Report of the Working Party

on the

Use of Cannabis for Medical Purposes

VOLUME II

MAIN REPORT

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GLOSSARY

Acute effects	The immediate effects of using a drug
AIDS	Acquired Immune Deficiency Syndrome
AMA	Australian Medical Association
Analgesic	A drug which reduces pain
Anandamide	A natural cannabinoid found in the brain
Anorexia	Significant loss of weight, which can affect HIV patients; it is the result of limited nutrient intake, and may be caused by medications, diarrhoea, depression or mouth ulcers
Anti-emetic	A drug that reduces nausea and vomiting
APADA	Australian Pharmacists Against Drug Abuse
APSAD	Australian Professional Society on Alcohol and Other Drugs
ARGT	Australian Register of Therapeutic Goods
BMA	British Medical Association
Cachexia	Significant loss of lean body mass such as skeletal muscle, which can affect HIV patients, resulting from illnesses or infections
Cannabinoids	Chemicals that act upon cannabinoid receptor sites in the brain
Cannabis	All forms of the product of the cannabis sativa plant
carcinogenic	A substance that causes cancer
CB1 and CB2	Two types of receptors found in the cannabinoid system
CBD	Cannabidiol, a cannabinoid system agonist
CD&SA	The Canadian Controlled Drug and Substances Act
Chronic effects	The longer-term effects that may occur if drug use is continued over a long period of time, such as an increased risk of a specific disease
COPD	Chronic obstructive pulmonary disease
DAWN	The US Drug Abuse Warning Network
DEA	The US Drug Enforcement Administration
Dependence (drug)	A disorder in which persons experience loss of control over drug use, and continue to use the drug despite the problems it causes them
DHHS	The US Department of Health and Human Services
Double blind study	A study in which neither the patient nor the treating physician know whether the patient is receiving an active or placebo drug
Dronabinol	Synthetic THC, which is taken orally in a capsule with sesame oil
Emesis	Nausea and vomiting
Endogenous cannabinoids	Cannabinoids that naturally occur in the brain
Epilepsy	A disorder in which abnormal electrical activity in the brain produces seizures
F&DA	The Canadian Food and Drugs Act
FDA	The US Food and Drug Administration
Glaucoma	A disease caused by raised intra-ocular pressure that can cause blindness if untreated
HIV	The Human Immunodeficiency Virus which causes AIDS
Huntington's disease	A movement disorder that results from damage to area of the brain involved in movement control
Illicit drugs	Drugs which are prohibited by law
Immunosuppressive	Something which suppresses the body's immune system

INCB	The United Nations' International Narcotics Control Board
IND	A program of the FDA that allows patients with serious or life-threatening diseases to use experimental drugs before they are generally available
IOM	Institute of Medicine, US
IOP	Intra-ocular pressure; pressure within the eyeball
Marijuana	Leaves and flowering tops of the cannabis sativa plants
Marinol	The trade name for dronabinol
MS	multiple sclerosis
MS Society	Multiple Sclerosis Society of NSW
Nabilone	A synthetic drug that has similar actions to THC
Narcotic	A legal term for drugs prohibited by international drug treaties that includes opioids, cocaine and cannabis
NCR	The Canadian Narcotic Control Regulations
NDA	An investigational New Drug Application, one step in the process in the US for approving drugs for medical use
NIDA	The US National Institute on Drug Abuse
n-of-1 clinical trial	Trial in which a single patient is observed over time, with periods in which a drug is used and not used, and behaviour and symptoms measured regularly over this time under double blind conditions
NORML	The US National Organization for Reform of Marijuana Legislation
ONDCP	The US Office of National Drug Control Policy
Parkinson's disease	A movement disorder that results from damage to area of the brain involved in movement control
Placebo	An inactive drug that is indistinguishable in appearance from the active drug with which it is being compared
PLWHA	Association for People Living With HIV/AIDS
R&D	Research and development
RACP	Royal Australian College of Physicians
Randomised controlled trial	A trial where participants are randomly assigned to an experimental (i.e. the active drug) or a control (a placebo drug) group
RCT	Randomised controlled trial
SAP	The Canadian Special Access Program
SCOST	House of Lords Select Committee on Science and Technology
Temporal lobe	An area on either side of the brain that is involved in memory and emotion
TGA	Therapeutic Goods Administration (Australia)
THC	Delta-9-tetrahydrocannabinol, the principal psychoactive ingredient of cannabis
Titrate	To measure the dose of a drug against its effects
Tourette's syndrome	A movement disorder that results from damage to area of the brain involved in movement control
TPP	The Canadian Therapeutic Products Programme

PART ONE: INTRODUCTION TO THE REPORT

1 INTRODUCTION

1.1 CONTEXT OF THE REPORT

In the past decade or so there has been controversy in a number of countries over potential medical uses of the C*annabis sativa* plant and the unique chemical substances (cannabinoids) this plant contains. In the USA citizen-initiated referenda in a number of states have legalised the use of cannabis for treating the problems associated with certain medical conditions. These include:

- control of nausea/vomiting associated with cancer chemotherapy;
- appetite stimulation in patients with HIV-related wasting syndrome;
- control of muscle spasticity (e.g. that associated with multiple sclerosis and spinal chord injuries);
- pain management (e.g. analgesic, anti-inflammatory);
- anti-convulsant effects (e.g. epilepsy);
- treatment of glaucoma;
- bronchodilation (asthma treatment).

In the past three years two major reports have been published on the medical uses of cannabis and cannabinoids – one by the UK House of Lords Select Committee on Science and Technology (SCOST), the other by the US Institute of Medicine.[1]. Both reports recommended research into the clinical uses of cannabinoid compounds and crude cannabis plant products. While awaiting the results of these trials, the reports recommended that, for compassionate reasons, cannabis should be made available as an interim measure to patients with a limited range of life-threatening and chronic health conditions who may benefit from its medical use.

In recent years, patient advocate groups and organisations such as the Australian Medical Association and the Law Society of New South Wales, have called for cannabis to be made legally available for medical use in Australia. The South Australian government commissioned an inquiry into the issue and legislation has been introduced into the Parliaments of South Australia and the Australian Capital Territory. To date, however, no state or territory has passed legislation. A Bill that was initially passed in the ACT was subsequently withdrawn.

This report summarises the deliberations of a group of clinicians, researchers and lawyers who were asked by the Premier to advise the New South Wales Government on:

- whether patients with some medical conditions should be allowed to use cannabis for medical purposes;
- if so, how this might be achieved, while taking into account the clinical needs of patients and the legal and social issues, and without legalising or decriminalising the recreational use of cannabis.

When he convened the Working Party, the Premier made it clear that any proposals to make cannabis available for medical use could not involve legalising or decriminalising the recreational use of cannabis products (see Appendix B – Terms of reference of the working party).

[1] Throughout this report we use the term cannabis to refer to all products of the plant Cannabis sativa. We prefer this to the American term marijuana, which is a Spanish word used to describe the leaves and flowering tops of the plant.

1.2 THE APPROACH OF THE WORKING PARTY

In considering the potential medical uses of cannabis and cannabinoids, the Working Party divided the subject into two parts: i) medical and therapeutic issues; ii) legal and regulatory issues.

These issues raised the following questions.

- Are cannabis and its constituent *cannabinoids* safe and effective medications for nausea and vomiting, HIV-related wasting, spasticity in multiple sclerosis and other neurological conditions, glaucoma, epilepsy, and chronic pain unrelieved by other analgesics?
- Is *smoking* a safe and effective way of delivering cannabinoids to treat these conditions?
- How do the safety and efficacy of cannabinoids and cannabis for these conditions and symptoms compare with those of other treatments?
- Are cannabis or its constituent cannabinoids likely to satisfy the criteria for registration as pharmaceutical drugs?
- What additional research should be undertaken to clarify the medical uses of cannabis or cannabinoids?

A critical issue is the standard of proof required to assess the safety and efficacy of cannabis for medical purposes. The standard regulatory requirements for pharmaceutical drugs include animal studies and randomised controlled clinical trials. In contrast, much of the evidence offered in support of the medical uses of cannabis and cannabinoids comes from uncontrolled clinical observations and patient reports, and raises questions as to the significance of this evidence.

If cannabis or cannabinoids are considered safe and effective in treating some medical conditions, the issue then arises whether they should be made available to patients who may benefit from their use, given that any use of cannabis is currently prohibited by law.

In considering the scientific evidence, the Working Party began by looking in detail at the report of the US Institute of Medicine (IOM). The IOM is a national scientific advisory body created by law to provide independent scientific advice to the American government on scientific and medical issues of major public importance. The Working Party gave particular weight to the IOM report, *Marijuana and Medicine,* because the committee that prepared this report represented a wide range of relevant expertise. The committee also commissioned comprehensive reviews of the research literature by leading researchers in the field, and sought submissions from patients and advocates for and against the medical uses of cannabis. The IOM report provides a comprehensive, up-to-date review of the medical and scientific issues and it would have been difficult to find better within the time frame available to the Working Party.

The IOM report was of less relevance in addressing legal and regulatory issues because of legal and constitutional differences between Australia and the US. To identify the legal options for making cannabis available for use in medical research and clinical practice, the Working Party commissioned a comprehensive review of the relevant national, international and state legislation. We also considered other reports and the information contained in invited submissions from various interested individuals, professional groups and patient advocacy organisations. In addition, we sought submissions from leading proponents and opponents of the medical uses of cannabis and cannabinoids (see Appendix C – List of submissions received), as well as from other interested professional bodies.

2 CANNABIS AND MEDICAL USE

2.1 CANNABIS AND CANNABINOIDS

Cannabis preparations are largely derived from the female plant of *Cannabis sativa*. Their primary psychoactive constituent is delta-9-tetrahydrocannabinol (THC)[2]. The THC content is highest in the flowering tops, declining in the leaves, lower leaves, stems and seeds. Marijuana (THC content 0.5 percent to 5 percent) is prepared from the dried flowering tops and leaves; hashish (THC content 2 per cent to 20 per cent) consists of dried cannabis resin and compressed flowers; hash oil may contain between 15 percent and 50 percent THC[3].

Cannabis may be smoked in a "joint" the size of a cigarette, or in a water pipe. Tobacco may be added to assist burning of marijuana or hashish. Smokers typically inhale deeply and hold their breath to maximise absorption of THC by the lungs[4]. Marijuana and hashish may also be eaten but cannabis is most often smoked because this is the easiest way to achieve the desired level of intoxication[5].

A typical joint contains between 0.5 and 1.0g of cannabis. The THC delivered varies between 20 and 70 percent[6], with a bioavailability that ranges from 5 percent to 24 percent[7]. As little as 2 to 3mg of available THC will produce a brief "high" in occasional users; regular users may use five or more joints a day. In human experiments, 10, 20 and 25mg of THC have been used as low, medium and high doses[8].

Like the opioids, cannabinoids act on a specific receptor that is widely distributed in the brain regions involved in cognition, memory, reward, pain perception and motor coordination[9]. These receptors respond to endogenous ligands which are considerably less potent and have a shorter duration of action than THC[10]. A specific cannabinoid antagonist that has recently been identified, promises to improve our understanding of the role of cannabinoids in normal brain function[11].

In the remainder of this report the term cannabis is used to refer to unpurified plant substances, including the leaves or flower tops, whether these are consumed by ingestion or smoking. The "effects of cannabis" include the composite effects of its various components, including THC. Not all the effects of cannabis are necessarily due to THC. Cannabinoids are compounds related to THC, whether found in the cannabis plant, in animals, or synthesised in chemistry laboratories. The term "cannabis and cannabinoids" will be used when referring to the effects of either cannabis or its constituent cannabinoids.

[2] Adams and Martin (1996).
[3] Adams and Martin (1996).
[4] Hall, Solowij and Lemon (1994)
[5] Hall, Solowij and Lemon (1994)
[6] Hall, Solowij and Lemon (1994)
[7] WHO (1997)
[8] Hall, Solowij and Lemon (1994)
[9] Adams and Martin (1996).
[10] Adams and Martin (1996).
[11] Adams and Martin (1996).

2.2 PATTERNS OF RECREATIONAL CANNABIS USE

Cannabis has been tried by a third of *all* adults in the USA, and by most *young* adults in Australia[12]. Rates of use are highest among young Australian adults in their early 20s and decline with age[13]. In the USA, studies which have followed up young people from their teens into their early 30s have shown that most cannabis use is intermittent and time-limited: most users stop in their mid to late 20s, and very few engage in daily cannabis use over a period of years[14]. In US and Australian surveys, about 10 percent of those who ever use cannabis become daily users, and another 20 to 30 per cent use weekly[15].

2.3 A BRIEF HISTORY OF MEDICAL CANNABIS USE

The medical properties of cannabis were well recognised in ancient China where physicians used it for the relief of constipation, gout, malaria and loss of appetite, and pain in childbirth[16]. In Western medicine, cannabis appeared in the Herbal (i.e. pharmacopoeia) of Dioscorides of about 60 AD, and in all subsequent herbals. In 1842, Dr W O'Shaughnessy, a British army surgeon who had served in India, reintroduced cannabis into British medicine. In Victorian times, cannabis was widely used for a variety of ailments, including muscle spasms, menstrual cramps, rheumatism, and the convulsions of tetanus, rabies and epilepsy; it was also used to promote uterine contractions in childbirth and as a sedative to induce sleep. With the development of new and better synthetic drugs in the 20th century herbal remedies generally fell into disuse. However, cannabis, extract of cannabis and tincture of cannabis remained in the British Pharmaceutical Codex (list of registered and approved drugs) until 1949. They were only removed from the Codex in 1954[17].

In Australia, the use of cannabis for any *medical* purpose was prohibited in the 1920s[18]. The use of cannabis for *any* purpose, medical or non-medical, is illegal in all Australian states and territories, but penalties for personal use and possession vary.

2.4 CONTEMPORARY MEDICAL CANNABIS USE

As there have been no comprehensive surveys of medical use of cannabis in representative samples of the population in Australia, the UK, or the US, we do not know what proportion of the population uses the drug, or how many of those who use do so for medical reasons; nor do we have good data on the patient characteristics and medical conditions for which cannabis is used. The limited survey data available come from small and possibly unrepresentative groups of patients. These results must be treated as partial and tentative.[19].

The IOM report summarised surveys of clients of the Californian Buyers' Clubs and 43 submissions

[12] Hall et al (1998)
[13] Hall et al (1998)
[14] Bachman, Wadsworth, O'Malley, Johnston and Schulenberg (1997)
[15] Hall et al (1998)
[16] SCOST (1998), section 2.5
[17] SCOST (1998), section 2.6
[18] Manderson (1993)
[19] IOM (1999), p. 20

received from individuals who used cannabis for medical purposes[20]. These showed that the largest group of medical cannabis users are people with HIV/AIDS, with smaller groups who have chronic pain, depression and musculoskeletal disorders. Patients are typically in their 30s or 40s and male, and the majority are HIV positive. The same was true of patients who spoke at IOM workshops[21].

The IOM report stressed the limitations of these data, which are based on self-reported diagnoses. While they provide a clear view of some patients' belief in the therapeutic value of cannabis, they represent only cases where cannabis use was beneficial and so present a biased picture. Also, we do not know what proportion of patients who tried cannabis for similar conditions found it unhelpful.

The House of Lords Select Committee (SCOST) reported that medical use of cannabis was "quite widespread" in the United Kingdom but could not provide a good estimate of its prevalence. Various estimates have been made, by the British Medical Association (BMA), the UK Alliance for Cannabis Therapeutics, and the Multiple Sclerosis Society[22]. The latter reported that a survey of MS patients found that 1 percent had used cannabis – a figure the MS Society considered an underestimate. The SCOST report suggested that the use of cannabis for medical purposes was "sometimes connived at by the medical profession"[23]. The report said that "substantial numbers of patients with various conditions are illegally self-medicating with cannabis and are convinced that they derive medical benefit, although scientific evidence for or against such a conclusion is largely lacking"[24].

2.5 SUMMARY: CANNABIS AND MEDICAL USE

- Cannabis preparations are largely derived from the *Cannabis sativa* plant. Delta-9-tetrahydrocannabinol (THC) is the primary psychoactive constituent;
- Cannabis may be smoked in a "joint", the size of a cigarette, or in a water pipe. It may also be eaten, but is most often smoked because this is the easiest way to titrate the desired dose;
- The "effects of cannabis" include the effects of THC as well as all other ingredients of cannabis. Not all the effects of cannabis are necessarily due to THC;
- The medical properties of cannabis have been recognised since ancient times.. Cannabis was reintroduced into British medicine in the mid 1800s. With the advent of synthetic drugs in the 20th century herbal remedies generally fell into disuse, although cannabis was not removed from the British Pharmaceutical Codex until 1954;
- There have been no population-based surveys of medical use of cannabis in Australia, the UK or the US;
- The Institute of Medicine used information from clients of cannabis buyers' clubs and individual submissions: most medical cannabis users were noted to have HIV/AIDS, with smaller groups having chronic pain, depression or musculo-skeletal disorders. Patients were typically males in their 30s or 40s.

[20] IOM (1999), p.22
[21] IOM (1999) , p.24
[22] SCOST (1998), section 5.2
[23] SCOST (1998), section 5.6
[24] SCOST (1998), section 1.3

- It is not possible to estimate how many people currently use cannabis for medical purposes, or how many would do so if it were legally available.

3 RECENT REPORTS ON MEDICAL USE OF CANNABIS & CANNABINOIDS

3.1 THE UK HOUSE OF LORDS (SCOST) REPORT

The inquiry by the House of Lords Select Committee (SCOST) into the medical use of cannabis and cannabinoids examined:

- "calls for the law to be changed to permit wider medical use of cannabinoids, and to permit the medical use of cannabis itself"[25].
- "the scientific and medical evidence to determine whether there was a case for relaxing some of the current restrictions on the medical use of cannabis"[26].

3.1.1 CANNABIS AND THE LAW IN THE UK

In the UK, cannabis and cannabis resin are Class B controlled drugs under the *Misuse of Drugs Act 1971* and the Misuse of Drugs Regulations 1985. Cannabinol and its derivatives (defined as THC and 3-alkyl homologues) are classified as Class A controlled drugs, which attract more severe penalties. Under the Regulations, cannabis, cannabis resin, and cannabinol and its derivatives (other than dronabinol) appear in Schedule 1, which means that, unlike those drugs appearing in Schedule 2, they cannot be administered for medical purposes. These Regulations also empower the Home Secretary to license anyone to produce, possess or supply any controlled drug, including a Schedule 1 drug; to license cultivation of cannabis plants; and to approve premises for smoking cannabis for research purposes.

This means that cannabis and most of its derivatives may not be used in medicine in the UK. They may be used for research but only under Home Office licence. Only two psychoactive cannabinoids – nabilone (a synthetic cannabinoid with similar effects to THC) and dronabinol (synthetic THC) – may be used for medical purposes. Two non-psychoactive cannabinoids – cannabidiol and cannabichromene – are not controlled drugs and so could be prescribed as unlicensed medicines but it appears that no one is currently doing so. Those advocating law reform want to transfer cannabis from Schedule 1 to Schedule 2 in the 1985 Regulations, permitting its use under certain conditions for medical purposes (for more detail on the legal situation in the UK, see Appendix G - Regulatory models in other jurisdictions).

There are no data on the number of prosecutions for medical cannabis use. The UK Alliance for Cannabis Therapeutics reported 15 cases of people charged with cultivation, possession and/or supply in medical situations since 1996. In 11 of the 12 cases where the outcome was known, the prosecution was abandoned or a conditional discharge given. One person was sentenced to 50 hours' community service.

3.1.2 FINDINGS AND RECOMMENDATIONS

The SCOST report recognised that there was insufficient evidence either to prove or disprove claims that cannabis has medical value. Nevertheless, the report concluded that there was enough anecdotal evidence "to convince us that cannabis almost certainly does have genuine medical applications, especially in treating the painful muscular spasms and other symptoms of multiple sclerosis (MS) and in

[25] House of Lords Select Committee on Science and Technology (SCOST) (1998).
[26] SCOST (1998), section 1.5.

the control of other forms of pain"[27].

The committee recommended that: "Clinical trials of cannabis for the treatment of MS and chronic pain should be mounted as a matter of urgency"[28], including trials of smoked cannabis. Recognition of the dangers of using smoking to administer any medicine that would be eventually licensed led the committee also to recommended that: "Research be promoted into alternative modes of administration (e.g. inhalation, sub-lingual, rectal) which would retain the benefit of rapid absorption offered by smoking, without the adverse effects."[29]

The report expressed dissatisfaction with the fact that it was Government policy to allow the Regulations to permit the prescription of cannabis to be amended only if sufficient evidence were produced the Medicines Control Agency to license cannabis[30]. Under this policy, cannabis would not be made available for medical use for several years, leaving many to suffer the very unpleasant symptoms of MS in the meantime. The committee recommended that the Government should transfer cannabis and cannabis resin from Schedule 1 of the Misuse of Drugs Regulations to Schedule 2. This would allow doctors to prescribe an appropriate preparation of cannabis as an unlicensed medicine and on a named-patient basis, and authorise doctors and pharmacies to supply the drug if prescribed. This change would also allow research without a special licence from the Home Office.

The committee argued that the current approach makes criminals of people whose intentions are innocent, adds to the burden of enforcement agencies, and brings the law into disrepute. The committee recommended that the Government immediately consult the Advisory Council on the Misuse of Drugs, as it is required to do by law to move cannabis out of Schedule 1[31]. Under the 1971 UN Convention on Psychotropic Substances, transfer of other cannabinoids from Schedule 1 to Schedule 2 requires the agreement of the World Health Organisation (WHO). To facilitate research, the committee recommended that the Government should raise the rescheduling of the remaining cannabinoids with the WHO[32].

The committee's recommendations were made primarily on "compassionate" grounds in the belief that the law was inconsistently enforced and hindered medical research. The report also argued that:

- rescheduling would prevent people charged with cannabis offences from claiming medical use as a bogus defence;
- allowing police and courts simply to ask to see a prescription would eliminate the need for these bodies to investigate individual medical histories.[33].
- if doctors were permitted to prescribe cannabis, medical professional bodies should advise them on how to do so responsibly
- professional regulatory bodies would need to develop safeguards to prevent diversion of cannabis for improper uses (e.g. that cannabis-based medicines should not be prescribed for people with, or predisposed towards, schizophrenia or cardiovascular conditions; nor, pending further research, to pregnant women[34]).

The committee also recommended that, on the basis of the available scientific evidence, cannabis and its

[27] SCOST (1998), section 8.2.
[28] SCOST (1998), section 8.3
[29] SCOST (1998), section 8.4
[30] SCOST (1998), section 8.5
[31] SCOST (1998), section 8.6
[32] SCOST (1998), section 8.10
[33] SCOST (1998), section 8.15
[34] SCOST (1998), section 8.16

derivatives should continue to be controlled drugs[35]. The rationale for this recommendation included:

- the adverse psychic effects of cannabis;
- its addictive qualities if used regularly;
- its impairment of cognitive functions;
- the risks for people with cardiovascular conditions; and
- the possibility that cannabis smoking may increase the risk of cancers to the mouth, throat and lungs, and cause similar respiratory disorders to tobacco smoking [36].

3.1.3 SUMMARY OF FINDINGS AND RECOMMENDATIONS

- There was insufficient scientific evidence to either prove or disprove claims about the medical value of cannabis. From the anecdotal evidence, however, it appears that cannabis does have medical applications, particularly in the treatment of MS and other forms of pain;
- There was support for clinical trials of cannabis (including smoked cannabis) in particular for the treatment of MS and chronic pain;
- Given the dangers of smoking as a route of administration, the report recommended research into alternative routes of administration (e.g. inhalation, rectal and sublingual);
- Given that many thousands were currently suffering the symptoms of MS, the Committee recommended the Government transfer cannabis from Schedule 1 to Schedule 2 of the Misuse of Drugs Regulations 1985, allowing doctors to prescribe cannabis as an unlicensed medicine, and doctors or pharmacies to supply it;
- Government consultation recommended with WHO, regarding the rescheduling of other cannabinoids;
- Safeguards were needed to ensure proper prescription and to avoid the diversion of medically prescribed cannabis to improper purposes;
- Cannabis and its derivatives should continue to be controlled drugs, given the evidence of the harms it causes.

3.2 THE US INSTITUTE OF MEDICINE (IOM) REPORT

In January 1997, the Office of National Drug Control Policy (ONDCP) at the White House asked the Institute of Medicine (IOM) to review the scientific evidence to assess the potential health benefits and risks of cannabis and its constituent cannabinoids. The review, which began in August 1997, was published in March 1999 as *Marijuana and Medicine: Assessing the Science Base*[37].

3.2.1 CANNABIS AND THE LAW IN THE USA

Cannabis is illegal in the United States. It was removed from the US pharmacopoeia in 1942 because it was "believed to be a harmful and addictive drug that caused psychoses, mental deterioration, and

[35] SCOST (1998), section 8.22
[36] SCOST (1998), section 8.19
[37] Institute of Medicine (IOM) (1999)

violent behavior"[38]. Cannabis and THC are found in Schedule 1 of the *Controlled Substances Act 1970*, the most restrictive Schedule available.

One cannabinoid – dronabinol (a capsule containing synthetic THC in sesame oil) – has been approved for marketing in the US (as Marinol). Dronabinol was approved by the Food and Drug Administration (FDA) in 1985 for the treatment of nausea and vomiting associated with cancer chemotherapy, and in 1992 for the treatment of anorexia in patients with AIDS.

Dronabinol is found in Schedule 2 the Controlled Substances Act; this is the second most restrictive category, which is reserved for medically approved substances with "high potential for abuse". The manufacturer of Marinol petitioned the DEA to reschedule dronabinol from Schedule 2 to Schedule 3 ("medical substances with some potential for abuse"). Although, by 1999, the DEA had announced a proposal to reschedule Marinol, no formal action had been taken[39].

In the 1970s eleven US states decriminalised cannabis, although some of these later recriminalised it. The IOM report notes that, during the 1980s, some HIV/AIDS patients found that cannabis relieved their symptoms, most dramatically those symptoms associated with HIV-related wasting[40]. Prosecutions followed in which those charged with unlawful possession of cannabis claimed the "medical necessity" defence on the grounds that they were using the drug to treat medical conditions. A minority of courts accepted these claims[41].

By June 1998, eight US states – California, Connecticut, Louisiana, New Hampshire, Ohio, Vermont, Virginia and Wisconsin – had laws permitting physicians to prescribe cannabis for medical purposes or allowing a medical necessity defence. In November 1998 ballots in five states – Arizona, Alaska, Oregon, Nevada, and Washington – favoured medical use of cannabis. Although the District of Columbia also voted on this subject, it was prevented from counting the votes by an amendment to the federal appropriation ill. Exit polls suggested that most voters had approved the measure[42].

Public support in the US for patient access to cannabis for medical use appears to be substantial. Public opinion polls taken during 1997 and 1998 found that 60 to 70 per cent of respondents were in favour of medical use of cannabis. The results of the referenda in these states were inconsistent with federal laws and so their implementation raised "complex legal questions"[43] (For more detail on the legal situation in the US, see Appendix G - Regulatory models in other jurisdictions).

3.2.2 EFFECTS OF ISOLATED CANNABINOIDS

The IOM report notes that great advances have been made in the basic science of cannabis and cannabinoids over the last 16 years. It seems, for example, that THC mimics chemicals that are naturally present in the brain (so-called 'natural cannabinoids'). Researchers have been trying for the past decade to discover these cannabinoids and work out their role. By using 'tagged' cannabinoids to identify potential binding sites in the brain they found one type of receptor (CB_1), which was widely distributed throughout the brain and was bound only to THC. This led to the discovery of a natural cannabinoid (anandamide) which uses the CB_1 site.

[38] IOM (1999), p.16
[39] IOM (1999), p.204
[40] IOM (1999), p.18
[41] Herstek (1998)
[42] IOM (1999), p.17
[43] IOM (1999), p.17

The IOM report summarises the state of knowledge about cannabinoid biology as follows:

- cannabinoids are likely to have a natural role in pain modulation, control of movement, and memory;
- the natural role of cannabinoids in immune systems remains unclear;
- tolerance develops in the brain to cannabinoids;
- dependence on cannabinoids appears possible, but is observed under a narrower range of conditions than with other drugs such as nicotine or opioids; and
- withdrawal symptoms can be observed, but appear to be mild compared to those produced by opioids or benzodiazepines[44].

Different cannabinoid receptor types found in the body appear to play different roles; while some effects of cannabinoids appear to be independent of these receptors. The variety of mechanisms through which cannabinoids can influence human physiology explains the variety of potential therapeutic uses for drugs that might act on cannabinoid systems.

The first recommendation of the IOM report was that: "Research should continue into the physiological effects of synthetic and plant-derived cannabinoids and the natural function of cannabinoids found in the body. Because different cannabinoids appear to have different effects, cannabinoid research should include, but not be restricted to, effects attributable to THC alone."[45]

3.2.3 EFFICACY OF CANNABINOID DRUGS

The IOM report concluded that cannabinoid drugs had potential therapeutic value in relieving symptoms of pain, nausea and vomiting and in stimulating appetite, but that the most promising data was in relation to the treatment of muscle spasticity. These therapeutic effects were most well established for THC[46]. The effects of cannabinoids on the symptoms studied were "generally modest" and, in most cases, more effective medications exist; but as people vary in their responses to medications there will always be a subpopulation of patients who do not respond well to other medications. The IOM concluded that:

- cannabinoids are "moderately well suited" for chemotherapy-induced nausea and vomiting and HIV-related wasting;
- that, smoking cannabis "is a crude THC delivery system and one which also delivers harmful substances"[47].

The report recommended clinical trials of cannabinoids drugs for symptom management with the aim of developing rapid-onset, reliable, and safe delivery systems, such as deep lung aerosols, nasal sprays, nasal gels and sublingual preparations. Phase 1 clinical studies are underway for the delivery of dronabinol by these means. The IOM report was not confident that cannabinoid-based drugs, other than dronabinol, would become available because of insufficient incentive for private enterprise to develop and market them.

