(1-naphthoyl)pyrroles, 1-(1-naphthylmethyl)indenes, and 3-phenylacetylindoles. At the present moment new unknown analogs are being detected in Australian forensic laboratories.

None of these analogs cross-react with cannabis (THC) based immunoassay screening systems and require chromatographic identification using mass spectrometry [24].

### 1.4.3 Hallucinogens

LSD and to a lesser extend MDMA have been the most common hallucinogens available in Australia, although LSD has had a limited availability for many years.

A series of drugs known as derivatives of NBOMe are potent substances with effects similar to MDMA but are active as trace amounts on blotting paper[3] in the same way as used for LSD. Of the phenethylamines, 25C-NBOMe [2-(4-chloro-2,5-dimethoxyphenyl)-N-(2-methoxybenzyl)ethanamine], 2C-N (2,5- dimethoxy-4-nitrophenethylamine), 2C-G (2,5-

[3] Trace amounts of drugs absorbed onto blotting paper are sufficient to cause significant physiological responses when placed on the tongue.

dimethoxy-3,4-dimethylphenethylamine) and three representatives of the 25-NBOMe series containing alkyl group at position 4 are known. 25I-NBOMe is a recreational drug used since 2010 and is known as "N-Bomb", "Smiles," and "25I" [25].

None of these analogs cross-react with existing immunoassay screening systems and therefore require targeted chromatographic identification using mass spectrometry.

## 1.5 Alcohol and Alcoholism

Alcohol is still the most common abused drug in Australia. Consequently it is likely to be most common cause for impaired practitioners. Impairment due to alcohol (chemically ethanol) usually becomes measureable over 0.02% (0.02 gram/100mL) in blood using a sensitive psychometric test. In practice it is difficult to prove alcohol impairment at blood concentrations much below 0.10%, although individuals will vary in their response to alcohol. Epidemiologically only at blood concentrations over 0.05% are associated with an increase in crash rate in drivers.

The process of measuring alcohol[4] is well established using either one of the commercial breath testing instruments or through a blood test in a laboratory.

Breath testing is conducted widely by police on drivers and providing the measuring instrument has been properly maintained and calibrated results are accepted in courts. Screening devices are less accurate than evidentiary devices, and depending on the instrument and its maintenance can lead to erroneous results, results are widely different from the true breath reading.

Blood analyses are the most accurate method for determining the presence of ethanol and assessing the degree of alcohol exposure. Laboratories capable of performing this test will need to use gas chromatography (GC). This will be the case in most if not all pathology laboratories[5].

Urine alcohol can be performed, but the relation to a likely blood alcohol concentration can be problematic since it can vary widely between subjects and whether the person is still absorbing alcohol [26]. As a general rule when drivers are in the elimination phase (about 1-2 hours after last drink) the average urine to blood concentrations ratio is about 1.3.

Since the elimination rate of ethanol is zero-order about one measure of alcohol is removed each hour which accords to about 0.015% per hour. Hence a person with a blood alcohol concentration of 0.10% (twice legal limit for driving) will have eliminated this alcohol almost

[4] This refers to ethanol, and not any of the other alcohols.

[5] Some laboratories may still use biochemical screening kits based on alcohol dehydrogenase (ADH) for screening purposes.

completely within 7 hours. In alcoholics who have developed a tolerance to the drug and have induced their enzymes will eliminate this much alcohol in less time (perhaps 4-5 hours).

Over the last 10 years it has become known that a minor metabolite of alcohol, known as ethanol glucuronide (EtG), can be used as a marker of alcohol exposure (degree of alcoholism) in hair. This substance is involatile and accumulates in hair with repeated use. In a number of European Countries (e.g Switzerland, Italy, France and Germany) magistrates order a hair EtG for recidivist drivers caught drink driving. The Society of Hair Testing[6] recommends a cut-off of 30 ng/mg[7]. Results above this concentration suggests chronic excessive alcohol consumption in the month or two prior to the sample being taken [27, 28].

This test is not currently available in Australia as a routine test in local pathology laboratories but at least one forensic laboratory can measure this substance in hair. If demand were to increase dramatically the number of laboratories conducting this test would also increase. This test would only be useful if alcohol dependence was suspected and there was no other way to determine this.

Other markers for alcohol dependence exist, such as fatty acid ethyl esters (FAEE) and carbohydrate deficient transferrin (CDT) [28-30].

## 1.6 Analysis

The analysis of appropriate human fluids for any of the drugs listed above and those not listed is complex and cannot be covered by one test.

This section is not intended to provide a thorough review of analytical techniques; this would be outside the scope of this report, but it is pertinent to provide some details of analytical techniques used by laboratories since this should provide readers an improved understanding of the limitations (and strengths) of the more common methods employed.

The analytical process of measurement can be split into two; the initial screening test, and the confirmation step. The screening step provides a relatively quick process to establish if a drug, or drug class, is likely to present in a given specimen, whilst the second (confirmation) step ensures that the drug is present and may also provide an estimate of the amount present. The confirmatory test is required when drugs are detected in the initial test.

Consequently, analytical methods can be broadly classified into screening procedures, and confirmation procedures, however there are also specific methods available for a particular drug or for a narrow range of drugs.

[6] See www.soht.org and consensus on alcohol markers

[7] There are moves to reduce this cut-off to 7 ng/mg in hair.

### 1.6.1 Screening procedures

This is the most important part of the drug testing process since it defines the extent to which drugs or drug metabolites can be detected, and is sometimes called the "initial test". Methods are required to have sufficient sensitivity and coverage of substances in order to provide a reasonable basis for their detection, should they be present. While there is no one ideal methodology it is more often than not that more than one method is required to allow a sufficient coverage of substances.

Immunoassay screens for common drugs-of-abuse are commonplace and often used as the first test. These assays are based on the interaction of the target drug or drug metabolite and a labelled form of the same drug or of the antibody that can be detected in some way (usually by colour) with a corresponding antibody that recognizes (binds) the target drug or drug metabolite. These are usually available in the form of commercial kits and are "run" using automated analysers in a similar way to standard biochemical tests.

A negative immunoassay result means that the sample does not contain a measureable amount of that drug or drug class. Immunoassays require little or no sample preparation and a laboratory can often screen hundreds of samples daily. However, positive results must always be confirmed by a more specific technique (e.g. chromatography-mass spectrometry [GC-MS] or liquid chromatography-mass spectrometry [LC-MS]) since they only give an indication of a drug or drug group being present.

Examples of immunoassay screening test kits are CEDIA (cloned enzyme donor immunoassay), EIA (enzyme immunoassay including enzyme multiplied immunoassay or EMIT), ELISA (enzyme linked immunosorbent assay) and FPIA (fluorescence polarization immunoassay) and kinetic interaction of microparticles in solution (KIMS). EMIT and CEDIA are commonly used for urine, while ELISA is used for blood, oral fluid (saliva) and hair.

These are useful methods when specimens are screened for various classes of drug. Most commonly these have been opiates and benzodiazepines. Unfortunately, no immunoassay-based kit is able to detect all members of the same class of drugs equally. In the case of opiates, immunoassays generally only detect morphine, codeine and possibly the heroin metabolite 6-acetylmorphine. They generally do not detect other opiates, let alone members of the wider opioid family that includes pethidine, oxycodone, methadone and fentanyl [31].

Even for benzodiazepines, while the kits are able to detect the prevalence of higher dose forms such as diazepam, oxazepam and temazepam they are less likely to detect use of the more potent members such as clonazepam, flunitrazepam, bromazepam, lorazepam and triazolam [32].

It is not common for private pathology laboratories conducting drugs of abuse screening (such as in urine) to use another form of screening technique besides immunoassay screens, however some of the more specialised laboratories employ chromatographic screens [33, 34]. These can either include GC or HPLC techniques, or better, one of more forms of mass spectrometry (MS) [33, 35, 36]. More recently, high resolution MS (HRMS) has been used successfully as a screening tool to identify drugs and drug metabolites in urine using their

accurate molecular mass [37, 38]. However, HRMS is not used routinely in pathology laboratories, rather, forensic facilities and sports doping laboratories.

Thin-layer chromatography (TLC) has been used by some laboratories and may continue to be used for drug screening purposes, particularly for drugs that fall outside the usual immunoassay screening panels. However, this technique is insensitive and will not detect the more potent abused drugs.

The advantage of chromatographic screening methods and in particular those that combine chromatographic separation with one form of MS is that the methods can detect a far larger selection of drugs with higher sensitivity and specificity. An additional advantage over higher sensitivity is that it leads to longer detection times.

In Australia it has been commonplace to test for common abused drugs that fall into five classes, i.e. amphetamine-based stimulants (ATS, or sometimes known as sympathomimetics), benzodiazepines, cannabinoids (THC metabolites), cocaine metabolites and some opiates. Unfortunately, this list only covers few of the more common drugs likely to be abused by health professionals.

Table 2 summarises the type of screening test needed to detect various substances mentioned earlier as being the most common abused by health professionals. The green highlighted rows are those detected by use of common immunoassays. Core immunoassay refers to standard “drugs of abuse” panel of drug class tests conducted by most pathology laboratories (green) and included in the Australian Standard for drugs of abuse testing in urine (AS/NZS 4308:2008).

**Table 2. Types of Screening Tests Required for Selected Drugs**

| Target Drug | Urine Screening Drug Test |
|---|---|
| Opioids | |
| Fentanyl | Special immunoassay and/or MS |
| Heroin (diacetylmorphine) | Core Immunoassay (AS/NZS 4308) |
| Codeine | Core Immunoassay (AS/NZS 4308) |
| Methadone | Special immunoassay and/or GC |
| Morphine | Core Immunoassay (AS/NZS 4308) |
| Oxycodone | Special Immunoassay and/or GC |
| Pethidine (also known as meperidine) | Special immunoassay and/or GC |
| Tramadol | Special immunoassay and/or GC |
| Sufentanil | MS |
| Anaesthetics | |
| Nitrous oxide | GC or MS |
| Ketamine | Special immunoassay and/or GC and/or MS |
| Halothane | GC or MS |
| Propofol | GC or MS |
| Benzodiazepines and related hypnotics | |
| Alprazolam | Core Immunoassay (AS/NZS 4308) |
| Diazepam | Core Immunoassay (AS/NZS 4308) |
| Clonazepam | Core Immunoassay (AS/NZS 4308) |
| Flunitrazepam | Core Immunoassay (AS/NZS 4308) |
| Midazolam | Core Immunoassay and/or GC or LC |
| Nitrazepam | Core Immunoassay (AS/NZS 4308) |
| Oxazepam | Core Immunoassay (AS/NZS 4308) |
| Temazepam | Core Immunoassay (AS/NZS 4308) |
| Zolpidem | Special immunoassay and/or GC or LC |
| Other Common Drugs of Abuse | |
| Cocaine | Core Immunoassay (AS/NZS 4308) |
| MDMA | Core Immunoassay (AS/NZS 4308) |
| Methamphetamine | Core Immunoassay (AS/NZS 4308) |
| Cannabis (marijuana) | Core Immunoassay (AS/NZS 4308) |
| Other "Designer" drugs | |
| Piperazines (and dozens of related stimulants) | MS |
| Cathinones (and dozens of related stimulants) | MS |
| Synthetic cannabinoids (>1000 members) | MS |

Legend:
GC – one of more forms of gas chromatography which can be connected with MS,
LC = one or more forms of liquid chromatography which can be connected with MS,
MDMA = 3,4-methylenedioxy-methamphetamine,
MS = mass spectrometry, in one or more of its various forms

Notes:

1. Core immunoassay refers to standards "drugs of abuse" panel of drug class tests conducted by most laboratories (green) and included in AS/NZS 4308:2008.
2. Special immunoassay refers to an actual test kit for that particular substance, as an especially requested test.
3. All positive screen results are presumptive and require confirmation by mass spectrometry.
4. Heroin use is normally detected through its urinary metabolite, 6-acetylmorphine.
5. In urine cannabis and its products are normally confirmed by presence of carboxy metabolite.
6. Class test for benzodiazepines will detect other members of this class, but not equally.

### 1.6.2 Confirmation procedures

Any positive result obtained from a screening test must be confirmed by a confirmatory test using mass spectrometry (MS). Any result relying simply on a screening result can lead to a false presumption of drug use, since not all screen results will be confirmed.

When an immunoassay positive response is obtained it will be necessary to identify which drug within a drug class is present, if any. In all situations a confirmation test must be based on one form of MS. This ensures that a positive identification is made irrespective of the type of screening method employed, unless the screening method itself is based on MS (which is rare in pathology laboratories).

There are literally hundreds of confirmation methods published using GC-MS or LC-MS (or LC-MS/MS)[8], so there is no need to list one or more methods here. While there are some rare exceptions, the use of MS in combination with a different screening method is invariably sufficient to confirm the presence of the substance being reported. In LC-MS which has become the most common analytical method in many laboratories the mass spectrometer is actually running in tandem mode (MS/MS) in which a key fragment ion of the drug molecule in question is further fragmented. This MS/MS mode has much higher specificity than single stage MS alone and also has much higher sensitivity, largely due to lower background noise (see Table 3).

**Table 3. Examples of Confirmation Techniques**

| Technique | Detector | Abbreviation | Common Applications |
|---|---|---|---|
| Gas Chromatography[1] | Flame ionisation | GC-FID | Alcohol (ethanol) |
| | Nitrogen phosphorous | GC-NPD | Basic drugs |
| | Electron capture | GC-ECD | Benzodiazepines |
| | Mass spectrometry | GC-MS | Most drugs |
| High Performance Liquid Chromatography[1] | Ultra-violet or multi-wavelength | LC-UV | Most drugs |
| | Mass spectrometry | LC-MS[3] | Most drugs |

[1] some applications use chemical derivatisation of the drug extracts to facilitate chromatography and improve mass spectral definition; [2] some applications use micro-columns providing much quicker run times; [3] this is invariably now tandem MS abbreviated as MS/MS.

Laboratories with the capability of performing GC-MS or LC-MS/MS for routine analyses (screening and/or confirmation) have a much greater ability to detect a wider range of drugs than methods not relying on MS techniques and can also detect much lower concentrations.

Confirmation methods usually incorporate a quantitative component, or semi- quantitative component, such that a concentration of the reported substance can be provided.

[8] Almost all LC-MS methods actually utilize tandem LC-MS or abbreviated as LC-MS/MS. Methods relying on single stage LC-MS will not usually have sufficient specificity for confirmatory purposes.

Laboratories performing these tests are required to have suitable validated procedures [39], perform suitable quality control checks in each batch and above all have their procedures and facilities accredited by NATA[9].

### 1.6.3 Drug-specific procedures

Numerous procedures exist in the literature that detect and quantify specific drugs or classes of like drugs. It would be too difficult to review all these here except to mention that many GC-MS or LC-MS/MS procedures are published for some of the more important drug classes. Recent reviews are also available [40, 41].

Typical class procedures include:

- Amphetamine-type stimulants
- Antidepressants
- Antihypertensives and other cardiovascular drugs (various classes)
- Antipsychotics
- Benzodiazepines and related hypnotics and anxiolytics
- Designer stimulants
- Diuretics
- Opioids
- Synthetic cannabinoids
- Volatile substances

Increasingly chromatographic methods allowing simultaneous detection and quantitation of large numbers of drugs-of-abuse are being published, now mainly using LC-MS/MS [42, 43].

Often over 100 substances can be detected in one chromatographic system, particularly using LC-MS/MS. This can enable rapid screening of a large number of potential analytes that is not possible using the more traditional immunoassay technology that focuses on one drug class at a time with often limited detectabilities of some members of the class.

Unfortunately these targeted methods are often limited to forensic laboratories. It is vital that an appropriate laboratory is chosen to conduct the testing when more than the standard limited-panel of drugs are required.

[9] National Association of Testing Authorities, see www.nata.asn.au

## 1.7 Cut-offs

The term cut-off is widely used in the "non-forensic" drug testing industry[10]. A cut-off is a concentration below which the laboratory does not report a result.

For example in urine testing, as defined in AS/NZS 4308:2008, the cut-off for morphine is 300 ng/mL. This means that even if the laboratory is able to confirm the presence of morphine at 290 ng/mL it will not report a positive result, rather it will report "not detected" or "below the cut-off", or if a presumptive (screen) result was obtained for opiates it would be report as "not confirmed" or a similar wording.

There are various reasons for this use of cut-off concentrations. Most importantly, in the case of morphine, when it is present at 300 ng/mL or less the result cannot be interpreted as 'use of morphine", or even use of heroin (since morphine is the major active metabolite), since morphine may be present in users of codeine without the presence of codeine at these relatively low concentrations. Indeed, in the USA, the morphine cut-off for urine testing is 2000 ng/mL for the same reason. Unfortunately, when using 2000 ng/mL many users of morphine and heroin may be missed.

Other reasons for use of cut-offs exist for other drugs. For example, the cut-off for cannabis attempts to exclude passive consumption (low amounts of cannabis inhaled from ambient air near cannabis users). While this cut-off concentration generally succeeds, it never can completely rule out passive (or other forms of inadvertent) exposure. It also limits the detectability of users of cannabis.

In practice laboratories do not report urine concentrations until they exceed the cut-off and the uncertainty of measurement. For example, if the 95% confidence interval (error) for morphine quantification is 20%[11] or 60 ng/mL (i.e. 20% of 300 ng/mL) then the laboratory will not report a concentration of morphine below 360 ng/mL.

The table below shows the AS/NZS 4308:2008 cut-off concentrations for screening and confirmatory purposes. The only "opiates" included are codeine, morphine and the heroin metabolite 6-acetylmorphine. This means that other opiates are not likely to be reported (and probably not even looked for by the laboratory), and certainly no opioids (synthetic morphine-like drugs).

Similarly, cut-offs apply to all other mentioned substances or classes of substances, hence concentrations below these will not be reported.

This approach is quite fair for the provider of urine and provides some safety from inadvertent exposure from whatever source. It also limits somewhat the detectability of the

[10] Note, in forensic laboratories cut-offs are not typically used, rather limits of detection which will be substantially lower than the cut-offs listed in AS/NZS 4308.

[11] This is a typical error, and may be more or less depending on the laboratory method.

drugs, although one could expect detection for the more common drugs of abuse (those listed in AS/NZS 4308:2006) to be a day or three.

However, it does mean that users of these drugs may miss returning a positive result since their urine concentration has slipped below the cut-off, usually due to consumption of drugs two or more days earlier.

**Table 4. AS/NZS 4308:2008 Cut-Offs**

**Screening Cut-offs**

| Drug/Drug class | Cut-off concentration (µg/L or ng/mL) |
|---|---|
| Amphetamine-type stimulants | 300 |
| Benzodiazepines | 200 |
| Cannabis metabolite | 50 |
| Cocaine metabolites | 300 |
| Opiates | 300 |

**Confirmatory Cut-offs**

| Drug | Cut-off concentration (µg/L or ng/mL) |
|---|---|
| Amphetamine | 150 |
| Methamphetamine | 150 |
| MDMA | 150 |
| MDA | 150 |
| Benzylpiperazine | 500 |
| Phentermine | 500 |
| Ephedrine | 500 |
| Pseudoephedrine | 500 |
| Morphine | 300 |
| Codeine | 300 |
| 6-Acetylmorphine | 10 |
| 11-nor-Δ9-THC carboxylic acid[1] | 15 |
| Benzoylecgonine[2] | 150 |
| Ecgonine methyl ester[2] | 150 |
| Diazepam | 200 |
| Temazepam | 200 |
| Oxazepam | 200 |
| α-Hydroxy-alprazolam[3] | 100 |
| 7-amino-clonazepam[3] | 100 |
| 7-Amino-nitrazepam[3] | 100 |
| 7-Amino-flunitrazepam[3] | 100 |

[1] cannabis metabolite, [2] cocaine metabolites, [3] metabolites of respective benzodiazepine. α-Hydroxy-alprazolam is also known as 1-hydroxy-alprazolam.

## 1.8 Costs

It is too complex to assess the costs of drug tests because they do vary substantially depending on the drug or drugs required to be tested, the specimen submitted and the laboratory conducting the testing.

Drugs of abuse panels such as amphetamines, benzodiazepines, opiates, cocaine and cannabis in urine using immunoassay screens are the cheapest test and would typically cost less than $50 per sample. Any positive requiring confirmation using mass spectrometry could cost about $100 or so.

However, when less common drugs are requested, such as one or more of the potent opioids, the cost can escalate sharply particularly if a range of drugs are required to be tested and/or specimens other than urine are involved. It is beyond this brief to provide more details here since it will require specificity as to the range of drugs to be tested and their frequency of testing (volume of work), and of course costs will depend on the laboratory chosen and their expected volume of work.

Given the increased laboratory capability required for this testing it is unlikely that many, if any, pathology laboratory can perform this complex work through a simple pathology request. It would be advised for AHPRA and the National Boards to develop an understanding of the capability of specific state-based or national laboratories for a panel of drugs (and other targeted substances) with appropriate detection limits or cut-offs. Targeted professionals would then need to be directed to a facility that could do the appropriate testing.

## 1.9 Specimens

There are various specimens that can be tested for drug use. Most commonly in the drugs of abuse testing arena urine has been employed. However, there will be situations where another specimen might be more useful to detect exposure to a substance.

Other specimens such as blood, saliva (now usually referred to as oral fluid), and hair are used as alternatives to urine and can provide important additional information. Each of these specimens has their own relative advantages depending on the reason for the test being conducted. These are summarised below.

### 1.9.1 Blood

Blood is normally only useful to establish if recent ingestion has taken place and can assist in determining if the person is drug affected at the time of collection as distinct from past use of a drug appearing in urine. Blood (as serum) is the specimen of choice for therapeutic drug monitoring (TDM), in the event compliance to a therapeutic drug is being checked, or if a properly prescribed drug is being abused.

When blood is collected the analytical tests will need to be directed to this specimen. Tests designed for urine cannot be used since blood concentrations of drugs are often quite low since blood generally contains the parent drug while metabolites are often targeted in urine. The analytical difficulty for blood testing is also quite high compared to urine, especially if a specific drug is not targeted.

However, since urine concentrations cannot be used to determine how much drug was consumed and only provides a very approximate guide as to time of ingestion, blood is the preferred specimen when more precise information over substance use is required.

While blood can easily be taken at any pathology collection centre, the analysis of possible impairing drugs in blood is much more difficult and is not generally available in commercial pathology laboratories. These laboratories may conduct blood testing for some of the more common drugs that have a defined therapeutic range, such as many of the anticonvulsants, digoxin, lithium, and anti-rejection drugs.

Blood concentrations for the higher risk drugs of abuse discussed here are not so common and could only be conducted by a few specialist laboratories in Australia.

Once a blood result was to be obtained the interpretation will require detailed knowledge of the pharmacokinetics of the drug and its clinical use.

### 1.9.2 Hair

Hair can prove to be a useful specimen for the analysis of drugs of abuse [44, 45]. Studies have shown that most, if not all drugs and poisons are secreted into hair following exposure. Hair is particularly useful to establish drug use many weeks to months prior to collection, since specimens such as blood and urine will only provide evidence of use from hours to at most a few days.

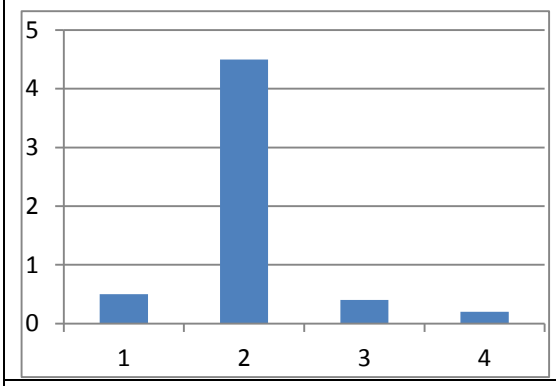
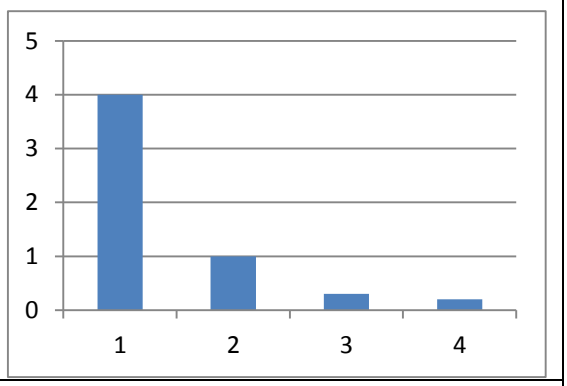
This provides hair a distinct advantage over urinalysis where proof of abstinence from drugs of abuse is required and may avoid regular urinalysis.

Unfortunately, contamination of hair can occur because substances enter hair by a number of processes. Incorporation by entrapment from the blood bathing the growing follicle is the primary mechanism, but drugs can also be incorporated through direct contact of mature hair with sweat and/or sebaceous secretions.

The interpretation of hair results must only be used in combination with other sources of information. This could be information on likely drug usage or previous urine drug results. Sometimes metabolite patterns of drugs can be useful to distinguish internal exposure from environmental exposure. For most drugs the parent drug is the dominant substance in hair. Heroin, cocaine, and the amphetamines and benzodiazepines are present largely as the parent compound, although 6-acetylmorphine and morphine are also present in the hair of heroin users. However both are also readily formed spontaneously from heroin. Similarly, cocaine is hydrolysed to benzoylecgonine, the major metabolite of cocaine.

There are a number of factors that affect retention of drugs into hair. These include the physiochemical properties of substances (basic>neutral>acidic), mechanism of incorporation (blood, sweat, sebaceous secretions), hair colour and type (African and Asian hair show greatest retention for basic drug), bleaching of hair (eg cocaine), other hair treatments including shampooing (eg cocaine as well as laboratory methods such as decontamination and extraction procedures; hence a hair concentration of drug cannot be converted into likely doses or frequency of doses. In practice, it is best to have the hair shaft cut into at least a few segments (often in 1 cm lengths that corresponding approximately to one month of growth) and compare the concentrations of any detected drug between segments. A relatively large concentration in one (or a few) segment and small amounts in the other segments could mean usage in the month represented by that segment and transfer of drug into the adjoining segments through sweat and sebaceous secretions, or even from external contamination (see **Table 5**).

**Table 5. Possible scenarios involving drug detection in hair segments**

| | |
|---|---|
|  |  |
| Type 1: likely use of substance in month 2 | Type 2: likely use of substance in month 1 |

Horizontal axes refers to months (1-cm segments) from scalp with "1" closest 1-cm to scalp and vertical axis refers to concentration of drug in ng/mg hair.

The detectability of a drug in a hair shaft or even a hair segment depends also on the amount of drug ingested over the period of time represented by the length of the hair segment. For example, the use of one dose of a potent drug such as fentanyl may not be detected in a hair segment even with the use of sensitive mass spectral methods since the concentration may be too low to detect.

Cocaine users (or persons exposed to cocaine) have been shown to eliminate cocaine in hair for some months since last use [46, 47]. It is likely that regular use of other drugs, particularly drugs that have high penetration into tissues such as amphetamines, most opioids, possibly anaesthetic drugs could also eliminate quite slowly from deep tissues and can appear in hair many weeks to months after last use. This means that hair testing could expose users of these drugs well after use, providing of course head hair is still available.

Hair is normally collected from the back of the head (nape) and is stored at room temperature in a sealed plastic bag. The amount of hair collected will depend on the type of analysis required, however at least 50 mg should be collected. A pencil thickness is often a convenient amount that will allow repeat testing if required. Hair kits are usually available from the testing laboratory.

Unfortunately, few laboratories in Australia perform hair testing and the cost of segmental analyses for even common drugs of abuse is very expensive compared to urine tests and would usually amount to well over $100 per sample particularly if the sample is positive.

### 1.9.3 Saliva (Oral Fluid)

Saliva or oral fluid as it is now more commonly termed is excreted primarily by the parotid, submaxillary and sublingual glands and also by other smaller glands such as buccal, labial, and palatal glands [48]. The fluids secreted by these glands differ considerably from each other and their composition is affected by time of day, food, age, gender, state of health, and by drugs. Saliva is made of the usual electrolytes as well as mucus and amylase and has a protein content of less than 5 % of plasma.

Drugs may enter these secretions in the growing hair follicle by passive diffusion from blood, ultrafiltration and active secretion. However, volumes of oral fluid are generally small, often 1-mL or less; hence there will be limited ability to repeat analyses by the laboratory. Some subjects will not be able to provide sufficient oral fluid on demand either due to their physiology operating at that point in time or because drugs consumed by them have reduced oral fluid secretions (e.g. amphetamines and cannabis reduce secretions).

Interpretation of saliva drug concentrations is more difficult than blood since oral fluid concentrations are dependent on the degree of protein binding in blood and oral fluid, and the degree of ionization (dependent on the physiochemical properties of the drug and pH of oral fluid). Alcohol, THC, the amphetamines and opioids (and most other basic drugs) are present in saliva in concentrations similar to or higher than blood (plasma/serum), while benzodiazepines (and most other acidic drugs) are present in much lower concentrations than blood.

Contamination of the oral cavity by recently ingested food (or even drug) artificially, but temporarily, raises the local concentration in these secretions. Cannabis is the best example: its presence in saliva is almost exclusively a result of oral contamination.

The main advantage of testing for drugs in oral fluid is the relative ease of collecting this specimen (does not require toilets or phlebotomists) and in the case of un-unionised workers the desire to only detect drugs used quite recently when they might be impaired as distinct from past recreational use. As a rule of thumb drugs are normally detectable in oral fluid for a few hours to a day, but this depends, as usual, on the dose and type of drug and the screening method employed.

The Australian Standard AS4760:2006 provides guidance on the collection of oral fluid for drugs of abuse testing, on-site screening and laboratory confirmation.

Oral fluid testing for drugs of abuse is widely practiced in road-side testing by police [49-51] and in many workplaces around Australia including many of the larger logistic companies and CASA[12].

### 1.9.4 Sweat

Another potential fluid that can be used to detect substance abuse is sweat. All drugs will be secreted into sweat and "sweat patches" are available commercially to allow sweat to absorb over a period of several hours to days. Patches are applied to skin not visible externally and accumulate any substance appearing in sweat over the length of time the patch is attached.

The patch is made of an adhesive layer on a thin transparent film of surgical dressing and a rectangular, absorbent, cellulose pad about 3-4 cm long. This allows the patch to breathe and water vapour can escape, whereas the drugs and other non-volatile components (salts) are retained on the absorbent pad. The patches are tamper resistant and have unique serial numbers for identification.

These have been used mostly overseas in the USA and Europe to a limited degree to detect continued use of drugs of abuse, e.g. cocaine, amphetamines and heroin etc, but can be used for other drugs, since they will appear in sweat [52-54]. Once the patch is removed they are sent to a laboratory for testing. The absorbed drugs can readily be washed out of the patch and analysed by conventional methods.

The potential advantage of this method is that a sweat patch can provide a week long history of any drug use, if left on for a week. The disadvantage is that the wearers of the patch can readily remove the patch (but cannot reattach the patch). This of course will lead to suspicion although irritation of the skin can occur and can provide a valid reason for removing the patch.

As far as I am aware no laboratory in Australia analyses sweat patches, although it would not be difficult to implement if the demand was present. I would consider this as an option for the future rather than at present.

### 1.9.5 Urine

By far the most common specimen used to assess exposure to drugs of abuse is urine. This specimen contains remnants of drugs and/or drug metabolites consumed in the recent past. It is also available in abundance and is relatively convenient to collect at a medical (pathology) collection centre[13].

[12] Civil Aviation Safety Authority

[13] Locations where a toilet is available with some security and privacy.

The concentration of drugs and their metabolites are usually relatively high, and invariably higher than the corresponding blood concentration, and are easier to detect analytically. This applies to the common drugs of abuse, methamphetamine, cocaine, cannabis, benzodiazepines, and opiates such as codeine, heroin and morphine.

There is great variation in the urine concentration of drugs (and indeed other substances) due to metabolic variability and water output of the kidneys. Dehydration (or failing kidneys) will produce higher concentrations than a normally hydrated person. Conversely, water loading will dramatically reduce concentrations of drugs and other substances. Consumption of water in a short period of time in excess of 1 L is needed to cause water loading.

In practice, for most drugs when a drug positive test is obtained it is reasonable to infer ingestion has occurred within a few days although this will depend a lot on the dose and frequency of administration, and of course the drug. Table 6 provides some detail over expected detection times in urine for selected drugs.

However, urine concentrations have no particular meaning and cannot be used to infer a dose or narrow down a time of ingestion.

**Table 6. Likely detection times in urine for selected drugs**

| Drug/drug metabolite | Detection time in urine[1] |
|---|---|
| 6-Acetylmorphine (heroin metabolite) | 6 hours |
| Benzodiazepines (alprazolam, diazepam, temazepam) | 1-7 days depending on half-life of drug |
| Buprenorphine | 1-4 days |
| Cannabis metabolites | 3-28 days depending on frequency of use |
| Cocaine metabolites | 1-3 days |
| Codeine | 1-2 days |
| Fentanyl | 1-4 days |
| Gamma-hydroxy-butyrate (GHB) | 6 hours |
| Hydromorphone | 1-2 days |
| Ketamine | 1 day |
| Methadone | 3-7 days |
| Methamphetamine/amphetamine | 2-4 days |
| 3,4-Methylenedioxymethamphetamine (MDMA) | 2-4 days |
| Morphine | 1-2 days |
| Oxycodone | 1-2 days |
| Pethidine | 1-4 days |
| Zolpidem | 1-4 days |

[1] These detection times will depend on dose, pharmacokinetic differences, and which metabolite is targeted, as well as on other factors, and are therefore only indicative. For cannabis, significantly longer detection times are seen with persons using the drug repeatedly. Some screening kits based on immunoassay will detect more metabolites than others.

An Australian Standard AS/NZS 4308:2008 provides guidance on the collection of urine, its transportation and analysis either at the collection centre (known as point of care testing, or on-site testing) and/or in the laboratory. Laboratories can be accredited against this standard and reports can be issued under this standard use “cut-offs” to avoid mis-interpretation of the source of drug. Laboratories advertising this service, i.e. drugs of abuse testing in urine to AS/NZS 4308 are accredited by NATA.