[44] IOM (1999), p.70
[45] IOM (1999), p. 71
[46] IOM (1999), p.177
[47] IOM (1999), p. 179

3.2.4 RISKS ASSOCIATED WITH MEDICAL USE OF CANNABIS

According to the IOM, the most contentious aspect of the medical cannabis debate is not whether cannabis can alleviate particular symptoms, but the degree of harm associated with its use. The report:

- noted that the majority of data on harmful effects is based on smoked cannabis;
- concluded that the primary adverse effect of acute cannabis use is diminished psychomotor performance;
- warned that is was inadvisable to drive "any vehicle or potentially dangerous equipment while under the influence" of cannabis[48];
- concluded that the short-term immunosuppressive effects of cannabis use were not well established but, if they exist, they do not preclude legitimate medical use
- that the acute side effects "are within the risks tolerated for many medications"[49].

The chronic effects of cannabis raised greater concern for medical use. These fell into two categories: the effects of chronic smoking, and the effects of chronic use of THC. Numerous studies suggest that chronic exposure to cannabis smoke is associated with an increased risk of respiratory disease, cancer, lung damage and poor pregnancy outcomes; hence smoked cannabis was considered "unlikely to be a safe medication for any chronic medical condition"[50]. The IOM recommended that studies be carried out to define the health risks of smoking cannabis.

Another concern about chronic use of cannabis for medical purposes was the risk of dependence on the psychoactive effects of THC. The report concluded that:

- "a distinctive marijuana withdrawal syndrome has been identified, but it is mild and short-lived"[51] compared with the profound syndrome of alcohol or heroin withdrawal;
- a little over than 4 percent of the general population were dependent on cannabis at one time in their life, with the risk of dependence less than those of other drugs (including alcohol and nicotine);
- a vulnerable subpopulation of cannabis users (adolescents with conduct disorders, individuals with psychiatric disorders, and people with other forms of substance abuse problems) can develop dependence.

The IOM investigated concerns that cannabis may be a 'gateway' drug, leading to use of more harmful substances. Despite, finding that patterns in progression of drug use from adolescence to adulthood are "strikingly regular", the report concluded that there was "no conclusive evidence that the drug effects of marijuana are causally linked to the subsequent abuse of other illicit (substances)."[52]

The report found "little evidence" to support concerns that:

- decriminalisation of cannabis necessarily leads to a substantial increase in use;
- medical use of opioids has produced drug addiction in many individuals;
- the debate about medical use has altered adolescents' perceptions of the risk of cannabis use.

The report concluded that "present data on drug use progression neither support nor refute the

[48] IOM (1999), p.5.
[49] IOM (1999), p.126.
[50] IOM (1999), p.126.
[51] IOM (1999), p.126.
[52] IOM (1999), p. 6.

suggestion that medical availability would increase drug abuse. This question is, however, outside the scope of issues normally considered when assessing the medical value of drug use and so should not be a factor in evaluating the therapeutic potential of cannabis or cannabinoids."[53]

3.2.5 SUMMARY OF RECOMMENDATIONS

- Research was recommended into the physiological effects of synthetic and plant-derived cannabinoids (including THC) and the function of cannabinoids found naturally in the body;
- Evidence suggests that cannabis and cannabinoids may be of benefit to relieve nausea and vomiting due to cancer chemotherapy; to treat AIDS-related wasting; as an analgesic; and to treat muscle spasticity in movement disorders such as MS;
- Smoked cannabis was not recommended for long-term medical use. Smoking is a poor delivery system, and cannabis plants contain variable mixtures of active compounds. The future (if any) of cannabinoid drugs lies in developing some with more certain composition;
- For some patients (e.g. who are terminally ill or have debilitating symptoms) the long-term risks of smoking are less relevant. Since many patients currently risk legal, social and health problems to use cannabis, clinical trials of cannabis use for medical purposes are warranted, provided that:
    - trials last less than 6 months;
    - there is documented failure of all approved medications to provide relief;
    - symptoms are expected to be relieved by rapid onset cannabinoid drugs;
    - the treatment is administered under medical supervision and its effectiveness is assessed;
    - supervision, similar to that provided by an institutional review board process, is available to provide guidance within 24 hours of a submission by a physician;
- Clinical trials are a first step to develop rapid-onset, non-smoked cannabinoid delivery systems;
- Until a non-smoked, rapid onset cannabinoid drug delivery system becomes available, people could (with informed consent) be used as experimental subjects in closely-monitored clinical trials of a harmful delivery system such as smoking.

[53] IOM (1999), p.127.

3.3 OTHER REPORTS ON THE MEDICAL USE OF CANNABIS

- **Australian National Task Force on Cannabis** (1994)[54] recommended "controlled research into the efficacy of synthetic cannabinoid products" for chemotherapy-associated nausea, HIV-related wasting, and glaucoma, and as anticonvulsant, antispasmodic and analgesic agents.

- **Health Council of the Netherlands –** 1996 report, *Marijuana as medicine,*[55] compiled by the Standing Committee on Medicine. In assessing the efficacy of cannabis and cannabinoids, the committee studied literature published during the past 25 years. The committee concluded that there was "insufficient evidence" to justify the medical prescription of cannabis.

- **South Australian Parliamentary** – Report on cannabis (1996)[56] concluded that there were clear indications that cannabis may be of particular therapeutic value as an appetite stimulant in HIV-related wasting, in relief of nausea associated with cancer chemotherapy, and as an analgesic. It also concluded that further research was required to investigate these possibilities.

- **Council on Scientific Affairs** (1997) **–** Report to the American Medical Association (AMA) House of Delegates on *Medical Marijuana*[57] recommended that adequate and well-controlled studies of smoked cannabis in patients who have serious conditions for which preclinical, anecdotal or controlled evidence suggests possible efficacy (e.g. HIV wasting syndrome; severe acute or delayed emesis induced by chemotherapy; multiple sclerosis; spinal cord injury; dystonia and neuropathic pain).

- **British Medical Association** (1997) – For the conditions and symptoms mentioned above, the BMA report, *Therapeutic uses of cannabis,*[58] recommended further research to establish suitable methods of administration, optimal dosage regimens and routes of administration.

- **U.S. National Institutes of Health** (1997) – Report*, Workshop on the medical utility of marijuana,*[59] found that cannabis looks promising enough to recommend new controlled studies of its use in treating the following symptoms/conditions: appetite stimulation and wasting, chemotherapy-induced nausea and vomiting, neurological and movement disorders, analgesia, glaucoma.

- **World Health Organization** (1997) – Report, *Cannabis: a health perspective and research agenda,*[60] recommended further basic pharmacological and experimental investigation of the therapeutic uses of cannabinoids and clinical research into their effectiveness. Also recommended more research on the basic neuropharmacology of THC and other cannabinoids so that better therapeutic agents may be found.

[54] Ali and Christie (eds) (1994)
[55] Health Council of the Netherlands (1996)
[56] Gowing, Ali, Christie & White (1996)
[57] Council on Scientific Affairs (1997)
[58] British Medical Association (1997)
[59] National Institutes of Health (1997)
[60] World Health Organization (1997)

4 SUMMARY OF SUBMISSIONS TO THE WORKING PARTY

4.1 PHARMACOLOGY AND BOTANY OF CANNABIS

[(*Pharmaceutical Society of Australia (NSW Branch)*]: Cannabis is a complex mixture of components and it is not clear which of these, alone or in combination, would be the most effective in treating various conditions.

[*Pharmacy Guild of Australia (PGA) (NSW)*]: The inherent variability and versatility of the Cannabis sativa plant, in terms of chemical identity and purity, make it almost impossible to produce a standardised product to satisfy the criteria set down by the Therapeutic Goods Administration (TGA). Medical use of a plant in its crude form cannot seriously be considered, but its alkaloids or synthetic derivatives should be used. Cannabis contains over 420 chemicals including over 60 cannabinoids. Although research on these chemicals is limited, some have been found to include known carcinogens. Smoked cannabis may produce many more chemicals – up to 2000. The last time a crude plant product was used pharmaceutically in Australia was when a compound of stramonium leaves was marketed as *Elliott's Asthma Cigarettes*. The fact that there are over 100 varieties of *Cannabiss sativa* of varying strengths makes it a very unstable species.

[*Australian Pharmacists Against Drug Abuse* (APADA)]: Cannabis is known to interact adversely with various substances such as selective anti-depressants, tricyclics, benzodiazepines, alcohol, amphetamines and sympathomimetic amines, serotonin re-uptake inhibitors, physostigmine, chlorpromazine, and opioids

4.2 CURRENT USE BY PATIENTS

[*Australasian Society for HIV Medicine*]: Estimates suggest that 30 percent of HIV positive gay men smoke cannabis at least weekly – twice the rate of HIV negative gay men.

[*Australian Committee for Medical Cannabis (ACMC)*]: Individuals currently self-medicate using cannabis for the following conditions: migraine and headaches, seizures, stress, anxiety, insomnia, dysmenorrhoea and premenstrual symptoms.

[*The Kookie Project*]: This organisation supplies patients living with HIV/AIDS and cancer with a number of cannabis products that improve their day-to-day living conditions. They are aware that their current activity is unlawful but are otherwise law-abiding citizens engaged in a form of civil disobedience to assist those who are seriously ill and suffering.

[*People Living With HIV/AIDS (PLWHA*)]: For many people living with HIV/AIDS, the use of cannabis is a vital component of their overall treatment regime and management strategies. Cannabis is used to maintain their life-extending allopathic treatments, making some of the side-effects they experience less acute and providing a better quality of life and more treatment choices. The issue cannot be treated academically but must give close consideration to the lived experience of those already using cannabis and gaining benefit from it.

4.3 HEALTH RISKS

[*NSW Nurses' Association*]: There are numerous health risks associated with smoking cannabis, including a risk of cancer, respiratory problems and acute epiglottitis. Also, smoking cannabis in a an in-patient health facility would contradict the NSW Department of Health's 1999 Smoke Free Workplace Policy.

[*Salvation Army (SA)*]: Cannabis smoking is a cancer risk; it may also cause people living with HIV to progress more quickly to AIDS.

[*Royal Australasian College of Physicians* (RACP)]: The use of cannabis may be harmful to some patients, such as those with mental health problems, but the risk of exacerbating mental health conditions should not, on its own, be considered sufficient reason to preclude the use of cannabis for medical purposes.

[*APADA*]: There are recognised health risks associated with cannabis consumption. These vary according to the duration of use e.g. using cannabis to manage nausea during chemotherapy would be considerably less risky than using it for long term treatment of conditions such as chronic pain, glaucoma, epilepsy or spastic motor diseases. Also, cannabis use may cause people living with HIV to progress more rapidly to AIDS.

[*Royal Australian and New Zealand College of Psychiatrists* (RANZCP)]: Problems associated with the use of THC include:

- impaired fitness to drive a motor vehicle;
- it is a common entry-point to broader drug abuse and dependence;
- lowered motivation and drive; and
- a well-recognised ability to produce a wide variety of usually brief psychotic symptoms (particularly sensory disturbances and paranoia).

Cannabis use is associated with the following mental health problems.

- *Development of an organic psychosis*: Symptoms include mild impairment of consciousness, distortion of time sense, a dream-like euphoric state, progressing to a fragmentation of thought processes and hallucinations.
- *Production of first onset psychosis*: In the 1990s a majority of people presenting with psychosis for the first time have used cannabis. Some young people presenting with a first onset of schizophrenia may have been using cannabis consistently from the age of 12 years. While these young people undoubtedly have a vulnerability to schizophrenia, THC is believed to have a role in precipitating the onset of the illness. The magnitude of this effect continues to be investigated.
- *Influence on the course of schizophrenia and bipolar disorder*: In the 1990s, substance abuse disorders emerged as the major co-morbidity of mental illness. Co-morbid substance abuse disorder, usually including THC, occurs in about 50 percent of young patients.

[*SA*]: Rehabilitation programs for cannabis addiction indicate that the psychoses associated with cannabis use are particularly intense, and include suicidal and violent thoughts.

[*APSAD*]: Although the existence of cannabis dependency has been proved, its intensity is mild compared to the dependency caused by many other drugs used in medicine. The effect of cannabis on mortality is negligible; the effect on morbidity is modest.

4.4 ROUTE OF ADMINISTRATION

[*Pharmaceutical Society of Australia (PSA) (NSW Branch)*]: Cannabis products would have to be standardised and in a form that would allow patients to titrate the desired dose. A cigarette-type is not acceptable; medical practitioners prescribing such a product and pharmacists dispensing it may be liable to legal action if patients develop smoking-related conditions.

[*ACMC*]: The long-term future of cannabis is unlikely to be in its smoked vegetable form.

[*Ms Lucy Charlesworth*]: Hepatitis C-positive people who self-medicate with cannabis often prefer smoked cannabis due to the rapidity of onset and the ability to titrate doses.

[*PGA (NSW)*]: Most users mix cannabis with tobacco. This practice raises both the health issues associated with tobacco use and the conflict with public health anti-tobacco messages. Also, because of a number of uncontrollable variables such as aspiration volume, frequency of inhalation, method of smoking ('joint' vs. 'cone'), smoking would not allow accurate prediction of the dose-related therapeutic response.

[*RACP*]: A high priority for future research is the development of delivery systems that will permit rapid titration of dose but avoid smoke inhalation. Except in extreme cases, delivery of cannabis via smoking is unsatisfactory. On the other hand, smoking does allow the patient to titrate the dose.

[*Kookie Project*]: Supplies cannabis in a butter or in cookies because of belief that smoking is harmful and not an appropriate way of delivering cannabis for therapeutic purposes.

[*PLWHA*]: Most patients prefer to smoke cannabis owing to the rapid onset of action and the ability to better titrate doses.

[*APADA*]: Cannabis doses may not be accurately titrated in the smoked form, particularly by naïve users.

[*SA*]: Development of pharmaceutical forms of cannabis or its derivatives (e.g. Marinol) should be encouraged: prescription name will deflect the negative associations of cannabis.

[*Australian Pharmaceutical Manufacturers Association Inc.*]: If cannabis were to be used for medical purposes, it must be in an appropriately formulated pharmaceutical preparation to ensure that a standardised and consistent dosage can be administered. Use of an unassayed or uncontrolled product, such as dried cannabis leaf in cigarette form, would not be acceptable, as there would be no way of controlling the dosage or adequately evaluating the comparative benefit of the substance compared with other products.

[*APSAD*]: Smoking is generally an unsatisfactory means of delivery, but it does have the benefit of allowing patients to titrate dose. More satisfactory means of administration may only be a few years away and this is a high priority for research.

4.5 INDICATIONS FOR MEDICAL CANNABIS USE

4.5.1 ANTI-EMESIS AND ANTI-NAUSEA IN CHEMOTHERAPY TREATMENT

[*Breast Cancer Action Group (BCAG)*]: While first line medications are used by most patients, a number of breast cancer patients use cannabis to address the side-effects of chemotherapy or radiotherapy (e.g. chronic and acute pain, nausea, loss of appetite, depression).

[*RACP* and *APSAD*]: In some patients, the nausea and vomiting associated with cancer chemotherapy are resistant to all conventional treatments. In a proportion of these patients cannabis use has been shown to alleviate these distressing symptoms.

[*RACP*]: It is difficult to defend the current situation where the use of cannabis in patients with a limited life expectancy remains illegal. Also of concern is the illegality of medical use of substance that produces a genuine therapeutic benefit.

[*APADA*]: The anti-emetic properties of cannabis are not as effective as those of other groups of drugs such as serotonin re-uptake antagonists, corticosteroids and substituted benzamides.

4.5.2 WASTING CONDITIONS AND APPETITE STIMULATION

[*RACP*]: Current evidence suggests that cannabis may assist some patients with cancer or HIV-related wasting by increasing appetite and calorie intake, but evidence of actual weight gain or diminished weight loss is unimpressive.

[*PLWHA*]: Cited the example of a seriously-ill male, suffering from the final stages of HIV/AIDS, who found that ingesting cannabis allowed him to eat more and enjoy a longer span and quality of life than the prognosis had suggested.

[*APADA*]: A study of dronabinol (synthetic THC), supporting a New Drug Application to the US Food and Drug Administration, showed that, in terms of appetite stimulation, it was as effective as another drug, megestrol, but not in terms of significant weight gain.

[*Catholic Health Australia (CHA) Inc.*]: Cannabis is reported to increase food enjoyment and the number of times individuals eat per day. There are, however, risks associated with the development of bacterial pneumonia in immune-compromised patients.

4.5.3 MULTIPLE SCLEROSIS AND SPASTICITY

[*Multiple Sclerosis (MS) Society of NSW*]: There is a shortage of scientific evidence showing any significant effect of either inhaled or orally administered cannabis. Suitable drugs are readily available and subsidised in Australia unlike in the UK and Ireland. It is not difficult for a patient to obtain access to GPs and neurologists, which reduces the need for self-medication.

Many MS patients already suffer cognitive impairment and it is almost certain that cannabis would exacerbate this problem. The prevalence of suicide among people living with MS and cautioned that cannabis use may increase this propensity.

The effect of cannabis on the demyelination process in the central nervous system is unknown and could make this process worse.

[PGA *(NSW)*]: Although there are some suggestions that cannabis has value for treating spasticity, the tendency of MS to spontaneous remission makes any evaluation difficult. Also, there is a limited research base in terms of MS.

[*CHA Inc.*]: There may be a role for cannabis in the treatment of the epileptic and dystonic disorders, although the long-term risks of smoked cannabis need to be quantified when considering chronic therapy for neurological conditions.

4.5.4 PAIN MANAGEMENT

[*ACMC*]: THC has analgesic properties and cannabis may prove to be a less addictive analgesic than morphine.

[*PGA (NSW)*]: THC and its synthetic derivatives have been shown to be effective in most animal models of pain. However, despite the fact that THC probably acts through the release of opioid peptides, there is no evidence at this stage that it is superior to centrally-acting opioids.

[*RACP*]: The role of cannabis in modulating chronic pain is attracting considerable interest and deserves further study, although there is not at present an incontrovertible case for giving cannabis a role in the routine management of chronic pain.

[*APSAD*]: In the light of recent advances in knowledge of the basic pharmacology of cannabis, future use of cannabis for pain modulation is likely.

[CHA *Inc.*]: There is a narrow therapeutic margin between the doses of cannabis which produce useful analgesia and those which produce unacceptable adverse CNS effects.

[*PLWHA*]: For about 10 years, a 38-year-old, HIV positive woman has found cannabis very helpful for muscular pains associated with her condition. She ingests cannabis in the form of cookies.

4.5.5 GLAUCOMA

[*Royal Australian College of Ophthalmologists*]: Although cannabis has been found to assist in the effective lowering of ocular pressures in patients suffering from glaucoma, the College does not advocate the use of cannabis for ophthalmological purposes at this stage.

[*ACMC*]: There is ample evidence to link cannabis with reduction in intraocular pressure (IOP), although the mechanism that produces this effect is not understood.

[*PGA (NSW)* and *APADA*]: Although there is evidence that cannabis can reduce IOP, the doses required to do this are high. There are concerns about the possible health effects, because any glaucoma treatment would have to be long-term..

[*CHA Inc.*] Cannabis may have some potential for lowering IOP but tolerance to its cardiovascular effects may also develop.

4.5.6 HEPATITIS C

[*Ms Lucy Charlesworth (L.C.)*]: Many Hepatitis C positive people find cannabis most effective and often the most appropriate medicine to alleviate symptoms of nausea, vomiting, general pain and headache, and specific pain such as nerve, muscle and joint pain. Because of liver dysfunction, some analgesics, such as aspirin and paracetamol, can be dangerous for HCV people owing to liver dysfunction.

4.5.7 STRESS RELIEF

[*L.C.*]: Chronically ill people use cannabis to reduce the emotional stress caused by their illness and life situation.

[*PLWHA*] advised that some patients use cannabis in order to sleep, given that certain HIV therapies can induce insomnia which otherwise can only be addressed by sleeping tablets.

4.6 NEED FOR CLINICAL TRIALS AND FURTHER RESEARCH

Virtually all the submissions referred to the need for further research and clinical trials of cannabis.

[*RACP*]: The multiplicity of psychoactive agents in cannabis and the legal problems in securing intellectual property rights over cannabis may deter the pharmaceutical industry from researching its therapeutic applications.

[*PLWHA*]: An important way of providing access to cannabis should be via participation in clinical trials, but this should not be the sole option as it could exclude non-metropolitan people living with HIV/AIDS.

[*APSAD*]: The prohibition on recreational use of cannabis is a major impediment to research evaluating possible therapeutic applications.

4.7 SUPPLY OF MEDICAL CANNABIS

4.7.1 LEGAL ISSUES

[*RACP*]: Legislation would need to define thresholds for cultivation, purchase, possession and administration of cannabis, and take into account the possibility that some patients in poor health would be unable to cultivate cannabis themselves.

[*NSW Nurses' Association*]: Some form of decriminalisation should be considered as this would reduce some of the legal issues and concerns for medical and nursing practitioners who are aware their patients are smoking cannabis for therapeutic purposes or are advising their parents about this issue. Any form of decriminalisation of cannabis must be accompanied by an education campaign about the risks involved (e.g. driving under the influence, use by people vulnerable to psychosis, and use by young people). It would also be necessary to reschedule cannabis under either Schedule 4 or Schedule 8 of the *Poisons and Therapeutic Goods Act* and provide explicit guidelines and policies governing its prescription – including identified diagnosis and approved conditions for which cannabis can be prescribed.

[*PLWHA*]: Having to engage in illegal activities to acquire cannabis causes distress and unnecessary complication for seriously ill people. Cannabis should be readily available for both urban and non-urban dwellers. One HIV positive male, who believed he was the target of homophobia from arresting police officers, was charged with possession. He received both a fine and community service, partly because he had a much earlier criminal record. The stress and cost of the court case made this patient very ill. Another HIV positive patient said he hated buying cannabis because "it makes me feel like a criminal". The inconsistent quality and availability of supply also causes concern and stress for patients. Cost is a problem, too, because illness has forced many patients to leave work and rely on benefits.

[*ACMA*]: Medical cannabis users face both the threat of criminal sanctions and the need to associate with the black market to obtain supplies.

[*Pharmacy Guild of NSW (PGNSW)*]: Has strong objections to approval of *Cannabis sativa* as a medical product should the Working Party recommend that patients be allowed to grow their own plants and consume unsupervised quantities of this restricted substance.

[*Australian Pharmaceutical Manufacturers Association Inc.*]: Commonwealth legislation may hinder access to cannabis, particularly if it has to be imported.

[*RACP*]: Authorities maintain separate and very different policies on recreational and therapeutic use of certain substances.

[*CHA Inc.*]: The Catholic tradition also distinguishes between recreational use and therapeutic use. Any investigation of potential therapeutic use must consider the balance of risks and benefits.

[*BCAG*]: Some cancer patients who might otherwise benefit from cannabis may be afraid to buy it on the streets because of the risk of prosecution and the uncertainty about purity and consistency of supply. Also, cost is often prohibitive. Further research should be undertaken to find other methods of administration.

4.7.2 COMPASSION CLUBS

[*PLWHA*]: One or more growers, who can provide cannabis of consistent quality, price and accessibility, should be licensed. Also, one or more of the informal cannabis distribution networks should be licensed to provide cannabis products within formalised guidelines.

[*Nimbin Hemp Embassy* and *NSW Compassion Club*]: Organisations such as these could have a role in providing supplies of cannabis to ill people.

[*L.C.*]: A Director in the Mid North Coast Area Health Service (writing in a private capacity) has suggested that patients who are unable to grow their own cannabis might be able to obtain low-cost supplies from buyers' cooperatives or compassion clubs.

4.7.3 PRESCRIPTION AND DISPENSING

[*RACP* and *APSAD*]:It is unlikely that cannabis could lawfully be prescribed in Australia, as it would not obtain approval from the Therapeutic Goods Administration. A minimalist approach, which provides exemptions from prosecution for people with certain conditions, could, however, be adopted. An expert committee would need to define criteria for identifying and selecting suitable medical conditions, and

periodically review new evidence. A second committee would be required to consider individual applications and supporting evidence.

[*APSAD*]: It is unlikely that cannabis could be lawfully prescribed in Australia, as this would require approval by the Therapeutic Goods Administration: the TGA only accepts applications for pharmacological preparations, not for natural products.

[*PSA (NSW Branch)*]: If the Government permits the use of cannabis in this State it should to be classified in Schedule 8 of the NSW *Poisons and Therapeutic Goods Act*. Pharmacists have the facility to store and dispense Schedule 8 products with minimal diversion to illicit uses.

[*L.C.*]*:* A NSW Cannabis Board could be set up to oversee licensing of premises and registration of individual growers. The Board could also issue certificates allowing to people to possess and purchase cannabis if they have letters from health care professionals confirming their health problem or indicating that they would benefit from using cannabis.

[*Australasian Society for HIV Medicine*]: Some HIV positive patients discuss their use of cannabis with their medical practitioners, placing these people in an awkward position.

[*PGA (NSW Branch)*]: There is no place in modern medicine for *Cannabis sativa* to be regulated as a medical product that can meet the criteria of the *Therapeutic Goods Act* (Cth). The Working Party should reject any method of delivery of *Cannabis sativa* that was not appropriately prescribed, dispensed and monitored by professionally-trained personnel.

[*RACP*]: Current data from clinical trials of cannabis are insufficient to warrant considering it drug of first choice for any medical condition. There are, however, sufficient data to conclude that some patients with certain medical conditions may benefit from using cannabis, with little risk of serious harm. Failure to relieve suffering when this is achievable is ethically questionable.

[*PLWHA*]: Cannabis for medical purposes should be accessible via a script from a GP or specialist as long as that person is a registered HIV prescriber.

[*APMA Inc.*]: Two pharmaceutical preparations, nabilone and dronabinol (Marinol), are currently available, although neither is on the Therapeutic Goods Register. Under the Special Access Scheme (SAS), these drugs could be made available on prescription to people with serious or life-threatening illnesses; except that the Commonwealth's Therapeutic Goods Regulation 12A (1) excludes drugs of abuse such as cannabis from availability under the SAS. To change this, cannabis would have to be re-scheduled under both Commonwealth and State legislation.

[*APSAD*]: Although some cannabis trials have been conducted and their findings published, there is insufficient data at present to consider cannabis as a first-line drug for any medical condition. There is, however, sufficient data to conclude that some patients with certain conditions may benefit from its use, with little risk of serious harm.

4.8 MESSAGE TO THE COMMUNITY/PUBLIC ACCEPTABILITY

[*RACP*]: The therapeutic use of cannabis in public settings, such as hospitals, in the presence of members of the public who may not approve, is an ethical issue.

[*Salvation Army*]: The potential sociological impact of using cannabis for medical purposes must be investigated, as this is likely to promote undue acceptance in the wider community.

[*CHA Inc.*]: If cannabis is approved for medical purposes, there would also need to be a education campaign to make sure that the public does not receive the wrong messages about its use.

PART TWO: MEDICAL AND THERAPEUTIC ISSUES

5 CANNABINOIDS AND ANIMAL PHYSIOLOGY

5.1 CURRENT STATE OF RESEARCH

Recent research has provided more information about the actions of cannabinoids in the human body. In particular, it has clarified how the active components of cannabis, such as THC, act on certain sites in the brain and body known as the cannabinoid receptors. Research has also identified "endogenous cannabinoids"–, cannabinoids that occur naturally in the human brain and body and act like THC to stimulate cannabinoid receptors in the brain.

These findings provide explain the psychological and physiological effects of cannabis observed in in humans, and its potentially therapeutic effects. Better understanding of the biological effects of cannabis has also led to the development of synthetic cannabinoid drugs whose effects are distinct from those of the active molecules in the cannabis plant. The account that follows is largely based on the IOM report, supplemented by recent research studies.

5.1.1 CANNABINOID RECEPTORS

The most important recent advance in understanding the biology of cannabinoids has been the identification of two types of molecular target in the human body on which the active drugs in cannabis act[61]. These are the cannabinoid receptors CB_1 and CB_2. The CB_1 receptor is found primarily in the brain and is responsible for the psychological effects of THC. The CB_2 receptor is found in the immune system[62] but its precise role remains unclear.

CB_1 and CB_2 receptors belong to a large group of G-protein coupled receptors found in the membranes of nerve cells that are involved in chemical signalling between those cells. The genetic sequences of approximately 140 G-protein coupled receptors have been discovered and the roles of around 50 of these are now known. The human genome is thought to contain approximately 1,000 genes encoding G-protein coupled receptors, which makes them one of the most important classes of proteins. Approximately 40% of all therapeutic drugs interact with this type of molecule.

The biological role of the brain cannabinoid system in humans is still being actively researched. The distribution of CB_1 and CB_2 receptors has been mapped in some detail, and the cellular functions of cannabinoid receptors are now quite well understood. The localisation of cannabinoid receptors in the brain, immune and reproductive tissues is consistent with many of their therapeutic and other effects. The sites of cannabinoid receptors include brain systems known to be involved in mood, motor control, memory formation, regulation of food intake, pain modulation and aspects of immune, and reproductive functions[63].

[61] Pertwee (1997).
[62] Munro, Thomas and Abu-Shaar (1993).
[63] Pertwee (1997) and Herkenham (1995).

One of the primary effects of cannabis in humans is, for example, disruption of short-term memory[64]. This effect is consistent with the abundance of CB_1 receptors in the hippocampus, the brain region most closely associated with memory. The effects of THC temporarily decrease neuronal activity in the hippocampus and its inputs. Similarly, pain perception is controlled mainly by nerve systems within the brain, and cannabinoids clearly play a role in the control of pain in those systems. Pain-relieving and pain-preventing mechanisms also occur in peripheral tissues, and endogenous cannabinoids appear to play a role in peripheral tissues[65].

Cell culture and animal studies have established that cannabinoids are immunomodulators, meaning that they increase some immune responses and decrease others[66]. The variable responses to cannabinoids depend on such factors as drug dose, timing of delivery, and type of immune cell examined. Large concentrations of cannabinoids affect multiple cellular targets in the immune system. Little is known, however, about the immune effects of chronic low-dose exposure to cannabinoids.

There is hope that synthetic cannabinoids, which selectively target CB_1 and CB_2, receptors or variants of these, will eventually be developed. The differences between the two receptors suggest that it should be possible to design therapeutic drugs that would act only on one or other receptor. This potentially offers a powerful method for producing biologically selective effects. In spite of the difference between the receptor subtypes, most cannabinoids in cannabis, particularly THC, bind to both CB_1 and CB_2 receptors. Some synthetic cannabinoids act preferentially at one receptor or the other, raising hopes that cannabinoid drugs with distinct therapeutic profiles can be developed. Synthetic cannabinoids have also been developed that block rather than stimulate cannabinoid receptors. The therapeutic potential of these agents is largely unexplored.

5.2 ENDOGENOUS CANNABINOIDS

The existence of a nervous system receptor for cannabis implies that there is an endogenous substance (i.e. one produced naturally) that acts on this receptor. The search for endogenous cannabinoids has yielded several compounds that act selectively on cannabinoid receptors. The best studied are anandamide and 2-arachidonyl-glycerol (2AG)[67] but their physiological roles are not yet understood. They probably perform a broad range of natural functions in the brain, which may be better understood in the next few years.

Drugs that act on the endogenous cannabinoids might have therapeutic uses. For example, drugs that selectively inhibit neuronal uptake of anandamide would increase the brain's own natural cannabinoids, thereby mimicking some of the effects of THC. A number of important psychotherapeutic drugs act by inhibiting neurotransmitter uptake. For example, antidepressants like fluoxetine (Prozac) inhibit serotonin uptake and are known as selective serotonin re-uptake inhibitors, or SSRIs. Another way to alter levels of endogenous cannabinoids would be to develop drugs that act on the enzymes involved in anandamide synthesis.

[64] IOM (1999), p. 53
[65] IOM (1999), p 53.
[66] Klein, Friedman and Specter (1998).
[67] Mechoulam, Hanus and Fride (1998); Felder and Glass (1998).

5.3 CHRONIC EFFECTS OF CANNABIS: TOLERANCE, DEPENDENCE AND ADDICTION

Many drugs produce tolerance, physical dependence, and withdrawal symptoms. These properties are common to many drugs of abuse but also to a variety of medicines. Tolerance is the most common response to repetitive use of a drug and is the condition in which, after repeated exposure to a drug, increasing doses are needed to achieve the same effect.

Chronic administration of cannabis results in tolerance to many of the acute effects of THC and cannabis in both animals and humans. Tolerance to cannabis may result from both *pharmacokinetic* changes (in absorption, distribution, metabolism and excretion of the drug) and *pharmacodynamic* changes (interactions with target cells). There is some uncertainty about the relevance of animal findings to human use given differences in route and dose. The IOM report reasoned that some biochemical adaptations to chronic cannabinoid administration may be the same in both animals and humans, but that the magnitude of those changes in proportion to the doses used would be less in humans[68].

Physical dependence on cannabinoids has been observed only under experimental conditions of "precipitated withdrawal" in which animals are first treated chronically with cannabinoids and then given an antagonist, a drug that blocks the CB_1 receptors[69]. Experimental animals generally do not self-administer cannabinoids in the way that they do highly addictive drugs like heroin and cocaine. This led to the conclusion that they were not reinforcing and rewarding but more recent studies have shown that THC can be rewarding in *mid-range* doses[70]. Low doses of THC are ineffective and high doses are aversive to animals. Physical dependence can be demonstrated in animals, but in humans the long half-life and slow elimination of THC from the body prevent most users from experiencing abstinence symptoms[71].

5.4 ACTIONS OF CANNABIS INDEPENDENT OF THE CANNABINOID SIGNALLING SYSTEM

Some effects of active compounds found in cannabis are independent of their effects on cannabinoid receptors. THC and cannabidiol, for example, can be neuroprotective through their antioxidative activity, meaning they can reduce the toxic forms of oxygen that are released when cells are under stress[72]. Other likely examples of the activity of cannabinoids on different areas are its effects on the activation of membrane-bound enzymes, arachidonic acid release, and perturbation of membrane lipids. The concentrations of THC or CBD needed to produce these effects are, however, generally much higher than those that would be achieved by smoking cannabis.

[68] IOM (1999), p.56
[69] Tsou, Patrick and Walker (1995)
[70] Lepore, Vorel, Lowinson, and Gardner (1995)
[71] IOM (1999), p. 57
[72] Hampson, Grimaldi, Axelrod and Wink (1998)

5.5 SUMMARY: CURRENT STATE OF RESEARCH

The most far-reaching recent advances in cannabinoid biology have been:

- the identification of two types of cannabinoid receptions (CB_1 and CB_2) – the CB_1 receptor is primarily located in the brain and mediates the psychological effects of THC, while the CB_2 is found in the immune system but its role remains unclear;
- the discovery of anandamide, a substance which is produced naturally by the body and which acts at the cannabinoid receptor sites, producing effects similar to those of THC.

Research has also revealed that:

- cannabinoids probably play a role in pain modulation, in memory, and movement control;
- tolerance to and dependence on cannabinoids is developed as with other drugs;
- therapeutic drugs (cannabinoids as well as non-cannabinoids) could act upon the cannabinoid system through a number of pathways in the brain.

6 THE MEDICAL VALUE OF CANNABIS AND CANNABINOIDS

When cannabinoids and cannabis are advocated for medical use it is primarily for relief of symptoms rather than to cure any underlying disease that causes such symptoms. Cannabis use is most commonly advocated for symptomatic relief of nausea, vomiting, appetite loss, and chronic pain[73].

Because cannabis has been more widely used recreationally than therapeutically much more is known about its adverse effects than its therapeutic effectiveness. Research on its therapeutic uses has also been hampered by a lack of funds and regulatory disincentives. As a consequence there is a marked contrast between the amount of basic research conducted on the biology of the cannabinoids, and the relatively small number of clinical studies of their medical efficacy.

The Working Party follows conventional medical standards in preferring evidence from randomised controlled trials (RCTs). RCTs are clinical experiments in which patients with the condition under study (e.g. chronic pain) are randomly assigned (e.g. by the toss of a coin) to receive either an active drug (e.g. THC) or an inactive comparison treatment. Ideally, the comparison drug would be a "placebo", meaning an inactive drug that was indistinguishable in appearance from the active drug. To control for any effects that THC may have on subjective symptoms like pain and nausea, the drug and placebo would be tested under "double blind conditions" (in which neither the patient receiving the drug nor the treating physician is aware of which patient received which drug). When RCTs are not possible, evidence may be accepted from "single patient" controlled trials in which treatment and placebo conditions are compared in the same patient under double–blind conditions using objective endpoints. The following analysis of the medical value of cannabis and cannabinoids is based upon material presented in the IOM report.

6.1 PAIN MANAGEMENT

Cannabinoids would have potential as an analgesic if they:

- were more effective for particular conditions than available pain-relieving or analgesic medications;
- had a broad clinical spectrum of efficacy and a unique side effects profile;
- had "synergistic interactions" with other analgesics, (i.e. enhanced the effects of other analgesic drugs when taken in conjunction with them;
- had side effects which could be useful in some situations;
- were effective among patients who had become tolerant to the effects of opioid analgesics.

Animal studies suggest that cannabinoids may be useful analgesics with mild to moderate efficacy. The CB_1 receptor acts on pathways that partially overlap with those affected by opioids but it acts through pharmacologically distinct mechanisms. This means that cannabinoids and opioids probably have different side effects and may have additive effects or act synergistically to produce analgesia.

Overall, the few controlled studies of the analgesic efficacy of cannabinoids have been inconclusive. Three experimental pain studies in humans produced mixed results[74], but they were poorly controlled so it is unclear that analgesia was produced in these paradigms. Two studies with acute clinical pain also had limitations that prevent strong conclusions from being drawn[75].

[73] IOM (1999); see Ashton (1999) for another review of the evidence
[74] Clark, Janal, and Nahas (1981); Hill, Schwin, Goodwin and Powell (1974); Libman and Stern (1985)
[75] Raft, Gregg, Ghia and Harris (1977); Jain, Ryan, McMahon and Smith (1981)

The most encouraging data on the effects of cannabinoids on chronic pain are from three clinical studies of patients with severe, persistent cancer pain that had resisted traditional analgesics[76]. These studies, which were all double blind and placebo controlled, demonstrated that cannabinoids have moderate analgesic effects equivalent to those of codeine, without its severe side effects, while improving mood, well–being, anxiety and appetite.

6.1.1 CONCLUSIONS: PAIN MANAGEMENT

As the IOM report indicated, more research is needed on the basic circuitry underlying cannabinoid analgesia and on the possibility of synergistic interactions with α_2-adrenoceptor agonists. The IOM view was that cannabinoids could improve the analgesic properties of opioids among patients in whom improved management is clearly needed. These included:

- Chemotherapy patients treated for mucositis, nausea and anorexia;
- Post-operative pain patients as an opioid adjunct to reduce nausea and vomiting;
- Patients with spinal cord injury, peripheral neuropathic and central post stroke pain;
- Patients with chronic pain and insomnia;
- AIDS patients with cachexia, AIDS neuropathy or any significant pain problem.

6.2 NAUSEA & VOMITING

Nausea and vomiting can occur under a variety of conditions but most reports of the anti-emetic effects of cannabis or cannabinoids are based on chemotherapy-induced emesis. This effect makes biological sense because there are numerous cannabinoid receptors in the brain centres that control emesis[77]. Recent animal research has provided supportive experimental evidence of the anti-emetic effect of THC[78]. There is also good clinical reason for a focus on chemotherapy-induced nausea and vomiting because it is a major side effect of treatment that can be so devastating that patients abandon therapy or suffer diminished quality of life.

Most of the studies of cannabinoids for patients receiving chemotherapy were done in the 1980s on THC, nabilone and levonantradol[79]. Many of these were poorly controlled. The cannabinoids studied showed *some* anti-emetic efficacy by comparison with the anti-emetic agents then available (viz prochlorperazine) but they were only modestly effective, typically failing to stop nausea in two thirds of patients. In one better-controlled study, THC produced complete control of emesis in 13% of case as against 47% who received metoclopramide. It achieved "major control" of vomiting (two or fewer episodes) in 27% as against 73% in the comparator[80]. The same has been true of the anti-emetic effects of nabilone and levonantradol [81].

There is weaker evidence of the antiemetic effects of smoked cannabis, and no controlled studies

[76] Noyes et al., 1975a, 1975b; Staquet, Gantt and Machin (1978)
[77] IOM (1999), p.146
[78] Limebeer and Parker (1999)
[79] IOM (1999), p.148
[80] Gralla et al., (1984)
[81] IOM (1999), p. 149

showing that smoked cannabis is superior to oral THC[82]. The most worrying side effects of THC have been orthostatic hypotension, dizziness and dysphoric effects, especially among those who have not had prior experience with cannabis.

Clinical and research interest in the anti-emetic potential of THC has declined because of the development of effective new antiemetics, which have dramatically reduced nausea and vomiting. These selective serotonin type 3 receptor agonists, such as, ondansetron, have achieved complete control over nausea induced by cisplatin in 75% of cases and up to 90% for less emetogenic chemotherapy. Side effects include headache and constipation but are generally well tolerated.

6.2.1 CONCLUSIONS: NAUSEA AND VOMITING

- Cannabinoids might have a role as adjunctive treatments that enhance the anti-emetic effects of other agents;
- They may also be useful for patients for whom current drugs have not been effective;
- The report of the US Institute of Medicine (IOM) recommended studies of the effects of adding cannabinoid drugs to other drug treatment for chemotherapy–induced emesis, particularly in persons who did not responded to standard treatments alone;
- The IOM allowed that there may be a very limited role for smoked cannabis in patients with severe nausea and vomiting who are unable to keep a pill down, but only if no alternative delivery systems were developed that produced a similarly rapid onset of the effects of THC. The antiemetic effects of cannabis could outweigh the possible harms of smoked cannabis in such seriously debilitated patients.

6.3 WASTING SYNDROME & APPETITE STIMULATION

Wasting syndrome in HIV/AIDS has been defined by the US Centers for Disease Control and Prevention as "the involuntary loss of more than 10% of baseline average body weight in the presence of diarrhoea or fever of more that 30 days that is not attributable to other disease processes."[83] Wasting can occur through anorexia (loss of appetite) or cachexia (disproportionate loss of lean body mass such as skeletal muscle). Anorexia, which may be caused by throat infections, ulcers, the adverse effects of medications, diarrhoea, neurological disease; depression, fatigue, or poverty, can accelerate wasting by limiting intake of nutrients. Cachexia is the result of tissue injury, infection or tumour.. Anorexia (starvation) can be reversed by providing food, but cachexia requires control of the underlying disease.

Despite the reported frequency of cannabis use for this purpose, little has been published about the effectiveness of either cannabis or cannabinoids for this purpose. THC in the form of dronabinol has been shown to be of benefit in short–term trials[84], and it has been registered for this purpose in the US.

High doses of megestrol acetate (Megace) - a synthetic progesterone derivative - stimulate appetite and produce weight gain in HIV/AIDS patients. THC does not appear to add to its effects[85]. Some patients

[82] Levitt et al. (1984); Vinciguerra, Moore, and Brennan (1988)
[83] IOM (1999), p.154
[84] Beal et al., (1995, 1997)
[85] Timpone et al., (1997)

do not like dronabinol because of its psychoactive side effects, the difficulty of titrating the dose, the delayed onset of effects, and the prolonged duration of the effects[86].

There are anecdotal reports of the effectiveness of smoked cannabis for the treatment of HIV/AIDS-associated anorexia and weight loss[87], but there have not been any controlled studies. A clinical trial is underway in California. A major concern with the use of smoked cannabis in HIV-infected patients is that they might be more vulnerable than other cannabis users to immunosuppressive effects of cannabis and to infectious organisms found in cannabis plant material.

6.3.1 CONCLUSIONS: WASTING SYNDROME AND APPETITE STIMULATION

- Cannabinoids may be promising agents for HIV/AIDS patients for treating the HIV wasting syndrome, nausea, appetite loss, pain, and anxiety;
- Some medications are more effective than cannabis but not equally effective in all patients;
- A rapid onset delivery system should be developed and tested in HIV/AIDS patients, for whom smoking is not recommended;
- For patients with terminal cancer, harms caused by smoking are of little consequence. For patients with terminal cancer who are suffering debilitating pain or nausea and in whom all indicated medications have failed to provide relief, the medical benefits of smoked cannabis probably outweigh the harm.

6.4 NEUROLOGICAL DISORDERS

Cannabis has been claimed to provide relief of three types of neurological disorders: muscle spasticity, particularly in MS and spinal chord injury; movement disorders such as Parkinson's and Huntington's disease and Tourette's syndrome; and epilepsy. It is not a cure for these disorders, but it may relieve some of their associated symptoms.

6.4.1 MUSCLE SPASTICITY

Muscle spasticity is the increased resistance to passive stretch of muscles and increased deep tendon muscles. Painful and debilitating involuntary contractions may occur. The main reasons for considering cannabis for this problem are numerous anecdotal reports of benefit among patients with MS and spinal cord injures (SCI). Animal studies have suggested that cannabinoids affect motor areas in the brain[88].

Multiple sclerosis

About 90% of MS patients eventually develop muscle spasticity, in the form of stiffness, spasms, cramps, aches or pain. Recent animal research found that THC reduced both tremor and spasticity among diseased mice, suggesting that the cannabinoid system may be involved in control of these

[86] American Medical Association Council on Scientific Affairs (1997)
[87] Clark (1995); Grinspoon & Bakalar (1993)
[88] Glass et al. (1997); Herkenham et al. (1991); Miller & Walker (1996); Sanudo-Pena & Walker (1997)

functions[89]. A survey of 112 MS patients[90] supported the use of cannabis for MS, and some open studies suggested it is of benefit[91]. Clinical data do not well support anecdotal evidence, but this may be due to the limitations of these studies' rather than to any limitations of cannabis' efficacy[92]. The survey results suggest that it would be useful to investigate the potential therapeutic value of cannabinoids in relieving symptoms associated with MS (this has recently been shown in animal experiments)[93], preferably using objective measures of spasticity and mild sedatives as controls to assess the sedating and spasticity specific effects of cannabinoids. The regular use of *smoked* cannabis is not advisable in a chronic illness such as MS.

Spinal cord injury

Muscle spasticity is also common SCI patients, 60% of whom are younger than 35 years and need long-term care. As with MS, surveys of these patients suggest that cannabis reduces spasticity, nausea and insomnia. The clinical data are too limited to decide whether cannabis or cannabinoids have a role in the treatment of muscle spasticity. Carefully designed clinical trials of THC need to be done, such as have been proposed in the UK[94].

6.4.2 MOVEMENT DISORDERS

Movement disorders are caused by abnormalities in areas of the brain that are connected to areas of the cortex that control motor functions. They result in abnormal skeletal muscle movements in the face, limbs and trunk. The disorders most often mentioned as candidates for medical cannabis use are dystonia, Huntington's disease, Parkinson's disease and Tourette's syndrome.

There is limited research evidence that cannabis is useful for treating movement disorders. There is evidence showing that the muscle spasms or "tics" experienced by people with Tourette's Syndrome are relieved by THC[95]. Since stress often transiently exacerbates movement disorders, the anxiety-relieving effects of cannabis or cannabinoids may help some patients with movement disorders. However, the health risks of regular cannabis smoking could be a risk for persons already suffering from chronic health conditions. Studies of animal models of the efficacy of cannabinoids on the symptoms of movement disorders would be ideal. In the absence of these, there would need to be clinical trials that include controls for the anxiety-reducing effects of cannabis.

6.4.3 EPILEPSY

There are only case reports of cannabis being used to control of epileptic seizures[96]. One observational study suggested that cannabis use was protective against seizures[97] but this study has major limitations. Most of the evidence for the anti-convulsant properties of cannabinoids concerns cannabidiol (CBD) rather than THC. The IOM concluded that clinical studies of cannabinoids in epileptics were not indicated.

[89] Baker, Pryce, Croxford, Borwn, Pertwee, Huffman and Layward (2000)
[90] Consroe et al. (1997)
[91] Clifford (1983); Petro & Ellenberger (1981); Ungerleider et al. (1987)
[92] IOM (1999), p. 161
[93] Achirona, Mirona, Lavieb, Margalitc and Biegonb (2000)
[94] SCOST (1998)
[95] e.g. Muller-Vahl, Kolbe, Schneider and Emrich (1999)
[96] British Medical Association (1997)
[97] Ng et al. (1990)

6.4.4 CONCLUSIONS: NEUROLOGICAL DISORDERS

- Studies of the therapeutic value of cannabinoids in relieving symptoms associated with MS would be useful. Regular cannabis smoking is not advisable in a chronic illness such as MS;
- Carefully designed clinical trials of THC are indicated for persons with SCI;
- For movement disorders, the most promising reports concern symptomatic treatment of spasticity, treatment of Tourette's syndrome, and perhaps cannabis' anxiety-relieving effects;
- Regularly cannabis *smoking* is not advisable for persons already suffering from chronic health conditions. Studies of animal models of the efficacy of cannabinoids on these symptoms would be useful. In the absence of these, there would need to be clinical trials that include controls for the anxiety-reducing effects of cannabis;
- Most of the evidence for the anti-convulsant properties of cannabinoids concerns cannabidiol (CBD) rather than THC. Clinical studies of cannabinoids in epileptics are not indicated.

6.5 GLAUCOMA

Elevated intra-ocular pressure (IOP) is a chronic condition that produces blindness if untreated[98]. IOP must be controlled continuously to reduce the risk of blindness. Although glaucoma is one of the most frequently cited medical indications for cannabis, evidence does not support its use with this condition. Cannabis and THC taken orally or intravenously reduce IOP by 25%[99], but the effect lasts only about three to four hours. Its effects are too short-lived, and the high doses that are required to produce them cause side effects that preclude the lifelong use of cannabis or cannabinoids to treat glaucoma[100]. The potential harmful effects of chronic cannabis smoking outweigh its modest medical benefits. A cannabinoid drug with longer lasting effects on IOP and less psychoactivity than THC could be of benefit[101].

6.5.1 CONCLUSIONS: GLAUCOMA

- The potential harmful effects of regular cannabis smoking required for a chronic condition such as glaucoma would outweigh the benefits. Cannabis is not indicated for the treatment of glaucoma;
- A longer-lasting cannabinoid drug with fewer psychoactive effects than THC might be beneficial.

6.6 INFLUENCE OF PSYCHOLOGICAL EFFECTS ON THERAPEUTIC EFFECTS

The psychological effects of THC and similar cannabinoids raise three issues for their therapeutic use. First, patients with no previous experience with cannabis may find the psychological effects disturbing. Second, in movement disorders or nausea, in which anxiety exacerbates symptoms, the anti-anxiety

[98] Alward (1998)
[99] e.g. Crawford and Merritt (1979)
[100] IOM (1999), p.174
[101] IOM (1999), p. 177

effects of cannabinoid drugs may create a false impression of the drug's therapeutic effects. Third, for cases in which symptoms are multifaceted, the combination of THC effects might provide a form of adjunctive therapy. Patients with HIV-related wasting could benefit from a medication that simultaneously stimulated appetite while reducing anxiety, pain, and nausea.

6.7 SUMMARY: THE MEDICAL VALUE OF CANNABIS AND CANNABINOIDS

- Advances in cannabinoid science suggest that there are opportunities to develop medically useful cannabinoid-based drugs to relieve:
  - pain;
  - nausea; and
  - stimulate appetite.
- In patients with HIV/AIDS or who are undergoing chemotherapy, cannabinoid drugs may provide relief for a range of symptoms that is not provide by any other drug;
- The data are weaker for muscle spasticity and movement disorders such as Tourette's syndrome, but promising;
- The least promising conditions for medical uses of cannabinoids are epilepsy and glaucoma.

7 THE RISKS OF CANNABIS USE

7.1 USE AND DEPENDENCE

Millions of Australians and Americans have tried cannabis but fewer become regular users (5% have used in the past month compared to 32% of adults in their lifetime)[102]. Recreational cannabis use is most common among 18-25 year olds, with use declining rapidly thereafter[103]. The age distribution of medical users is very different, with such use most often occurring after 35 years[104].

Anthony and colleagues[105] compared the risks of dependence on cannabis with that of other drugs by estimating the proportion of those who have ever used each drug who became dependent on it. They estimated that 9% of lifetime cannabis users were ever dependent on it. The equivalent figures were 32% for tobacco, 23% for heroin, 17% for cocaine, 15% for alcohol and 9% for tranquilliser sedatives like valium. Factors that predicted an increased risk of dependence were: being: male, being under 35 years, being white, and having another psychiatric disorder, such as, alcohol dependence, anxiety, depression or an antisocial personality disorder.

Hence, cannabis users appear to be less likely to develop dependence than users of other drugs (including alcohol and nicotine). Cannabis dependence appears to be less severe than dependence on other drugs[106]. Some adolescents and persons with psychiatric disorders are more likely than the general population to become dependent on cannabis.

7.1.1 CONCLUSIONS: USE AND DEPENDENCE

- The possibility of dependence is an important consideration when considering approval of the therapeutic use of cannabis;
- On the other hand, some controlled substances that are currently approved medications also produce dependence after long-term use;
- This issue is a normal part of patient management and does not present undue risk to them.

7.2 PROGRESSION FROM CANNABIS TO OTHER DRUGS

The pattern of involvement with recreational drug use from adolescence to adulthood is very regular. Typically, cannabis use follows alcohol and tobacco use and precedes other illicit drug use. This pattern of involvement has raised societal concerns about whether the use of cannabis encourages the use of more dangerous drugs, i.e. whether cannabis is a "gateway drug".

[102] Hall, Johnston and Donnelly (1999)
[103] Hall, Johnston and Donnelly (1999)
[104] IOM (1999), p. 93
[105] Anthony, Warner and Kessler (1994)
[106] IOM (1999), p.98

We need to distinguish two interpretations of the gateway analogy[107]. The first is the 'stepping stone' hypothesis according to which progression from cannabis to other drugs is due to the pharmacological properties of cannabis. The second is that cannabis use provides an increased opportunity to use other illegal drugs. The latter interpretation is the one favoured in the scientific literature, and it is better supported by the available data[108].

The extent of involvement with cannabis is an important predictor of progression to the use of other drugs. Daily cannabis users are more likely than their peers to be extensive users of other substances. The best predictors of other illicit drug use are: earlier first use of alcohol or nicotine, daily cannabis use, and mental health problems[109]. As the IOM report stressed, however, progression to any illicit drug use is not synonymous with heavy or persistent drug use[110].

As the IOM report stressed, data on drug use progression comes from studies of *non-medical* or recreational cannabis use by adolescents. It is unlikely that the same pattern of progression would occur if cannabis was used for *medical* purposes by adults who were over the age of 35 years.

7.2.1 CONCLUSIONS: PROGRESSION FROM CANNABIS TO OTHER DRUG USE

- Data on drug use progression comes from studies of *non-medical* or recreational cannabis use by adolescents;
- It is unlikely that the same pattern of progression will occur among persons using cannabis for *medical* purposes who are generally over the age of 35 years.

7.3 LINK BETWEEN MEDICAL DRUG USE AND DRUG ABUSE

Some opponents of medical uses of cannabis have claimed that education about the harms caused by cannabis use will be undermined if cannabis is used for medical purposes. The IOM addressed this issue by examining three types of evidence:

- experience with the medical use of opioids;
- the impact of decriminalising cannabis use on rates of cannabis use in some US states, 1973-78; and
- effects of the 1996 medical cannabis campaign on the perceived risks of cannabis use in California and other US states.

In the case of medical opioid use, the IOM argued that fears of iatrogenic addiction "have proven unfounded"[111] and that needless fear of producing addicts through medical treatment had caused "needless suffering" among patients who received inadequate medication. Very few opioid addicts begin by using prescribed opioids, and diversion of pharmaceutical opioids is not a major source of illicit opioids in the US. Medical use of cannabis, the IOM argued, was unlikely to be more of a problem than

[107] Kandel, Yamaguchi and Chen (1992)
[108] IOM (1999), p.99
[109] IOM (1999), p.100
[110] IOM (1999), p.100
[111] IOM (1999), p.102

medical uses of opioids[112].
In the case of decriminalisation, a number of studies have failed to find any impact of decriminalisation on rates of cannabis use. This includes Johnston et al's study examining the impact of decriminalisation on rates of cannabis use[113] and Model's study of cannabis mentions in DAWN emergency room data between 1975 and 1978[114]. These findings are also consistent with MacCoun and Reuter's[115] analysis of the impact of Dutch experience with decriminalisation on rates of cannabis use.

US household surveys of drug use have assessed perceived risks of cannabis use. These indicate that the perceived risk of weekly cannabis use decreased *nationally* between 1996 and 1997 but there was not any greater rate of decrease in California where proposition 200 was passed[116].

7.3.1 SUMMARY: LINK BETWEEN MEDICAL DRUG USE AND DRUG ABUSE

- Some opponents of cannabis use for medical purposes argue that this will undermine attempts to inform people of the harms associated with cannabis use. The IOM report, which examined this issues from three different angles, drew the following conclusions;
  - The medical use of *opioids* has not resulted in a large number of iatrogenically dependent persons;
  - Decriminalising cannabis use does not appear to have resulted in observable changes in the prevalence of cannabis use;
  - The 1996 Californian medical cannabis campaign was not associated with a change in voters' perceptions of the risks of cannabis that differed from US states where no such campaigns were held.

7.4 PSYCHOLOGICAL HARMS

There are a number of reasons to be wary of assuming that the heath and psychological effects of non-medical cannabis use will predict the health hazards of its medical uses:

- The circumstances in which a drug is used influence a drug's psychological effects;
- Laboratory research studies of cannabis have for ethical reasons only included participants who have had prior experience with cannabis. People who might react negatively either do not take part, or have been screened out of such studies so the incidence of adverse reactions to cannabis in naïve medical users cannot be judged from available laboratory evidence;
- Most laboratory studies have looked at the effects of single doses rather than the repeated use that would occur in the treatment of a medical condition. The laboratory studies do, however, give some indication of the possible adverse effects to assess in clinical trials.

[112] IOM (1999), p.102
[113] Johnston, O'Malley, and Bachman (1989)
[114] Model (1993)
[115] MacCoun and Reuter (1997)
[116] SAMHSA (1998)

7.4.1 PSYCHIATRIC DISORDERS

There is disagreement in the literature about whether cannabis use can produce an acute psychosis or not, but most commentators agree there is little evidence of a persistent cannabis-induced psychosis[117]. The association between cannabis and schizophrenia is not well understood. The scientific literature indicates general agreement that heavy cannabis use can precipitate schizophrenic episodes but not that cannabis use can cause the underlying disorder. People with schizophrenia or with a family history of schizophrenia are likely to be at greater risk for adverse psychiatric effects from the use of cannabis[118].

7.4.2 COGNITION

Cannabis acutely affects cognition and produces characteristic changes in blood flow to the temporal lobe. The findings of studies purporting to show dramatic structural changes in the brains of heavy uses have not been replicated with more sophisticated techniques. Recent evidence suggests that after a brief period (19-24 hours) of cannabis abstinence, long-term heavy cannabis users are relatively impaired on a cognitive task[119]. It is uncertain whether longer-term cognitive changes occur in long-term heavy cannabis users because of the difficulty in ensuring that these studies have adequately matched cases and controls prior to cannabis use[120].

7.4.3 PSYCHOMOTOR PERFORMANCE

Cannabis use affects psychomotor performance on a number of tasks. Although there are inconsistencies between studies, the functions that are most disrupted are: body sway, hand steadiness, rotary pursuit, driving and flying simulation, divided and sustained attention, and the digit-symbol substitution test[121]. There is also some evidence of "hangover" effects on the performance of pilots in a flight simulator. The cognitive impairments associated with acutely administered cannabis limit the activities that people could do safely or productively, such as driving or operating dangerous equipment.