Laboratories conducting urine drugs of abuse screening use a combination of immunoassay and/or chromatographic methods to screen the specimen for the presence of the targeted drug or drug class. Drug classes include opiates, benzodiazepines and amphetamines of which more than one member of each class can be detected.

Immunoassays use antibodies to detect the presence of specific drugs or metabolites and are the most common method for the initial screening process since they can be used in automated large scale testing laboratories. For example, for opiates this immunoassay test would detect use of codeine, morphine and the heroin metabolite, 6-acetylmorphine[14]. Depending on the immunoassay test kit used it may detect other opiates, such as hydromorphone. A summary of the cross-reactivities to three common urine immunoassay kits are shown below. Note; none of these are likely to detect use of fentanyl, oxycodone, tramadol or pethidine (meperidine).

This table also shows that all products do not perform equally; the green highlighted sections show the drugs likely to be detected in urine. The Triage kit shows the highest specificity, whereas the EMIT II plus kit will pick up other related opiates. The latter may be important if other opiates need to be screened. This table also illustrates that whatever immunoassay screening kit is used by the laboratory a positive result needs to be confirmed and the opiate causing the response identified.

**Table 7. Cross-Reactivities of Selected Opioids to Three Common "Opiate" Urine Immunoassays**

| | EMIT II plus | CEDIA | Triage |
|---|---|---|---|
| Morphine | 300 | 300 | 300 |
| Codeine | 200 | 240 | 300 |
| 6-Acetylmorphine | 400 | 400 | 300 |
| Buprenorphine | ND | ND | ND |
| Hydromorphone[1] | 500 | 500 | ND |
| Hydrocodone[2] | 250 | 600 | ND |
| Methadone | ND | ND | ND |
| Oxycodone | 1500[3] | ND | ND |
| Pholcodine[4] | 390 | Unknown | Unknown |
| Oxymorphone[2] | ND | ND | ND |
| Pethidine | ND | ND | ND |
| Fentanyl | ND | ND | ND |
| Buprenorphine | ND | ND | ND |

All urine concentrations are in ng/mL. Cross-reactivity is based on using morphine cut-off of 300 ng/mL, and are approximate.
ND = not likely to be detected in urine
[1] Dilaudid or Jurnista in Australia; [2] not available in Australia; [3] poor cross-reactivity and will only detect drug for about 12 hours; [4] anti-tussive

[14] This is sometimes referred to as 6-monoacetylmorphine, or 6-MAM.

In some sectors, i.e workplace drug testing, urine screens for drugs of abuse are conducted at the point of collection using hand-held or "on-site" kits[15]. These can provide a "quick" preliminary result to see if the worker is possibly using a drug of abuse, in which case they will usually be stood down until the confirmatory result is returned a day or two later from the laboratory. These tests kits have a similar design to laboratory-based test kits, but can be less reliable in some circumstances and with some kits. Guidelines on their use are also contained within AS/NZS 4308:2008.

Unfortunately, the most common result is "opiate-positive", usually caused by use of codeine. Standing people down (or imposing sanctions) based on use of an over-the-counter drug that is unlikely to cause impairment, unless grossly misused is problematic, although this is widely employed in wider workplace drug testing programs in safety-critical industries. These on-site kits usually include the most common drugs of abuse, ie amphetamines, benzodiazepines, cannabis, cocaine and opiates and rarely other drugs or drug classes including opioids.

## 1.10 Workplace Drug Testing

Testing employees for drugs of abuse is extensively practised in the USA with many millions of tests conducted annually. This includes the armed forces, all federally employed public servants, aviation, rail, many state-owned agencies, and numerous private companies. Most of these tests rely on urine for a combination of post-incident and random testing. Hair is also used but predominately for pre-employment screening to ensure, as far as testing can, that a future employee does not use recreational drugs.

The federal mandated scheme in the USA started with the Drug-Free Workplace Act of 1988 which requires some Federal contractors and all Federal grantees (employees) to provide drug-free workplaces as a precondition of receiving a contract or grant from a Federal agency. In the USA, alcohol and drug testing is widespread across all sectors [55]. This includes the top Fortune 1000 companies where about 80% have some type of alcohol and drug testing program.

In recent years alcohol and drug testing in Australia has expanded with the introduction of occupational health and safety (OH&S) legislation in all states that obligates employers to provide a safe workplace for all employees and visitors. Employers face significant fines if found guilty under these laws. In Australia a large number of corporations and other agencies test employees for drugs of abuse – essentially those covered in AS/NZS 4308:2008 for urine and AS4760:2006 for oral fluid. The major industries/groups that use drug testing are:

- Armed forces (army, air force, navy)
- Aviation

[15] Sometimes referred to as point-of-care drug testing.

- Custodial services (prisoners, parolees etc)
- Mining
- Petrochemical
- Police (some jurisdictions)
- Transportation by rail and trucks (logistics)

This testing is a combination of random (for deterrence), regular, post-incident (i.e. crash investigation) and targeted (suspicion of alcohol and/or drug abuse). The numbers of tests conducted and trends over years are not generally available, although anecdotally the incidence of positive tests has reduced since testing started.

All Australian States (and ACT) conduct random testing for alcohol and drugs (methamphetamine, Ecstasy[16] and cannabis) on drivers of motorised vehicles, with about 200,000 tests annually for drugs and several million for breath alcohol. The test is based on the use of oral fluid (saliva) and has a positive rate for drugs of about 2-3%. This same group gives a positive rate for breath alcohol of about 1%,

In Australia, a number of the unions have been arguing for employers to use oral fluid, rather than urine, to not penalise workers in safety-critical occupations using drugs during their days-off but coming to work unimpaired. The argument here relates largely to individual rights to privacy and being able to do what they please when not at work providing they are fit for work when rostered to do so.

The most common recreational drug, other than alcohol in this cohort, is cannabis. The pharmacological effects of this drug largely occur for up to several hours, yet urine metabolites can be detected for days, when impairment cannot be detected using standard field sobriety tests. Oral fluid testing using cut-offs defined in AS4760:2006 would only produce positive readings for up to several hours. Indeed over the last several years a number of workplaces now use oral fluid for routine testing of employees, such as the logistic companies and CASA.

Drug testing, in whatever specimen, does not provide a measure of impairment or fitness for duty. It only indicates prior use of a targeted substance, usually illicit drugs.

The primary argument for drug testing, particularly random or regular testing is that it identifies the "drug user", a person who may have a dependency to alcohol or drugs and may therefore be at a higher risk of a safety incident, or have a higher rate of absenteeism, or produce a higher risk of criminal behaviour (e.g theft) at the workplace. Most drug and alcohol workplace policies give them an opportunity for rehabilitation, but reoffending may result in losing their job.

Other than in drivers on roads where many of these drugs have been shown to increase crash risk [56-59], there is essentially no data on drug use and incidents or accidents at a workplace, other than anecdotal reports which suggest such a link.

[16] Chemically 3,4-methylenedioxy-methamphetamine

There is no such data in health professionals in terms of alcohol and drug use contributing to poor performance, increased poor diagnoses or poor surgical outcomes or even a higher rate of negligence claims with indemnity insurers. The reason for this is probably not that there is no association; but that data is rarely made available and/or epidemiological studies that are able control sufficient variables are almost impossible to perform.

## 1.11 Substance Testing in Sports

Competitive sport utilises a different form of testing. The majority of competitive (professional) sports have accredited laboratories that test for the presence of banned substances. Any presence that can be confirmed is a positive and athletes caught with a positive test for a banned substance face periods of suspension.

The most well-known agency, the World Anti-Doping Agency, or WADA publishes a list of prohibited substances both in and out of competition[17]. These include but are not limited to:

- Anabolic steroids and other anabolic agents
- Beta-blockers
- Blood doping agents
- Beta-blockers
- Cannabis like substances
- Diuretics and masking agents
- Glucocorticosteriods
- Numerous peptide structures including growth hormones
- Opioids such as morphine, fentanyl, oxycodone, methadone, pethidine, heroin
- Stimulants, both amphetamine like and beta2-agonists

Numerous sports and codes within particular sports have variations to this list and the way they deal with the positive test result in terms of process and sanctions. However, almost all of the banned substances have no cut-off; hence any amount that can be confirmed by the laboratory is reported. Most of the tests are conducted on urine, and some in blood.

The Australian Sports Anti-Doping Authority[18] (ASADA) has useful information on its website and illustrates that different drugs are banned for different sports, depending on the physiological effect of the substance on the athlete.

These laboratories use state-of-the-instrumentation that enables them to cover a large range of substances quickly and with very low detection limits. In this respect the anti-doping laboratories resemble forensic laboratories.

[17] See http://www.**wada**-ama.org/en

[18] See http://www.asada.gov.au/

## 1.12 Forensic Drug Testing

Forensic applications of testing operates in some ways like anti-doping testing in competitive sport in that laboratories cover a large range of substances without the use of cut-offs to limit detectability. As for anti-doping testing most of the analytical systems used are based on chromatographic separation and detection by mass spectrometry. This enables the detection of very low amounts of drugs, often for days to weeks after last use.

These laboratories use a combination of blood, oral fluid and urine, and some also use other tissues including hair.

In Australia these laboratories are accredited by NATA under the forensic science accreditation scheme and issue reports and certificates to various clients including courts. Each State and Territory has its own laboratory, although the range of tests and ability to conduct non-forensic or contract testing varies from one facility to another.

Typical forensic applications include:

- Testing urine and/or hair for trace amounts of substances in drug-facilitated assaults[19];
- Testing blood for impairing substances in persons suspected of an assault,
- Testing blood for impairing substances in cases of suspected impaired driving;
- Testing oral fluid in drivers for presence of a banned substance;
- Testing blood and/or urine in victims (living and deceased) for impairing or toxic substances.

In all of these cases mass spectrometry is used to ensure a reliable and sensitive detection has occurred and the result is confirmed. These analyses do not use cut-offs, rather report any substance above the threshold detection or reporting limits set by that laboratory. These reporting limits are much lower than those cut-offs used in AS/NZS 4308:2008.

These laboratories have the potential to offer a drug testing service to AHPRA and its National boards to detect a larger number of relevant target drugs at lower detection limits than that offered under AS/NZS 4308:2008.

[19] This may include sexual assaults (alleged rapes) and other crimes where an impairing substance may have been given to sedate the victim.

## 1.13 Which specimen to Use

The choice of specimen will depend on the purpose of the testing.

If the primary purpose is to determine whether a person has used one or more un-prescribed drug in the recent past then urine testing is by far the most cost-efficient modality.

Urine can readily be collected in sufficient volume on demand and allows laboratories to detect drugs and/or drug metabolites for a few days or so after last use. While hair offers a much longer window of detection (providing head hair is present), as discussed earlier, interpretation of results may not be straightforward and the cost is far higher than urine testing. Oral fluid may provide a narrower window of detection and provides a closer resemblance to blood concentrations than the other two specimens, however unless evidence of very recent use and/or likely impairment is sought urine is the best general specimen to use. The other specimens may be used to compliment urinalysis.

**Table 8** summarises some of the pros and cons for testing in urine, oral fluid and hair. Reliability and detectability refers to the ability to detect drugs of abuse with urine having the highest rating since it can detect drugs for longer and can also detect benzodiazepines, whereas oral fluid detects drugs for a shorter period of time and is not able to detect benzodiazepines with sufficient detectability and hair is mainly used for longer term exposure and is not that good to detect acute or low dose exposure.

The collection of oral fluid and hair typically take less time on average than urine, however analytical costs tend to be higher. The laboratory costs for urine samples tend to be less than that for oral fluid, while hair costs will be substantially higher.

**Table 8. Summary of the pros and cons for three specimens**

| Parameter | Urine | Oral Fluid | Hair |
|---|---|---|---|
| Drug Detectability | +++ | ++ | + |
| Collection Time | + | ++ | +++ |
| Relative costs | +++ | ++ | + |
| On-site Screening possible | Yes | Yes | Not possible |
| Equipment requirements for on-site testing[1] | $20-50 per collection kit | $30-50 per collection kit[2] | Not applicable[3] |
| Standards | AS/NZ 4308 | AS 4760 | No, but guidelines by SoHT |

+ the greater number of + symbols suggests a better outcome; for "relative costs" +++ is cheaper than +
[1] estimate only, and will depend on number of drugs targeted, volume and type of kit used
[2] costs may also include a reader that may amount to several thousand dollars per unit.
[3] collection kits will incur a cost; an estimate of the cost is $10 per kit
SoHT = society for hair testing, see www.soht.org.

## 1.14 Adulteration and Substitution

It is well known that some subjects will try to affect the outcome of the test, particularly tests based on the use of urine. This falls into two types: attempts at adulterating the urine to reduce or prevent the detection of drug and drug metabolites, or substitute their urine with another.

Checking urine soon after collection can assist in determining if the urine specimen is valid particularly if it has not been observed by the collector at the pathology centre [60]. These checks include:

| | |
|---|---|
| Urine colour | note colour, particularly if pale |
| Urine Temperature | 33-28 $^{o}$C within 4 minutes of collection |
| Urine pH | usually within range 4.5 to 8.0 |
| Specific Gravity: | should be within range 1.003 to 1.020 |
| Creatinine concentration: | should be greater than 50 mg/100mL |

The Australian Standard AS4308:2008 requires a check of colour and temperature. When urine collection is not directly viewed / witnessed the Australian Standard also specifies a number of aspects that relate to the physical space in the cubicle, such as use of "blueing agent" and sealing of taps (if present) for washing hands to prevent dilution of urine with water.

Water loading is one of the more common attempts at masking drug presence in urine. This is affected by consuming large volumes of water shortly before a collection occurs. Volumes of water required are usually well in excess of 1 litre. This causes urine to be very pale and effectively dilutes the drug concentration[20]. This can easily be detected by visual inspection of urine colour and measurement of creatinine concentration[21]. The specific gravity will also be very low [61].

Adulteration agents can be added to urine to either mask the drug by interfering with the immunoassay kit or by changing the drug metabolite in the specimen. The latter may occur by use of an oxidising agent, for example. Adulteration test kits are commercially available and should be used when urine collection is not witnessed. These include devices such as the Intect 7 (Branan Medical Corp, Irvine, CA), Mask Ultra Screen (Kacey, Asheville, NC), AdultaCheck 4, and AdultaCheck 6 (both from Chimera Research and Chemical Inc, Tampa, FL). These tests can detect use of bleach, glutaraldehyde, pyridinium chlorochromate (PCC), nitrites and oxidants.

[20] Some people will try to colourise the urine by ingesting Vitamin B complex tablets.

[21] Adulteration check-sticks include creatinine, allowing point of collection creatinine concentration (approximate) to be obtained.

Witnessed collections of urine avoid most of these issues although it is most uncommon for witnessed collections to occur, largely because of privacy concerns. If urine collections conform to the Standard AS/NZS 4308:2008 and the above tests are conducted the risk of an adulterated specimen is very low. If witnessed collections were to occur this would impose significant issues for most if not all collection centres and would require availability of both male and female collectors.

Where a doubt occurs it is always possible to request a DNA analysis on the urine and compare this with a DNA sample taken from a buccal swab or small sample of blood. Storage time in the laboratory or negative urine specimens will need to be checked to ensure sample is still available for re-testing.

It is less easy to adulterate an oral fluid collection since this is always done in the presence of the subject. Nevertheless, subjects can rinse their mouth immediately prior to collection either with water or one of the internet products which act much like water itself. This can temporarily lower the concentration of drug in oral fluid secretions, but generally do not have the same effect as water loading can for urine drug concentrations. In any event the turn-over of oral fluid in the mouth is about 10 minutes; hence any reduction is only temporary [62, 63].

In the case of hair it is known that subjects bleach or colourise hair in order to either remove drug or change the nature of the drug entrapped in hair [44]. This is rarely successful since drugs entrapped inside the hair shaft are very difficult to extract *in situ*. A somewhat common technique to avoid drug detection is to shave off all head hair, although this should raise significant concerns for AHPRA and National Boards and require other forms of monitoring. The use of axillary hair, while containing entrapped drug within the hair shaft, is much more prone to contamination since its growth rate is so much slower than head hair and is therefore not recommended for testing.

## 1.15 Frequency of Collections

One of the issues confronting organisations requiring repeat testing for drugs of abuse is how often this testing needs to be done in order to reasonably exclude drug use by the subject.

The answer depends on a number of factors including the drug(s) likely to be ingested by the subject, the dose that might be used and the type of specimen collected and ultimately the need for such a strategy.

In the case of urine the common drugs of abuse such as amphetamines, opiates, benzodiazepines, cocaine and cannabis are excreted over at least 2-3 days and may even be a little more for amphetamines and cannabis. This also applies to most of the other drugs listed in **Table 7**. Twice weekly urine testing provides coverage for most of this time for these drugs, although 3-times weekly will provide essentially complete coverage. If urine testing is subject to frequent random orders by professional registration boards then it will very

difficult for drug-using subjects to never get caught out, although they will at times escape being detected if a urine test is not ordered within a few days of their use.

For some of the other drugs the frequency is more difficult to assess. Heroin, for example, is detected through a combination of 6-acetylmorphine and morphine, although 6-acetylmorphine is normally only present in urine for up to about 6 hours.

If use of gamma-hydroxy-butyrate (GHB) is suspected then its detection in urine is also limited to about 6 hours. Since all persons exhibit small endogenous concentrations of GHB; usually up to about 5 mg/L, concentrations around this number and below cannot be distinguished from actual use of GHB.

Neither of these two latter drugs are likely to be commonly used by health care professionals. The more common abused drugs listed in Table 1 are mostly detected by more specialised techniques, hence the laboratory method and detection limit will often dictate the detection period as much as the dose used and the pharmacokinetics of the drug. As a guide **Table 8** provides a rough guide for detection time in urine for substances with different terminal elimination half-lives in blood. For example, a drug with a half-life of 12 hours in blood should be detectable for about 2 days since if half the drug is removed every 12 hours, four-times 12-hours will leave only 1/16$^{th}$ of the original amount in the body. Hence if a drug is consumed on Sunday it may not be detected on Tuesday and almost certainly not later in the week.

**Table 8. Approximate urine detection windows against pharmacokinetic half-life in blood**

| | Day of Week | | | | | | |
|---|---|---|---|---|---|---|---|
| **Blood Pharmacokinetic Half-life** | **Sunday** | **Monday** | **Tuesday** | **Wednesday** | **Thursday** | **Friday** | **Saturday** |
| **6 hours** | | | | | | | |
| **12 hours** | | | | | | | |
| **24 hours** | | | | | | | |
| **48 hours** | | | | | | | |

Likely coverage (in purple) for urinalysis for drugs of abuse based on terminal elimination half-life in blood and substance taken on Sunday morning.

**Table 9** summarises the pharmacokinetic terminal elimination half-life of the more unusual substances that can be abused by health professionals and likely concentrations that are required for detection of drug and/or its metabolite in urine, and for comparison, hair.

**Table 9. Minimum Concentrations Required to Detect Target Substance in Urine and Hair**

| Drug | Half-life (hours)[1] | Urine (ng/mL)[2] | Hair (ng/mg) |
|---|---|---|---|
| Alprazolam | 6-22 | 100 (as α-hydroxy-alprazolam, see AS4308:2008)[C] | 0.05 [64] |
| Buprenorphine | 24-72 (sublingual) | 0.5 (including norbuprenorphine and hydrolysed) [65] | 0.2 [66] |
| Fentanyl | 1-6 | 2 (also norfentanyl) [67-69][C] | 0.02 [70, 71] |
| Hydrocodone | 3-9 | 100 [72] | 0.02 [71] |
| Hydromorphone[3] | 2-4 | 50 (little data available) | 0.2 [73] |
| Ketamine | 2-4 | 25-50 (ketamine and norketamine) [74-76][C] | 0.05 (ketamine and norketamine) [77] |
| Methadone | 15-30 | Also EDDP (200) [72][C] | 0.02 [71] |
| Midazolam | 1-3 | 200 (using conventional benzodiazepine screening kits in hydrolysed urine) [78], although much lower cut-offs are desirable | 0.05 [79] |
| Morphine | 2-4 | 300 (as total morphine, see AS4308:2008)[C] | 0.2 [71] |
| Oxycodone | 2-3 | 100 [72, 80, 81][C]<br>50 [82] | 0.2 [71] |
| Pethidine | 2-6 | 100-200 (also norpethidine) [72, 83][C] | 0.02 [84] |
| Propofol | 0.5-1.0 | 200 (glucuronide and quinol metabolites) [85] | 0.02 (parent drug and glucuronide) [79, 86] |
| Tramadol | 5-7 | 100-200 (tramadol and O-desmethyltramadol)[C] | 1 [71] |
| Zolpidem | 2-4 | 5-25 (carboxy-4-methyl metabolite is more useful as target analyte) [87, 88] | 0.005 [64] |

The minimum concentrations in urine and hair are suggestions based on literature and refer both to likely detection limits but some also refer to amounts found in actual cases and should be used as a guide to provide the best ability to detect these drugs in health professionals.
EDDP = 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine, a methadone metabolite.
[1] terminal elimination half-life in blood as most common range [89]
[2] most of these drugs are not targeted in the urine standard AS4308:2008.
[3] also a metabolite of hydrocodone and a minor metabolite of morphine.

For example, alprazolam, currently the most commonly abused benzodiazepine[22] has a pharmacokinetic terminal elimination half-life of 6-22 hours with an average about 12 hours. The drug is excreted in urine largely as the 1-hydroxy-metabolite (also known as α–hydroxy-

[22] This benzodiazepine will be schedule 8 as of February 2014, thereby restricting its use substantially.

alprazolam). This drug is covered by the Australian and New Zealand Standard (AS/NZS 4308:2008) and lists a urine cut-off as 100 ng/mL. Using this cut-off persons using reasonable doses should be detected by routine urinalysis for benzodiazepines for about 2 days after last use.

However, most laboratories using chromatographic screening techniques (such as some forensic laboratories) will be able to detect much lower concentrations of alprazolam metabolite. For example, using LC-MS/MS detection limits for 1-hydroxy-alprazolam of 0.05 ng/mL can be obtained [90], some 200 times lower than the 100 ng/mL cut-off recommended by AS/NZS 4308:2006. This will lengthen the urine detection time substantially and may extend the detection time to about 1 week after last use.

## 1.16 Relapse Rates in Health Care Professionals

Treatment of substance-dependency across the whole population of persons treated for this condition is well documented, although not unexpectedly the success depends as much on the program and the substance being abused as much as it does across individuals. For example, the treatment of opioid-dependent persons has been one of the more common types of programs in the community, largely associated with heroin abuse, although of course for health care professionals (HCP) this will often involve pharmaceutical opioids. Typically, at least in Australia, these programs have used methadone, and more recently buprenorphine and naltrexone have also been used with varying success as well as other pharmacotherapies. In a meta-analysis of opioid detoxification programs buprenorphine and methadone appear to be the most effective [91].

The treatment of dependency to benzodiazepines, while a significant community problem, can be treated without specific pharmacotherapies quite effectively [92].

This report is not intended to provide guidelines on which program is best suited for a HCP, this can only be accomplished by a recognized provider of drug dependency treatment services. However, the author provides some information from peer-reviewed literature on published evaluations of the success of selected programs particularly as they relate to HCPs.

For HCP there have been some published studies. For example in the USA a study reported in the Journal of the American Medical Association (JAMA) of 292 substance-dependent health care professionals enrolled in the Washington Physicians Health Program, an independent post-treatment monitoring program over a 11-year period to end 2001 found that 25% had at least one relapse. The risk of relapse was increased in those who used a major opioid or had a coexisting psychiatric illness, or a family history of a substance use disorder. The presence of more than one of these risk factors or a previous relapse further increased the likelihood of relapse [93].

A 5-year longitudinal cohort study of 904 medical practitioners identified with substance abuse and admitted to a state-run physician health program gave excellent outcomes including102 anaesthetists who had a higher rate of opioid abuse than other doctors [94].

The relapse rate of surgeons over a 5-year longitudinal cohort study over a number of state-run physician health programs in the United States was no different to other medical practitioners and most were able to successfully return to medical practice following treatment for chemical dependency [95].

None of these studies elaborate on the frequency of drug tests, however presumably some form of drug testing has occurred to determine the extent, if any, of continued substance abuse. The frequency of these tests will depend very much on the provider of treatment services and may not necessarily cover every day of their treatment.

# Section 2 – Responses to Specific Issues

## 2.1 Introduction

This section uses the technical information provided in Section 1 to answer particular issues raised by AHPRA in relation to the testing of impairing substances in health care professionals. See Appendix 4 for a list of these specific issues of concern to the sponsor.

Responses to these issues are dealt in a thematic fashion rather than responding to each of the questions in turn.

## 2.2 Range of Impairing Substances to be Tested

As the previous section illustrated the range of impairing substances that can be abused by health professionals is far greater than the list of substances covered in the Australian Standard (AS/NZS 4308:2008). In fact, almost all of the substances of concern are not covered by the Standard. Of note are:

- pharmaceutical opioids (other than codeine and morphine) such as fentanyl, hydromorphone, methadone, oxycodone, pethidine, tramadol;
- strong stimulants other than benzylpiperazine, methamphetamine and MDMA;
- the anxiolytics/hypnotics zolpidem and midazolam;
- designer cannabinoids; and
- anaesthetic substances such as ketamine and propofol.

This would mean health professionals with access to pharmaceutical substances would easily escape being picked up for drug use when a urine sample is only tested for drugs listed in this Standard. Furthermore, if a medical practitioner was known to have an addiction to morphine (and found positive by testing to AS/NZS 4308) then by replacing this drug with one of the other opioids would not be detected if testing was restricted to those two opiates listed in the Standard.

Consequently, it is strongly recommended that AHPRA and National Boards extend the list of drugs of interest well beyond those listed in the Standard. This would also apply to routine testing where no particular substance is suspected.

The drugs of most concern will be the pharmaceutical opioids fentanyl, hydromorphone, methadone, oxycodone, pethidine, tramadol, and ketamine, zolpidem and midazolam should be included in all routine tests. Other impairing substances might be included (or just target tested) if there is a suspicion of their use, e.g. ketamine, propofol or one of the designer drugs (stimulants or synthetic cannabinoids) etc.

## 2.3 Providers of Services

Extending the list of impairing substances to be screened will create significant difficulties in finding a provider(s) of such services. It is likely that not all pathology providers currently being used will be able to provide this service.

It is not practicable or desirable to allow the health professional to determine their own pathology laboratory . The health professional, even if they were determined to do the right thing, would not be in a position to determine the technical requirements required for more extensive testing. Ideally, a laboratory would be able to use more sophisticated methods than a series of immunoassay kits to screen for the listed drugs, indeed by extending the list of impairing drugs to be tested the cost effectiveness against the cost of more traditional screening (such as by immunoassay testing), declines. This would mean some form of chromatographic screening such as that done by all of the forensic laboratories would become routine. While these forms of chromatographic testing do not need to be limited to forensic laboratories the capability needs to exist in a pathology laboratory that is also cost effective and timely.

It is not my brief to recommend any particular laboratory, AHPRA would need to clearly specify its requirements and either seek expressions of interest from various providers and/or request tender submissions. Laboratory costs will depend not only on the range of impairing substances (and also specimens if these were to change from just urine), the expected volume of work and the expected turn-around time.

The turn-around time for methods using chromatographic screens (either GC-MS or LC-MS/MS) do not need to be any longer than using immunoassay technology. A number of laboratories can provide results within a day or two of receipt, if required.

However, AHPRA should expect significant cost increases once testing goes beyond those drugs listed in the Standard.

Depending on the laboratory or laboratories chosen by AHPRA it may be necessary to engage an accredited collection service if the selected laboratory(s) do not have collection centres or even convenient collection centres. This will incur a fee.

This arrangement will have the added complication of needing to transport the specimen to the nominated laboratory ensuring adequate security and preserving chain-of-custody. This already occurs in many centres, hence this arrangement, if it were to occur, could be organised without too much difficulty, but again this will be at a cost and may not be as timely as exists for many of the routine tests.

## 2.4 Accreditation

While the use of suitably accredited facilities is required all Australian providers of pathology services will be NATA accredited for medical testing (a requirement if providers wish to

obtain Medicare reimbursement for the cost of the test). Additionally, all providers of forensic services are also accredited by NATA, but to a forensic standard which includes a range of additional requirements over those required under medical testing, such as security and chain-of-custody requirements.

Only some laboratories have been assessed as compliant to the requirements of the urine standard; and this will include some of the forensic facilities as well. Most of the requirements of the urine standard that can create difficulties relate to the collection of the specimen. It is possible to have an accredited collection centre from one agency (pathology provider) submit the specimen to another provider, or a provider uses a recognised collection centre for any collections.

If urine is collected then the collection agency would have accreditation to this part of the standard. If another specimen is collected (e.g. hair) then specific protocols will need to be applied that are consistent with best practice, as detailed in Section 1.

Ultimately the greatest need is the ability of a laboratory to be able to provide the range of testing that is extensive and appropriate to the case as well as being reliable, timely and cost efficient.

## 2.5 Interpretative Issues in Testing

As discussed in Section 1 a range of factors affect clearance of drugs in a person and of course a particular concentration in a specimen. Interpretation is not always straightforward hence it is recommended that an appropriately qualified person review laboratory results that is consistent across Australia and through the health professional groups, and where necessary, communicate with the laboratory any abnormalities. This issue is discussed further later.

In urine testing the most common issues are:

- Low creatinine concentration;
- Detection of morphine when codeine may have been consumed; and
- Ingestion of poppy seeds

The detection of low creatinine by the laboratory will produce a warning on the report, if the sample is analysed at all. AS/NZS 4308:2008 advise quite correctly that a repeat specimen be ordered if the creatinine concentration is below 50 mg/l and flag as low creatinines in those up to 200 mg/L (see Section 1 for more details). Physiologically persons can have naturally low urine creatinine (between 50-200 mg/L). In a study involving 45,000 urine specimens 2.6% of men and 1.5% of women had a urine creatinine below 200 mg/L [96].

The most common reason for very low creatinines is water-loading, designed to reduce the concentration of drugs in urine and avoid detection. While a repeat urine test can be ordered, if the time period is more than several hours then there will be a possibility that the substance

that may have been present is no longer detectable, particularly when using cut-offs listed in AS/NZS 4308:2008.

This practice cannot be easily stopped (in a minority of persons), although practitioners could be warned against this practice. It is known that some individuals have naturally low urine creatinine, however if repeat urine tests show an essentially normal creatinine it is unlikely that there is a physiological reason for one low creatinine.

When morphine is detected in urine at concentrations below about 2000 ng/ml it is not possible to distinguish from use of morphine alone, consumption of poppy seed products, consumption of codeine alone, or even use of heroin.

Codeine is metabolised to morphine in 92% of the population, although only about 10% is metabolised to codeine. Since codeine is excreted quicker than morphine and its conjugates, the ratio of codeine to morphine gradually reduces until about 1 day post dosing the ratio is less than unity and eventually even the codeine is no longer detectable using a cut-off of 300 ng/mL (as defined in AS/NZS 4308:2008) [97, 98]. Hence at morphine concentrations (total morphine after hydrolysis) at around 2000 ng/mL or lower it is possible that morphine has derived entirely from codeine use.

Poppy seeds contain morphine and smaller amounts of codeine and other alkaloids (including thebaine), largely as a contaminant from other parts of the plant, although the content varies substantially from one source of poppy seed to another.

Depending on the source of the seeds and the amount consumed urine will be positive for opiates (morphine) for a few to several hours . While poppy seeds are often found in small amounts in common bakery items (bread and bagels etc), some cultural groups naturally use substantial amounts in cakes and other similar products, for example central Europeans and Jewish people consuming more than 50 grams of poppy seed in one sitting [99]. The morphine content in poppy seeds varies widely and is known up to almost 0.3 mg per gram seed hence 50 grams of seed in a cake amounts to about 15 milligrams of morphine [100-102].

However, rarely do morphine concentrations above 300 ng/mL persist beyond several hours post consumption; hence it will not be difficult to abstain from such products several hours before a urine drug test.

If morphine is detected in urine and it is above 2000 ng/mL and consumption of poppy seeds recently has been ruled out then consumption of morphine or use of heroin can be reasonably suspected. The presence of 6-acetylmorphine (hydrolysis produce of heroin) will confirm use of heroin, but this metabolite is usually only present up to about 6 hours post injection of heroin. Oral heroin is never associated with 6-acetylmorphine in urine due to first-pass (hepatic) metabolism.

The interpretation of hair results can be problematic. This is detailed in section 1. As a general rule I would not advise use of hair results in isolation to prove use of an impairing substance. Rather, it can be an useful adjunct to other information that points to active substance abuse.

## 2.6 Frequency of Testing

As detailed in Section 1 the frequency of testing will depend on a number of factors including the likely risk of re-offending and substance(s) used.

As far as detection windows are concerned for urine testing the following table provides some general information. The detection window is very much dependent on the dose, or doses used if multiple doses have recently been used, the analyte (target drug or metabolite) and the cut-off or detection limit.

Laboratories using chromatographic detection systems, particularly those using mass spectrometry are likely to have detection windows twice as long as those using immunoassay screening test kits. While chromatographic based tests will be more expensive they will need to be used less frequently than those based largely on immunoassay test kits and are also able to detect a larger number of drugs.

**Table 10. Approximate urine detection windows for selected drugs**

| | Days of Coverage for Urine Tests | | | | | | |
|---|---|---|---|---|---|---|---|
| **Drug** | **1** | **2** | **3** | **4** | **5** | **6** | **7** |
| Ketamine | | | | | | | |
| Midazolam | | | | | | | |
| Pethidine | | | | | | | |
| Zolpidem | | | | | | | |
| Morphine | | | | | | | |
| Tramadol | | | | | | | |
| Oxycodone | | | | | | | |
| Alprazolam | | | | | | | |
| Fentanyl | | | | | | | |
| Diazepam | | | | | | | |

Likely coverage (in heavy shaded areas) for urinalysis for drugs of abuse using most common cut-offs. Light shaded areas are predicted likely detection periods using other metabolites as target and/or lower detection limits.

In workplace testing, other than post-incident or targeted, collections of urine (or oral fluid) are taken randomly. This substantially reduces the ability to detect a drug user when testing modalities do not cover the entire period of employment.