7.4.4 AMOTIVATIONAL SYNDROME

One of the most controversial claims is that heavy cannabis use can produce an "amotivational syndrome" - a term which generally refers to "young people who drop out of social activities and show little interest in school, work or other goal directed activity"[122]. There is, however, little convincing evidence of a causal relationship between cannabis use and these behavioural characteristics.

[117] Hall (1998)
[118] Hall (1998)
[119] Solowij (1999)
[120] Solowij (1999)
[121] Hall, Solowij and Lemon. (1994)
[122] IOM (1999), p.107

7.4.5 SUMMARY: PSYCHOLOGICAL HARMS

- There is evidence to suggest that heavy cannabis use can precipitate schizophrenic episodes among persons with schizophrenia or with a family history of schizophrenia, but not cause the underlying disorder;
- There is evidence to suggest that heavy, long-term cannabis users may be subtly impaired on complex cognitive tasks;
- There is little convincing evidence that cannabis causes an "amotivational syndrome";
- Measures of mood, cognition, and psychomotor performance should be incorporated into clinical trials of the efficacy of cannabis or cannabinoid drugs;
- The psychological effects of cannabinoids, such as anxiety reduction, sedation and euphoria, can influence their potential therapeutic value. They are potentially undesirable in some patients and situations and beneficial in others.

7.5 PHYSIOLOGICAL HARMS: TISSUE AND ORGAN DAMAGE

7.5.1 IMMUNE SYSTEM

The health consequences of immunomodulation by cannabis are unclear[123]. It is not known whether cannabis smoking leads to higher rates of infections, tumours, allergies, or auto-immune responses. The problem is how to duplicate the 'normal' cannabis-smoking pattern while removing other lifestyle factors that may also have an effect, such as alcohol and tobacco use. Epidemiological studies of long-term human cannabis users are required.

7.5.2 CANNABIS SMOKE

Tobacco is a major cause of lung cancer and emphysema and cannabis smoke contains many of the components of tobacco smoke. For the same cigarette weight, as much as four times the amount of tar may be deposited in the lungs of cannabis smokers as in the lungs of tobacco smokers[124]. This is because cannabis cigarettes are usually unfiltered, cannabis smokers inhale more deeply, and they hold their breath longer than tobacco smokers. However, cannabis cigarettes are rarely packed as tightly as tobacco cigarettes, less of each cannabis cigarette is smoked, and many fewer cannabis cigarettes are smoked per day than tobacco cigarettes[125].

Habitual cannabis smoking may reduce the ability of the lung's immune system to destroy fungi, bacteria and tumour cells and to release proinflammatory cytokines[126]. All of these effects suggest that cannabis might be an immunosuppressant. If so, the respiratory risks of cannabis smoking should be seriously considered before using it in a patient with pre-existing immune deficits, such as, HIV and cancer

[123] IOM (1999), p.109
[124] Hall, Solowij and Lemon (1994)
[125] Hall, Solowij and Lemon (1994)
[126] Tashkin (1999)

patients, and patients receiving immunosuppressive therapies (for example, transplant patients)[127].

Research shows elevated rates of chronic bronchitis among cannabis smokers and suggests that tobacco and cannabis smoking have additive effects[128]. Bronchial tissue changers that have been observed in habitual cannabis smokers include reddening and swelling and increased mucus secretion (which probably explains the high rates of coughing and phlegm production in cannabis smokers). More recent studies report increased rates of cellular and molecular abnormalities in bronchial epithelium cells in cannabis smokers (with similar changes observed in smokers of 21 cannabis joints per week to those seen with 25 tobacco cigarettes per day). The rates of these changes are highest in those who smoke both cannabis and tobacco[129].

There is conflicting evidence on the effects of cannabis smoking on small airways. Bloom and colleagues[130] found impairment while Tashkin and colleagues[131] did not, at higher levels of use. As a result, the question of whether usual cannabis smoking habits are enough to cause chronic obstructive pulmonary disease (COPD) is unanswered.

Conclusions: cannabis smoking

- Chronic cannabis smoking might lead to acute and chronic bronchitis and extensive microscopic abnormalities in the cells lining the bronchial passageways, some of which may be premalignant. These symptoms are similar to those of tobacco smokers;
- The combination of cannabis and tobacco smoking augments these effects;
- It is unclear whether chronic cannabis smoking causes COPD.

7.5.3 HIV/AIDS PATIENTS

HIV/AIDS patients are the largest group to report medical cannabis use. They are immune compromised and cannabis use has been linked to progression to AIDS in HIV positive persons and to premature mortality from AIDS[132]. The IOM study group cautioned against a causal interpretation of the latter findings because potential confounding factors were not fully controlled in these studies.

It remains unclear whether cannabis smoking is an independent risk factor in the progression of AIDS in HIV positive men[133]. There was no increased risk in the Multicenter AIDS Cohort Study over 18 months[134] or in the San Francisco Men's Health Study over 6 years[135] but there was an increased risk in the Sydney AIDS Project over 12 months[136]. However, the latter result had the shortest follow up and it used an old definition of AIDS, which may have meant that many of their cases had AIDS at baseline,

127 IOM (1999), p. 113
128 Tashkin (1999)
129 Tashkin (1999)
130 Bloom, Kaltenborn, Paoletti, Camilli and Lebowitz (1987)
131 Tashkin, Coulson, Clark, Simmons, Bourque, Duann, Spivey and Gong (1987)
132 Sidney et al. (1999)
133 IOM (1999), p.p.115
134 Kaslow et al (1989)
135 Di Franco et al. (1996)
136 Tindall et al. (1988)

making this finding less reliable[137].

The greatest concerns regarding HIV/AIDS patients are the possible effects upon immune systems via direct immune suppression and exposure to an added burden of pathogens. Such patients may be vulnerable to the harms of smoking cannabis.

Conclusions: HIV/AIDS patients

- It remains unclear whether cannabis smoking is an independent risk factor in the progression of AIDS in HIV positive men;
- The causes for concern regarding medical cannabis use among HIV/AIDS patients are possible immune system effects through:
  - immune suppression by cannabis;
  - exposure to pathogens;
  - smoking as a route of administration.

7.5.4 CARCINOGENICITY

The gas and tar phases of cannabis and tobacco smoke contain many of the same carcinogenic compounds, namely, polycyclic aromatic hydrocarbons such as benzopyrene[138]. Their concentrations are higher in cannabis tar and more is deposited on the lung than tobacco tar[139]. The possible carcinogenicity of cannabis smoking is a concern but it has been difficult to collect epidemiological data on the issue because fewer people smoke cannabis and those who do may under-report their use.

Case studies suggest that cannabis smoking may contribute to the development of respiratory cancer. The most impressive finding is the over-representation of cannabis smokers among people with lung cancer and cancers of upper aerodigestive tract that develop before the age of 45[140]. Such cancers are rare before age of 60 even in tobacco smokers. This suggests that long-term cannabis smoking could potentiate other risk-factors, such as tobacco smoking, and that it may be a more potent risk factor than tobacco and alcohol use in the early development of such cancers. A recent case-control study has found an elevated risk of cancer among cannabis smokers[141].

Sidney and colleagues[142] examined rates of cancers among cannabis smokers in their mid 40s and found only an elevated risk for prostate cancer. We should beware of over-interpreting the null result for lung cancer in this study because this type of cancer requires a long exposure that few of these men had had (given that the average age at follow up was only 43 years). Cellular and molecular studies strongly suggest that cannabis smoke is carcinogenic.

[137] IOM (1999) p.116
[138] Tashkin (1999)
[139] Hoffmann et al. (1975)
[140] e.g. Taylor (1988); IOM (1999), p. 117
[141] Zhang et al. (1999)
[142] Sidney et al. (1999)

7.5.5 CONCLUSIONS: CARCINOGENICITY

There is reasonable but not conclusive evidence that cannabis causes the types of cancers that are caused by tobacco smoking. Cellular, genetic and human studies all suggest that cannabis smoke is an important risk factor for respiratory cancer. The following research would clarify matters:

- More case-control studies of the association between cannabis smoking and respiratory cancers;
- Molecular studies of respiratory cancer progression in cannabis smokers, e.g. molecular markers such as TP53, P16, NAIZ and GSTML;
- Prospective studies of populations with HIV seropositivity or a high risk of HIV infections both in existing cohorts and as part of any clinical trials of cannabis in HIV/AIDS;
- Regular recording of cannabis use by patients;
- Additional cellular, animal and human studies to investigate the effects of THC and cannabis on immune function.

7.6 CARDIOVASCULAR SYSTEM

Cannabis smoke and oral THC raise heart rate by 20-100% in 10-20 minutes after use, slowly reducing over 3-5 hours[143]. Blood pressure can increase on reclining, producing postural hypotension. Chronic oral THC reduces heart rate in humans but tolerance develops to these effects after a "few days" of frequent daily use[144]. These effects are not a health risk for healthy young recreational users but they pose a greater risk for older patients with cardiovascular disease. THC may accordingly be contraindicated in patients with cardiovascular disease who should be advised against smoking cannabis.

7.6.1 CONCLUSIONS: CARDIOVASCULAR SYSTEM

- Tolerance to the cardiovascular effects of THC develops quickly;
- However, the increases in heart rate caused by THC are of concern for patients with cardiovascular disease, who should be advised not to use cannabis.

7.7 REPRODUCTIVE SYSTEM

Animal studies show that THC inhibits reproductive functions by suppressing Leuteinising Hormone (LH)[145]. A small number of acute human studies are consistent with animal studies but studies of regular cannabis users tend not to show effects on LH, probably because tolerance develops to any inhibitory effects. Cannabis or THC could possibly decrease human fertility in both sexes in the short term. THC may also affect implantation of the embryo during early pregnancy[146]. Cannabis smoke is also likely to be

[143] Hall, Solowij and Lemon (1994)
[144] Hall, Solowij and Lemon (1994)
[145] Jackson and Murphy (1997)
[146] IOM (1999), p. 122

harmful to foetal development. Fertility and foetal development are important concerns for many younger adults but they are unlikely concern people who have seriously debilitating or life threatening diseases that occur in later life, and who use cannabis short-term for medical purposes[147].

There are few consistent findings on the effects of cannabis use during pregnancy on birth outcomes[148]. The most consistent finding has been a small reduction in birth weight, which could be due to tobacco since most of these women also smoked tobacco. The Ontario Prenatal Prospective Study has found modest and equivocal effects of maternal use on behavioural development[149] but the IOM study group was reluctant to attribute these effects to maternal cannabis use because they could be related to the reasons why the mothers used cannabis while pregnant rather than to cannabis use itself[150]. Nonetheless, smoking cannabis during pregnancy is not advisable.

7.7.1 CONCLUSIONS: REPRODUCTIVE SYSTEM

- Animal studies have shown that THC suppresses leuteinising hormone, but these findings were not replicated in studies of regular human cannabis users, probably because tolerance develops to these effects;
- There are inconsistent data on the effects of cannabis upon pregnancy, however smoking during pregnancy is not advisable.

[147] IOM (1999), p.123
[148] Cornelius, Taylor, Geva and Day (1995)
[149] e.g. Fried, Watkinson and Gray (1998)
[150] IOM (1999), p.125

7.8 SUMMARY: THE RISKS OF CANNABIS USE

- Most of the evidence on cannabis' harmful effects is based on smoked cannabis. Except for the psychoactive effects of cannabis (which are due to THC), it is not possible to distinguish the drug effects from the effects of inhaling smoke;
- The primary *acute* adverse effect of cannabis use is impaired psychomotor performance, which affects a persons' ability to safely drive or operate complex equipment;
- The immunosuppressive effects of cannabis are not well established. If they exist at all, they are probably not great enough to preclude medical use.
- The acute side effects of cannabis use are within those tolerated for other medications;
- The *chronic* effects of cannabis are of greater concern for medical use:
    - Chronic cannabis smoking increases the risk of cancers, lung damage and poor pregnancy. Smoking is not a safe route of administration for any chronic medical condition;
    - There is a small risk of dependence on THC. People most at risk are those with psychiatric disorders (including substance dependence) and adolescents with conduct or substance use problems; they should be advised against using cannabis;
- Cannabis cigarettes are not ideal delivery systems in that they deliver a variable mixture of cannabinoids as well as a variety of other biologically active substances (including possible contaminants such as fungi or bacteria);
- The available data suggest that medical use of cannabis would not be a problem if it was as closely regulated as the use of other medications with abuse potential (e.g. the opioids);
- Three factors influence the safety of cannabis or cannabinoid drugs for medical use: the delivery system, the use of plant material, and the side effects.
    - *Smoking as a delivery system for cannabis* is undesirable as it is clearly harmful, especially in people with chronic conditions;
    - *Cannabis plant material,* because of its uncertain composition and hence equally uncertain effects, is an undesirable form of medication.
    - *Side effects of cannabinoid drugs* are within the acceptable risk associated with approved medications – in fact, some of the side effects, such as anxiety reduction and sedation, might be desirable for some patients. As with many medications there are people for whom they would probably be contraindicated.
- Studies of the individual health risks of *smoking* cannabis should be conducted, particularly among populations in which cannabis use is prevalent.

8 THE DEVELOPMENT OF CANNABINOID DRUGS

The future medical uses of cannabinoids lie in pharmacological drug development in which the chemical structures of cannabinoids are manipulated to design better therapeutic drugs. Several new cannabinoids have been developed for human use but none has yet reached the stage of human testing. Any new drug has to clear a number of hurdles before it is registered. The regulatory and marketing experiences of dronabinol in the US suggest that these barriers may be substantial for therapeutic cannabinoid drugs and even greater in the case of using the cannabis plant for medical purposes. Given the prominence of US pharmaceutical research and the size of the American drug market, the US regulatory process has a large impact on drug development. US regulatory experiences also provide a useful indication of how difficult it may be to develop and obtain regulatory approval for new medical cannabinoid drugs in Australia.

8.1 US FEDERAL DRUG DEVELOPMENT POLICY

Two US Federal agencies regulate controlled substances for medical use: the Food and Drug Administration (FDA) and Drug Enforcement Agency (DEA). The FDA is responsible for the regulation of human testing and the introduction of new drugs into the market place. The DEA determines the schedule and establishes production quotas to prevent diversion of drugs with a potential for abuse. In the US, cannabis is a Schedule 1 drug, meaning that it is classified as a drug with no medical uses and a high abuse potential; consequently, the DEA is involved in the regulatory process. This adds considerable complexity and expense to clinical research on the therapeutic uses of cannabis[151].

FDA approval of a drug often takes over a decade and the pre-clinical and clinical research required to obtain approval cost pharmaceutical companies substantial sums. The National Institute of Health may sponsor drug development programs to stimulate development and marketing in the private sector, e.g. drugs for HIV, cancer, addiction and epilepsy.

The following stages describe the process of developing a new drug and obtaining regulatory approval to market it:

- discovery, synthesis and purification of a substance with biological activity and possible therapeutic value;
- animal testing for safety and efficacy and possible human utility ('preclinical phase');
- Investigational New Drug Application (NDA) to undertake human clinical trials.

These three stages take an average of 5 years but this may vary with the complexity of the drug, the availability of patients for clinical trials, the typical duration of use of the drug and the ease of measuring its therapeutic effects. For every drug that reaches clinical testing, thousands are synthesised and tested. Only one in five that are clinically tested secures FDA approval for marketing through an NDA[152].

An NDA requires clinical data as well as information on chemistry, manufacturing and controls, pharmacology and toxicology, human pharmacokinetics and bioavailability. In the case of new cannabinoids an NDA would also require an assessment of "abuse liability". In 1996, the median time for FDA review of an NDA was 15 months. According to the IOM, the estimated cost of a developing

[151] IOM (1999), p.194
[152] IOM (1999), p.195

and eventually marketing a single drug is in the range of US $200 - $350 million[153].

When the FDA approves an NDA for a new drug, the manufacturer can only market the drug for the "approved indication". Any physician is free to prescribe the drug for other indications ("off label use") but the company cannot market it for any such use unless it submits an "efficacy supplement" to obtain approval for the new indication. This process costs of the order $10 - $40 million in additional clinical research and compliance with the regulatory process. A new formulation of a drug that has been previously approved drug requires separate approval. The company needs to establish the bioequivalence, safety and efficacy of the new and existing formulation. This type of approval would, for example, be required for an inhaled form of Marinol.

FDA also has an Orphan Drug program that provides incentives to manufacturers to develop drugs to treat "orphan diseases", diseases that affect 200,000 or fewer people in the US. This program could be used to obtain approval for using cannabinoids to treat Huntington's Disease, MS and SCI. It could also be used to obtain approval to treat subpopulations of patients with more prevalent diseases, e.g. patients with Parkinson's disease and early moving motor dysfunction.

The FDA Treatment-IND program (set up in 1987) allows patients "with serious and life-threatening diseases to obtain experimental medications, such as cannabis, before their general marketing"[154] but only if that no other comparable drugs are available.

8.2 DRUG ENFORCEMENT AGENCY

The DEA controls substances with a potential for 'abuse', which is defined "as nonmedical use that leads to health and safety hazards, diversion from legitimate channels, self-administration, and other untoward results"[155]. Schedule I includes drugs that have "no accepted medical use" and "high abuse potential"; Schedule II is the most restrictive category for drugs that have an accepted medical use. The DEA makes its decision on the schedule in which a drug should be classified on the recommendation by the Secretary of Department of Health and Human Services (DHHS). This recommendation is based on *in vitro* human and animal studies, including animal studies of drug self-administration and drug discrimination. The DEA usually accepts the recommendation of the DHHS.

Cannabis and THC are included in Schedule I, as are any cannabinoids found in the plant, and any "similar" synthetic cannabinoids. Investigators who wish to study natural cannabinoids have to submit their research protocols to DEA for approval. This does not necessarily apply to cannabinoids that are not found in the plant, although their future status depends upon their chemical and pharmacological relationship to THC, and their abuse potential.

Pharmaceutical firms regard scheduling as a major limitation on their ability to market a drug. Scheduling: restricts access to the drug; deters physicians from prescribing it; stigmatises the drug; adds expense in the form of abuse liability studies; and federal and state scheduling processes may delay the drug's arrival on the market.

[153] IOM (1999), p.197
[154] IOM (1999), p.198
[155] IOM (1999), p.198

8.3 DEVELOPMENT AND MARKETING OF MARINOL

Marinol is the trade name for dronabinol, a synthetic form of THC. The preclinical and clinical research on Marinol for the treatment of nausea and vomiting in cancer chemotherapy was primarily supported by the US National Cancer Institute, with 25% of costs contributed by Unimed, the pharmaceutical company that now markets it. Approval of Marinol's use in HIV-related wasting required two additional Phase III clinical studies that took 3 years and cost $5 million[156].

Marinol is synthesised in the laboratory rather than extracted from the *Cannabis sativa* plant. It is delivered via a capsule in which THC is dissolved in sesame oil. Only 16-20% of an oral dose of THC reaches the circulation; the onset of effects is slow; and peak plasma levels are not reached for 2-4 hours[157]. Its common side effects include: anxiety, depersonalisation, dizziness, euphoria, dysphoria, sleepiness and abnormal thinking. These affect about a third of patients but only a small proportion stop using it as a result[158].

Marinol was placed in Schedule II - medically approved but with "high potential for abuse". Unimed asked for it to be rescheduled to schedule III - drugs with "some potential for abuse" - on the grounds that there is no evidence of abuse or diversion, and it is unlikely to be abused because of its slow onset of action and dysphoric side effects. Unimed estimate that a less restrictive schedule for Marinol would lift sales by 15-20% by reducing paperwork and regulatory disincentives to prescribing[159]. In July 1999, dronabinol was re-scheduled by the DEA with the support of the FDA and NIDA from Schedule II to Schedule III (C-III) on the basis of evidence of low abuse liability[160].

Annual sales of Marinol are estimated to be $20 million in the USA, with 80% of use by patients with HIV, 10% by patients undergoing cancer chemotherapy and 20% by patients using it for off-licence reasons, including anorexia and disturbed behaviour in Alzheimer's disease. Approval of its use for HIV expanded its market, which had been shrinking as more effective anti-emetic drugs become available for cancer patients undergoing chemotherapy. Much of its recent market growth has been among HIV patients who are receiving combination anti-retroviral therapy, to stimulate appetite and reduce nausea and vomiting.

Unimed gained orphan status on Marinol for 7 years (from 1992) for use in anorexia associated with HIV. They have a use patent on its use in Alzheimer's disease. According to Unimed, the main rate-limiting factors in the market growth of Marinol are a lack of awareness among physicians of the drug's efficacy, its adverse effects, and its restricted availability.

Unimed applied for an IND in 1998 to develop new formulations that would deliver Marinol to the circulation more rapidly and directly. These include: deep lung aerosol, nasal spray, nasal gel, and sublingual preparation. Inhalation is considered the most promising method, owing to the rapid onset of effects and potential for better dose titration by the patient. It may, however, also carry an increased potential for abuse. Transdermal administration works best for hydrophilic drugs rather than lipophylic ones like THC. The estimated cost of approving a new formulation is estimated to be $7-10 million[161].

Advocates of medical cannabis argue that smoked cannabis is much less expensive than Marinol. The IOM study group suggested that this is true only if one ignores the costs of engaging in a criminal act

[156] IOM (1999), p.203
[157] IOM (1999), p.203
[158] IOM (1999), p.203
[159] IOM (1995)
[160] Federal Register: July 2, 1999, Volume 64, number 127, pp 35928-35930
[161] IOM (1999), p.206

and the risks of poor quality control. Marinol costs $200 a month for treating HIV but it is less expensive when used for short-term periods in cancer chemotherapy. Both costs are reduced by health insurance reimbursements. The estimated cost of cannabis at $2-16 per gram via buyers' clubs means that Marinol is less expensive than smoked cannabis if patients smoke two or more joints per day[162].

8.4 MARKET OUTLOOK FOR CANNABINOIDS

The decision to launch pre-clinical research and clinical trials is dictated by a drug company's judgment about whether there will be an adequate return on investment. The R&D costs of cannabinoids are likely to be similar to those of neuropharmaceuticals and anti-inflammatory drug, two drug categories with the highest R&D costs. There will also be the additional costs of meeting DEA regulatory requirements.

The potential market for cannabinoids is influenced by the current and projected patient prevalence, the sales of existing drugs, the availability of competing products, and the duration of disease (e.g. disease with an early age of onset and a need for long term use). Factors that affect market return include the company's ability to patent the drug, the availability of other forms of market protection, access to health insurance reimbursements, restrictions on access because of drug scheduling, social attitudes towards the drug, its adverse effect profile, and its interactions with other drugs. Naturally occurring substances such as THC cannot be patented; only new cannabinoids can be patented.

The IOM identified five cannabinoids that were under development, most of which were at the pre-clinical phase. This included THC administered by different routes and the use of the cannabis as a botanical plant. There may be other cannabinoids under development that have not been made public.

The IOM made three points about these cannabinoids:

- virtually all were being developed by individuals or small pharmaceutical companies, suggesting it is a commercially risky venture;
- no plant component other than THC was being developed by a pharmaceutical company, probably because of concerns about their Schedule I status and the fact that it would not be patentable (although orphan drug status could be given);
- some cannabinoids were being developed for neuroprotection.

According to the IOM the market prospects for new cannabinoids are difficult to assess. Only one (dronabinol) has been marketed and its market is modest. The experience of those being developed will affect future efforts, but at the moment development appears to be high risk.

Cannabinoids may be developed for profitable markets that reflect large unmet medical needs, especially its use for pain management. Cannabinoid antagonists and inverse agonists may also have some therapeutic potential. They would not be schedule I drugs because of their low abuse potential. They could, in principle, improve memory, stimulate immune response, and suppress appetite and anxiety, all of which are impaired by THC.

[162] IOM (1999), p.207

8.5 ROUTES OF ADMINISTRATION OF CANNABINOIDS

8.5.1 PRESENT DELIVERY SYSTEMS

Most recreational cannabis users smoke the dried plant. This produces uncertain dosage because of the variable amounts of THC in the cannabis preparation and variations in the way the preparation burns and is smoked. The products of smoking are deleterious to health, and smoking is not an acceptable method of drug delivery for some people. Any medical use of cannabis requires the development of a rapid-onset, reliable, and safe delivery systems without the adverse effects of smoking. Claims that these systems are "close to being developed" are incorrect.

Direct drug delivery methods (e.g. via injection into the brain and spinal cord) place the drug directly where the intended receptors are located. *Indirect* delivery methods involve absorption into the blood, for blood-borne delivery to the intended receptors. Although direct routes have been useful in animal laboratory research, no direct delivery system is presently realistic in humans. Indirect systems include intravenous administration, transpulmonary (inhalation) administration, and oral and rectal administration. Direct routes of administration make selection drug action possible, but the cost of greater invasiveness. Indirect routes are much less invasive but they treat the whole body making it difficult to obtaining therapeutic effects without side effects. At present, the main feasible indirect delivery methods to humans are inhalation by smoking, intravenous injection (for research purposes), and oral and rectal administration.

Lungs absorb THC very rapidly when cannabis is smoked, although the amount absorbed varies according to smoking style. There is further variation when the larger inhaled aerosol particles are absorbed from other parts of the respiratory tract and swallowed. There is a brief but significant lag between smoke inhalation and perceived effect. This delay, which is caused by the variations in the rate of absorption and the speed with which cannabinoids are carried to their receptors, makes it difficult for users to titrate their doses to obtain the desired effect. Controlled delivery by inhalation from the range of high-tech devices and intranasal sprays now being used for other drugs (e.g. for asthma and pain) is not presently feasible with THC because of its chemical characteristics – principally its lack of water solubility and resinous nature.

It is simple to administer most drugs orally but, anatomically and physiologically, this is the most complex method of administration. In the case of THC, however, with its uncertain and low bioavailability and slow absorption, oral administration does not allow patients to adjust their dosage rapidly and reliably, and so achieve for the desired effect with least side effects. Sublingual and buccal THC lozenges are not presently feasible and, without significant improvements in formulation, are unlikely to be better than oral administration.

Rectal administration of THC gives greater bioavailability than oral administration, but with even slower absorption. While this method may be a suitable for maintaining the effect over long-term administration, it is generally less acceptable to Australian patients than most other routes.

Because THC is widely distributed in body tissues, with extensive uptake in fatty tissues, low levels persist over a prolonged period. This property also makes improbable that it can be efficiently delivered by a "skin patch" formulation, although newer technology using iontophoresis (or electroporation) may be more useful.

At the present state of (public domain) knowledge, aqueous solutions are normally required for the novel

dosage forms that have been suggested for cannabis and/or THC. Making a drug, such as a cannabinoid, intrinsically water soluble involves a number of chemical synthetic steps – typically making a salt through incorporation of an ionising functional group such as an acid or an amine, either with or without a prodrug strategy. The alternative is to make a cannabinoid preparation solution e.g. by cyclodextrin complexation or dispersion through manipulation with pharmaceutical additives.

8.5.2 FUTURE POSSIBILITIES

A number of companies that produce innovative dosage forms of drugs have been asked for their views on possibility of developing a cannabinoid preparation that would retain the benefit of rapid absorption offered by smoking without its adverse effects. Most believed that such a development was possible but that it would take a considerable time, especially if new cannabinoids were involved. They were not convinced that the financial incentives were sufficient to undertake the development work without significant seeding funds.

Two issues were raised: the preferred drug for delivery; and the mode of delivery. The preferred drug on present knowledge is THC. The best route of administration (and thus relevant formulation) is less certain.

Some companies have developed sophisticated forms of transpulmonary delivery using breath activated systems that allow rapid titration of dose to response. However, these require aqueous drug solutions, which precludes THC. An alternative technology could be used to generate aerosol by ultrasonic or jet energiser using cannabinoids in suspension or dispersed in an aqueous matrix. Even if such a development plan was successfully undertaken by a major company, the end cost of such a sophisticated device is likely to be too high for the target patient population.

Sublingual and buccal drug administration could be developed pharmaceutically from drug suspension or nonaqueous medium, although models for these dosage forms are normally based upon solutions. Both rectal and passive transdermal administration are unlikely ever to fulfil the need for rapid titration of dose to effect. Active (iontophoretic or electroporation) transdermal systems may be successful as these have been used with large molecules, including hydrophilic proteins.

Although there is still much work to be done, success could lead to the development of new methods for administering cannabinoids to patients for therapeutic purposes and to significant gains in intellectual property.

At this stage there are no feasible, reliable and inexpensive methods for delivering cannabinoids and effectively titrating dose to response.

In terms of future long-term development, further experimentation is needed into:

- making cannabinoids more water soluble;
- determining the intrinsic pharmacological and cannabinoid receptor binding actions of any new derivatives;
- determining whether the actions of the derivatives is due to biodegradation to their parent cannabinoids;
- examining their potential for innovative delivery, e.g. by aerosols into the lungs or by iontophoresis, using relevant animal models,
- evaluating any promising new cannabinoids and their routes of delivery in human subjects under controlled conditions, in the usual manner for early drug development.

This would require a significant program of experimentation that would require major sponsorship from the National Health and Medical Research Council with a pharmaceutical industry partnership.

For the immediate future, it would seem that an ultrasonic nebulizer, invented locally, has great promise. Any development-application from government sources would be well-placed in this area, especially if they also funded local development of more water soluble cannabinoids. Relatively inexpensive research could also be done into formulating cannabinoid suspensions into solid lozenge dosage forms that might be suitable for buccal or sublingual routes. Appropriate research skills are available locally and the requisite funding is within the reach of the State government sources with or without pharmaceutical industry partnership. In any event, monitoring of international research and collaboration with groups working on these issues in other countries should be fostered.