It would be difficult if not impractical to order tests to cover the entire length of time a health professional is being monitored. Currently at least some of the National Boards have regimens based on the following based on likely risk, viz:

- Group 1 – testing 12 - 16 times per month
- Group 2 – testing 8 - 12 times per month
- Group 3 – testing 4 - 8 times per month

- Group 4 – testing 2 - 4 times per month
- Group 5 – testing 1 - 2 times per month
- Group 6 – testing up to five times per year

Presumably when drugs such as zolpidem and pethidine are suspected of being abused higher-risk practitioners would fall into Group 1 and have testing conducted every 2-3 days. This would be generally sufficient to cover even shorter acting drugs such as zolpidem and pethidine, and will also cover drugs listed in AS/NZS 4308:2008.

For longer acting drugs a less frequent regimen would be appropriate, although for drugs listed in **Table 10,** other than diazepam, and perhaps fentanyl, testing every 2-3 days will provide complete coverage.

Depending on the risk of re-offending and the occupation it would be justifiable to conduct less frequent testing even for short half-life drugs. Persons dependent on drugs will find it difficult to stop use, even after they have been identified as drug users; a more random approach to testing will eventually detect repeated use of the suspect drug(s). In any case AHPRA and National Boards will need to assess the risk of any reoffending in practitioners conducting more highly specialized techniques, such as working in an operating theatre, against those in less risky areas of activity.

When frequent repeated urine tests are required consideration should be given to use of hair. This will require less frequent testing and could provide coverage for a few months depending on the length of hair, however it will mean that during the period of hair growth no information will be available to indicate (at least from chemical tests) whether reoffending is occurring. Consequently, this specimen may be of greater use once rehabilitation has occurred and the risk of reoffending is low.

However, a newly identified drug-using practitioner could be ordered to have a hair test to provide a prior history of drug use, providing sufficient length of hair is available (greater than 2 cm gives about 2 months of history if 2 segments are analysed). Note there is a small lag of about 1-2 weeks before hair appears through the skin.

## 2.7 Consent and Privacy

It is common practice to seek consent from a person who is being selected (or targeted) for drug testing. Indeed this is built into the requirements for the Australian urine and oral fluid standards. My advice is that this should continue to be the case for future testing policies.

AHPRA and National Boards will need to determine the policy if the practitioner refuses to take part in the testing and does not sign the consent form. Presumably if this occurs a National Board have the power to propose to suspend the practitioner from their usual activities; the presumption being that the practitioner is using impairing drugs and likely to be impaired whilst working. The legalities of these options are outside the expertise of the contractor, hence will need to be assessed by an appropriately qualified person.

Ideally, the name of the practitioner is not disclosed on the specimen and on the request-to-test form, rather a unique ID number (known to AHPRA), date of birth and possibly a third identifier (i.e. registration number) if possible. This means that only AHPRA (and any agent involved in the investigation that needs this information) will be aware of the results. This will require all test results to be sent to one person rather than other practitioners (i.e. a doctor's general practitioner) who may not have the expertise to interpret a result, let alone decide on the most appropriate course of action.

Inherent in the signed consent is the requirement by AHPRA and any party involved in the analysis and interpretation to meet the needs of the Privacy Act (and indeed other legislative requirements if relevant). This would be assisted by the use of a Review Officer (see later) to whom all results are submitted and who is able to make an interpretation for the respective board.

## 2.8 Review of Test Results and Test Review Officers (TRO)

The complexities in deciding what drug tests to be performed in a suspected practitioner and by what laboratory, together with the difficulties in assessing (at least some) laboratory reports, means it requires a specialist role within AHPRA. To rely on persons who do not have this specialist knowledge will weaken the process and increase the risk of a practitioner "slipping through" the system, and may even on occasions be falsely accused when laboratory reports are not properly interpreted.

This does not mean that any of the personnel currently performing this function in AHPRA do not have these skills or are not performing their job properly; the author cannot evaluate this, however whatever person(s) perform this function should have the appropriate skills and qualifications and ideally should be limited in number to ensure sufficient consistency in interpretations.

Within the drug-testing industry that serves workplaces the use of a review officer to perform these functions is quite common, and is indeed mandated in many industries. Indeed this is suggested in the Australian Standard and is very common in the USA. An example of the qualifications and experience required of such a person is referenced for information [103]. These persons are termed Medical Review Officers (MRO).

Other models exist with use of other appropriately skilled persons and could be called Test Review Officers (TRO), but the main requirement is knowledge of the analytical processes and capabilities of relevant laboratories and sufficient knowledge of the drugs concerned and how their presence can be best interpreted in whatever specimen is analysed.

Given the volume of work it would be anticipated that this function could be shared between professional registration boards or even between jurisdictions. This would also help to standardise the approach for AHPRA. Ultimately, of course this would be a matter for AHPRA and how this might be best funded.

## 2.9 Deterrence Effect of Substance Testing

One of the questions raised in this brief is whether testing for drugs or alcohol has a deterrent effect and potentially reduces the risk of reoffending as an impaired practitioner.

There is effectively no research into this area for health care practitioners that the author can find in the peer reviewed literature.

It is presumed that regular drug testing in these professionals not only reduces the frequency of re-offending but ultimately leads to rehabilitation in most persons (usually with treatment from a recognised provider). Indeed this is true generally for persons treated for alcohol and drug dependency, although the success rate will almost certainly depend on the program and drug being treated and of course the individual. For example, opioid dependency has received most research. A meta-analysis concludes that pharmacotherapies (either methadone or buprenorphine) are more clinically effective and more cost-effective than no drug therapy in dependent opiate users [104]. Opioid-dependent persons stabilised on pharmacotherapies and not continuing to abuse drugs are usually capable of performing their usual functions.

The only assessment of likely effectiveness of substance testing that can be made where information is available is on alcohol and drug use in drivers and how this increases the risk of an injurious crash and how widespread drug testing can lead to a deterrent effect. Survey of night club attendees prior to widespread random drug testing on the roads in Victoria suggested that such a program would deter drug use and driving [105]. Unfortunately there are no follow up surveys to indicate whether deterrence has actually occurred. In truth this is difficult to assess given the changing drug scene (availability of drugs have changed with time leading to greater access to drugs) and other variables that affect road driving safety.

Cost benefit analyses have also been performed to determine the degree to which drug testing in drivers and other road policing activities can lead to reduced road trauma [106, 107].

Research in this area is highly recommended particularly in the higher risk practitioner groups identified in this report.

## 2.10 Recreational Use of Impairing Substance Outside Work

As discussed in Section 1.10 testing for impairing substances (alcohol, illicit drugs) is widespread across a number of work groups in Australia and is still growing. Random drug testing is largely restricted to the higher risk occupations and is designed to detect employees who abuse substances and who may be at a higher risk of adverse health outcomes and poorer work performance including a higher rate of absenteeism, accidents and criminal behaviour.

It is also used to deter motorists from taking alcohol or drugs and driving, and hopefully reducing road trauma in its various forms.

One could argue that health professionals could be subject to random or routine alcohol and drug testing. All of these persons treat or care for patients, and if impaired by alcohol or drugs, the quality of treatment or care is likely to be reduced.

This would be a costly program given the numbers of these practitioners across Australia, and with the rural practitioners quite difficult to implement, even if cost were not a factor. Drug testing, whatever the type and extent, will not determine if the practitioner was necessarily impaired by that substance, particularly if urine had been used for testing. Hence, all the testing may expose is some form of recreational use that may not impact on his/her professional practice. Of course, if testing shows the presence of a non-prescribed drug (such as an opioid) this may raise the question over the source of drug as well as health and professional practice issues. This information can be supplemented by observations of co-workers for changes in behaviour that may be linked to an evolving substance-abuse problem.

Given the available literature substance use and abuse leading to impairment and negligent practice is more likely with the higher risk professions, such as anaesthetics and surgery, although other health professional groups have had substance abuse issues identified by AHPRA. The higher risk groups could be subject to regular or random testing rather than only after a complaint is made suggesting substance abuse.

While this is not possible under current national law this may be something AHPRA could consider in the future.

If regular or random testing were to be considered to deter drug abuse and identify at-risk health professionals, AHPRA would need to modify the way it orders drug tests and requires the practitioner to pay for the test.

Alternatively, AHPRA may wish to test in blood (or oral fluid) where at least some comment could be made (in at least some cases) on the magnitude of the concentration and how this may relate to normal prescribed use and likely impairment. For example, if fentanyl was detected in blood at 3 ng/mL one would expect the drug to have a significant narcotic analgesic effect as distinct from much lower concentrations.

This would only work if the blood specimen were taken close to the alleged impairment. This is probably unlikely in most cases due to time taken to initiate an action following notification (appears to be several days in many cases). In such a case AHPRA would even be more likely to have to rely on more sophisticated chromatographic tests (at least for most drugs of interest) than immunoassay tests to achieve the necessary detection limits.

Hence from a practical viewpoint urinalysis is much easier to confirm presence of a non-prescribed substance and to use other measures to inform over the nature and extent of the complaint. Evidence from colleagues working with the allegedly impaired practitioner about his/her behaviour at the relevant time will also be useful, as well as evidence of any misappropriation of drugs.

## 2.11 Drug Intelligence

Given the range of substances abused in the community change with time it would be prudent to review the policy from time to time to ensure no substances are being missed.

In Australia information on changes in use and availability of illegal substances is published by the Australian Crime Commission (ACC) through its website[23]. Annual reports are issued as well as Illicit Drug Data Reports.

Global information is provided regularly by the United Nations Office on Drugs and Crime (UNODC)[24]. The world Drug Report is the most relevant with the 2013 report now available.

The European Union, through its agency the European Centre for Drugs and Drug Addiction (EMCDDA)[25] provides useful up-to-date data on its web site over drug availability and trends within the European Union as well as providing risk assessments for some of the emerging drugs.

Key laboratories engaged in forensic toxicology maintain an awareness of changes in drug availability and of course will have information on drug detections. They could be used as a source of intelligence, perhaps on an annual or biennial basis.

Alternatively, a suitably qualified individual could be asked provide such information to AHPRA on an annual or biennial basis.

## 2.12 Possible Future Models

For discussion purposes two models are suggested that are capable of providing more information to AHPRA and National Board about the veracity or otherwise of a complaint against a health professional that relates to prescribed or non-prescribed misuse or abuse of an impairing substance.

This is divided into those practitioners suspected of substance abuse for the first time and those practitioners who have been found to abuse these substances and who are required to undergo further testing to establish abstinence.

[23] http://www.crimecommission.gov.au

[24] http://www.unodc.org

[25] http://www.emcdda.europa.eu

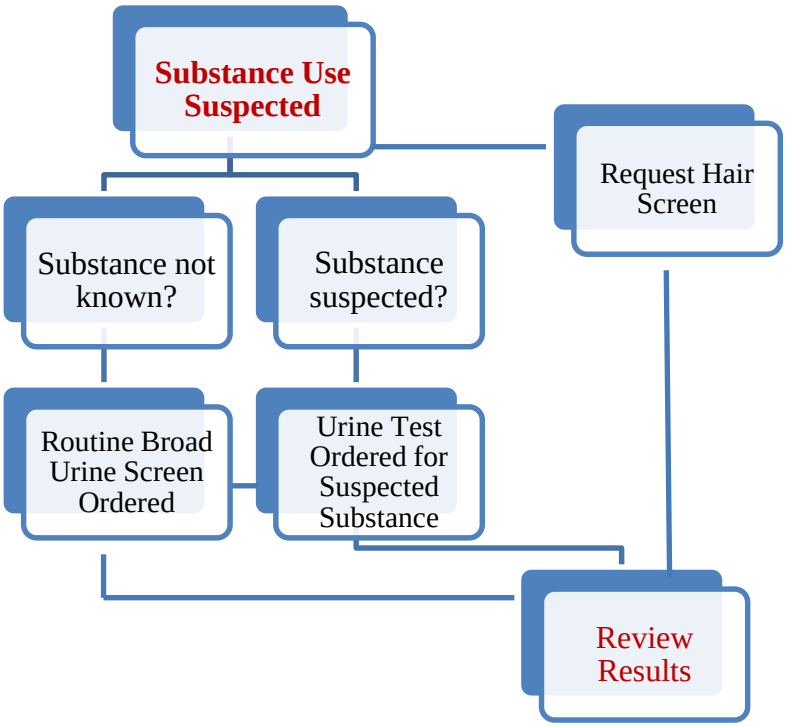
### 2.12.1 First-Time Testing of Practitioners

The flow chart below illustrates a possible model that could be used to investigate any health practitioners suspected of substance abuse (by complaint received or other information). In this model both urine and head hair is collected as soon as AHPRA are made aware of the allegation or suspect substance abuse through the notification.

Urine is analysed for any suspected substance as well as a broad range of impairing substances as outlined earlier by a previously approved laboratory. Hair is analysed by segmental analyses, such as 1-cm increments from the skin for a similar range of impairing substances, again by a previously approved laboratory.

Once results are available a Test Review Officer (TRO) reviews the results of the tests and a decision made with all the other material available to AHPRA though its investigation including a medical assessment of the professional.

**Figure 1: Flow Chart for First-Time Testing**




The urine test, as it does currently, provides information on the presence of any impairing substance through recent use (days) and the hair can provide information dating back some months, depending on the length of hair available for testing. The use of hair adds information to the urine test and provides an increased ability to detect past non-prescribed use of relevant substances.

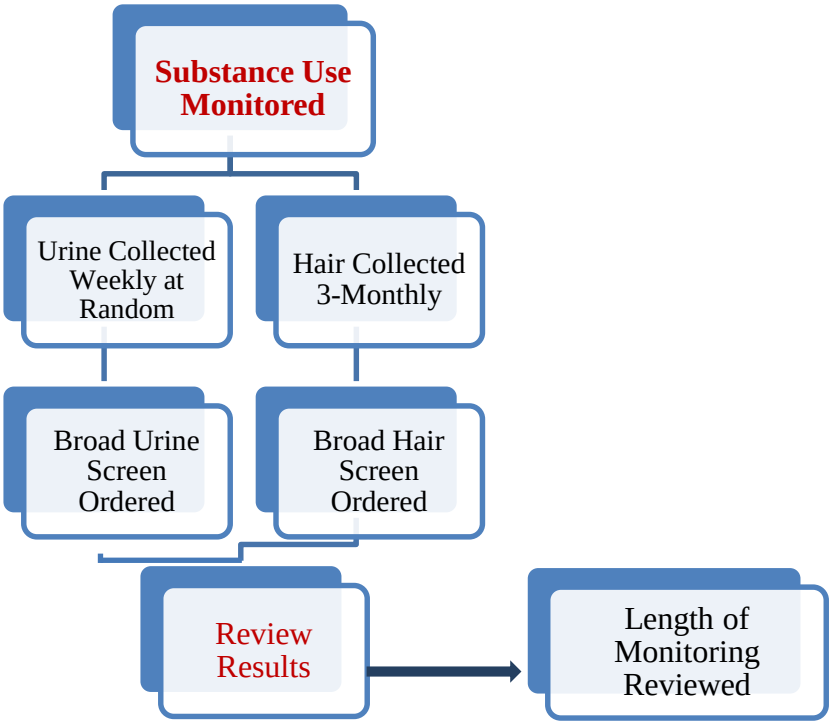
Depending on the results of the tests, and other information provided to AHPRA more testing may be required.

### 2.12.2 Repeat Testing of Impaired Practitioners

Once practitioners have been shown to misuse or abuse prescribed or non-prescribed impairing substances either because of detection in a previous test or through their own admissions AHPRA will need to ensure the practitioner does not re-offend, particularly when working in their registered profession.

A possible model would again be to combine urine testing with occasional hair testing. To avoid 2 or 3-daily repeat urine tests for many months or even years it is recommended to have one urine test weekly, but not any particular day of week, rather randomly as determined by AHPRA, and a 3-month hair test conducted on the last three 1-cm segments. A substance used in the preceding 3-months is still likely to be detectable even if hair is not sufficiently long for a 3-cm cut (as will more likely apply to men) since drugs leach slowly from tissue depots.

**Figure 2: Flow Chart for Repeat Testing**




The frequency of these tests can of course be varied depending on risk of re-offending and the occupation of the health professional and their risk of harm to themselves and their patients.

This model attempts to provide a “middle ground” to reduce the frequency of urine testing while still providing information to AHPRA on any re-offending.

Depending on the results of these tests and of course other information AHPRA will need to review the frequency of testing and the duration of monitoring.

In all of these tests, particularly when using hair continuing alcohol dependency can also be assessed by a chemical test, such as ethyl glucuronide.

## 3.0 Recommendations

The author is aware that AHPRA has the intent to develop nationally consistent, evidence-based approaches for the assessment and management of health practitioners, who are impaired, by developing:

a) An evidence-based approach for assessing, testing and managing (regulatory management) health practitioners who may be impaired, consistent with the National Law. Management includes monitoring, including biological testing, and
b) Indicators for when and how to use a range of monitoring modalities, primarily chemical testing.

To this end the following recommendations are made to ensure this intent can be reasonably achieved.

1. AHPRA and National Boards to develop a policy (and associated standard procedures) on what drugs (and other substances) require testing and their respective detection limits (or cut-offs) for particular specimens, and for particular circumstances taking into account:
    a. List of substances to be screened when no particular substance is suspected, and/or
    b. Targeted testing when a substance is suspected.