8.6 REGULATION OF AND MARKET OUTLOOK FOR CANNABIS

In the US, there are two IND for clinical studies of cannabis in the treatment of HIV anorexia and of migraine. Anyone wanting to do clinical research on cannabis has to obtain DEA approval and obtain supplies of cannabis from NIDA. Both can be obtained if the study is funded by an NIH approved grant. A major obstacle to marketing cannabis is having a sponsor with sufficient resources to meet the requirements of FDA and DEA. While in principle a botanical product like cannabis could get FDA approval in oral form as a dietary supplement, in fact, DEA is only likely to approve a new drug[163].

Bringing cannabis to market as a new drug is uncertain for at least three pharmacological reasons: it is a botanical product, it is smoked, and it is a drug with abuse potential. Plants are more difficult to bring to market than pure chemical products because of concerns about product consistency, uncertain potency of the active ingredients, microbiological and other contamination, and the stability of active and inactive ingredients over time.

A handful of botanicals (digitals, psyllium and senna) are still on the market but all were registered before the introduction of current regulatory standards, which they would not meet. The fact that cannabis is smoked poses a major additional regulatory challenge because of the health risks of smoking. The use of alternative systems, such as vaporisers, would relieve though probably not eliminate the problem.

The regulatory hurdles to market posed by the Controlled Substances Act are not insurmountable. Cannabis would have to be rescheduled by the DEA as having "accepted medical use", namely, that "the drug's chemistry must be known and reproducible, there must be adequate safety studies proving efficacy, the drug must be accepted by qualified experts, and the scientific evidence must be widely available."[164]. If cannabis was rescheduled it would have to be to Schedule II because the Single Convention on Narcotic Drugs restricts its classification to this category.

Assuming all these hurdles can be cleared, there remain formidable problems in finding a market for medical cannabis. There is the typical $200-$350 million costs of new drug development, the additional cost of meeting the tougher standards for botanicals, and the DEA requirements for a controlled substance. Experience with development and marketing of dronabinol may reduce some of these problems but the cannabis plant is not a patentable product.

[163] IOM (1999), p.215
[164] IOM (1999), p217

8.7 SUMMARY: THE DEVELOPMENT OF CANNABINOID DRUGS

- Cannabinoids are an interesting group of compounds with potential therapeutic applications;
- There is a surge of scientific interest in their development but the road to market for any new drug is likely to be expensive, long, risky, and studded with obstacles. Experience with dronabinol is atypical because of the US government's heavy investment in its R&D;
- The development of medical cannabinoids is likely to be risky judging by the paucity of products in development and the small size of the firms sponsoring them;
- The market outlook in the US is not favourable for medical approval of the cannabis plant or the compounds contained within it. Commercial interest in bringing them to market appears nonexistent, probably because they are placed automatically in the most restrictive schedule;
- It does not currently appear feasible that there exist alternative routes of administration of cannabinoids that would be reliable and inexpensive, which would eliminate the use of smoked cannabis while making dose titration easier;
- Further research is needed into:
    - making cannabinoids more water soluble;
    - examining the consequences of water solubility on the actions of these derivatives at receptors;
    - determining whether the actions of these derivatives is due to their biodegradation to their parent cannabinoids;
    - examining their potential for innovative delivery;
    - evaluating novel cannabinoids and/or their routes of delivery in human subjects under controlled conditions.
- Locally invented nebulisers and inhalers hold great promise; any development-application funds arising from government sources would be well-placed in this area;
- Research into sublingually-administered lozenges may also be promising, and deserve further investigation.

PART THREE: LEGAL AND REGULATORY OPTIONS

This section explores the legal issues raised by the report's recommendations concerning the use of cannabis or cannabinoids for medical purposes in New South Wales. The question of medical use is quite separate from issues such as decriminalisation or legalisation for non-medical use; these were not considered by the Working Party.

Decisions concerning the medical use of cannabis and cannabinoids must be based on sound scientific evidence of their therapeutic value. The first part of this report has provided the basis upon which such decisions can be made. This second part considers various legal and regulatory models for facilitating both the therapeutic use of cannabis and the performance of therapeutic trials for selected medical conditions. The objective was to explore and develop models, which would permit the use of cannabis and cannabinoids for therapeutic purposes and scientific trials in New South Wales, without contravening any existing legislative and regulatory requirements.

9 INTRODUCTION

Cannabis is a prohibited drug in all States and Territories in Australia. Before examining in detail the various proposals for regulating the medical use of cannabis, it is first necessary to consider what legal constraints might be imposed upon such action by international law. Australia's domestic drug laws are influenced, and to some extent determined, by the obligations set out in international conventions to which Australia is a party. This is why the requirements of international drug conventions can limit the range and scope of legal strategies available for dealing with the medical use of cannabis.

This section of the report identifies the key international drug conventions to which Australia is a party, as well as the obligations and limitations these conventions place on our drug related laws. The underlying assumption is that it is desirable for any legislative scheme dealing with the use of cannabis or cannabinoids for medical purposes in New South Wales to comply with Australia's obligations under international law.

Although these conventions aim to eliminate the use of illicit drugs, they also recognise that some of these drugs can be useful for medical and scientific purposes. Further, to use cannabis for research and clinical purposes would not place Australia in breach of any its international treaty obligations. In some participating States, for example the UK, it is lawful to possess cannabis and most of its derivatives for the purposes of medical research. The definition of "medical and scientific purposes" may be considered sufficiently broad to allow the prescription of cannabinoids and/or the certification of cannabis use for the treatment of certain medical conditions.

9.1 INTERNATIONAL CONVENTIONS GOVERNING MEDICAL USE OF CANNABIS IN AUSTRALIA

Until 1900, there were very few legal controls on the sale and use of drugs in Australia, including cannabis.[165] The classification of cannabis as illegal in Australia is due, in part, to international efforts to control the production of opium. This, in turn, marked an international trend towards drug prohibition. The Hague Convention of 1911-12 confined the use of opium, cocaine, morphine and heroin to that required for medical purposes; the Geneva Conventions of 1925 and 1931 added cannabis to the list of illegal substances.[166] Collectively, these international instruments established the framework for Australia's future drug laws.[167] They prohibited the non-medical use of cannabis and so, in 1926, the Australian government elected to control cannabis importation under the *Customs Act 1901*.[168] Legislation was subsequently enacted in the various States to prohibit the unauthorised use of cannabis.[169]

Domestic drug laws worldwide are the result of eleven International Conventions. At this time, the drug conventions ratified by Australia and affecting our domestic drug laws are the United Nations Single Convention on Narcotic Drugs 1961, the United Nations Convention on Psychotropic Substances 1972, and the United Nations Convention Against Illicit Traffic in Narcotic Dangerous Psychotropic Substances 1988.

States which are signatory to international conventions have an obligation to ensure that their domestic laws are consistent with the requirements of those conventions. In Australia, where the Commonwealth Government alone signs the conventions, following consultation with the States and Territories, their provisions do not automatically become part of domestic law unless carried into effect by legislation. This often requires individual States and Territories to implement their own complementary legislation. Generally, as a matter of principle, States and Territories comply but they are not expressly prevented from passing or retaining inconsistent laws. It is, therefore, the responsibility of the Commonwealth Government, which has the power under section 109 of the Australian Constitution to override an inconsistent State or Territory law to ensure nation-wide implementation of these agreements.

The following international agreements to which Australia is signatory, affect the use of cannabis for medical purposes.[170]

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165 G Griffith and M Swain, *The Medical Use of Cannabis: Recent Developments*, NSW Parliamentary Library Research Service, Briefing Paper No 11/99 p.31

166 Kyriangis M, "Marijuana – Just What the Doctor Ordered? A Review of the Medico-Legal and Political Debate in the United States of America on Medicinal Use of Marijuana and Implications for Australia", 20(3) UNSWLJ 594 at 634.

167 G Griffith and M Swain, *The Medical Use of Cannabis: Recent Developments*, NSW Parliamentary Library Research Service, Briefing Paper No 11/99 p.31.

168 Ibid.

169 Victoria in 1927; South Australia in 1934; New South Wales in 1935; Queensland in 1937; Western Australia in 1950; and Tasmania in 1959.

170 The following section concerning international conventions is informed by and based on the analysis of J Norberry, (1991) "Legal Issues" in *Feasibility Research and the Controlled Availability of Opioids, Volume 2, Background Papers*, National Centre for Epidemiology and Population Health, Australian National University, Canberra, pp.87-115.

9.1.1 UN SINGLE CONVENTION ON NARCOTIC DRUGS 1961

The United Nations Single Convention on Narcotic Drugs sought to codify all existing conventions, and the obligations of signatory states under the provisions of those conventions. Australia ratified the Single Convention on 1 December 1967. Other countries whose drug policies may be of interest have also ratified the Convention. The United Kingdom ratified on 2 September 1964, Canada on 11 October 1961 and the Netherlands on 16 July 1965.

The Convention "replaces the eight treaties that had previously regulated international dealings in drugs".[171] Its objectives of confining the use of controlled drugs to medical and scientific purposes are achieved by restricting the production of "narcotic drugs" to the assessed requirements of member countries, and by establishing controls to eliminate diversion of legal supplies to the illicit market. The earlier assessment system has been retained and operates under the supervision of the International Narcotics Control Board (INCB).[172] This system requires Governments to estimate annually the amount of narcotic drugs that will be needed to satisfy all medical and scientific requirements in the country for the next year. The INCB evaluates, confirms and publishes the amount of narcotic drugs for each government. Each government may then manufacture or import narcotic drugs within that amount, and distribute them to medical facilities for the treatment of patients. Governments are obliged to adhere to their estimates and to provide annual reports on quantities of drugs required and used.[173] If, however, there are unforeseen increases in medical demand, governments may submit supplementary estimates to the Board at any time. These requests are treated expeditiously.

Narcotic drugs are listed in Schedules to the Convention. Schedule I includes the major opioids plus cocaine and cannabis. Schedules II and III contain less powerful opioids such as codeine. Schedule IV contains drugs considered as having particularly dangerous properties. Cannabis is also included in Schedule IV where drugs are subject to all the control measures specified by the Convention for Schedule I drugs. In addition, Article 2(5) requires that:

> *(a) A Party shall adopt any special measures of control which in its opinion are necessary having regard to the particularly dangerous properties of a drug so included; and*
>
> *(b) A Party shall, if in its opinion the prevailing conditions in its country render it the most appropriate means of protecting the public health and welfare, prohibit the production, manufacture, export and import of, trade in, possession or use of any such drug except for amounts which may be necessary for medical or scientific research only, including clinical trials herewith to be conducted under or subject to direct supervision of the Party.*

Although cannabis is included in Schedule IV of the Convention, the additional controls set out in Article 2(5) are only to be adopted if, in the opinion of the Party, they are deemed necessary. In sum, these additional controls are not mandatory. The kind of controlled availability of cannabis proposed in this report (i.e. one that recognises the need for precautions in relation to non-medical uses) should comply with the "special measures of control" referred to in Article 2(5)(b).

[171] Royal Commission into the Non-Medical Use of Drugs in South Australia (1979) *Final Report,* p.225.
[172] Ibid.
[173] Ibid.

Two additional provisions are of central importance in understanding the effect of the Single Convention upon the formulation and content of Australia's national drug laws. These are:

- Article 4, which contains a so-called "general obligation" upon States to "… take such legislative and administrative measures as may be necessary…to limit exclusively to *medical and scientific purposes* the production, manufacture, export, import, distribution of, trade in, use and possession of drugs" (italics added). This provision applies to cannabis.
- Article 36, which requires States to treat as "punishable offences" specified conduct with respect to certain drugs contrary to the convention. "Specified conduct" includes the "possession" but not the use, of drugs. This provision also applies to cannabis.

It is clear from the record of proceedings that the conference on the Single Convention intended:

- each State to decide for itself, in light of the views of the medical profession, whether a particular substance should be completely prohibited;[174]
- States to have the widest possible freedom in the treatment of patients and in the prescription of drugs;[175] and
- that the safeguards to be adopted should be decided by each government based on general health interests.[176]

There remains, however, some contention about the precise requirements of the principal drug conventions. The meaning of the term "for medical or scientific purposes", for example, is not defined. In the circumstances, these words should be given their ordinary meaning in the context of the overall aims and objectives of the conventions. The spirit and intention of the drug conventions is to eliminate the illicit availability of narcotic drugs in the community. Any interpretation of the term "medical and scientific purposes" is limited by the fact that the "purposes" must be compatible with the stated aims and intentions of the conventions.[177]

To avoid international condemnation, any proposed therapeutic use of cannabis must be clearly and unequivocally "medical and scientific".[178] Research indicates that cannabis and cannabinoids may alleviate symptoms of a wide range of health conditions, such as HIV-and cancer-related wasting, pain unrelieved by conventional treatments, some neurological disorders, and nausea/vomiting in some cancer patients undergoing chemotherapy. Australia would need to demonstrate that any proposed legislation or administrative action was compatible with its obligations under the international drug conventions to which it is party.

In short, the conventions recognise the need to use narcotic drugs for medical purposes and the meaning of "medical and scientific" purposes is sufficiently broad to encompass the prescription or certification of cannabis for the treatment of medical conditions. The primary aim of the conventions is, however, to limit the use of narcotic drugs in the community. Consequently, any proposals for using cannabis or cannabinoids for medical purposes must be grounded on evidence of their therapeutic value; otherwise they risk being seen as "back door decriminalisation".[179]

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[174] United Nations Conference for the Adoption of a Single Convention on Narcotic Drugs: Official Records, Vol. I, document E/CONF.34.24., per Mr HS Warren (Australia) p.17.
[175] Ibid., per Mr JH Koch (Denmark) p.11.
[176] Ibid., per Mr JH Koch (Denmark) p.11.
[177] Gowing L, Ali R, Christie P, and White J, (1988) *Therapeutic Uses of Cannabis*, Drug and Alcohol Services Council, South Australia, University of Adelaide, p.16.
[178] Ibid. At p.17.
[179] Ibid. At p.17

Another dilemma posed by the requirements of the Single Convention is whether States are obliged by Article 36 to apply penal sanctions for unauthorised personal use/possession. It is arguable that States are not bound to apply penal sanctions to such conduct because Article 36 is concerned solely with conduct relating to trafficking and so the reference to "possession" is relevant only to possession for the purposes of distribution, not personal use.[180] Even if a wider interpretation of Article 36 is applied, States are not required to impose mandatory penal sanctions. They may instead impose minor penalties, such as fines or censure, (e.g. the expiation fee approach adopted in South Australia and the Australian Capital Territory).[181]

9.1.2 UNITED NATIONS CONVENTION ON PSYCHOTROPIC SUBSTANCES 1972

This treaty came into force in Australia on 17 August 1982 and was ratified by Canada on 9 December 1988. Its provisions are essentially administrative. The main purpose of the treaty is to supplement the international system of controlling the legal manufacture and distribution of psychotropic substances. The penal provisions (Article 22) are of relatively minor importance. Delta-9-tetrahydrocannabinol (e.g. dronabinol) is listed as a psychotropic substance under Schedule II of the Convention, to which certain measures of control apply (e.g. possession permitted only under legal authority).

9.1.3 UNITED NATIONS CONVENTION AGAINST ILLICIT TRAFFIC IN NARCOTIC DRUGS AND PSYCHOTROPIC SUBSTANCES 1988

This convention was ratified by Australia on 16 November 1992; by Canada on 5 July 1990; by the United Kingdom on 28 June 1991; and by the Netherlands, with some reservations, on 8 September 1993.

The 1988 convention requires participating states to prevent the illicit cultivation of plants containing narcotic or psychotropic substances. The cannabis plant is expressly included.[182] Further, the convention clearly distinguishes between possession for the purposes of trafficking, and possession for personal consumption.

Article 3 obliges parties to adopt whatever measures are necessary to criminalise the following activities which are "contrary to the provisions of the 1961 Convention as amended…": production, manufacture, distribution, sale, importation, exportation, and possession for personal consumption of narcotic drugs and psychotropic substances. Article 3(4)(d) permits treatment, education, after-care, rehabilitation or social re-integration as an alternative (or in addition) to conviction or punishment for offences involving possession, purchase or cultivation for personal use, regardless of the seriousness of the offence.[183]

[180] Ibid. At p.16
[181] Ibid, p.16
[182] Advisory Committee on Illicit Drugs, *Cannabis and the law in Queensland – A Discussion Paper*, July 1993, at 27.
[183] Woltring H, (1990) "Examining existing drugs policies: The 1988 UN Convention – Help or Hindrance", *Criminology Australia*, April/May, pp.19-20.

9.1.4 CONCLUSIONS: INTERNATIONAL CONVENTIONS

The controlled availability of cannabis and cannabinoids for medical or scientific purposes would not place Australia in breach of any international treaty obligations. In fact the practice of other participating states such as the UK, where it is lawful to possess cannabis and most of its derivatives for the purposes of medical research could be seen as a guide to the interpretation of the relevant treaties.

The definition of "medical and scientific" purposes in international treaties is sufficiently broad to encompass the prescription or certification of cannabis and cannabinoids for the treatment of medical conditions.

Any model of controlled availability that was designed to facilitate the treatment of individuals with certain specified medical conditions could be said to have a medical purpose. So, too, could a controlled availability model (such as a clinical trial subject to rigorous evaluation) that was designed to test certain hypotheses in relation to the therapeutic properties of cannabis and cannabinoids.

The meaning of the words "medical" and "scientific" must, however, be interpreted in ways that are compatible with the aims of those who drafted the treaties. The models of controlled availability proposed in this report would satisfy those requirements.

The 1961 Single Convention is of particular importance in determining whether the controlled availability of cannabis and cannabinoids would place Australia in breach of international treaty obligations. Its provisions have been described as "regulatory" as opposed to "prohibitionist"[184] because they place a dual obligation upon governments: to ensure adequate availability of narcotic drugs for medical and scientific purposes and at the same time prevent the illicit production, trafficking and use.

Clearly, legalisation (i.e. total deregulation permitting availability of drugs for purely recreational purposes) is the one policy option not acceptable under the Convention.[185] As long as a medical or scientific purpose is satisfied, the government has a number of policy options. One example would be the cultivation, trade in and distribution of cannabis, by either a state enterprise or a licensed private enterprise, to individuals who qualify under appropriate programs.

[184] Ibid, at p.19.
[185] Ibid, at p.19.

9.1.5 SUMMARY: INTERNATIONAL CONVENTIONS

- Australia is a signatory to international conventions that aim to restrict production, manufacture, export, import, distribution, trade, and possession of narcotic drugs (which includes cannabis) to medical and scientific purposes;
- The spirit and intention of international drug conventions is to eliminate the availability of illicit drugs in the community. The conventions recognise, however, the need to use narcotic drugs for medical purposes;
- Under these conventions, any use of cannabis or cannabinoids for medical purposes must be based on evidence of its therapeutic value;
- A medical purpose might be argued for a model designed to facilitate the treatment of individuals with certain specified medical conditions;
- A scientific purpose might be argued for a controlled availability model (such as a clinical trial) designed to test certain hypotheses in relation to the therapeutic properties of cannabis;
- The meaning of "medical and scientific purposes" is sufficiently broad to encompass the prescription or certification of cannabis or cannabinoids for the treatment of medical conditions.

9.2 COMMONWEALTH LEGISLATION[186]

Commonwealth powers in respect to trade and commerce and external affairs have a critical bearing on the proposed controlled availability of cannabis in New South Wales.

The Australian Constitution provides for the specific powers of the Commonwealth Parliament. For the Commonwealth Parliament to act validly, it must act solely on the basis of one of these powers – most of which are covered by s51 of the Constitution. "There is no specific power to legislate in relation to criminal law generally or drugs in particular".[187] The major Commonwealth legislation, the *Customs Act* claims validity on the basis of the power accorded by the Constitution to legislate with respect to "trade and commerce with other countries"(s51(i)).[188] The customs legislation focuses entirely on imported and exported drugs; it is not concerned with cannabis crops grown in Australia. Where there is doubt about the origins of a particular drug, prosecutors can prosecute under State legislation that covers imported drugs as well as those grown in Australia.[189]

Since 1984, the Commonwealth has been able to exercise increased powers in the regulation of drug-related activities. This is because the High Court decision in *Commonwealth v Tasmania*[190] gave an expansive interpretation of the "external affairs" power enunciated in s51(xxix) of the Constitution. The issue in that case involved the extent to which the Commonwealth Parliament could legislate to give

[186] The section "Commonwealth Legislation" in this report is informed by and based on the analysis of Norberry J, "Legal Issues" (1992) in *Feasibility Research into the Controlled Availability of Opioids, Volume 2, Background Papers*, National Centre for Epidemiology and Population health, Australian National University, Canberra, pp.87-115.
[187] D Brown, D Farrier, D Neal, and D Weisbrot, (1996) *Criminal Laws, Materials and Commentary on Criminal Law and Process in New South Wales*, The Federation Press, p.1056.
[188] Ibid.
[189] Ibid.
[190] The Commonwealth of Australia v Tasmania (The Tasmanian Dam Case) (1983) 158 CLR 1.

effect to an international convention.[191] As a result of this case, the Commonwealth Parliament can properly legislate to give effect to any international obligations created by a convention to which Australia is a party.

Several of the following Commonwealth Acts purporting to implement the provisions of international conventions rest their claim to constitutional validity on the external affairs power.

9.2.1 CUSTOMS LEGISLATION

Customs Act 1901 (Cth)

Under s.50(1) of the *Customs Act 1901* the Governor-General may, by regulation, prohibit the importation of goods into Australia. Prohibitions on these imports may be absolute or qualified, prohibiting, for example, importation in specified circumstances, or from a specified place, or unless specified restrictions or conditions are complied with (s.50(2)).

Section 51(1) of the Act provides that "[g]oods, the importation of which is prohibited under section 50, are prohibited imports". Section 50(3) allows the Customs (Prohibited Imports) Regulations to establish a system of licences and permissions in relation to the importation of prohibited goods.

The importation of a prohibited import constitutes an offence under the Customs Act. Section .233B of the Act creates a special offence in respect of the importation of narcotic goods. ["Narcotic goods" are defined in s.4(1) as "goods that consist of a narcotic substance". A "narcotic substance" is defined as a substance or thing specified in column 1 of Schedule VI (this includes cannabis) or any other substance or thing for the time being declared by the regulations to be a narcotic substance.] It is, therefore, an offence under s.233B to possess, without reasonable excuse, a prohibited import that is classified as a narcotic good. Those holding the requisite licenses and permits issued under the Customs (Prohibited Imports) Regulations would have such an excuse.

Customs (Prohibited Imports) Regulations

Until 1991, the importation of *all* drugs (including therapeutic substances) was governed by the Customs (Prohibited Imports) Regulations. When the *Therapeutic Goods Act 1989* (Cth) was introduced (see below), controls on the importation of drugs *for therapeutic purposes* were transferred to therapeutic goods legislation – the Customs (Prohibited Imports) Regulations (Amendment).

Prohibited imports: Schedules to the Customs (Prohibited Imports) Regulations designate categories of prohibited imports. The opioids, together with many other drugs, including cannabis, are listed in Schedule IV. The Regulations treat cannabis in the same way as other drugs listed in Schedules I or II of the Single Convention.

Under regulation 5(1) importation of drugs into Australia is prohibited except in certain circumstances. A person wishing to import a drug must apply in writing for both a licence (r.5(1)(a)(i)) and a permission (r.5(1)(a)(ii)) from the Secretary of the Department of Health and Aged Care (Cth)(r.5(4)). Current licensees include drug companies, universities, police and government departments.

[191] Ibid.

A licence to import drugs: The Regulations (r.5(7)) provide that a licence shall not be granted unless:

- such information as is reasonably required by the Secretary of the Department of Health and Aged Care (Cth) is supplied by the applicant;
- the applicant is a fit and proper person to be granted a licence to import drugs;
- any agents or employees of the applicant are also fit and proper persons; and
- the premises on which the applicant proposes to keep the drugs are secure.

Regulation 5(9) provides a number of conditions to be met by the licence holder. These concern the security, disposal of drugs, record keeping requirements and report-making obligations. The Department of Health and Aged Care (Cth) or the Comptroller-General of Customs may specify the taking of certain security precautions to ensure that "there is no danger of loss or theft of any drug in the possession of the holder of the licence".

A permission to import drugs: This is granted for a particular shipment of a drug. Before permission is issued, a person must first have obtained a licence to import. The Regulations (r.5(10)) provide that a permission shall not be granted by the Secretary of the Department of Health and Aged Care (Cth) unless:

- any information reasonably required by the Secretary of the Department of Health (Cth) is provided by the applicant; and
- the applicant has made proper arrangements for the safe transportation and custody for the drug after it has been delivered for home consumption.

In addition, applicants must satisfy particular requirements in respect of drugs included in Schedules I and II of the Single Convention on Narcotic Drugs. (Schedule I includes cannabis as well as heroin, morphine and methadone.) These additional requirements, set out in r.5(10(b)),are as follows.

- Where the applicant requires the drug for the manufacture of another drug, then the applicant must be the holder of a manufacturer's licence under the *Narcotic Drugs Act 1967* (Cth) (if applicable), and also (if applicable), the holder of a manufacturer's licence from the particular State or Territory in which the manufacturer's premises are located;

- Where the applicant requires the drug for the purposes of his business as a seller or supplier of drugs, the applicant must be appropriately licensed under the relevant State or Territory law;

- A permission may also be granted in relation to the use by the applicant of a Schedule I or II drug if the use is for *medical or scientific purposes*. The legislation does not require an applicant to be licensed or otherwise authorised under State or Territorial law. In practice, it is, however, unlikely that a permit would be issued unless the legislative requirements of a particular State or Territory had been met since, once imported, possession of the substance by the applicant would be in breach of those requirements.

For Schedule I and II drugs a permission to import must specify a quantity of a drug that, together with already authorised and anticipated imports, "exceeds the amount that, in accordance with the

requirements of the Single Convention, has been determined to be the maximum amount of that drug that may be imported into Australia during the relevant year" (r.5(12)).

This maximum amount is determined by the Department of Health and Aged Care (Cth) in accordance with Australia's obligations under the Single Convention and is notified annually to the International Narcotics Control Board (INCB). One of the reasons for this notification is to prevent a build up of stocks in excess of those required for medical and scientific purposes.

For cannabis to be legally imported into Australia, the Department of Health and Aged Care (Cth), would have to notify the INCB of an estimated maximum amount for cannabis and the INCB would notify other parties to the convention. At present, Australia has not notified the INCB of any estimated maximum amount for cannabis importation. Consequently, exporting countries, such as the Netherlands, which are parties to the Single Convention, would not be able to export cannabis to Australia (nor could it be imported) without breaching the convention. Although the Department of Health and Aged Care makes annual estimates of drug importations, it is possible to give the INCB supplementary estimates.

In keeping with Australia's obligations, any imported cannabis must be used for medical or scientific purposes only.

9.2.2 NARCOTIC DRUGS ACT 1967

Following ratification by Australia of the Single Convention on Narcotic Drugs 1961 the Commonwealth introduced the *Narcotics Act 1967* to implement controls over the manufacture of drugs. The Commonwealth also amended the Customs Act to make sure that licitly produced drugs for medical purposes would not leak into the illicit drugs market and to strengthen controls over their importation. Other amendments dealt with drugs in transit through Australia.

9.2.3 THERAPEUTIC GOODS ACT 1989 (CTH)

The *Therapeutic Goods Act 1989* (Cth) is crucial to the controlled availability of cannabis and cannabinoids in New South Wales because, under Part 4A (s.31) of *Poisons and Therapeutic Goods Act 1966* (NSW), Commonwealth therapeutic goods laws also apply to this State.

The Therapeutic Goods Act establishes an Australian Register of Therapeutic Goods (ARTG) which records therapeutic goods approved for supply; the Act also makes special provision for unregistered goods that are intended for use in clinical trials. There are currently no cannabis or cannabinoid products registered on the ARTG. Two products – nabilone (a synthetic cannabinoid) and dronabinol (synthetic THC) – are available in Canada, the US and the UK, but the pharmaceutical companies who supply these products overseas do not wish to pursue their registration in Australia.

9.2.4 POSSIBILITIES FOR MAKING CANNABIS AVAILABLE FOR MEDICAL USE IN NSW

There are various possibilities for making cannabis and cannabinoids available in New South Wales but, as outlined below, most of these are not currently viable.

Registration on the ARTG

Under therapeutic goods legislation, before any product can be marketed in Australia it must be registered on the ARTG. Consequently, a product containing any cannabinoid from a natural or synthetic source would have to be registered. To obtain approval for registration, the application must provide pharmaceutical, toxicological and clinical information. This information is carefully evaluated by the Therapeutic Goods Administration (TGA) to establish that the quality, safety and efficacy of the product put forward for registration. As this is an expensive and lengthy process applications are not usually lodged unless the sponsor considers the product commercially viable. Owing to the health risks associated with smoking, cannabis *in smoked form* will never comply with TGA requirements. Since cannabis is a crude plant product, even if it were administered in ways other than smoking, it would still be unlikely to comply with registration requirements under the Therapeutic Goods Act.

- Drugs cannot be registered except on application from a pharmaceutical company and it is unlikely that any pharmaceutical company would seek to register a natural plant product that cannot be patented.
- There are very few data from controlled clinical trials on the efficacy of cannabis for treating the recommended conditions
- There are serious concerns about the safety of smoked cannabis, especially in the treatment of chronic medical conditions;
- Quality is also problematic, because crude forms of cannabis contain variable amounts of THC and other cannabinoids.

All this adds up to the fact that it would not be possible to manufacture of cannabis for use as a therapeutic good.

Australian Orphan Drug Program

This program is designed to overcome sponsors' reluctance to develop products not deemed commercially viable. Under this program, the TGA waives application fees and other charges associated with registration and the initial evaluation of data. Approval time is also usually shorter than the statutory 225 working days.

Strict rules apply to the classification of a drug under this program. Generally, the disease for which the drug is intended as treatment should have no less than 2000 victims. Also, the drug should have the same quality and standards of safety and efficacy as other marketed drug products.

Orphan drugs may be eligible for pharmaceutical benefits listing, which means subsidised costs to patients.. Overseas manufacturers of cannabis derivatives are likely to give more thought to this option but it is still doubtful whether they would lodge an application.