    This list(s) will contain drugs specified in AS/NZS 4308:2008, their required detection limit or cut-off and other drugs not specified in the Standard that require testing, such as fentanyl, hydromorphone, methadone, pethidine and other opioids, tramadol, ketamine, propofol, zolpidem etc.

2. AHPRA and National Boards to develop a policy (and associated standard procedures) as to what specimens should be collected for particular circumstances (relevant notifications, return to work etc); such as:
    a. Routine or random screening of drugs in urine (and alcohol in breath or urine) for a range of substances;
    b. Testing of drugs in blood (and alcohol in breath or urine) in particular circumstances when impairment may be present or knowledge of likely dosing is required;
    c. Targeted or random testing of drugs using alternative specimens, such as hair when a longer range assessment of substance abuse is suspected and/or frequent urine testing cannot occur or is not practicable, in addition to alcohol in breath or urine.

3. AHPRA and National Boards to develop a policy (and associated standard procedures) as to the length of time specimens collected from practitioners should be stored, for both:
    a. Negative test reports (non-positive to initial test request), and
    b. Positive test reports.

    These retention times allows, with proper authority, the ability to test for further substances, and at least for positive reports time for any dispute resolution to occur.

4. AHPRA and National Boards to develop a policy on the frequency of routine or random testing required for particular type of practitioner, taking into account the circumstances and risk of recurring substance abuse and the substance(s) used and taking into account the possibility of using specimens other than urine in some cases.

5. AHPRA to identify key laboratories that are able to perform the testing required and establish formal working relationships and associated prices to targeted practitioners. Ideally, AHPRA should identify laboratories that can provide a screening service based on mass spectrometry with chromatography separation since this will enable a larger range of relevant substances to be detected with improved detection limits (over immunoassay screening approaches). These laboratories may not necessarily exist in each jurisdiction; hence consideration will need to be given to ensure appropriate transportation from the collection centre (such as storage temperature and timeliness) and chain-of-custody is maintained.

6. AHPRA to establish similar formal arrangements to ensure collection of the appropriate specimen and that collection accords with appropriate standards, i.e. AS/NZS 4308:2008 for urine, and if relevant, AS4760:2006 for oral fluid and the international accepted practice for hair collection such as that recommended by the Society of Hair Testing.

7. For each practitioner that is required to undergo testing for an impairing substance ensure an appropriate test request form or order has been actioned by AHPRA and signed by the practitioner and that both the collection agency and testing laboratory are aware of the specific testing orders before collection has occurred, and the laboratory also has clear instructions of any required drug and their respective detection limits or cut-offs.

8. AHPRA to engage test review officers (TRO), or other suitably qualified individuals, who have the expertise to interpret drug results for AHPRA and National Boards. The function of this person(s) would be to review all results and assist the respective boards determine any further testing, i.e. further testing in the same or other specimens. This person(s) would need to be thoroughly familiar with analytical techniques used in this capacity, the pharmacokinetics of drugs and factors that can influence test results (such as use of other drugs, diseases and genetic factors involved in drug metabolism).

9. Two models are recommended if additional testing is required using a combination of random urine tests with a hair test for:
    a. First time offending suspected practitioners and
    b. Those practitioners requiring regular monitoring.

    These models are illustrated in section 2.12.

10. It is recommended that AHPRA and National Boards provide information, or sponsor such data collection, into the prevalence of substance abuse in health professionals across Australia, and to encourage data analysis to identify the extent of the problem and how this changes with time. This would also stimulate possible third-party research projects into the success or otherwise of programs designed to identify at-risk practitioners (anonymously), their treatment outcomes, and how their addiction is best managed.

11. In time, if changes to the National Law can occur, it is recommended that AHPRA and the National Boards have the ability to introduce random testing for impairing substances for the higher risk practitioners, such as those working in operating theatres without the requirement for a notification to occur. This would provide a preventive and deterrence role and additionally provide some information to AHPRA and the National Boards on the extent of non-prescribed drug use in a cohort of health professionals.

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## Appendix 1. Monographs

The following provide brief summaries of selected drugs that are part of usual "pathology" laboratory drug screens and are known to be abused by some health professionals.

The monographs focus mainly on the concentrations likely to be detected, or need to be targeted, using both screening and confirmation techniques.

Some references are included for information but are not meant to be an exhaustive list.

*Terminology and Abbreviations*

| | |
|---|---|
| Half-life | time taken to halve a blood or urine concentration. |
| Terminal elimination | elimination phase due to excretory processes rather than absorptive or distributive phases. |
| Cut-off | a minimum reporting concentration designed to allow easy detectability of analyte and be able to detect reasonable use of target drug. |
| Sustained-release | tablet or capsule forms designed to deliver drug over a longer time frame allowing less frequent oral administration. |
| CEDIA | cloned enzyme donor immunoassay |
| GC-MS | Gas Chromatography-Mass Spectrometry |
| LC-MS/MS | Tandem Liquid Chromatography-Mass Spectrometry |
| EMIT | Enzyme multiplied immunoassay technique |
| SSRI | serotonin reuptake inhibitors |
| SNRI | mixed serotonin noradrenaline reuptake inhibitors |
| MDMA | 3,4-methylenedioxymethamphetamine (Ecstasy) |

*Units*

Nanogram per millilitre (ng/mL) has the same numerical number as microgram per litre (µg/L) and are therefore considered equivalent.

## Alprazolam

This benzodiazepine belongs to the triazolo class of anxiolytics used in the treatment of anxiety and depression as well as to improve the symptoms of agoraphobia and panic disorders. In Australia it is available as various generic forms. For example Xanax® one of the nine generic forms is available as 250 micrograms, 500 micrograms, and 1 mg and 2 mg tablets. Daily doses usually range up to about 2 mg daily, although higher doses are occasionally justifiable.

Alprazolam is rapidly absorbed orally and plasma concentrations up to about 50 ng/mL are observed after multiple dose administration. One week of regular use leads to 3-4 fold higher concentrations.

Alprazolam clearance is reduced by cigarette smoking but increased when other substances interfere with CYP450 3A4 metabolism, such as azole antifungals (ketoconazole, itraconazole), cimetidine, some SSRI antidepressants, diltiazem, isoniazid, macrolide antibiotics such as erythromycin and clarithromycin, grapefruit juice, ergotamine, cyclosporin, amiodarone, nifedipine, and HIV protease inhibitors, as well as others, hence these drugs can affect detection times in specimens.

In healthy subjects the terminal elimination half-life of alprazolam in blood ranges from 6 to 24 hours with a mean of about 12 hours.

Alprazolam is metabolized to 1-hydroxy-alprazolam and 4-hydroxy-alprazolam and it is these forms that dominate urine including their respective conjugates. Their half-lives appear to be similar to that of alprazolam. About 50% of a dose is excreted within 24 hours, and 94% within 72 hours.

The urine cut-off for 1-hydroxy-alprazolam is 100 ng/mL in AS/NZS4308:2006 is adequate when using standard immunoassay test kits (i.e. EMIT, CEDIA etc), however much lower limits are possible using mass spectrometry which should allow detection for several days after last use. Methods capable of detecting much less than 1 ng/mL are known, both for blood and urine [90, 108, 109].

The drug can be detected in hair with detection limits of about 2-5 pg/mg [110, 111].

## Cannabis and cannabinoids

$\Delta^9$-Tetrahydrocannabinol (THC) is the active form of cannabis (marijuana). The strength of cannabis usually varies from 2-4%, but can exceed 10%. It is normally inhaled through cigarettes smoked in a similar fashion to tobacco or inhaled through a water pipe, or "bong". It can also be consumed orally through food products, such as cookies.

Peak blood concentrations following the smoking of standard doses can exceed 100 ng/mL. This usually occurs within minutes. The elimination half-life of THC is about 1-4 hours in the initial elimination phase and is 2-3 days in the terminal phase when blood concentrations are usually less than 2 ng/mL.

Concentrations of THC in blood of 5 ng/mL or higher generally indicate use within a few hours, although there is considerable individual variability. In rare cases THC concentrations over 5 ng/mL in blood may persist for several hours to days particularly after high and/or regular doses due to saturation effects. For example 24 hours after smoking cannabis blood concentrations of THC has been reported in a high-cannabis use person (1 joint per day) as high as about 4 ng/mL (plasma 6.4 ng/mL) and carboxy-THC of 92 ng/mL. Even higher concentrations are possible in extreme situations.

The extent of cannabis effects during the "intoxication" phase of 1-3 hours post-dose may diminish with time due to tolerance. However, it is still likely that consumption of "street" doses of cannabis will lead to significant adverse effects on the brain even in regular users, but again usually in the few hours after a dose. Chronic and/or long term use is likely to lead to impairment over a longer period of time and of a higher intensity.

Persons under the influence of cannabis will experience impaired cognition (reasoning and thought), poor vigilance and impaired reaction times and coordination. Epidemiological studies have shown that recent use of cannabis does increase crash risk when driving motor vehicles (including motor cycles) [112-114].

11-Nor-$\Delta^9$-tetrahydrocannabinol-9-carboxylic acid (often referred to as carboxy-THC or 11-carboxy-THC) is one of the main metabolites of THC and is found in the blood and urine of cannabis users. Because of difficulties in measuring THC accurately, some laboratories may only measure this inactive metabolite rather than THC in blood.

In urine carboxy-THC is the target analyte and it is present in substantial amounts also as a glucuronide conjugate; hence laboratories need to hydrolase the urine prior to analysis for this metabolite.

Urine concentrations of carboxy-THC peak average at 90 ng/mL and 150 ng/mL within 6 hours following the smoking of 1.75% (16 mg) and 3.55% (34 mg) cannabis cigarettes [115]. Similar urinary concentrations are observed after 10 mg smoked and 5 mg intravenous administration [116]. There is a large variation in the amounts excreted between, and within, studies. Detectable carboxy-THC in urine persists for up to 12 days following low-moderate doses of cannabis (16 to 36 mg smoked, or 5 mg intravenous) [115-117]. Higher doses (56

mg over 2 days) give detection times in urine up to 25 days in regular users of marijuana [118].

Variation in urine concentrations of cannabinoids occurs for a number of reasons including variable rates of metabolism, release of THC from fat and tissues, and variations in urine output. Creatinine measurements in urine are used to correct for renal function. However, it is still common to have fluctuating urine concentrations for some days following last use, including situations where one day level is below cut-off and another day the level is above the cut-off. A low water output will concentrate any products, compared with a high urine flow. Kidney function will also affect drug excretion. For this reason, if carboxy-THC concentrations in urine are used to produce sanctions or affect employment status, it is recommended to correct urinary cannabinoids for creatinine content. A mono-exponential model based on the Marquardt-Levenberg algorithm, has provided a way to determine recent from past use of cannabis [119].

The oral availability of cannabis is about 6 %, which means that only 6 % of the ingested THC is absorbed into the blood stream. The remainder is metabolised prior to entry into the blood stream, or is not absorbed. Consumption of marijuana-laced brownies (cookies) containing the equivalent of 1-2 cigarettes produces significant behavioural and physiological changes as well as significant carboxy-THC in the urine. Detection times in urine range up to 12 days using a 20 ng/mL cut-off and 8 days using a 75 ng/mL cut-off [120]. The activity is higher than expected from THC concentrations due to a much higher production of 11-hydroxy-THC, which is also biologically active.

Carboxy-THC is easily measured in urine using standard immunoassay kits as screening procedures (see AS/NZS 4308:2008) with a cut-off of 50 ng/mL (following hydrolysis). Confirmation can occur by GC-MS using a 20 ng/mL cut-off, or by other forms of MS [121, 122].

In hair THC is the dominant form and can be detected by MS procedures using a 0.1 ng/ng cut-off. Increasingly the carboxy metabolite is also being targeted in hair to avoid issues of environmental contamination such as from side stream smoke but the cut-off required is much lower at 0.2 pg/mg.

The synthetic forms of cannabis, such as JWH-018, AM-694, JWH-018, JWH-073, JWH-122, JWH-200, JWH-250, CP-47,497, CP47,497-C8 do not cross react with immunoassays or mass spectrometric methods designed for THC and its metabolites (see also section 1.4.2). Hence specific kits designed to detect at least some of these analogs are required, or MS methods designed to detect various synthetic cannabinoids.

## Codeine

Codeine is available as numerous over-the-counter preparations by itself or in combination with paracetamol, ibuprofen, aspirin and others with dose strengths ranging from 5-10 mg of the phosphate as a simple combination analgesic over-the-counter sales to 30 mg strength as a prescription only medicine. As an anti-tussive it is available as numerous combinations with one or more of paracetamol, pseudoephedrine, chlorpheniramine, or phenylephedrine as a cough syrup or tablet.

Typical daily doses are 15-60 mg but may range up to 240 mg daily. Once absorbed the codeine is rapidly excreted with a half-life in blood of about two hours.

Codeine is metabolized to morphine to the extent of about 10% in most persons. This means urine usually contains both codeine and morphine. Codeine is normally well in excess of the morphine concentration, but during the tail end of excretion (over the last few hours) the codeine to morphine concentration ratio decreases and may even be under unity. This is due to the longer half-life of morphine compared to codeine.

In a review of 547 urine results of codeine users the average codeine and morphine concentrations were 12 and 1.2 μg/mL. There were six cases with morphine concentrations of about 1.7 μg/mL; these had codeine concentrations ranging from 0.3 to 20 mg/L (Victorian Institute of Forensic Medicine data). In a published study involving the administration of 10-40 mg of codeine to nine subjects the excretion of both codeine and morphine in urine was evident for up to 3 days. At the 40-mg dose morphine concentrations in urine were up to 10 μg/mL at between 6-30 hours post dose. Corresponding codeine maximum concentrations ranged up to 56 μg/mL [123]. In another study 13 healthy volunteers were given 25 or 50 mg codeine orally and had their urine assessed for codeine and morphine content. For the 50 mg dose the proportion of the codeine dose excreted as morphine ranged from 2 to 12% and the overall codeine to morphine ratio ranged from 2 to 23 over the whole excretion cycle [97]. The significant production of morphine from a number of codeine preparations was also shown by another study. Codeine and morphine were detectable in urine within 1 hour of administration [124].

Codeine use has also been shown to produce small amounts of hydrocodone in urine [125]. Furthermore hydrocodone is known to be metabolized to hydromorphone [126]. Both of these are potent opioids available in their own right, although only hydromorphone is available in Australia.

Codeine is readily measured by conventional opiate immunoassays (and is listed in AS/NZS4308), GC-MS or LC-MS/MS techniques. In AS/NZS4308 the urinary cut-off is 300 ng/mL. It is also readily detected in the hair of users. The main difficulty with codeine is distinguishing the morphine in urine from other sources including morphine itself as well as heroin. When present with 6-acetylmorphine it probably derives from heroin since the opium poppy (and poppy seeds) does contain some codeine as well as the morphine.

## Fentanyl

Fentanyl is a potent opioid with approximately 50-100 times the potency as morphine on the mu-opioid receptor. It is used for chronic pain management and surgical anaesthesia. It is currently available in Australia as intravenous formulations (100 microgram in 2mL, 500 microgram in 10mL), as well as lozenges (200-1600 microgram), skin patches (12 to 100 microgram/hour) as well as a combination injection with ropivacaine. It is one of most common opioids abused by health care professionals [93]. It has also been associated with a number of deaths from abuse of patches, including Australia [127].

Fentanyl has a low oral bioavailability hence in settings other than surgical anaesthesia it is delivered by buccal absorption or from patches. Serum concentrations depend on the dose but generally range from about 1-3 ng/mL.

Fentanyl is extensively metabolized and only a few per cent of the original dose is excreted unchanged in urine, primarily in the form of norfentanyl and desproprionyl fentanyl. In surgical settings it is delivered intravenously in which case a significant proportion of dose is excreted as norfentanyl in urine during the first 12 hours [128, 129].

Analysis of urine to determine prior exposure to pethidine requires use of specific immunoassay kits for screening since the drug will not be detected by conventional "opiate" kits. Urine screening kits for fentanyl are available and generally detect the parent compound with a cut-off of 2 ng/mL (0.002 mg/L) with good specificity. Some also cross-react with the despropionyl metabolite [68], although the norfentanyl metabolite is the most abundant in urine and is detectable for much longer than the parent drug in urine. Detection times in urine depend on screening method and dose, but may only be 1-2 days if fentanyl only is targeted, but may extend to about 4 days if norfentanyl is also measured.

Confirmation tests have traditionally used GC-MS although more recently LC-MS/MS methods have been published which have detection limits in urine of 0.3 ng/mL or better [128, 130, 131]. In hair fentanyl has been detected. Methods using GC-MS are known [132] but LC-MS/MS has much higher sensitivity and can detect concentrations down to 0.002 ng/mg hair [71, 110] and is therefore much more likely to detect occasional use of fentanyl.

Other fentanyl like drugs include alfentanil, remifentanil, sufentanil, α-methyl-fentanyl, 3-methyl-fentanyl, para-fluoro-fentanyl and carfentanyl. Many other fentanyl derivatives are known, many of which are more potent than fentanyl on the mu-opioid receptor [133, 134]. These are generally not detectable by "fentanyl" immunoassay screening kits, or even mass spectrometric methods unless they are specifically targeted by the laboratory.