Under s.19 of the *Therapeutic Goods Act 1989* (Cth) there are two ways the Secretary of the Department of Health and Aged Care may authorise the importation and/or use of a drug not registered on the ARTG. These are: the Personal Import Scheme and the Special Access Scheme.

Personal Import Scheme

Under this scheme individuals may import for medical uses (and at their own expense) a drug that is not registered on the ARTG. They may import no more than 3 months' supply at the maximum dose and must have a doctor's prescription for the medication, where this is required by State law. Since, however, narcotic, psychotropic and other drugs subject to the Customs (Prohibited Imports) Regulations may not be imported under the Personal Import Scheme, this is not a viable option.

Special Access Scheme

Under this scheme, certain categories of patients may obtain access to a drug. The controls applied depend on the category of patient for whom the drugs are intended.

- *Category A* (*patients who are terminally or seriously ill with life-threatening conditions*): These patients do not have to obtain TGA approval to use/import the drug; in effect, the treating doctor approves the use.
- *Category B (patients who are suffering from a life-threatening condition, even if they are not critically ill):* These patients need TGA approval to use. Drugs approved for use by patients in this category have generally been the subject of at least Phase 1 clinical trials in humans.
- *Category C* (*patients who are suffering from a serious but not life-threatening illness*): These patients also need TGA approval to use the drug. Drugs approved for use by patients in this category must have been put through exhaustive clinical trials to test their efficacy and safety for human use. Normally the drugs would have been subjected to all the clinical trials needed to support a marketing application.

It was under the Special Access Scheme that the synthetic cannabinoid, dronabinol, was imported and used for the treatment of HIV wasting syndrome. This is not, however, a viable option to consider as majority of eligible patients did not gain access to the drug: they had to bear the full costs themselves and, for most, this was too expensive.

9.2.5 CRIMES (TRAFFIC IN NARCOTIC DRUGS AND PSYCHOTROPIC SUBSTANCES) ACT 1990 (CTH)

This legislation is designed to implement the provisions of the 1988 convention in relation to trafficking in narcotic drugs and psychotropic substances. The Act criminalises certain defined activities that constitute an offence against a law of the Commonwealth, a State or Territory, or a foreign country (s.9). As it is "not intended to exclude or limit the operation of any other law of the Commonwealth or any law of a State or Territory" (s.5(1)), it should not affect lawful activities involving cannabis or cannabinoids.

9.2.6 CONCLUSIONS: COMMONWEALTH LEGISLATION

The Commonwealth has a critical role to play in any scheme for making cannabis or cannabinoids available for medical purposes in New South Wales.

The Commonwealth controls the source of cannabis imported into this country for clinical trials and it is an offence to import cannabis without the mandatory Commonwealth licences and permissions. The Commonwealth also has extensive powers in relation to the use of therapeutic goods within New South Wales. Smoked cannabis will never comply with TGA requirements for registration as a therapeutic good. Crude forms of cannabis, even if administered in other ways, are also unlikely ever to comply.

The reasons are as follows.

- Drugs cannot be registered except on application from a pharmaceutical company and it is unlikely that any pharmaceutical company would seek to register a natural plant product that cannot be patented;
- There are very few data from controlled clinical trials on the efficacy of cannabis for treating the recommended conditions;
- There are serious concerns about the safety of smoked cannabis, especially in the treatment of chronic medical conditions;
- Quality is also problematic, because crude forms of cannabis contain variable amounts of THC and other cannabinoids.

This means that cannabis cannot be manufactured for use as a therapeutic good.

If a model allowing the controlled availability of cannabis and cannabinoids in NSW were to proceed unlawfully legislative sanctions already exist. In addition to these, the Commonwealth could legislate (for example, using its external affairs powers) to proscribe the model and penalise its participants. It is not clear whether this course of action would succeed; and it would certainly be tempered by political considerations.

An important consideration is whether some or all of these obstacles at the Commonwealth level could be overcome if the cannabis used were sourced and supplied in New South Wales alone.

9.2.7 SUMMARY: COMMONWEALTH LEGISLATION

- Under the "external affairs" power of the Australian Constitution, the Commonwealth Parliament can legislate to give effect in Australian jurisdictions to our obligations under international conventions.
- For cannabis to be imported into Australia legally for medical/scientific purposes, the Department of Health and Aged Care (Cth), would have to notify the INCB of an estimate for cannabis;
- The Commonwealth has extensive powers in relation to the use of therapeutic goods within NSW. Cannabis as a crude plant product is very unlikely to ever be registered as a therapeutic good in Australia;
- Without being registered as a therapeutic product on the ARTG, cannabis may not be produced or prescribed for use as a therapeutic product;
- The registration of cannabinoids as therapeutic goods in Australia may be achieved through sponsorship by a pharmaceutical company, or under the Orphan Drug Program. Neither of these appears likely to happen at the moment.
- Narcotic, psychotropic and other drugs subject to the Customs (Prohibited Imports) Regulations may not be imported under the Personal Import Scheme. Hence, this is not an option that can be considered for the medical use of cannabis and cannabinoids;
- Dronabinol (a synthetic cannabinoid) was available under the Special Access Scheme for patients with HIV wasting syndrome. Since patients must pay the full cost of drugs under the SAS (which is considerable), access to cannabinoids (e.g. dronabinol) under this scheme is not considered viable.

9.3 THE RELATIONSHIP BETWEEN STATE AND COMMONWEALTH LEGISLATION

According to s.109 of the Commonwealth Constitution, Commonwealth legislation prevails over inconsistent State legislation, as long as the former represents a valid exercise of the Commonwealth Parliament's constitutional powers.

In the case of *Stevens*,[192], Justices of the NSW Court of Criminal Appeal found that there was some overlap between the *Drug Misuse and Trafficking Act 1985* (NSW) and the narcotic offences provisions of the Customs Act (Cth), but that, because the aims of the two Acts were different, there was no inconsistency.

> *"The purpose of the two acts is different, one being to control imports of narcotics, the other to control and create offences in respect of the possession and supply of narcotics in NSW for the benefit and protection of the community in NSW. The Commonwealth Act, it may be said, erects, in s.233B, a barrier or defence against narcotics coming into Australia, whilst the Drug Misuse and Trafficking Act is a measure that enables the State to police the use of and trafficking in* narcotics in NSW. *The two laws will, in given circumstances overlap and apply to the same sets of circumstances but the purpose of each remains fundamentally different. As the purpose of the two Acts is entirely different they are not, under s.109 of the Constitution, to be regarded as inconsistent" (at 82).*

[192] (1991) 23 NSWLR 75

9.4 NEW SOUTH WALES LEGISLATION

Two Acts are particularly important when considering the feasibility of using cannabis and cannabinoids for medical purposes in this State. They are: the *Drug Misuse and Trafficking Act 1985* and the *Poisons and Therapeutic Goods Act 1966*.

9.4.1 DRUG MISUSE AND TRAFFICKING ACT 1985

The objectives of the *Drug Misuse and Trafficking Act 1985* are to clarify the distinctions between:

- the statutory provisions governing the prohibition of drugs of misuse; and
- the statutory provisions governing the possession and supply of drugs for medical purposes.

The Act makes a clear distinction between prohibited *plants* and prohibited *drugs*. Prohibited drugs are listed in Schedule 1 and their possession is prohibited unless authorisation has been obtained from the Director-General of the NSW Health Department, or the drugs fall within the appropriate schedule of that other key piece of State legislation – *Poisons and Therapeutic Goods Act 1966*. Prohibited drugs listed in Schedule 1 include: prepared opium, cannabis, heroin, cocaine and LSD. There is, however, little attempt to differentiate on the basis of the relative seriousness of the effects of different drugs or their potential to cause harm.[193]

The offences included in the Act cover all prohibited drugs. The only difference is that cannabis plants and leaves are treated less severely when it comes to the maximum allowable penalties for the most serious offences – supply, cultivation, and production.[194]

One important provision of the *Drug Misuse and Trafficking Act 1985* is that a person may use a drug for medical purposes without committing an offence, as long as the drug has been obtained legitimately. A legitimate source of supply could, for example, be someone authorised by the Director-General of the NSW Health Department to certify cannabis use or prescribe cannabinoids.

The following is a summary of the significant provisions of the *Drug Misuse and Trafficking Act 1985*.

- *Section 10:* It is an offence to possess prohibited drugs (including cannabis, which is listed in Schedule 1). It is, however, worth noting that Schedule 1 also contains drugs (e.g. morphine) which, under the Poisons Act, can legally be obtained for therapeutic purposes on prescription. It is not an offence if the person is licensed or otherwise authorised under the Poisons Act or if possession for scientific research, instruction, analysis or study has been appropriately authorised by the Director-General of the NSW Health Department s.10(2)(b). Possession by those caring for or assisting in the care of, another person for whom a prohibited drug has been lawfully prescribed or supplied may be exempt from criminal liability under s.10(2)(d), as long as possession is "for the sole purpose of administering, or assisting in the self-administration of, the prohibited drug to the other person in accordance with the prescription or supply" [s.10(2)(d)(ii)].

- *Section 11*: Possession of drug-using equipment is a summary offence. It is also an offence to sell, supply or display a bong (s11(A)).

- *Section 12*: The act of using the drug, commonly known as self-administration, is a summary offence.

[193] Brown D, et al (1996) at 1072.
[194] Ibid.

- *Section 13*: Administering a drug to another person is an offence. The only exceptions are when the person administering the drug is licensed or otherwise authorised under the Poisons Act or authorised by the Director-General of the NSW Department of Health., or when the prohibited drug has been lawfully prescribed (s.13(2)(a)).

- *Section 14:* It is an offence to allow one person to administer to another drugs that have not been lawfully prescribed and supplied, whether administration is by ingestion, inhalation, smoking or any other means of introducing a prohibited drug into any part of the body one's own body or the body of another person.

- *Section 19*: Prohibits the aiding and abetting of offences in New South Wales.

- *Section 23*: Offences relating to growing cannabis. It is not unlawful to cultivate, supply, or possess a prohibited plant if a person is "…acting in accordance with an authority granted by the Director-General of the Department of Health where the Director-General is satisfied that the cultivation, supply or possession of the prohibited plant is for the purpose of scientific research, instruction, analysis, or study"(s.23(4)(b)).

- *Section 25:* Defines a wide range of illegal activities associated with the distribution of drugs, not just the selling. The definition of supply includes: "to sell and distribute, and also includes agreeing to supply or offering to supply or keeping or having in possession for supply, or sending, forwarding, delivering or receiving for supply, or authorising, directing, causing, suffering, permitting or attempting any of those acts or things" (s.3). The supply of a prohibited drug is not unlawful if "…a person is licensed or authorised to do so under the *Poisons Act 1966*; or…a person acting in accordance with an authority granted by the Director-General of the Department of Health where the Secretary is satisfied that the supply of the prohibited drug is for the purpose of scientific research, instruction, analysis or study"(s.3).

- *Section 40:* Places the onus on the accused to prove that any alleged offence is not unlawful (s.40(A)(2)).

9.4.2 POISONS AND THERAPEUTIC GOODS ACT 1966

The *Poisons and Therapeutic Goods Act 1966* is designed to regulate the supply and distribution of pharmaceutical drugs and poisons.[195] Drugs covered by this Act include tranquillisers, pethidine and morphine. Possession and use of these drugs are legal only on a medical practitioner's prescription.

Poisons List

The Poisons Act, as it is generally known, sets out all the controls applicable to the supply and prescription of drugs for medical use in New South Wales. A Poisons List is annexed to the Act.

The level of control exercised over the use of a drug depends on the schedule of the Poisons List in which it is classified. Drugs are classified in the NSW Poisons List through proclamation by the State

[195] Zahra, P, Arden, R, Ierace, M. and Schurr, B. (1998) *Drug Law in New South Wales*, The Federation Press, Sydney, p172.

Governor on the advice of the Executive Council and on the recommendation of the Health Minister (s.8(6)) The Poisons List may be amended by applying, adopting or incorporating, with or without modification, a standard published by the National Health and Medical Research Council or any other published standard in force at a particular time or from time to time.

For cannabis and/or cannabinoids to be prescribed in New South Wales, they would first have to be classified in the appropriate section of the NSW Poisons List. This classification would need to ensure that availability was restricted to medical prescription only and that patients for whom the drugs had been lawfully prescribed were permitted to possess and use them. The following are the relevant schedules to the Act.

Schedule 8: This schedule contains drugs classified as narcotics. It includes THC, which means that this substance can only be supplied with a doctor's prescription. Under this schedule, NSW Department of Health approval to prescribe is generally required if the prescription is for "a drug dependant person" or any other person for a period of longer than 2 months. Also, the drug must be stored in a safe; stock is accountable (a drug register that records all purchase and supply details must be maintained); and dispensed prescriptions must be retained by the pharmacist who first dispenses them.

Major offences in relation to drugs classified under schedule 8 include:

- Illegal possession (s.10 of the *Drug Misuse and Trafficking Act*) – maximum penalty $2200 and/or 2 years' imprisonment or both.
- Illegal supply (s.23 of the *Drug Misuse and Trafficking Act*) – maximum penalty depends on the quantity supplied: e.g. penalty for a small quantity of cannabis leaf (30g) $5500 and/or 2 years' imprisonment.
- Unauthorised self-administration (s.12 of the *Drug Misuse and Trafficking Act*) – maximum penalty is $2200 and/or 2 years' imprisonment.

Schedule 4: Drugs in this classification include antibiotics and antihypertensives. Under this schedule supply is by doctor's prescription only, with very few exceptions. Department of Health approval to prescribe is not required. The drug must be stored in the pharmacy's dispensary but stock is not accountable. The pharmacist must make a record of each prescription dispensed but does not have to hold prescriptions at the pharmacy.

The major offence relating to this classification is illegal supply, which means supply without prescription (s.10(3)(b)). The maximum penalty is $1650 and/or 6 months' imprisonment. There are no offences for illegal possession.

Schedule 4 (plus inclusion in Appendix D to the Poisons and Therapeutic Goods Regulations): Drugs in this schedule are usually those subject to abuse (.e.g**.** benzodiazepines and anabolic steroids**)**. Supply is by doctor's prescription only, with very few exceptions. Health Department approval to prescribe is not required. Other basic controls are the same as for Schedule 4 drugs except that, in some cases, dispensed prescriptions must be held by the pharmacist who first dispenses them.

Major offences related to this classification include:

- Illegal supply (supply without prescription) (s.10(3)(a)) – maximum penalty $2200 and/or 2 years imprisonment.
- Illegal possession (no prescription issued) (s.16(1)) – maximum penalty $2200 and/or 6 months imprisonment.
- Possession for the purposes of supply (possession of larger quantities) (s.18(A)) – maximum penalty $2200 and/or 2 years' imprisonment.

Classification in the Poisons List would allow cannabis and cannabinoids to be prescribed by medical practitioners. As with other prohibited proscription drugs, all the other prohibitions would continue to apply.

10 PRESCRIBING ISSUES AND OPTIONS

Smoked cannabis cannot be prescribed because it does not, and is never likely to, meet the requirements of the Therapeutic Goods Act (8.3.3). Cannabis and cannabinoids delivered by other methods may, in time, qualify for TGA registration. When this situation arises, the following prescription models could be considered.

10.1 PRESCRIPTION WITH DEPARTMENT OF HEALTH (DOH) APPROVAL ON AN INDIVIDUAL PATIENT/DOCTOR BASIS

Under this model, doctors would have to apply in writing to the NSW Department of Health (DOH) each time they wished to prescribe for a patient. They would need clear guidelines to assist with this process. Although this model applies the greatest controls and would require considerable resources, it would also allow any doctor who made the appropriate application to be authorised to prescribe. Under this model, the government has ultimate responsibility for authorising drug prescription and might be exposed to damages if adverse health effects occurred.

10.2 PRESCRIPTION WITH DOH APPROVAL ON AN INDIVIDUAL PATIENT BASIS, BUT ONLY FOR A SPECIFIED CLASS OF DOCTOR

Under this model DOH authorisation would be restricted to an "approved" category of doctors. These could be specialists responsible for diagnosing conditions, or other doctors who had undertaken some form of additional training or accreditation. Doctors would have responsibilities and liabilities similar to those applying to the previous model. Both models would have in-built mechanisms to prevent "doctor shopping".

10.3 PRESCRIPTION WITH DOH APPROVAL AS A DOCTOR "AUTHORISED" TO PRESCRIBE FOR ANY PATIENT WHO MEETS CERTAIN SPECIFIED CRITERIA

Under this model, DOH approval would have to be obtained, but not on individual patient basis. The doctor would, however, have to be an "approved" prescriber of cannabis and cannabinoids. The government would need to develop guidelines for the appointment of approved prescribers. Appointment could be made subject to certain conditions (e.g. that DOH be notified of any prescriptions written for patients who have met the specified criteria). This model places more responsibility, and associated liability, on the prescribers. They would have to maintain detailed records and clinical notes, including details of patient identification. This model is more open to "doctor shopping" – a practice which could prove difficult to detect. Existing legislation requires patients to advise their doctors when they have obtained certain medications from another medical practitioner in the preceding 2 months. This requirement could be reversed, making the doctor responsible for obtaining this information from the patient. To protect the doctor from liability, the patient could be asked to sign some form of declaration.

10.4 PRESCRIPTION WITHOUT DOH APPROVAL, AND BY A NOMINATED CLASS OF DOCTOR, FOR ANY PATIENT WHO MEETS SPECIFIED CRITERIA

Under this model, DOH approval to prescribe is not required. Legislation would simply specify the criteria patients must meet to be eligible for prescription and the class of doctor authorised to prescribe. This model places all the responsibility and associated liability on the doctor.

11 CONTROLLED AVAILABILITY OPTIONS

There are various options for allowing controlled availability of cannabis and cannabinoids for medical purposes in New South Wales. These include: a non-enforcement agreement; amendments to existing NSW legislation; and the introduction of special legislation.[196]

11.1 NON-ENFORCEMENT AGREEMENT

Because importation of cannabis is regulated by both Commonwealth and State laws, a "non-enforcement" agreement would have to be made with the Commonwealth as well as with a wide variety of relevant agencies, including the Australian Federal Police and the Director of Public Prosecutions. The advantage of a non-enforcement agreement is that it would avoid the need to amend NSW statutes. On the other hand, principles of criminal justice militate against such an approach since all those involved would be denied their right to the sure and adequate protection of the law. Important considerations include: the uncertainties of this approach, the potential for things to "go wrong", and the possibility that all or any of the parties could revoke their agreement.

On 3 April 2000, NSW began a 12-month trial whereby police instead of arresting adults for possession of less than 15 grams of cannabis cautioned them and referred them to a telephone advice line where they could obtain further information about cannabis use. The scheme does not apply to those with previous drug convictions or those with serious criminal records. Only two such cautions are allowed. It relies on the exercise of police discretion and has no legislative basis. Police guidelines assist individual police in the exercise of their discretion whether to caution or arrest however ultimately it is up to the officer concerned. Arrest is always an option. It is a classic example of a non-enforcement scheme. The pilot has yet to be completed and evaluated.

11.2 AMENDMENTS TO EXISTING NEW SOUTH WALES LEGISLATION

If clinical trials of cannabis and cannabinoids were to be introduced it would be necessary to amend s.10 of the *Drug Misuse and Trafficking Act* to expand provisions that at present allow only for scientific trials. Even though it could be argued that s.10 already applies to clinical trials (which are of course "scientific"), it would still be prudent to make legislative amendments to this end.

Consideration might also be given to inserting a detailed omnibus provision into the *Drug Misuse and Trafficking Act* establishing a clinical trial or the like, "notwithstanding anything in this Act (or other Act)".

If cannabis and or cannabinoids could be lawfully prescribed under the *Poisons and Therapeutic Goods Act* very little amendment would be necessary. They would be treated in much the same way as other Schedule 4 or Schedule 8 drugs. In fact, to formalise this, the drugs would merely be required to be listed in either Schedule 4 or 8 of the Poisons List.

If a scheme involving medical certification were to be introduced, a number of amendments would need

[196] The "Controlled Availability Options" section of this report is informed by and based on the analysis of Norberry J, "Legal Issues" in *Feasibility Research into the Controlled Availability of Opioids, Volume 2, Background Papers*, National centre for Epidemiology and Population health, Australian National University, Canberra, pp.87-115.

to be made to the *Drug Misuse and Trafficking Act* to provide for those certified (and perhaps their carers and those involved in very small-scale cultivation) to obtain protections similar to those now extended to persons who obtain scheduled drugs on prescription. A sunset clause could be included with any such amendments. The exact amendments required will depend on the model adopted for ensuring that those in need of cannabis/cannabinoids for medical purposes may obtain and use the drug lawfully.

11.3 SPECIAL LEGISLATION

An alternative legislative approach would be to enact special legislation to provide for the controlled availability of cannabis and cannabinoids for medical purposes or to establish a clinical trial – perhaps, once again, with a sunset clause. The Act would need to over-ride other relevant pieces of State legislation and its provisions would depend on matters such as the design of a clinical trial and/or the source of the cannabis to be used.

11.4 SUMMARY: CONTROLLED AVAILABILITY OPTIONS

There are various approaches that could be adopted to permit controlled availability of cannabis and cannabinoids in New South Wales for medical purposes.

- A *non-enforcement agreement*. This would avoid the need for statutory amendments in New South Wales but would deny all those involved their rights to the sure and adequate protection of the law. The uncertainties of this approach, the potential for things to "go wrong", and the possibility that all or any of the parties could revoke their agreement should be considered;

- *Amendments to existing legislation*. In the case of research/clinical trials, the words "clinical trials" could be included in addition to existing exemptions under the research provisions of the Drug Misuse and Trafficking Act. The possession or cultivation of cannabis and/or cannabinoids for therapeutic uses, and certification of cannabis and cannabinoid use for a therapeutic purpose by a medical practitioner, could both be rendered lawful by amendments to the *Poisons and Therapeutic Goods Act*;

- *Special legislation*. Special legislation could provide for the controlled availability of cannabis and cannabinoids for therapeutic purposes or clinical trials.

11.5 LEGISLATION IN NSW AND OTHER JURISDICTIONS

The types and seriousness of offences under existing drugs legislation and the penalties these offences attract vary enormously from one jurisdiction to another (see Appendix E – Legislation). Within jurisdictions there are often inconsistencies between the intent of the legislation and the way minor cannabis offences are dealt with in practice. The penalties imposed by some courts, for example, do not necessarily reflect the penalties provided for in legislation. In addition, legislation in the ACT and South Australia allows for minor cannabis offences to be dealt with out of court altogether through expiation schemes. Victoria's legislation, by way of contrast, provides for no conviction to be recorded against certain minor cannabis offenders and for the penalty to be adjourned.

This raises significant issues for patients who use cannabis for medical purposes and for any proposal to enable them to do so lawfully in NSW. For further discussion of jurisdictional issues pertaining to criminal liability see 16 - Criminal liability.

12 GENERAL REGULATORY MODELS AT THE STATE LEVEL

When considering the legal status of cannabis and cannabinoids and the possibility of law reform, it is important to be aware of Australia's international treaty obligations. Although there are some differences of opinion with regard to the range of legislative options available to Australia within the scope of international treaty obligations, the policy of total prohibition currently followed by most States and Territories is only one of the available options.

This section will consider a variety of potential regulatory models. The conclusion favoured, thus far, is to use existing regulatory mechanisms. So that the goals of harm reduction may continue to be pursued alongside any law reform in this area, regulatory policy must not only take into account legislative frameworks but also appropriate measures of social control, such as drug education and prohibitions on advertising. The following legislative options in relation to the use and possession of cannabis in NSW[197] provide a useful starting point.

- **Total prohibition with no expediency principle:** (as practised in most Australian States, including New South Wales and the Northern Territory) - more or less full enforcement of the criminal law relating to cannabis.

- **Total prohibition with an expediency principle:** to allow for the formal non-enforcement of minor infringements (as in the Netherlands), based on an administrative decision that it is not expedient (not in the public interest) to prosecute all or certain cannabis offences.

- **Total prohibition with an administrative decision to caution certain categories of offenders:** and/or to divert them into treatment programs rather than to subject them to criminal prosecution (presently being trialled in NSW and Victoria).

- **Total prohibition with non-criminal sanctions:** e.g., to replace criminal convictions with civil penalties such as "on the spot fines", (as in South Australia and the ACT).

- **Partial prohibition:** where criminal sanctions remain for some cannabis-related incidents (e.g. trafficking) but are removed from the purview of the law for others (a policy adopted in Spain).

- **Regulation** where government agencies, or agencies licensed by the government, are responsible for controlling the production, distribution and sale of cannabis: under a regime similar to that regulating the tobacco and alcohol industries. Trafficking outside the regulated system would continue to be a criminal offence and attract penalties. Activities associated with the use of cannabis or cannabinoids for medical purposes would not, however, be penalised. No full working model of this option is currently operating in any Australian jurisdiction, although there are examples of similar regulatory systems Australia – for instance, opium poppies are cultivated under government licence in Tasmania and authorities have been granted to trial low THC hemp in New South Wales since 1995. Drugs such as tobacco, alcohol and many pharmaceutical products are also subject to regulation. These examples illustrate two major models for regulating the availability of drugs that would otherwise be prohibited: regulated commercial sale and government monopoly.

[197] Using here the taxonomy developed in McDonald, D, Moore, R, Norberry, J, Wardlaw, N. and Ballenden , N. (1994), *Legislative Options for Cannabis in Australia*, National Drug Strategy Monograph No.26, AGPS, Canberra.

- **Free availability:** This would mean the absence of any legislative or regulatory restrictions on the cultivation, importation, sale, supply, possession or use of cannabis. At present, this is not a legal option available in any country.

13 SPECIFIC REGULATORY MODELS AT THE STATE LEVEL

13.1 SOURCE OF CANNABIS

There are four possible models for obtaining cannabis for medical use:

- importation;
- licensing or authorisation of companies or authorities to cultivate cannabis;
- using cannabis from illegal crops that have been seized;
- legal exemptions for people with certain medical conditions to grow cannabis for personal medical use ("grow your own"), or for others to supply them with cannabis ("compassionate supply").

13.1.1 IMPORTATION

Importation of cannabis for personal medical use would be illegal under Commonwealth law. Importation for scientific research or clinical trials could be authorised if appropriate regulations and procedures were complied with (see 9.2.1 - Customs Legislation).

13.1.2 LICENCES/AUTHORISATION

The Single Convention establishes a system of controls in respect to the cultivation of opium poppies and cannabis. In accordance with Articles 23 and 28, parties are required to establish a centralised government agency to carry out functions in relation to the cultivation of opium poppies and cannabis, and only cultivators licensed by this agency may be authorised to engage in cultivation. In Australia, the Therapeutic Goods Administration (TGA) fulfils this function at the Commonwealth level. Regulatory bodies at the State level, such as the Poppy Advisory and Control Board in Tasmania, are required to work in tandem with the TGA to ensure compliance with Australia's international treaty obligations.

It is conceivable that the NSW Government could licence companies/authorities to cultivate cannabis for medical and research purposes. Cannabis is, however, currently an unregistered drug within the meaning of the *Therapeutic Goods Act 1989* (Cth) - and is likely to remain so until other modes of administration are developed – so its cultivation could only be legally sanctioned if it were part of a clinical or scientific trial. The cost of establishing a regulatory body to oversee the licensing of cannabis cultivation for medical and research purposes would be considerable.

13.1.3 CONFISCATED PLANTS AND CROPS

Another possible source of supply for medical purposes would be cannabis seized in the course of law enforcement activities. For cannabis to be registered as a therapeutic product it must, however, undertake the rigorous standardisation process required of other therapeutic products under the Therapeutic Goods Act. As the concentration of THC varies significantly between plants - according to their source and the method of cultivation - guidelines setting standard requirements for the crude plant material would have to be developed. Registration of cannabis as a therapeutic product is unlikely at

present, given the lack of suitable delivery options; so the use of confiscated cannabis would be confined to the limited purpose of a clinical trial.

The *Drug Misuse and Trafficking Act* (NSW) (Part 3A) provides for the destruction or retention of prohibited drugs that have been seized by police. Under s.39J, for example, the Director-General of the Department of Health may request the Commissioner of Police to give such prohibited drugs to "a person or body specified" for the "purpose of scientific research, instruction, analysis or study".

While this course of action is not explicitly forbidden by the Single Convention, the long standing policy of the International Narcotics Control Board (the organization overseeing compliance with treaties) is that countries should not base a licit activity upon an illicit source.[198] Also, other parties to the Single Convention, such as Canada, have rejected the use of seized cannabis for medical purposes on the basis that it would be in contravention of international treaty obligations.[199]

13.1.4 GROW YOUR OWN

The 1961 Single Convention permits parties to cultivate cannabis under the control of government agencies (act 28(1)). Apart from the controls that apply to such large-scale licensed cultivation, the only specific obligation in relation to cannabis cultivation is under act 22, which provides that a party shall prohibit cultivation whenever prohibition is the "most suitable measure, in its opinion, for protecting the public health and welfare and preventing the diversion of drugs into the illicit traffic".[200] It is left to each party to decide whether total prohibition is the "most suitable measure". The NSW Government could, therefore, decriminalise privately cultivated amounts of medical cannabis that neither threaten the "public health and welfare" nor contribute to the "illicit traffic", without placing Australia in breach of its international obligations under the Single Convention.

Nothing in acts 4(1)(c) or 36(1) of the Single Convention contradicts this conclusion. The general obligation in act 4(1)(c), to take necessary legislative and administrative measures, applies to "manufacture" and "production" but not to the term "cultivation" which is defined quite separately in act 1(1). Although act 36(1) refers specifically to "cultivation", it is clearly focusing on activities in the chain of trafficking rather than on acts associated with personal use.[201]

In sum, Australia's international treaty obligations would not necessarily be compromised if a regulatory model giving legal exemptions to individuals with certain medical conditions to grow their own cannabis plants were to be adopted in New South Wales. If such a model were adopted, it would need to focus on distinguishing between cultivation for medical or recreational purposes. For example, to qualify for exemption, individuals might be required to present medical documentation (e.g. certification from medical practitioner; prescription, etc.) diagnosing a condition for which cannabis is an effective treatment and stating that the person may benefit from its use. In addition, the number of plants allowable per person should be restricted to the number considered necessary for them to maintain treatment of a specified health condition.