## Ketamine

Ketamine is an anaesthetic used only occasionally in clinical medicine as a short acting anaesthetic for induction or to supplement other anaesthetics, but is more commonly associated with its use and availability in veterinary practices, although clandestine production in Asia is suspected. It is among the most common of the abused drugs in many parts of Southeast Asia and has been known as "Special K" amongst other street names [135].

In clinical medicine it is available as Ketalar solution for injection (200 mg/2mL).

It has properties similar to phencyclidine (PCP) and lysergic acid diethylamide (LSD) producing an dissociative state with an intense out of body experience lasting about one hour. Methoxetamine is an analog that has recently become an abused drug in some parts of the world (such as USA) [136].

As for all anaesthetics it is rapidly taken up into tissues and has a terminal elimination half-life of about 2-3 hours. Ketamine is extensively metabolised by the liver to norketamine, by hydroxylation of the cyclohexone ring, by dehydration of the hydroxylated metabolites to form the cyclohexene and conjugation with glucuronic acid. Norketamine has some pharmacological activity and has similar concentrations to ketamine in plasma.

Ketamine is not a drug analysed routinely by pathology laboratories. Urinalysis focuses on a combination of the detection of ketamine and norketamine although dehydronorketamine is the main metabolite and can be detected for longer times. Commercial screening kits are available with urine cut-offs of 25 ng/mL (for ketamine). Confirmation tests based on GC-MS or LC-MS/MS can target a number of metabolites with a limit of detection of around 1-5 ng/mL and can detect use of ketamine for about 2-4 days depending on dose used and which metabolite(s) was targeted [75, 76, 137].

The drug and its norketamine metabolite can also be found in hair with a detection limit of 0.02 ng/mg [77].

## Midazolam

This benzodiazepine is available in Australia exclusively as solutions (5mg/5mL, 5 mg/mL, 15 mg/3mL, 50 mg/10mL) for sedation during minor surgery and to assist in the induction of anaesthesia, however in many parts of East and Southeast Asia and Europe it is available as a tablet or syrup for use as a sleeping aid and anxiolytic.

It is a short acting benzodiazepine of the imidazo-subclass and has a terminal elimination half-life of about 2 hours. It is metabolised mainly to 1-hydroxy-midazolam, although some 4-hydroxy and 1,4-dihydroxy metabolite are also formed, all of which are also conjugated with glucuronic acid. 60-80% of 1-hydroxy-midazolam is excreted into urine within 24 hours of a dose [138]. Very little unchanged midazolam is found in urine hence the need to target 1-hydroxy-midazolam.

Conventional commercial benzodiazepine immunoassay kits for urine are likely to detect this drug as a class test using a cut-off of 200 ng/mL [32], although it is not mentioned in AS/NZS 4308:2008 and therefore it is unlikely that routine testing will detect this drug. Given its short half-life and extensive metabolism it is not likely to be detected in urine for much longer than 1 day using these cut-offs.

Any presumptive positive result will require confirmation by either a GC-MS [78] or LC/MS/MS method to verify its presence [139, 140].

The parent drug is also detectable in hair but requires use particularly sensitive mass spectrometric methods due to the low concentrations of benzodiazepines in hair and requiring a detection limit of at least 0.05 ng/mg [64, 70, 79].

## Oxycodone

This opioid has become increasingly popular in Australia and overseas as a widely prescribed opioid, which has also become widely abused [141]. Oxycodone is a potent narcotic analgesic available as immediate and controlled release tablets, as a paediatric oral solution and as a solution for injection.

Doses used vary widely depending on severity of pain and the extent of tolerance to opioids but can exceed 50 mg daily.

Oxycodone is orally active with a bioavailability of 50-90% and is metabolised to oxymorphone by CYP2D6 and to noroxycodone by N-demethylation by CYP3A4, as well as to other minor metabolites including conjugates of oxymorphone. Oxymorphone is the major urinary metabolite and is also a potent opioid in its own right and is about 10 times more potent than oxycodone on mu-opioid receptor.

Single dose administration of Oxycontin (sustained release oxycodone) results in urinary oxycodone detectable for about 30 h post dose using a cut-off concentration of 50 ng/mL. If oxymorphone is measured (following hydrolysis of urine) detection times can approach 2 days [82].

Analysis of urine to determine prior exposure to oxycodone requires use of specific oxycodone immunoassay kits for screening since the drug will not be detected by conventional "opiate" kits. Cut-offs often applied to urine analyses are typically 100 ng/mL [80]. Chromatographic screening tests can detect 50 ng/mL or lower [82].

The drug and its nor-metabolite is relatively easy to detect (and confirm preliminary tests) by chromatographic means (GC-MS or LC-MS/MS) with limits of detection down to about 40 ng/mL, although lower concentrations are easily possible with modern instrumentation [142].

The drug can be detected in hair of "users" using conventional MS drug detection procedures designed for hair.

## Pethidine

Pethidine (or meperidine as it is known in the USA) is an opioid, acting on mu-receptors and related structurally to fentanyl with a potency about 1/8 of morphine. It has been subject to abuse by health professionals although less so in recent years due to the emergence of other opioids [16, 93].

Daily doses range from 50 to 150 mg of pethidine hydrochloride, by mouth or 25 to 100 mg by IM injection.

Blood concentrations following prescribed oral therapy use range up to about 0.5 mg/L. blood concentrations decline relatively rapidly with a pharmacokinetic terminal elimination half-life of about 3 hours.

Pethidine is metabolized to norpethidine which has about half to one quarter the potency as the parent drug on opioid receptors and is the main urinary metabolite (about 20% of dose). About 7% of the ingested dose is excreted unchanged in urine. Meperidinic and normeperidinic acids are the predominant metabolites although these not usually targeted by laboratories performing routine tests.

Analysis of urine to determine prior exposure to pethidine requires use of specific meperidine immunoassay kits for screening since the drug will not be detected by conventional "opiate" kits. Cut-offs often applied to urine analyses are typically 200 ng/mL. Chromatographic screening tests can detect lower concentrations.

The drug and its nor-metabolite are relatively easy to detect (and confirm preliminary tests) by chromatographic means (GC-MS or LC-MS/MS) with limits of detection down to about 1 ng/mL [67, 134, 143, 144].

The drug can be detected in hair of "users" using conventional drug detection procedures designed for hair [84].

## Propofol

Propofol is a short-acting general anaesthetic with sedative effects mediated primarily by the positive modulation of the inhibitory function of the neurotransmitter GABA through $GABA_A$ receptors. Sub-anaesthetic doses of propofol can elicit a euphoric response. It is known to be abused almost exclusively by health professionals who have access to this drug through their profession [145-147].

It is available as various water-based 10 mg/mL emulsions.

Plasma concentrations initially decline rapidly as a result of distribution with a half-life of a few minutes, followed by a slower half-life of 30-60 minutes. A slower terminal elimination phase occurs as it is removed from less poorly perfused tissues.

It is extensively metabolised to the 1- and 4-glucuronides and 4-sulfate conjugates of propofol and its quinol (oxidation product) [85]. Almost no free propofol is found in urine.

No commercial immunoassay screening kits are available for its analysis and would only be tested by relatively few specialist laboratories in the world, largely restricted to forensic facilities. All testing will need the use of GC-MS techniques for the parent drug and one or more of its metabolites in urine at concentrations that can detect at least 200 ng/mL, although much lower concentrations are required if detection is required days out from use [148, 149].

Hair analysis has been used to detect abuse of propofol down to about 0.02 ng/mg [70, 79].

## Tramadol

Tramadol is a centrally acting analgesic with opioid activity used in the treatment of moderate to severe pain in (oral) daily doses of 50 - 100 mg administered two to four times daily.

It is available in various forms including capsules, sustained release tablets, oral drops as well as solution for injection. There are numerous generic formulations. One of these Tramal® is available as immediate release capsules 50 mg, solution for injection 50 mg/mL, 100 mg/2 mL, sustained release tablets 50 mg, 100 mg, 150 mg & 200 mg and oral drops 100 mg/mL.

Tramadol is metabolised by N- and O-demethylation and glucuronidation or sulfation with O-desmethyl tramadol the most significant since it has most of the opioid activity. These involve the CYP450 3A4 and 2D6 enzymes. Hence drugs that affect one or both of these enzymes, or certain genotypes can affect clearance.

Tramadol inhibits serotonin and noradrenaline neuronal uptake and will consequently affect the activity of other serotonin active drugs, such as the SSRI/SNRIs and MDMA (Ecstasy).

In healthy subjects the terminal elimination half-life in blood ranges from 5 to 7 hours with a mean of about 6 hours. The O-desmethyl metabolite (sometimes known as M1) has a half-life of 6 –8 hours.

Neither tramadol nor their metabolites are detected by conventional opiate immunoassay assays, hence laboratories need to purchase separate kits for this drug or use chromatographic screening systems. The cut-off for tramadol in urine is often 200 ng/mL, however this may only detect tramadol for 2-3 days after last use. The use of mass spectrometry screening can achieve much concentrations as low as 5 ng/mL and allow detection of tramadol and O-desmethyl tramadol in urine samples for up to 7 days [150].

The drug is also detectable in hair but concentrations down to about 0.02 ng/ng are required to be detected [151].

## Zolpidem

Zolpidem belongs to the imidazopyridine group of compounds and is structurally unrelated to other hypnotic agents and selectively binds to a benzodiazepine subtype receptor. Pharmacologically it is closely related to the benzodiazepines (such as alprazolam, diazepam and midazolam). It is primarily marketed as a hypnotic with night time doses of 5-10 mg. It is available as 5 and 10 mg tablets. A sustained release form is also available.

The elimination half-life in blood is about 2 hours with it hypnotic effects lasting about 6 hours.

Zopiclone is extensively metabolised by the CYP450 enzymes with only a trace excreted unchanged in urine. The main metabolites are the N-oxide and the N-desmethyl form with a carboxy-metabolite being dominant and is the target analyte for urine testing.

Neither zolpidem nor its metabolites are detected by conventional benzodiazepine immunoassay assays, hence laboratories need to purchase separate kits for this drug or use chromatographic screening systems. The cut-off for zolpidem in urine is often 25 ng/mL, however this may only detect zolpidem for no more than 1 day after last use. The use of mass spectrometry screening can achieve concentrations as low as 5 ng/mL and allow detection of tramadol in urine samples for a few days [87, 152].

The drug is also detectable in hair but concentrations down to about 0.2 pg/ng are required to detect use of a single 10 mg dose [152].

## Appendix 2. Case Studies

These are largely fictitious cases or actual cases altered to provide anonymity and focus on key issues relevant to this report.

### Case Study 1 - Oxycodone

A medical practitioner suspected of opioid abuse was ordered to undertake a urine test. A urine sample was subsequently collected but found to be dilute (watery appearance and creatinine of 1.3 mmol/L). A repeat urine sample was ordered the following day that passed the integrity testing procedure and was subsequently analysed for drugs listed in AS/NZS 4308:2008. A negative result was obtained.

Repeat testing for oxycodone on the second urine using a chromatographic screen detected oxycodone in clearly measurable levels.

This case illustrates need to ensure specimen integrity testing to avoid attempts at watering down any excreted drugs using water-loading techniques, and the need to use techniques capable of detecting likely abused drugs.

### Case Study 2 - Fentanyl

A 38-year old anaesthetist was suspected of diverting fentanyl during operations. A urine sample was requested and analysed for 5 drugs of abuse classes (amphetamines, benzodiazepines, cannabinoids, cocaine and opiates) plus fentanyl. It was likely that the urine sample was collected at least several days since the complaint was made.

The urine specimen was assessed as satisfactory by colour, temperature at collection and creatinine concentration. The 5 drugs of abuse panel were analysed as per AS/NZS 4308:2008 and fentanyl was screened by immunoassay using a cut-off of 2 ng/mL. Urine testing of this specimen gave negative results.

Repeat urine was ordered one week later for similar testing and again found to be negative for targeted drugs.

Subsequently a hair sample was ordered. This was taken about one month after the original complaint was made. About 4-cm of hair weighing about 50 mg was taken from the nape of the head. This was subject to a standard washing protocol to clean hair and remove surface-bound drugs and was cut into four 1-cm long segments. The segments were analysed for fentanyl by tandem mass spectrometry with a detection limit of 5 pg/mg and screened for other drugs of abuse using a similar technique.

Fentanyl was detected in all 4 segments, although most was detected in the middle two segments at concentrations of 100 and 55 pg/mg with only traces in the other two segments.

Midazolam was also detected in the 2-cm segment (from root end) in trace amounts as well as some diazepam in the last 2 segments (two furthest from root).

These results strongly indicate that this person had used fentanyl as well as some midazolam (also used in surgical procedures) and diazepam. The absence of drugs in the urine test could be associated with abstinence once he was made aware of the complaint. Positive drug tests in hair could be the result of environmental or occupational exposure since he would handle these drugs almost daily; so this would need to be excluded if this was the only evidence pointing to use of these drugs.

More testing is recommended, particularly urine in the short term to monitor any possible re-use of these drugs.

## Case Study 3 - Propofol

Abuse of propofol by health professionals is well known with many reported deaths [153-155].

This case relates to a 29-year old female nurse who was suspected of being impaired by a substance. A urine specimen was ordered for drugs of abuse testing within a day of her suspected use. Routine testing for drugs listed in AS/NZS 4308:2008 gave a negative result.

Later investigation by the facility indicated missing propofol vials. The urine was later tested for propofol using GC-MS but was also found to be negative; however the method did not have low detection limits and the specimen was not hydrolysed prior to analysis. Subsequent reanalysis by another laboratory using GC-MS following hydrolysis found small amounts of propofol and its metabolites.

Propofol has a short pharmacokinetic half-life and is almost completely excreted in urine as conjugates. These conjugates need to be hydrolysed prior to any analysis using sensitive mass spectrometric methods. Such analysis would normally only be carried out if a suspicion of propofol abuse occurred.

# Appendix 3. Basic Pharmacokinetic Information

Pharmacokinetics refers to the time course of absorption, distribution into tissues, metabolism and excretion. Pharmacokinetics provides a useful way to define the time course of drug action, and the rate of removal and inactivation of drugs.

## Absorption

For drugs to exert any biological activity they must be delivered to the biological organism. Intravenous administration results in immediate and complete availability to the body, whereas oral administration results in a relatively slow and often incomplete availability (bioavailability) to the body. This will affect the amount of drug available to the person.

*Oral Absorption*

Drugs taken orally will have a delayed absorption since the drug will need to be transported to the small intestine for absorption to take place. Relatively few drugs are absorbed in the stomach, usually acidic drugs such as aspirin, and alcohol, and then only a small portion of the dose is absorbed in the stomach itself.

Gastrointestinal motility will affect transit time from the stomach to small intestine as it will affect the rate of transport from the small intestine into the blood. Food can often affect the absorption process both in terms of rate, as well as extent, leading to either an enhanced, a reduced, or unchanged bioavailability. For example, the absorption of ethanol can be markedly reduced by food.

*Other Routes of Administration*

Other routes of administration are used for drugs. These include intravenous, intramuscular, inhalation, dermal, nasal insufflation, inhalation, intravaginal, ocular, rectal and sublingual.

All of these routes have their own special pharmacokinetic properties that vary between drugs. Pharmaceutical preparations are specially designed for each route of administration to optimise the absorption process. Casual non-medical use of drugs given by routes not designed for the preparation will not usually give optimal absorption characteristics.

For example, heroin and the amphetamines are often injected intravenously, while cocaine is inhaled through the nose (nasal insufflation). The vapours of heroin and cocaine can also be inhaled leading to absorption through the lungs. Drugs such as many asthma medications and anaesthetics are delivered by inhalation of aerosols.

Intramuscular administration is a relatively common alternative site for medical use of benzodiazepines and other drugs. The rate and extent of absorption from this site would be expected to be somewhere between that of intravenous and oral administrations. For example, the benzodiazepine midazolam is rapidly absorbed intramuscularly with drug detectable after 5 min, and peak concentrations are obtained at 20-30 min.

Alprazolam is absorbed more rapidly sublingually than when given orally. Buprenorphine, a potent narcotic opioid is also usually given sublingually to improve its bioavailability.

Other routes of administration such as dermal, ocular and vaginal are uncommon with drugs of abuse but are used for particular medical purposes when drug needs to be delivered to a local site. Usually any lipid soluble drug can be absorbed at these other sites.

## Half-life

This is the most commonly used pharmacokinetic term used. It also defines the ability of the body to remove a drug. Half-life defines the time required for the body to remove half of the drug absorbed. Half-life is usually given in hours, although some drugs have half-lives of minutes or weeks.

Half-life is estimated by calculating the slope of the terminal part of the blood or plasma concentration versus time curve. At this stage it is assumed that no other competing process is operating, i.e. no absorption is still taking place, no distribution of drug into tissues is still taking place and that the decline in plasma concentration versus time is first order.

These assumptions are most important to remember, since they may seriously affect the calculation of half-life. The first order decline in plasma concentration is often only assumed. The plot of the logarithm of the plasma concentration versus the time should be linear in this terminal region. If the half-life is not linear, then half-life cannot be calculated with any accuracy and almost certainly means that there are either multi-compartmental losses of drug, or the processes of absorption and tissue distribution are still occurring.