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198 For a recent statement of this position see, (1999) International Narcotic Control Board Report, E/INCB/1999/1 at 109.

199 For example, see Health Canada, "Research plan for Marijuana for Medical Purposes: A Status Report", Therapeutic Products Programme, June 9 (1999) at http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/cds/marijuana/resear_e.html

200 Dawkins K, "International Law and Legalising Cannabis" in (1997) *New Zealand Law Journal* 281 at 282.

201 Ibid.

The "grow your own model" might not, however, be a realistic option for all patients; for example, some might not have access to a private and secure outdoor area or possess the capacity or funds to grow cannabis indoors. Also, the debilitating nature of the illnesses for which cannabis may be used medically, may prevent some patients from growing their own.

A legislative framework would have to be developed to provide exemptions for specific individuals or class of individuals requiring cannabis or cannabinoids for personal therapeutic use.

13.1.5 SUPPLY BY CANNABIS DISPENSARIES ("BUYERS" OR "COMPASSION" CLUBS)

It may also be necessary to consider whether anyone apart from patients with one of the specified conditions should qualify for exemption – for example, people who are not ill themselves but who, entirely without remuneration, supply patients who are too ill to grow their own.

Cannabis dispensaries (often known as buyers clubs or compassion clubs) have been set up in several cities around the world, including Australia, to supply cannabis to medical users on a non-profit basis. The voluntary "controls" under which these dispensaries operate vary a great deal. One dispensary might, for example, supply via mail order on receipt a letter and money (as proposed by the NSW Compassion Club); another might supply directly on receipt of a photo ID card "qualifying" the individual. These "controls" are not regulated and may be illusory. To preserve the distinction between supplying cannabis for medical as opposed to recreational purposes, and as a matter of good public policy, government regulation is the most responsible and appropriate way of sanctioning the supply of cannabis to those in need.

Australia's international obligations will determine whether activities, which fall outside of this proposed regime, *must* attract criminal liability. In the context of act 4(1)(c) of the Single Convention, it has been argued that the supply of small amounts of cannabis without remuneration or for insignificant remuneration, is falls outside the meaning of "distribution" and "trade".[202] "Offering", "offering for sale", "purchase", "sale", "distribution" and "brokerage" in act 36(1) can also be interpreted as referring only to commercial or trafficking transactions rather than donations or non-profit supply for personal use.[203] If compassionate supply of cannabis does not necessarily attract criminal liability under Australia's international obligations, the next question is whether the gratuitous or non-profit supply of small, or even large, amounts of cannabis for private, personal use *should* be excluded from criminal liability.

It is important to note that if "compassion" or "buyers" clubs were to supply cannabis commercially as a therapeutic good, they would contravene the Commonwealth Therapeutic Goods Act since cannabis is not a registered therapeutic good (see Section 9.2.4 - Possibilities for making cannabis available for medical use in NSW).

13.1.6 SUPPLY BY INDIVIDUALS

Cannabis could also be supplied to patients by concerned individuals rather than organised groups; for example by someone who cultivates cannabis solely for the purpose of supplying a sick relative. This raises questions as to whether these people should be granted legal exemptions and, if so, who else would be entitled to exemption.

[202] Ibid.
[203] Ibid.

Cultivation and supply

At present, the provisions of the *Drug Misuse and Trafficking Act* (NSW) relating to the cultivation and supply of prohibited drugs and plants would apply in these circumstances. "Supply" is very broadly defined by the Act: it includes *selling* or *giving away* drugs as well as simply *agreeing* to supply. In addition, there is "deemed supply": where a person is deemed guilty of supply for possessing quantities of drugs considered "traffickable". The Act divides trafficking offences into a number of categories – "indictable", "commercial" and "large commercial" – and higher penalties apply to charges of supply involving larger amounts of drugs. Penalties for the cultivation of cannabis, depend on the number of plants rather their gender, size or location. Generally, the fewer plants grown, the less serious the charge. It is also an offence to "take part" in the supply or cultivation of cannabis. For example, a person may be considered to be taking part in the cultivation and supply of cannabis if they allow their premises to be used for growing it.

Possession of prohibited drugs

Under s.10(2)(d) possession will not be rendered unlawful by a person who "(i) has the care of, or is assisting in the care of, another person for or to whom the prohibited drug has been lawfully prescribed or supplied, and (ii) has the prohibited drug in his or her possession for the sole purpose of administering, or assisting in the self-administration of, the prohibited drug to the other person in accordance with the prescription or supply".

Under s.40(A)(2) the onus of proving lawful supply rests with the accused. There is no equivalent provision in s.23 and s.25 regarding the cultivation and supply of cannabis. The only legal exemptions set out under these two sections concern activities undertaken in accordance with an authority by the Director-General of the Department of Health (NSW) and which are carried out for the purpose of scientific research, instruction, analysis or study. Consequently, if a model of regulation that allows for the lawful medical certification of cannabis were adopted, legislative amendments to the *Drug Misuse and Trafficking Act* in regard to cultivation and supply would be required. This could be achieved by inserting a similar exemption to that found under s.10(2)(d) or by extending the existing range of legal exemptions beyond those currently recognised in s.23(4) and s.25(4).

13.2 CONCLUSIONS: SOURCE OF CANNABIS

- Importation of cannabis for personal medical use would be illegal under Commonwealth law. Importation of cannabis for scientific research or clinical trials could be authorised if appropriate regulations and procedures were complied with;
- The only way in which *cannabis seized from illicit sources* could be used at this time, pending TGA approval, is for the limited purpose of scientific research or a clinical trial;
- The NSW Government could decriminalise privately cultivated amounts of medical cannabis - the *"grow your own"* model - without threatening "public health and welfare" nor contributing to "illicit traffic", and without placing Australia in breach of its international obligations under the Single Convention;
- This "*grow your own"* model might not be feasible for all persons, since many patients: a) might not have access to a private and secure outdoor area; b) might not have the capacity or funds to grow cannabis indoors; and c) might be too debilitated (by illnesses) to be able to grow cannabis for themselves;
- Cannabis dispensaries (*buyers clubs or compassion clubs)* have been set up in several cities including in Australia to supply cannabis to medical users on a non-profit basis. There are many difficulties surrounding these clubs with respect to their compliance with International Conventions; furthermore, since cannabis is not, and is unlikely to become, a registered product under the ARTG, as suppliers of a therapeutic product that was not registered they would be contravening the Commonwealth Therapeutic Goods Act;
- Concerned individuals such as a patient's carer might supply cannabis. This could be made possible by legislative amendments to the Drug Misuse and Trafficking Act in regard to cultivation and supply.

14 DISTRIBUTION / DISPENSING ISSUES

14.1 CERTIFICATION

It is necessary to distinguish between smoked cannabis, and cannabis or cannabinoids administered by other methods. If smoked cannabis cannot comply with the therapeutic goods provisions because of the inherent health risks, it cannot be generally prescribed. If and when cannabis can be delivered safely and in compliance with TGA requirements, a prescription model based on existing schedule 4 or schedule 8 drugs could be established.

In the meantime, if smoked cannabis is to be made available for recognised medical conditions, but cannot be prescribed, a medical certification scheme could be established. Guidelines would need to be developed for this medical certification scheme and should include the following requirements:

- that identified or approved conditions be diagnosed by a medical practitioner who would also be responsible for monitoring the patient's well-being and response to treatment.

- legal recognition that those with certification and possibly those who care for certified patients and obtain or cultivate cannabis on their behalf, use or possess the drug lawfully.

Certification would not see cannabis included in the Poisons List but would require appropriate amendments to the Drug Misuse and Trafficking Act to ensure that those certified were not prosecuted. A legal distinction would have to be drawn between those with certification, for whom cannabis possession would be lawful, and recreational users for whom it would not.

The following are some models for medical certification that smoked cannabis would benefit individuals with certain recognised conditions.

14.1.1 CERTIFICATION OF INDIVIDUAL PATIENTS WITH APPROVAL FROM THE NSW DEPARTMENT OF HEALTH

Under this model, a doctor would need to make an application to the Department of Health (NSW) before certifying a patient. Although this model would allow a register of certified patients to be kept, it would also be both costly and time consuming.

14.1.2 CERTIFICATION WITH DEPARTMENTAL AUTHORISATION OF APPROVED DOCTORS OR CLASSES OF DOCTORS FOR ANY PAITENT WHO MEETS SPECIFIED CRITERIA

Under this model, approval of medical certification on an individual patient basis would not be required. Instead individual doctors could be required to obtain Department of Health (NSW) approval to prescribe, or the Drug Misuse and Trafficking Act Regulations could specify a class of doctors authorised to certify.

14.1.3 CERTIFICATION BY APPROVED CLASSES OF DOCTORS FOR PATIENTS WHO HAVE ONE OR MORE SPECIFIED CONDITIONS

Under this model, no Department of Health (NSW) approval would be required before certification that a patient has or more of the specified conditions. The legislation would merely detail the criteria patients must meet before certification and the class of doctor eligible to certify. This model places all responsibility and associated liabilities on the doctor. Regulations could set parameters for the medical conditions eligible for certification and the classes of doctors eligible to certify.

Appropriate amendments to the *Drug Misuse and Trafficking Act* would be required to ensure that those certified possessed and used cannabis lawfully.

15 CIVIL LIABILITY AND OTHER ISSUES[204]

Civil liability is an important aspect of any model for regulating the availability of cannabis and/or cannabinoids for medical use, particularly if cannabis is to be made available outside the ambit of existing State/Commonwealth legislation and if smoking is to be considered as a method of administration. The key considerations are:

- what duty of care is owed to those individuals in receipt of cannabis or cannabinoids on compassionate grounds - either as part of a clinical trial or otherwise;
- how potential civil liability may be minimised or excluded.

15.1.1 LIABILITY IN TORT (NON CRIMINAL MATTERS)

Negligence

Liability in negligence does not flow from every instance of injury or loss. "Negligence is conduct falling below the standard demanded for the protection of others against reasonable harm".[205] In an action for negligence the plaintiff must show:

- that the person accused of a breach of duty (defendant) had a duty of care to the person complaining of the breach (plaintiff);
- that the defendant breached this duty of care; and
- the plaintiff suffered damage as a result of (and not too remote from) this breach.

Breach of duty (or negligence) consists of failure to take reasonable precautions to guard against reasonably foreseeable and not insignificant risks of injury to the plaintiff. Whether the risk is significant or not is determined by four factors: the likelihood of risk occurring; the likely seriousness of the consequences of any risk that occurs; the cost of guarding against any risk that might occur; and the social value of the defendant's activity. The test of whether the damage caused by negligence is too remote is basically whether it was a reasonably foreseeable consequence of the defendant's negligence. In many circumstances this test may be qualified to include unforeseeable damage.[206]

When considering the liability issues which may arise in relation to the controlled availability of cannabis or cannabinoids, it is worth looking at comparable situations – such as the duty of care medical practitioners owe to their patients or medical researchers to their subjects (although there seems to be little Australian or English case law involving the latter).

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[204] The "Civil Liability and Other Issues" section of this Report is informed by and based on the analysis of Norberry, J. (1991) "Legal Issues" in *Feasibility Research into the Controlled Availability of Opioids, Volume 2, Background Papers*, National Centre for Epidemiology and Population Health, Australian National University, Canberra, pp.87-115.

[205] Fleming J, (1992) *The Law of Torts*, The Law Book Company Limited, at p.105.

[206] Trindale FA, and Cane P, (1985) *The Law of Torts in Australia*, Oxford University Press, Melbourne, pp.279-80.

Patients/trial participants

Applying the principles referred to above, a duty of care would apply to all those in receipt of therapeutic cannabis or cannabinoids - whether as patients or as trial participants.

Third parties

A duty of care may also be owed to third parties and, if the tests for negligence were met, someone other than a patient or trial subject could succeed in an action for negligence. A parallel here might be motor vehicle accidents involving third parties. Courts have, for example, held that medical practitioners owe a duty of care not only to their pregnant patients, but also to the foetus. In the case of making cannabis or cannabinoids available in the treatment of individuals, damage to the foetus would need to be considered.

Once children are born they have their own legal rights that may be the subject of litigation.

Action for injuries or loss after a clinical trial

It is possible for an action for negligence to be pursued successfully after the trial has finished –- provided that the tests for negligence have been satisfied. The *Limitation Act 1969* (NSW) requires that a cause of action, "founded on negligence, nuisance or breach of duty" for damages for personal injury be commenced within a period of three years.[207] The limitation period starts running when the injury occurs rather than when the breach of duty took place.

15.1.2 CONSENT AND INFORMED CONSENT

All medical treatment and medical research must be carried out with valid consent. Failure to obtain a valid consent from a patient/subject could result in actions for negligence or trespass.

To be valid, consent must:

- be freely and voluntarily given;
- cover the procedure to be performed;
- be given by a patient/subject who is competent to/capable of giving consent;
- be informed to some degree.[208]

Consent may be nullified if given by a patient/subject who is under the influence of drugs.

[207] See s.18A of *Limitation Act 1969 (NSW)*.
[208] Dix A, Errington M, Nicholson K, Powe R (1988) *Law for the Medical Profession*, Butterworths, Sydney, p.84.

Informed consent

The legal status of the doctrine of informed consent is not clear in Australia. For consent to be valid, it must, however, be based on some information. A practitioner is potentially liable in relation to either trespass or negligence if he or she fails to obtain the consent of a competent patient before undertaking a medical procedure.[209] Information provided may include disclosure of any risks inherent in a procedure (such as the harmful effects of smoking if this is the cannabis treatment method).

In regard to the doctor-patient relationship, sufficient information should be provided so that the patient may make a rational decision about the proposed treatment.

Informed consent has seldom been an issue in relation to medical research or experimentation, although, it has been said that the Nuremburg Code of 1948 imposes an ethical obligation on the researcher, as against the medical practitioner, to obtain the free and informed consent of the subject. The substance of the obligation is, however, unclear.[210] The extent of the information necessary to satisfy informed consent requirements may also depend upon whether the case involves pure experimentation or experimental procedures which are part of a patient's therapeutic regime. [211]

Whatever model of controlled availability is adopted, whether for a clinical trial or otherwise, valid consent must be obtained from patients/subjects, including specific consent to any experimental part of the treatment.

Minors

A useful example is medical treatment or contraceptive advice. In a legal sense, the consent of a parent or guardian is a prerequisite to the treatment of a person below the age of 18 years. However, it has been suggested that "the common law recognises that [a minor] may have the capacity to consent on his own behalf. This exception will apply if the minor has sufficient capacity to understand the nature and effect of the procedures involved, however, the procedures must be for the therapeutic good of the minor and not be of a serious nature".[212] Caution, therefore, must be exercised before any certification of a minor occurred.

15.2 PRIVACY AND CONFIDENTIALITY

15.2.1 PRIVACY

The *Privacy Act 1988* (Cth) applies to medical research that is carried out by a Commonwealth instrumentality or that involves personal information held by a Commonwealth instrumentality. The current *Guidelines for the Protection of Privacy in the Conduct of Medical Research* under s.95 of the Privacy Act were issued in June 1995.

[209] *Ibid*, at p.92.
[210] *Ibid*, at p.99.
[211] *Ibid*, at p.99.
[212] *Ibid,* at p.86.

When medical research involves personal information held by a Commonwealth instrumentality, the guidelines recommend that the agency first use the provisions in the Act allowing "the release of personal information in certain circumstances which could include medical research". If this is not possible, the guidelines should be used to avoid breaching the Information Privacy Principles.

The guidelines recommend that medical research being conducted by a Commonwealth agency be conducted in conformity with the Information Privacy Principles, a Public Interest Determination, or the Guidelines themselves.

The *Epidemiological Studies (Confidentiality) Act 1981* (Cth) would be relevant to any trials being conducted by or on behalf of the Commonwealth in accordance with the regulations to the Act. As well as prohibiting the disclosure of identifying information obtained in the course of the study, this Act also prohibits those involved from disclosing information acquired in the course of the study.

The provisions of the Privacy Act in relation to personal information sought from a Commonwealth agency would still apply to any trial established under the auspices of a State authority.

15.2.2 CONFIDENTIALITY

Confidentiality is also an important issue. It relates to the storage and use of personal information about trial participants; the use of this information by trial personnel; the potential for actions for breach of confidence; and the potential for information to be used by the police and the courts. By the very nature of a trial involving controlled availability of cannabis or cannabinoids, mere disclosure of a subject's involvement may have adverse consequences for that person. Also, information about the activities of trial participants might be used in legal proceedings against that person; and not just in criminal proceedings: the information could also be used in family court matters where, for example, questions of custody or access were being considered. On the other hand, there may be legitimate public and law enforcement interests involved in the disclosure of certain information.

The following options should be considered:

- obtaining consents from trial participants;
- the use of waivers;
- appropriate security in relation to the storage and access of information;
- statutory limits on disclosure and the imposition of penalties for breach;
- the granting of legal privilege against disclosure to trial personnel; and
- provision for withdrawal of consent and the destruction of records where a subject withdraws from the trial.

One example demonstrates the importance of this issue: Health Canada is currently under threat of legal action after a confidential list of the names of some 128 individuals who had been corresponding with the federal department about using cannabis as a medicine was leaked from its controlled substances branch.

15.3 CONCLUSIONS: CIVIL LIABILITY

15.3.1 CONSENT

Although consent can be given verbally or implied, a properly worded consent form should be drafted; patients and trial participants should be given a careful explanation of what is involved; and their signature should be obtained. (N.B. they must be competent to/capable of giving this signed consent).

Pro forma consent forms are often used in conjunction with medical treatment in an attempt to provide some protection against liability. Often this protection is only minimal because such consent forms rarely contain detailed information, especially about the particular procedure being undertaken.[213] Their value may also be limited both by the words used on the form and the procedures adopted in securing the consent and signature of the patient.[214] Also, any ambiguity in the consent form is likely to work against the defendant in legal proceedings.

15.3.2 WAIVERS

By signing a waiver, a person forgoes his or her rights of legal action in respect of loss or damage suffered. A waiver, in writing, should be obtained before the relevant procedure takes place. Waivers apply only to the forfeiture of rights by the signatory; they do not bind third parties. In addition, courts are more likely to read waivers strictly – and thus, construing ambiguities and uncertainties against the defendant in an action for negligence.

15.3.3 STATUTORY EXEMPTION CLAUSES

Statutory exemption clauses are sometimes used to exempt from civil and/or criminal liability the actions of those operating under legislation. If appropriately worded, these clauses should cover third parties. The courts are likely to interpret the clauses strictly and so exclude, for example, actions for negligence. As a matter of public policy, it is open to question whether the rights of patients/trial participants, and particularly the public in general, should be curtailed in this way.

Although this part of the report is concerned primarily with legal issues, it is also important to consider how the public might respond if legislation relating to the controlled availability of cannabis or cannabinoids were to limit or abolish the right to take legal action.

Where legislation containing a sunset clause also includes statutory exemption from liability, it would be necessary to ensure that this exemption, and any other relevant provisions, would continue after the sunset clause came into effect.

15.3.4 SELECTION OF SUITABLE PATIENTS AND TRIAL PARTICIPANTS

In view of the negligence issues discussed above, careful consideration must be given to the inclusion of pregnant women in the trial and particular caution must be exercised in relation to minors.

[213] Ibid, at p.106.
[214] Ibid, at p.105.

15.3.5 CONFIDENTIALITY

The protection of confidentiality must also receive careful attention.

15.4 SUMMARY: CIVIL LIABILITY

There are various ways of ensuring that civil liability would be minimised if clinical trials of cannabis and cannabinoids were to be carried out, and/or if cannabis were to be considered for medical use by eligible patients. They include the following.

- Ensuring that patients/subjects give informed consent. This would mean that they were informed in a clear manner of the possible benefits of cannabis use for their condition(s), as well as the risks associated with cannabis use, particularly cannabis smoking;
- Obtaining a waiver that is worded clearly and unambiguously;
- Inserting statutory exemption clauses, to exempt persons acting under the legislation from civil and/or criminal liability for their actions;
- Carefully selecting clinical trial participants;
- Ensuring that patient/subject confidentiality is maintained.

16 CRIMINAL LIABILITY

Patients and trial participants/personnel face possible liability under both NSW criminal law and under the criminal law of other jurisdictions.[215]

16.1 NEW SOUTH WALES LAW

The current law proscribes activities such as the provision of a substance like cannabis or cannabinoids to a patient or trial subject. The law would need some amendment to protect patients and practitioners, trial personnel and participants from criminal liability if they were operating under a controlled availability model.

New South Wales should also consider providing statutory exemptions from aiding and abetting offences for trial personnel who are carrying out authorised activities in association with a clinical trial.

By way of contrast, some statutory provisions should not be altered in any way. For example, under Part 2 s.12 of the *Road Transport (Safety and Traffic Management) Act 1999* (NSW) it is an offence to use or attempt to use a vehicle under the influence of alcohol or any other drug *(cf Traffic Act, s 5 (2) and (2A))*. It is an offence even if the drug has been legally prescribed. If cannabis or cannabinoids were to be allowed for medical use in any form, this provision should not be relaxed.

16.2 LAWS IN OTHER JURISDICTIONS

As a general principle, the criminal law of a jurisdiction applies to all crimes committed within that jurisdiction regardless of the nationality of the alleged offender; also, in most circumstances, the criminal law of a particular jurisdiction does not have extra-territorial effect.[216] While the lawful cultivation of cannabis in New South Wales would not be a matter over which the courts of other States or Territories would have jurisdiction, difficult questions arise in respect of offences committed in other States or Territories. For example:

- What is the situation if an individual, who has obtained cannabis or cannabinoids lawfully in NSW, takes it into Victoria? and
- If the individual had the cannabis in the context of a clinical trial, could the trial personnel also be considered to have aided and abetted the commission of an offence under Victorian law?

There is a need to explore strategies to protect individual patients, trial participants and personnel from being prosecuted in the courts of other jurisdictions. One possible strategy would be to ask individuals lawfully in possession of cannabis in NSW to give a written undertaking not to take it into, or use it in, another state. A better option might be to enter into an arrangement with other state governments not to prosecute patients or trial personnel.

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[215] The "Criminal Liability" section of this Report is informed by and based on the analysis of J Norberry, (1991) "Legal Issues" in *Feasibility Research into the Controlled Availability of Opioids, Volume 2, Background papers*, National Centre for Epidemiology and Population Health, Australian National University, Canberra, pp.87-115.

[216] Bates AP, Buddin TL and Meure DJ (1979) *The System of Criminal Law, Cases and Materials in NSW, Victoria and South Australia*, Butterworths, Sydney, p.130.

- Individual patients, trial participants and trial personnel should all be made aware of the potential for exposure to criminal liability if they enter other jurisdictions with cannabis in their possession.

16.3 POLICE CONCERNS

The following police concerns also need to be addressed.

- That cannabis or cannabinoids supplied lawfully to one individual could be used unlawfully; if, for example, that person were to sell it to someone else;
- The possibility of trafficking by trial personnel. Should security checks of trial personnel be implemented and, if so, what should they encompass? Security measures and record keeping procedures at any point of administration or distribution would need to be stringent;
- The risk that patients or trial participants will supplement licit cannabis with cannabis that has been illicitly obtained/cultivated. What sanctions, if any, should apply in such circumstances and how would they affect policing?
- The conflict between the need to protect the confidentiality of patients/trial participants and the legitimate need of the police to know their identity so that law enforcement can be carried out and people in lawful possession of cannabis are not harassed. The police would, for example, have a legitimate need to know whether an individual was in lawful receipt of cannabis if they had reasonable cause to suspect that the person was committing a drug offence (e.g., the authenticity of a prescription or certification for cannabis or cannabinoids was doubtful).

One option would be a well-maintained register of individuals who are currently in lawful receipt of cannabis kept by the Department of Health, or, in the case of a clinical trial, by the hospital or facility responsible for conducting the trial. Police could apply for access to this information by making a request to a designated person. This designated person would decide whether the requesting officer had a "need to know" and, if appropriate, would proceed to make the request to the clinic or hospital. It is essential that these decisions be properly documented. Also, careful consideration should be given to the type of information to be kept on the register. Should it include, for example, a physical description of the subject for identification purposes, and information about dosage and dosage schedules?

Police cooperation is vital and so they must be fully consulted and informed about any proposed changes to current laws in relation to cannabis and cannabinoids – whether these changes are for the purposes of clinical trials or otherwise.

17 CONCLUSIONS: LEGAL AND REGULATORY OPTIONS

The law relating to cannabis and cannabinoids is a complex array of Commonwealth, State and Territory legislation. The following are some important legal which issues need to be addressed when considering possible options for making cannabis available for medical use in New South Wales.

- satisfying the Commonwealth that the proposed course of action would not place Australia in breach of its international treaty obligations;
- obtaining requisite licenses and permits from the Commonwealth for cannabis to be imported;
- complying with any obligations imposed by the TGA;
- addressing the statutory impediments to clinical trials in NSW;
- addressing questions of liability in negligence, consent, confidentiality, minors, etc. attempts to limit or exclude liability, especially using statutory exemption clauses, have ethical, political as well as legal implications;
- providing appropriate indemnities to medical professionals and clinical personnel;
- providing appropriate protection against criminal liability in New South Wales;
- providing information to both patients and medical professionals concerning criminal liability in other jurisdictions.

PART FOUR: REFERENCES AND APPENDICES

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APPENDIX A – WORKING PARTY MEMBERSHIP

Chair

Professor Wayne Hall
Executive Director, National Drug and Alcohol Research Centre
The University of New South Wales

Members – academic/clinical

Associate Professor MacDonald J Christie
Head of Department of Pharmacology, and Medical Foundation Fellow,
The University of Sydney

Professor Richard O Day
Professor of Clinical Pharmacology, The University of New South Wales
and Director of Clinical Pharmacology and Toxicology, St Vincent's Hospital

Professor Laurence E Mather
Professor of Anaesthesia and Analgesia (Research), The University of Sydney
Centre for Anaesthesia and Pain Management Research, Royal North Shore Hospital

Members – key stakeholder groups

Dr David Currow
Director, Nepean Cancer Care Centre and
Director of Palliative Care Services, Wentworth Area Health Service
Representing the NSW Cancer Council

Mr Robert Griew
Chief Executive Officer, AIDS Council of NSW

Ms Margaret Hole
Law Society of NSW

Professor Michael Kidd
Professor of General Practice and Head of Department of General Practice,
The University of Sydney
Representing The Royal Australian College of General Practitioners (NSW Faculty)

Dr Michael Noel
Career Medical Officer (Palliative Care), Wentworth Area Health Service
and Councillor, Australian Medical Association (NSW Branch)
Representing the Australian Medical Association (NSW Branch)

Members – NSW Government agencies

Commander Alan Baines
Acting Local Area Commander – Kings Cross
NSW Police Service

Mr Geoff Barnden
Director, Office of Drug Policy
The Cabinet Office

Mr Andrew Haesler
Director, Criminal Law Review Division
Attorney General's Department

Mr John Lumby
Chief Pharmacist and Manager, Pharmaceutical Services Branch
NSW Department of Health

Researchers

Ms Louisa Degenhardt
Ms Julia Grix

Secretary

Mr Carl Green
Office of Drug Policy
The Cabinet Office

APPENDIX B – TERMS OF REFERENCE OF THE WORKING PARTY

- To assess the efficacy and safety of cannabis for medical purposes.

- To review the extant medical and scientific literature.

- To establish what further research is required.

- To establish if and how cannabis can be effectively administered with the least harm to patients.

- To establish if and how cannabis, or any cannabinoid substances, should be supplied for medical use and how diversion for recreational use or dealing or trafficking could be avoided in these circumstances.

- To identify legal, ethical, pharmacological, physiological, mental, general health and community implications and issues concerning the use of cannabis for medical purposes.

- To make recommendations to the Expert Advisory Group on Drugs.

APPENDIX C – LIST OF SUBMISSIONS RECEIVED

Submissions invited

Australian Pharmacists Against Drug Abuse

Australian Pharmaceutical Manufacturers Association Inc.

The Australian Professional Society on Alcohol and Other Drugs

Australasian Society for HIV Medicine Inc.

Catholic Health Australia Inc.

GW Pharmaceuticals Ltd (UK licensed cannabis producer)

Multiple Sclerosis Society of New South Wales

New South Wales Nurses' Association

People Living With HIV/AIDS

Pharmaceutical Society of Australia (NSW Branch) Ltd

The Pharmacy Guild of Australia (NSW Branch)

The Royal Australian and New Zealand College of Psychiatrists (NSW Branch)

The Royal Australasian College of Physicians

The Royal Australian Society of Ophthalmologists

The Salvation Army (Australia Eastern Territory)

Submissions volunteered

Australian Committee for Medical Cannabis

Australian Parents for Drug-Free Youth

NSW Breast Cancer Action Group

Ms Lucy Charlesworth

The Kookie Project

Nimbin Hemp Embassy

APPENDIX D – DELIVERY SYSTEMS FOR MEDICAL CANNABIS

Laurence Mather, Professor of Anaesthesia and Analgesia (Research), University of Sydney at Royal North Shore Hospital, St Leonards NSW 2065.

Most recreational cannabis users smoke the dried leaves and flowers of the cannabis sativa plant. When they do so aerosol particles of active cannabinoids and other substances in the smoke are deposited on the mucosa of the respiratory tract. If the smoke is deeply inhaled, the particles are carried to the deeper portions of the respiratory tract, including the air sacs, where cannabinoids are rapidly and efficiently absorbed into the blood that perfuses the lungs. If the smoke is only lightly puffed, then the cannabinoids will be deposited in the upper portions of the respiratory tract where they are more slowly and less efficiently absorbed through the mucous membranes, of the mouth and upper respiratory tract. Some cannabinoids may be swallowed and absorbed orally. The pattern of deposition depends upon the velocity of the smoke aerosol particles, how deeply the smoke is inhaled, the sizes and composition of the smoke particles, the nature, density and composition of the material matrix, and the way that it is burned.