Half-life is calculated from the slope of this terminal region from:

$$\text{Half-life} = 0.693 / ß$$

Where $ß$ is the slope of the terminal part of the plasma concentration vs time curve.

The half-life is useful in estimating the concentration of drug in the recent past (back calculation). For example, a drug with a half-life of 12 hours and a blood concentration of 100 ng/mL will be expected to have a concentration of about 50 ng/mL, 12 hours later. This will reduce to about 25 ng/mL at 24 hours and about 12.5 mg/L after two days.

Half-lives of drugs vary enormously from one hour for cocaine to over two days for nordiazepam (metabolite of diazepam). The half-life for intravenous heroin is only minutes.

A half-life is not a constant for a particular drug, rather it varies from person to person, and within a person. It is not uncommon for half-lives for a drug to vary 100 %, even in healthy individuals. Consequently, where appropriate, any calculation involving half-life should take into account these factors.

The half-life of commonly used drugs is usually measured in young and otherwise healthy persons. A number of factors will affect half-life and clearance of drugs generally.

Congestive heart failure, kidney and liver disease are particularly important examples, others are advanced age (>64 years), very young children, obesity and other drugs.

## Metabolism

Essentially all drugs and chemical substances are broken down or are converted to another substance, or substances, prior to excretion. This process is termed metabolism, or bioconversion.

The human body has evolved a number of mechanisms to metabolise chemicals, the primary purpose of which is to enable the substance to be more readily excreted by the body, and thereby remove the substance. Metabolic processes can be divided into two or three main types. Phase 1 metabolism is an oxidative process modifying the molecule by changing the nature of a functional group or adding a functional group. Phase 2 metabolism is a conjugative process in which a sulphate or glucuronide ester is added to an existing functional group.

*Phase 1 Processes*

Phase I processes include hydroxylation, oxidation, dealkylation routes of metabolism.

The enzyme system responsible for most of the dealkylation, hydroxylation, and oxidation reactions are the cytochrome P450 series of enzymes which are found predominantly, but not exclusively, in the liver. One form, CYP3A is responsible for hydroxylating and dealkylating many of the benzodiazepines, and the N-dealkylation of opioids. This form has two sub-types termed CYP3A3 and CYP3A4. Another, CYP2D6, is responsible for the O-dealkylation of many of the opioids.

*Phase 2 Processes*

Conjugation reactions include formation of glucuronide and sulphate esters, as well as methyl, acetyl, glycyl and glutamyl conjugates. The glucuronide is probably the most common conjugate and is seen with the benzodiazepine family of drugs, with morphine and related opioids as well as hydroxylated amphetamines.

Glucuronidation occurs in which the enzyme uridine diphosphate glucuronide (UDP) glucuronyl transferase adds ß-glucuronide acid to either a nitrogen (N), oxygen (O) or sulphur (S) on a drug or drug metabolite. This enzyme is found predominantly in the liver but is also found in the lung, kidneys, brain and gastrointestinal tract. Glucuronides are mostly inactive, although a notable exception is the 6-glucuronide of morphine that is more active than morphine itself as an analgesic.

Sulphate esters are also common with hydroxylated compounds such as some asthma drugs ($ß_2$-stimulants) and steroids. The other conjugates are not as common, and are not important metabolites for the drugs of abuse.

The high polarity of the glucuronides and sulphates mean the kidneys are able to more rapidly excrete them than the parent drug.

## Excretion

Elimination of metabolites and any unchanged drug occurs primarily in the urine. In fact the urine accounts for the majority of excreted drug, either unchanged or predominantly as a metabolite.

A significant amount of many drugs is excreted in the faeces. Amounts vary from a few percent to over 30 % of the administered dose. Faecal excretion derives from unabsorbed drug, or absorbed drug which is secreted in bile (from the liver) and which is not subsequently re-absorbed.

Biliary excretion is more important for molecules, which have a higher molecular weight, such as conjugates. For example, PCP and the opioids are particularly good subjects for biliary excretion. Other drugs found in bile include the benzodiazepines, colchicine, cocaine and its metabolites, the tricyclic antidepressants (amitriptyline, dothiepin, imipramine, doxepin etc), other psychiatric drugs sertraline, trazodone, chlorpromazine, and thioridazine, as well as the sedatives ethychlorvynol and methaqualone, and many of the cardiovascular drugs. Ethanol is present in bile. Other drugs are also likely to be present in bile.

Elimination of volatile drugs in breath is a significant route for volatile drugs such as ethanol, volatile solvents, and gases.

## Duration of Action

The term half-life has been used to define the rate of removal of drug from the blood. This term has frequently been confused to also mean duration of action of the drug. While in some cases the half-life does provide a reasonable correlation with biological effect, in many cases it does not. For the effect of a drug to be related directly to the blood concentration it requires a direct correlation of the blood concentration with the tissue at which the drug is acting. For the drugs of abuse, the site of action is the brain, or discrete sections of the brain.

For a drug to enter these brain regions they will be subject to particular processes that allow entry into the brain. These are based on the physiochemical properties of the drug including the lipid solubility characteristics (lipophilicity) and retentive ability of the brain region. Drugs with higher lipid solubility will tend to enter the brain quicker and to a greater degree than those that are water-soluble.

Another complicating factor when dealing with correlation between pharmacokinetic half-life and duration of action is the non-linear dose-response relationship for drugs. This means that a doubling of a dose does not necessarily mean a doubling of effect. In fact, for most drugs there is a threshold dose, the minimum effective concentration, below which no significant pharmacological effect can be observed; and a maximum dose, above which toxicity or serious side effects may develop and often with no additional therapeutic response. These relationships are very important when the likely toxicological effects of drugs are considered.

## Metabolic Interactions

An important feature of the metabolism of many of the benzodiazepines is that other drugs may interfere with their metabolism. For example, cimetidine (an anti-ulcer drug), and a number of the newer generation of anti-depressants inhibit the metabolism of alprazolam, and potentially many other benzodiazepines by CYP3A. This occurs either by competitive inhibition of the enzyme(s) involved in their mutual metabolism or by inhibition of the enzyme(s) by the interfering drug. Many of the newer serotonin reuptake inhibitors, including fluoxetine, paroxetine, sertraline are relatively potent inhibitors of this enzyme. Other drugs are also known to induce metabolism or inhibit metabolic processes.

## Genetic Factors

In some circumstances genetic factors can influence the metabolism and excretion (as well as the effects of the drug).

The cytochrome P450 (CYP450) family of enzymes is the most clinically relevant and responsible for the metabolism of the majority of commonly used drugs. About 80% of all commonly used drugs are primarily metabolised by 8 CYP450s from 5 subfamilies (1A, 2B, 2C, 2D and 3A). Although most individuals possess normal CYP450 enzymatic activity, thus experiencing the expected response to recommended doses of drugs, some people experience variations in the normal function of these enzymes that can lead to either increased or reduced blood and tissue concentrations.

# Appendix 4. Project Brief

The aim of the Project in accordance with AHPRAs 2013 - 2014 Business Plan is to: *Establish nationally consistent approaches for the assessment and management of health practitioners with an impairment.*

The assessment and management of health practitioners who are impaired should:

- be consistent with the objectives and guiding principles in the *Health Practitioner Regulation National Law Act* (**'the National Law'**); and
- aim to keep health practitioners practising where safe and appropriate; and
- be informed by international research and published best practice.

The purpose of the Project is to establish nationally consistent, evidence-based approaches for the assessment and management of health practitioners who are impaired as a result of their health. In achieving this, the AHPRA and the Boards aim to protect the community by using and referring to nationally consistent policies, while also ensuring that decision making is consistent, fair and robust.

The Services are as follows:

- The Contractor is to provide AHPRA with a detailed report describing the most recent body of research and contemporary evidence to inform an approach to managing, assessing, testing and monitoring of health practitioners with a drug or alcohol impairment, such that a practitioner is safe to practise;
- The report will:
    - list categories of substance abuse and of impairment; and
    - list categories of substances which are the subject of abuse.
- The report must include a description of the current range of screening tests covering different impairment and addiction situations i.e. where, what, when, frequency and the evidence-basis for testing and monitoring, including the following:
    - What tests should Boards require (urinary testing, hair testing, breathalyser etc);
    - What to specifically request when testing;
    - Conditions under which to collect specimens including full protocol, chain of custody considerations and any specific testing requirements;
    - Frequency of testing and the basis for this (for example based on the practitioners' clinical status and progress);
    - Randomness of testing;
    - Minimum period of testing recommended taking into consideration individual clinical conditions (e.g. substance misuse vs. substance abuse vs. addiction) if relevant;
    - Trigger points to review monitoring regimes – increase or decrease intensity of monitoring;
    - In addition to biological testing, what other monitoring complements the regime to give confidence to the Boards and community that practitioners are unlikely to have relapsed.
- Based on the research, the report must propose protocols for the ongoing monitoring of practitioners with a risk of drug or alcohol abuse, misuse or addiction and the evidence for these protocols.
- The Reporting and timing of the Contractor's work effort is set out below under 'Key Deliverables'.

Further detail regarding the Services is set out in Appendix A to this Schedule 2, entitled *Management of the Impaired Practitioner – Supplementary matters and issues in relation to biological testing* outlines the requirements of the project.

## Appendix A – Further details regarding the Services

### Management of the Impaired Practitioner

# Supplementary matters and issues in relation to biological testing

### 1. Purpose

The purpose of the project is to establish nationally consistent, evidence-based approaches for the assessment and management of health practitioners who are impaired. In achieving this, the Australian Health Practitioner Regulation Agency (AHPRA) and the National Boards aim to protect the community by referring to nationally consistent policies, while also ensuring that decision making is consistent, fair and robust.

The assessment and management of health practitioners who are impaired should:

- Be consistent with the objectives and guiding principles in the National Law; and
- Aim to keep health practitioners practising where safe and appropriate; and
- be informed by international research and published best practice.

The Boards' involvement in health practitioners who are impaired is limited to their regulatory assessment and management.

The Board has no role in the *treatment* of health practitioners who are impaired.

### 2. The scope of the project

AHPRA is seeking:

- An evidence-based approach for assessing, testing and managing (regulatory management) health practitioners who may be impaired, consistent with the National Law. Management includes monitoring, including biological testing
- Indications for when and how to use a range of monitoring modalities, primarily biological testing.

Examples of questions that arise include:

- How should specimens (hair, blood, urine etc) be collected? For example, should they be supervised and by whom
- How should the request for testing be expressed to ensure that we are likely to receive the correct test report
- Should we be requiring any specific laboratory requirements. For example, are there specific accreditation requirements, should we be requiring the use of one laboratory only etc.
- What testing regime should we use – frequency, randomness etc.

### 3. Definitions and actions available under the National Law

The following definition of impairment is from section 5 of the National Law:

**Impairment**, in relation to a person, means the person has a physical or mental impairment, disability, condition or disorder (including substance abuse or dependence) that detrimentally affects or is likely to detrimentally affect:

(a) for a registered health practitioner or an applicant for registration in a health profession, the person's capacity to practise the profession; or

(b) for a student, the student's capacity to undertake clinical training—

(i) as part of the approved program of study in which the student is enrolled; or

(ii) arranged by an education provider.

As a result of forming a reasonable belief that a practitioner or student registered by a Board has an impairment, a Board, panel or tribunal may impose conditions on registration, accept an undertaking, suspend or cancel the registration of a practitioner or student, as defined under the relevant sections of the National Law (see Part 8 of the National Law, and in particular section 178).

### 4. Research, evidence and/or published best practice

Without limiting the scope of this project, the following are some of the issues that arise regularly that AHPRA and the Boards would like to have addressed and advised on in the Report.

Is there research, evidence and / or published best practice regarding:

a. The retrospective nature of urine drug screening and hair testing. It is recognised that the retrospectivity of urine drug screening and hair testing (compared with breathalyser and saliva testing), means the practitioner may have practised while intoxicated by drugs or alcohol by the time the results are received. Is there research re possible mitigation against this retrospectivity?

b. The metabolism (half-life) of various drugs and substances and how this would affect a Board's interpretation of test results?

c. Research into the ability of a well-informed practitioner to "beat the system" and a protocol(s) that mitigates against this.

d. Often, people with substance abuse disorder are prescribed other medications such as benzodiazepines or codeine-containing medications. Therefore, they will always return a positive result for that substance. Is there a way to determine the level of prescribed drug vs. misuse of the drug?

e. Additionally, the administration of or non-prescription medication e.g. cold and flu medication may affect a test result. Is there research into the management of false-positives?

f. We are aware that a practitioner with an addiction is at higher risk of seeking other drugs and/or relapse, in the first few years of recovery and a higher risk of late relapse even after not abusing for a long time. What is the evidence about how to manage this risk of relapse? Is there an expectation of complete abstinence demonstrated by 100% negative results as a normal course during rehabilitation – is there research that this is realistic?

g. Does screening/testing for drugs or alcohol have a deterrent effect and mitigate the risk or minimise the likelihood of a practitioner practising while intoxicated by alcohol or drugs?

h. What substances should we screen for? For example, will a drug user who uses morphine move onto something else, that is undetectable, if we start screening for morphine? Therefore, should we always be screening for synthetic opiates (for those people with opiate addiction), or do we need to screen for different substances?

i. Taking into account the changing nature of drug use and the need for regulatory bodies to "catch-up", how do we ensure that our screening protocols are up-to-date? What do we need to do to build into our planning/operations/strategies to identify new substances of abuse?

j. What can we learn from other industries e.g. civil aviation, police service, mining, legal, teaching etc

k. What is the role of hair analysis in monitoring practitioners who have abused drugs? Is there any evidence as to the why, when, what drugs to test for (over and above drug/s of use determined by admissions and/or evidence) that led to conditions being imposed

l. Blood-borne viruses: While this is a policy decision for the Boards, is there any research relating to practitioners with blood-borne viruses (say, if they are addicted to drugs administered intravenously e.g. fentanyl, propofol).

m. What protocol to use for the selection of a laboratory for testing urine, hair, etc e.g. NATA accredited?

n. barriers to consistency – e.g. availability and accessibility of urine collection centres compliant with AS4308 and UDS pathology providers in each State and Territory

o. Is there research or best-practice relating to authorisation/consent from the practitioner for testing

p. is there research or evidence re balancing testing costs with frequency of screening and number of drugs tested

## 5. Definition of tests which might be applied

Is there evidence of the tests which might be applied as follows?

### 5.1 Tests with real-time results – pre work-shift and during a work-shift (after breaks)

a. alcohol – use, application, regularity, reliability and outcomes of breathalyser tests

b. cannabis – use, application, regularity, reliability and outcomes of saliva tests

### 5.2 Tests with retrospective results (regularity to be determined by Board)

a. random urine screening – use, application, regularity, reliability and outcomes of urine screening

b. hair testing – use, application, regularity, reliability and outcomes of hair testing

c. liver function testing – use, application, regularity, reliability and outcomes of liver function testing

d. blood testing – use, application, regularity, reliability and outcomes of blood testing

e. any other relevant biological tests – use, application, regularity, reliability and outcomes

f. whether there are drugs not included in the AS4308 screen that all practitioners need to be tested for e.g. NSW tests for pethidine and tramadol in all cases

g. what diagnostic tests are required to confirm the presence of drugs detected in a screen (e.g. GCMS)

### 6. Timing and method of communication of tests required

What is the evidence or research around timing and method of communication of tests required?

a. In one state, a previous Board devised the following protocol and that has been adopted by some (but not all) other Boards for random testing for drugs. Group 1 are considered to be the most high-risk practitioners. The practitioners know which group they are in:
   - Group 1 – testing 12 - 16 times per month
   - Group 2 – testing 8 - 12 times per month
   - Group 3 – testing 4 - 8 times per month
   - Group 4 – testing 2 - 4 times per month
   - Group 5 – testing 1 - 2 times per month
   - Group 6 – testing up to five times per year

b. Is there any evidence that this sort of protocol is more effective than a protocol that has a maximum amount of testing (say per year) but gives little indication of the number of times per month?

c. What is the timing and regularity of testing for drugs with a very short half-life e.g. requirement to test before 12 noon?

d. What is the evidence / best-practice relating to when Boards might increase or reduce the frequency of random screening?

e. Are there recommended processes for testing when a practitioner is on leave – should AHPRA require testing while on holidays unless an application for leave from testing has been submitted by the practitioner and approved by the Board? Or should we communicate that no testing is required on holidays and request the practitioner to notify us of holidays?

f. Is there evidence in relation to limitations on overseas travel or absences from screening approved by the Board?

g. What are the time lags for results?

### 7. Outcomes of testing

Is there evidence and research regarding:

a. The interpretation and management of dilute samples including follow up with pathology laboratory of low creatinine levels

b. Masking of drugs

c. Ingestion of poppy seeds used as an excuse in positive opioid response

d. How to deal with drug use outside of practice (both in the case or practitioners with an impairment and under monitoring; and separately, those who take illegal drugs while not practising (weekends; while on leave)

e. Measures for following up with the practitioner regarding missed tests, test results that are positive, test results with low creatinine levels, and any other irregularities in collection of sample or results e.g. request by a practitioner to provide a sample without supervision, temperature of urine not within expected range

f. Evidence for the recommended duration of monitoring – how long should a Board require urine screening, hair testing, breathalyser, etc?

h. Research relating to evidence that monitoring is no longer required?