After they are absorbed and subjected to any first pass metabolism in the lungs, the cannabinoids and other substances are transported in the arterial blood to all regions of the body to produce their effects (and side effects). Cannabinoids are in this way indirectly delivered to the receptors in the central nervous system (including spinal cord) and elsewhere on which they act. Administration of cannabis by smoking is a reasonably efficient and inexpensive way to deliver cannabinoid drugs but it has several problems: variable the amounts of the active and other substances are delivered; the products of smoking are deleterious to health; and some people find that smoking is an unacceptable method of delivering a drug.

Recent reviews of the potential medical uses of cannabis conclude that there is sufficient anecdotal and pre-clinical evidence of the potential therapeutic uses of cannabinoids to warrant controlled clinical trials of THC and other cannabinoids for the control of nausea and vomiting, pain and muscle spasm, and for stimulation of appetite in AIDS and cancer-related wasting. [e.g. House of Lords, 1998; Joy *et al.*, 1999; Martin, 1999].

Smoking cannabis is a pharmaceutically and medically unacceptable way of administering cannabinoids because: it delivers an unreliable dosage by using an unstandardized natural plant product; it is an uncontrolled and potentially harmful delivery system that involves vaporization and pyrolysis. Oral administration of THC and other cannabinoids have limited value for medical purposes (Joy et al, 1999).

Clinical trials of the medical uses of cannabinoids require delivery of a standardized dose of standardized substance(s), preferably by devices that are *affordable* to patients. These recent reviews have both recommended that research be undertaken to develop "rapid-onset, reliable, and safe delivery systems" that do not involve smoking (e.g. House of Lords, 1998; Joy et al, 1999). This paper assesses the likelihood of developing these methods of delivery and dosage forms of medical cannabinoids.

A classification of drug delivery systems

Drug delivery systems can be classified as direct and indirect. *Direct* methods deliver the drug to the region of the receptors on which they act and the drug spreads to the receptors by diffusion and bulk flow of drug in solution. *Indirect* methods involve the drug being absorbed into the blood for delivery to the target receptors in the blood that flows to the region containing the relevant receptors. Direct routes allow for specific local action; indirect routes make it difficult to obtain therapeutic effects without side effects.

The more familiar forms of drug delivery, based on analogy with opioid analgesics, are listed in Table 1. Apart from topical administration, where drugs are used for their local actions, direct routes are more invasive and require a very skilled drug administrator. Direct routes can place opioids receptors in the brain (via intracerebroventricular injection) and spinal cord (via subarachnoid and epidural injections). Cannabinoids also bind to receptors designated CB_1 that occur in particular areas of the brain and spinal cord [Ameri, 1999]. Although direct routes have been used in animal laboratory experiments, there is to date no direct system of cannabis delivery in humans.

The principal indirect routes for opioid analgesics, include oral administration; intravenous, intramuscular, and subcutaneous injection; and sublingual, transpulmonary, rectal, vaginal, buccal, intranasal and transdermal absorption methods. Some of these indirect routes are feasible for cannabinoids which can be delivered by the bloodstream to the central nervous system CB_1 and peripheral CB_2 receptors. When more is known about these receptors, it may become possible to deliver cannabinoids to non-central nervous system CB_2 receptors by more direct, but relatively noninvasive, routes to produce greater selectivity of action. It remains to be seen whether any of the indirect methods achieve satisfactory separation of the desired therapeutic and the undesired side effects of cannabinoids.

Table 1: A synopsis of the usefulness of the various indirect routes used for the administration of drugs, for example, as used for opioid analgesics in pain management

	Absorption surface area	*Local perfusion*	*First pass metabolism*	*Reliability*	*Patient acceptance*
Oral	++	++	– (?)		+++
Intramuscular	+	++	+++		+
Intravenous	+++	+++	+++		+
Subcutaneous	+	++	+++		+
Transpulmonary	+++	+++	++(?)		+++
Rectal	+	+	++(?)		– (?)
Vaginal	+	+	++(?)		– (?)
Buccal	+	++	++(?)		++
Sublingual	+	++	++(?)		++
Intranasal	+	++	+++		++
Transdermal	+	+	+++		+++

+ indicates favourable outcome; – indicates unfavourable outcome; (?) indicates variability: due to the drug, the need for avoidance of swallowing, or patient preferences

Cannabinoid delivery

An orally administered cannabis preparation was introduced into Europe by Dr WB O'Shaughnessy, an Irish surgeon, in 1842, to relieve pain, muscle spasm, convulsions in tetanus, rabies, rheumatism and epilepsy. It was subsequently used for these and a range of other conditions, including increasing uterine contractions in child-birth. Usage later declined, probably because the preparations varied in potency, absorption and/or bioavailability after oral administration, making it difficult to optimise dosage. Cannabis was dropped from the 1932 British Pharmacopoeia but Cannabis, Cannabis Extract and Cannabis Tincture remained in the British Pharmaceutical Codex 1949 and could be prescribed by GPs until relatively recently. Cannabis Extract is an alcoholic extract of Cannabis BPC prepared from Cannabis BPC by percolation. Cannabis Tincture BPC is prepared by dilution of Cannabis Extract BPC. The monograph specified standards for alcohol content and density (weight per millilitre) but there was no standard for either the total content of cannabinoids or the proportions of individual cannabinoids.

Although a wide variety of cannabinoids has been partially or fully synthesised over the past 50 years,

research has been impeded by variability between cannabis plants in the amounts of cannabinoids and other substances. It is sometimes claimed that the mixture of cannabinoids found in cannabis plants is not pharmacologically equivalent to Δ^9-tetrahydrocannabinol (THC) but from a research perspective it is logical to use a pure substance rather than a mixture.

The supply of THC regulated cigarettes by the US National Institute of Drug Abuse (NIDA), and the recent selective breeding of cannabis plants seem to provide cannabis in which the amounts of naturally-occurring cannabinoids THC, cannabidiol (CBD) and cannabinol (CBN) are better controlled than cannabis grown under normal growing conditions [e.g. Cartwright and Mather, 1972]. This is integral to trials underway in the UK.

Issues with different routes of drug delivery

The main *anatomical-physiological* factors that increase the absorption of any drug are: (i) large surface area of absorbing membrane(s) exposed to drug, (ii) high velocity of local blood flow carrying drug away from the site (local perfusion), and (iii) low "first pass metabolism" or "first pass extraction" between the site of drug administration and the systemic blood circulation (*ergo* drug receptors).

Drugs absorbed from the gut are subject to favorable conditions of (i) and (ii) but not (iii). They are also subject to vagaries of gastrointestinal motility that may influence absorption for specific regions of the gut. Drugs absorbed from the lungs are favorable on (i), (ii) and (iii) but impose strict requirements on particle size and velocity of medication droplets. Aesthetic acceptability, difficulty and compliance of use, cost, and other factors can all affect the pharmacological usefulness of a drug. For this reason it is often said that the choice of route of administration (of pain relieving drugs) may be as important as the choice of drug for some patients.

The preferred reference route for comparison is **intravenous injection** that has been used in a number of studies to describe the intrinsic behaviour of individual cannabinoids within the body. Ohlsson *et al.*, [1980] reported on the THC plasma concentrations after smoked and orally ingested cannabis in comparison to intravenous injection. Wall *et al.* [1983] produced data on the time course of THC and its metabolite concentrations after oral and intravenous dosing. The pharmacokinetic properties of THC revealed by these studies are that it has extensive tissue distribution and low renal excretion, as would be expected of a very lipophilic substance. It also has a fairly low total body clearance and long terminal half-life (time taken for 50% loss) of 20 to 30 hours). The latter is consistent with its slow washout from tissues. However, the measured oral bioavailability (~6% [Ohlsson *et al.*, 1980; Wall *et al.* 1983] is less than that predicted from the total body clearance after intravenous administration (~10 L/h [Wall *et al.* 1983]), suggesting that some of the oral dose of THC might be lost before delivery to the liver.[217] Because THC is widely distributed in body tissues, with extensive uptake in fatty tissues, low levels persist over a prolonged period. With a half-life of 30 h, some of the effects of THC, such as appetite stimulation, may persist for 24 h or longer. The prolonged activity may also be due in part to an active metabolite, 11-hydroxy-Δ^9-THC, which is present in similar concentrations to THC [Wall *et al.* 1983].

For most recreational cannabis users the most common mode of administration is **transpulmonary**, that is, the inhalation of smoked material. Absorption of THC by this route is very rapid [Huestis *et al.,*

[217] The ratio of the total body clearance (~10 L/h) to the hypothesized liver plasma flow (drug delivery) to the liver (~50 L/h) gives an estimate of the fraction of dose subjected to first pass extraction if ingested orally. The value (~20%) is greater than the measured oral bioavailability (~6%) suggesting that some of an oral dose may be lost by extraction (to chemical degradation or metabolism) before delivery to the liver; this would be assumed, respectively, to be in the acid of the stomach contents or in the wall of the gut.

1992]. Pharmacokinetic calculations of the absorption rate or first pass extraction have not been reported in the literature (although these would only be approximations because of the rapidity of absorption and the imprecision of the dose and dosage method). Systemic availability of THC by smoking was estimated to average 18% [Ohlsson *et al.*, 1980] although variability due to smoking style would be expected. There is significant variability in early plasma THC concentrations even when a standard smoking protocol and standardized THC content cigarettes are used [Huestis *et al.,* 1992]. This can be ascribed to variability in the amounts of THC that escape pyrolysis, are vaporized, and delivered in the inspired smoke stream. Additional variability occurs after delivery when larger inhaled aerosol particles are deposited in the oro-pharynx and swallowed.

The deposition of pyrolysis products that condense as "tars" is a major pharmacological disincentive to smoking as a route (as it is with tobacco smoke). Attempts to clean the smoke aerosol by using vaporizers (rather than "pyrolyzers') and water traps do not acceptably reduce the ratio of tar to THC [Gieringer, 1996]. Attempts to produce cannabis with higher THC content to reduce the amount smoked (and tar delivered) for a desired dose of THC may prove to be more successful [e.g. Stix, 1998]. The only research pertinent to this issue is a study of 10 cannabis smokers which indicated that it was not easy to titrate smoke (and thus tar) to achieve a desired subjective "high" [Matthias *et al.* 1997]. This may be due, in part, to a significant lag between smoke inhalation and perceived effect that result from absorption in the lung and transport of the cannabinoid(s) to brain receptors.

Oral administration is the most useful route for administering systemically active drugs in patients with a properly functioning gut. It is simple to perform, requires little or no training, and can be used without time constraint. However, it is the most anatomically and physiologically complex route, with rate and extent of absorption affected by a multitude of factors, such as, the nature and timing of the last meal. Oral capsule cannabinoid preparations (notably Marinol™ and Cesamet™) are commercially available, and anecdotally cannabis "cookies" have a following. Nonetheless, the oral route does not allow patients to adjust their dosage rapidly and reliably to achieve the desired effect with a minimum of side effects. For this reason, the anecdotal evidence is that these preparations are not liked by many patients. They may also be more expensive than using the smoked plant. When judged by metabolite production [Wall *et al.* 1983], oral administration produces almost complete (90 to 95%) absorption of THC from the gastrointestinal tract but delivery into the systemic circulation is variable and slow because of extensive metabolism in the liver. Only 4 to 12% [chocolate cookie vehicle (Ohlsson *et al.*, 1980)] or 10 to 20% [sesame oil vehicle (Wall *et al.* 1983)] of the administered dose reaches the systemic circulation.

Rectal administration of THC (as the hemisuccinate ester) has been compared to oral THC in very limited published trials. The rectal route was found to give much greater systemic bioavailability than the oral route. A ~30-fold difference was found in one preliminary study [Mathes *et al.*, 1993] and a ~2-fold difference in a more rigorous trial but in only two patients [Brenneisen *et al.*, 1996]. The reason is that the majority of blood-borne drug is absorbed from the rectum which does not drain into the portal circulation (and thus avoids full first pass metabolism). However, the results from rectal administration are sensitive to the position of the suppository. If it is inserted too far it behaves more like oral administration; if it is not inserted far enough, it may be uncomfortable and come out. Rectal administration is not rapidly titratable to drug effect but it is suitable for long-term administration where maintenance of effect is required. It usually has a slower rate of absorption than oral administration, and it is generally aesthetically less acceptable to Australian patients than other routes.

Cannabis preparations

Medical and lay writers sometimes claim that novel inhalational (transpulmonary aerosol), intranasal (spray), sublingual (lozenge) or transdermal ("skin patch") dosage forms of cannabis or cannabinoids will

soon be available or are undergoing trial [e.g. Stix, 1998]. The assumption seems to be that because these dosage forms and routes have been or are being developed for opioid analgesics they are applicable to cannabinoids. However, no such cannabinoid delivery systems are in the public domain, and moreover, they are unlikely to be developed because the physicochemical properties of THC and its congeners, particularly their lack of water solubility, make them unsuitable formulations for these dosage forms.

THC is about 10,000 times more soluble in oily media than in water [Garrett and Hunt, 1974]. This property aids its uptake from respiratory tract mucous membranes into blood, and from blood into the central nervous system. However, it makes formulation of dosage forms extremely difficult, with the exception of oily preparations such as Marinol™ (which consists of THC in sesame oil dispensed in capsules).

When THC is intravenously injected in research studies, it is dissolved in alcohol and injected into a fast flowing intravenous fluid line, or it is dispersed in a detergent or protein solution. Most parenteral dosage forms require a water based solution or dispersion of drug. Notable exceptions are oily vehicles used for depot (usually intramuscular) injections, for rectal suppositories or vaginal pessaries, some organic polymer gels for transdermal skin patches and organic solvent based aerosols used for inhalation. The latter were typically based upon chlorofluorocarbon (CFC) solutions that also acted as the aerosol propellants [e.g. Mather *et al.* 1998] but CFCs are no longer used. Older studies of the uses of cannabis as a bronchodilator in treating asthma often used CFC based delivery systems [see Ashton, 1999].

Aqueous solutions of drugs are normally required for dosage by aerosols delivered and/or made by nebulizer methods, for intranasal sprays, and for sublingual and buccal lozenges. The important characteristic of sublingual and buccal lozenges is their retention at the relevant mucous membranes in the oral cavity. Some portion of sublingual and intranasal sprays are swallowed. It may be possible to develop a novel solid sublingual or buccal lozenge from a cannabinoid suspension preparation, but this would differ from the more usual matrix of a solid solution, e.g. the fentanyl oral transmucosal preparation commonly known as the fentanyl "lollipop".

A highly lipophilic substance does not readily lend itself to passive transdermal (skin patch) dosage where rapid titration of dosage to effect is required because of a depot of the substance forms under the skin [Grond et al., 2000]. More recent active (or iontophoretic or electroporation) forms of transdermal dosage may be more useful. These use a very weak electric current to induce transport (and absorption) the drug. Such systems have been found successful for delivering the opioid analgesic, fentanyl [Grond et al., 2000; Gupta et al., 1999] and hydrophilic peptide and protein molecules [Green, 1996]. THC is not a crystalline material; it is a resinous semisolid at room temperature which precludes the dry powder method of administration used in some inhalation devices.

Press releases from British GW Pharmaceuticals Ltd describing their sponsored trials originally specified their delivery form as transpulmonary [Boseley, 1998] but more recent press releases they state that the drug will be "sprayed under the tongue". Studies of morphine suggest that the majority of the dose deliver in this way is swallowed, producing a bioavailability and rate of absorption the same as oral administration [Podczeck, 1996]. A major (£950,000) 3-year project recently funded by the Medical Research Council (UK) to assess the therapeutic effect of THC in multiple sclerosis is reportedly using administering cannabis extract in sesame oil. It is unclear whether these changes in dosage method have arise from a closer analysis of water insolubility or from pilot bioavailability data. It is clear, however, that a transpulmonary system would be problematic, if not impossible, given public domain knowledge.

Because THC is not water soluble, several research groups have synthesized water-soluble cannabinoid derivatives to aid formulation [e.g. Zitko *et al.*, 1972; Pop *et al.* 1996a,b; Martin *et al.,* 1998; Pop *et al.*, 1999]. There are as yet no public domain data on these novel drug delivery forms but they are active

cannabinoids when assessed by pharmacological measures, they bind to cannabinoid receptors, or they are prodrugs. The THC hemisuccinate ester mentioned above [Mathes *et al.*, 1993; ElSohly, 1995; Brenneisen *et al.*, 1996] is a THC prodrug.

It may require a number chemical synthetic steps to make a drug, such as a cannabinoid, intrinsically water soluble. This typically involves making a salt through incorporation of an ionizing functional group, such as, an acid or an amine, either with or without a prodrug strategy. The alternative is to make a cannabinoid preparation solution e.g. by cyclodextrin complexation or dispersion through manipulation with pharmaceutical additives. Although there is still much work to be done, success would allow the development of novel dosage forms for use in human medicine, with significant gains in intellectual property.

Future possibilities

A number of companies involved in developing innovative dosage forms were asked their views on the potential for developing a cannabinoid preparation that retained the benefits of rapid absorption offered by smoking without its adverse effects. Most believed that it may be possible but predicted that it would take considerable time, especially if novel cannabinoid(s) were involved. They were not convinced that there were sufficient financial incentives to undertake this work in the absence of significant seeding funds. Two issues are at stake: the mode of delivery and the preferred drug for delivery.

The House of Lords report suggested that THC be administered by inhalation, sublingual and rectal routes. To this could be added an active transdermal dosage form and buccal as a special case of sublingual. Inhalation seems most attractive because it most readily replaces smoking.

Some companies have developed sophisticated transpulmonary breath activated systems for transpulmonary delivery of drugs via the mouth that allow rapid titration of dose to response. For example, AERx™ systems for morphine, fentanyl and insulin (Aradigm Corp., Hayward, California), work with aqueous drug solutions [e.g. Ward *et al.* 1997]. They use advanced design features such as a logic circuit that senses the volume and amount of breath drawn and permits the dose administration when these are within predefined specifications of breath flow. This provides a very tight control over the size of the drug particles so that they reach the deep regions of the lungs where efficient absorption occurs. It also uses a unique system to extrude the aqueous drug solution through a membrane to aerosolize the particles.

The current requirement for aqueous drug solutions precludes their use with cannabinoids. Alternative technology to generate aerosol, such as by ultrasonic energizer to aerosolize the particles of an aqueous solution (e.g. Sheiman Ultrasonic Research Foundation, Sydney, NSW; Aerogen Corp., Sunnyvale, California) could work with a suspension or dispersion of drug in an aqueous matrix.

Even if a major company were to develop such a device for cannabinoids, the cost of these sophisticated devices would be too high for the target patient population. Nonetheless, it is of special interest that a Sydney inventor (Dr Vladimir Sheiman) has developed a small, inexpensive ultrasonic driven battery-powered aerosol device [Sheiman, 1999] that might be able to deliver cannabis from a suspension. This device has a "chimney" type cell which has been found to be more effective than the traditional "pail" type cell [Serita, 1997].

Other inhalation systems are used for delivery of nicotine to reforming smokers but they do not give an aerosol for deep airway absorption. The majority of absorption occurs in buccal and upper respiratory tract membranes. Dry powder systems are used clinically to administer drugs for asthma therapy and

they are being explored for other substances, e.g. proteinacious substances for vaccines. It is uncertain whether these could be adapted to accommodate resinous substances such as THC.

Sublingual and buccal drug administration could be developed pharmaceutically from drug suspension but models for these dosage forms normally use solutions. Both have been used previously with water-soluble opioid analgesics for titration to effect within reasonable limits. However, their use with cannabinoid suspensions may only lead to a complex method of oral administration. Both rectal and passive transdermal administration are unlikely ever to fulfil the need for rapid titration of dose to effect. Active (iontophoretic or electroporation) transdermal systems could possibly be successful as these have been used with large molecules, including hydrophilic proteins.

THC would seem the preferred substance with present knowledge. For further developments such as more water soluble derivatives, approaches could be made to the Herbal Medicines Research and Education Centre (HMREC), Faculty of Pharmacy, University of Sydney. They have indicated that the development of water-soluble cannabinoid derivatives would fall within their interests and expertise. The HMREC was established in July 1997 to carry out high quality research and education on herbal and complementary medicines.

Recommendations

At this stage of (public domain) knowledge, there are no reliable, inexpensive, novel dosage forms of THC or other cannabinoids that can be administered for medical purposes to facilitate the titration of dose to response.

In order to develop these further experimentation is needed into: (a) making cannabinoids that are more water soluble by chemical derivatisation; (b) determining the intrinsic pharmacological and cannabinoid receptor binding actions of these new cannabinoids; (c) determining whether their actions are due to biodegradation to their parent cannabinoids; (d) examining their potential in animal models for innovative delivery, e.g. by aerosolisation into the lungs or by iontophoresis; (e) evaluating any promising approaches of novel cannabinoids or their routes of delivery in human subjects under controlled conditions in the normal manner for early drug development. These types of study comprise a significant program of experimentation that would require major sponsorship by the National Health and Medical Research Council, with or without pharmaceutical industry partnership.

In the immediate future, the Sheiman ultrasonic nebuliser, invented locally, has the greatest promise. Any funds for development-application funds that the government may provide would be well-invested in this area and in local development of water-soluble cannabinoids. At the same time, relatively inexpensive research could be done into formulating cannabinoid suspensions into solid lozenge dosage forms that might be suitable for buccal or sublingual routes. The necessary research expertise is available locally and the level of funding required is within reach of the State government, with or without pharmaceutical industry partnership. In any event, close monitoring and collaboration with international research groups working on these issues should be encouraged.

Representative literature

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Glossary of terms relevant to routes of drug administration

Bioavailability – the ratio of drug delivery to the systemic blood circulation when administered by one route compared to a reference route. This is often construed as *absolute* or *systemic (bio)availability* if the reference route is intravenous for which systemic bioavailability is, by definition, 100% because the drug is placed in the systemic circulation; otherwise it is *relative (bio)availability between two routes*. Drug delivery is usually measured as the time integral of drug blood concentrations, although other measures, e.g. drug effect, can used to measure, e.g. *physiological availability*. Both the *rate* and *extent of (bio)availability* are outcome variables. Most commonly, and almost generically, *"bioavailability"* is used in connection with drugs administered orally, but the term strictly applies to all routes (see "first pass metabolism").

Buccal – placed for across the mucous membrane of the cheek to avoid the portal circulation.

Epidural (spinal) –injected outside the spinal fluid chamber so that drug diffuses into spinal fluid.

First pass extraction, first pass metabolism – loss of drug dose due to metabolism (specifically, biotransformation to a different chemical entity, i.e. metabolite) and/or other reasons (such as high affinity binding) between the site of drug administration and the systemic blood circulation. Most commonly this is used in connection with drugs administered orally due to the drug being absorbed from the gut and carried in the portal circulation to (metabolising enzymes in) the liver before ongoing to the systemic circulation. Strictly applies to all routes due to the drug being carried in the blood from all drug administration portals to the lungs that have the capacity to metabolise, to various extents, some drugs (and to excrete others into breath) before delivery via the arterial blood to all parts of the body. First pass extraction due to high affinity binding is sometimes mistaken for metabolism. Losses due to binding are normally recovered over shorter or longer time courses: this is a controversial area in research.

Intracerebroventricular – injected into the ventricles (water filled chambers) of the brain.

Intramuscular – injected into a muscle.

Intranasal – sprayed up the nasal passages.

Intravenous – injected into a vein.

Oral – by mouth, delivers into the portal circulation.

Parenteral – other than by the gut.

Perineural – injected around nerve(s), typically for producing local anaesthesia.

Portal – point of entry (also, less commonly, used for a device for aseptic injection of drugs, usually placed under the skin, used for delivery of drugs to a different site, typically intrathecal).

Portal vein, portal circulation – collected venous blood drainage of the gut that delivers solutes to the liver.

Prodrug – a drug substance that is biologically or chemically converted in the body to a pharmacologically (more) active drug substance than that administered.

Receptor – a specific chemical entity that binds with a drug to produce a pharmacological outcome, i.e. induce, or block, a biological response.

Rectal – placed into the rectum in a suppository (a slowly dissolving dose form) to avoid the portal circulation.

Subarachnoid (spinal) – injected into the spinal fluid around the spinal cord.

Subcutaneous – injected under the skin.

Sublingual – under the tongue to avoid the portal circulation.

Systemic – from the whole body.

Topical – placed on the surface.

Transdermal – across the skin.

Transpulmonary – across the air sacs of the lungs.

Vaginal – placed into the vagina in a pessary (a slowly dissolving dose form) to avoid the portal circulation.

House of Lords Select Committee: Science and Technology Committee on Cannabis. Recommendations paragraph 8.4: "…we recommend that research be promoted into alternative modes of administration (e.g. inhalation, sub-lingual, rectal) which would retain the benefit of rapid absorption offered by smoking, without the adverse effects."

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Maximum Penalties for Indictable Offences under Drug Misuse and Trafficking Act 1985

	Summary			Indictment					
	small[1] s 30	*indictable* s 31	*less than commercial*[2] s 32(2)	*less than commercial*[3] s 32		*commercial* s 33		*large commercial* s 33(3)	
	all drugs	all drugs	cannabis	cannabis	all others	cannabis	all others	cannabis	all others
Cultivate prohibited plant: 23(1)(a), 23(2)(a)	$5, 500 and 2 years	$11, 000 and 2 years	$11, 000 and 2 years	$220, 000 and 10 years	$220, 000 and 15 years	$385, 000 and 15 years	$385, 000 and 20 years	$550, 000 and 20 years	$550, 000 and life
Supply prohibited plant: 23(1)(b), 23(2)(b)	$5, 500 and 2 years	$11, 000 and 2 years	$11, 000 and 2 years	$220, 000 and 10 years	$220, 000 and 15 years	$385, 000 and 15 years	$385, 000 and 20 years	$550, 000 and 20 years	$550, 000 and life
Possess prohibited plant: 23(1)(c), 23(2)(c)	$5, 500 and 2 years	$11, 000 and 2 years	$11, 000 and 2 years	$220, 000 and 10 years	$220, 000 and 15 years	$385, 000 and 15 years	$385, 000 and 20 years	$550, 000 and 20 years	$550, 000 and life
Manufacture prohibited drug: 24(1), 24(2)	$5, 500 and 2 years	$11, 000 and 2 years	$11, 000 and 2 years	$220, 000 and 10 years	$220, 000 and 15 years	$385, 000 and 15 years	$385, 000 and 20 years	$550, 000 and 20 years	$550, 000 and life
Supply prohibited drugs: 25(1), 25(2)	$5, 500 and 2 years	$11, 000 and 2 years	$11, 000 and 2 years	$220, 000 and 10 years	$220, 000 and 15 years	$385, 000 and 15 years	$385, 000 and 20 years	$550, 000 and 20 years	$550, 000 and life

[1] All quantities in the Schedule to the Act are based on a range with the exception of "less than commercial" quantities dealt with on indictment, which can overlap with small and indictable quantities. All other quantities thus cover a discrete range - for example, an indictable quantity is more than the "small" quantity but less than, or equal to an "indictable" quantity.

[2] A "less than commercial" but more than "indictable" quantity of all prohibited drugs other than cannabis cannot be dealt with summarily.

[3] On indictment, the less than commercial quantity can be any amount - that is, it may include "small" or "indictable" quantities.

Maximum Penalties for Indictable Offences under Drug Misuse and Trafficking Act 1985 (continued)

	Summary			**Indictment**					
	small s 30	*indictable* s 31	*less than commercial* s 32(2)	*less than commercial* s 32		*commercial* s 33		*large commercial* s 33(3)	
	all drugs	all drugs	cannabis	cannabis	all others	cannabis	all others	cannabis	all others
Supply (except cann. leaf) to minor: 25(1A), (2A)[4]	$5, 500 and 2½ years	$11, 000 and 2½ yrs	$11, 000 and 2½ yrs	$264, 000 and 12 years	$264, 000 and 16½ yrs	$462, 000 and 25 years[5]	$462, 000 and 25 years	$660, 000 and 24 years	$660, 000 and life
Ongoing drug dealing: 25A	--	--	--	--	--	--[6]	**$385, 000 and 20 years**[7]	--	--
Conspiring to commit offences: 26	$5, 500 and 2 years	$11, 000 and 2 years	$11, 000 and 2 years	$220, 000 and 10 years	$220, 000 and 15 years	$385, 000 and 15 years	$385, 000 and 20 years	$550, 000 and 20 years	$550, 000 and life
Aiding, abetting in or outside NSW: 27, 28	$5, 500 and 2 years	$11, 000 and 2 years	$11, 000 and 2 years	$220, 000 and 10 years	$220, 000 and 15 years	$385, 000 and 15 years	$385, 000 and 20 years	$550, 000 and 20 years	$550, 000 and life

[4] Penalties for supplying to minors are confusingly set out in two places under the legislation: ss 30-33 (general) and 33AA(2) (dealing specifically with minors).
[5] The offence excludes cannabis leaf. Therefore, the penalties in relation to cannabis are for cannabis plant, oil and resin.
[6] The offence of commercial dealing does not apply to any form of cannabis.
[7] The offence of commercial dealing does not depend on the quantity of the drug supplied. It is therefore, the only indictable offence which is constructed in this way. The penalties for the offence are equated with commercial supply because this is the assumption underpinning the offence.

APPENDIX G - REGULATORY MODELS IN OTHER JURISDICTIONS

UNITED KINGDOM

As the House of Lords Report recognises, the UK regime is one of the most restrictive in the world.[218]

The regulation of cannabis in the United Kingdom under the *Misuse of Drugs Act 1971* is extremely complex. Schedule 2 to the Act classifies cannabis itself, and cannabis resin, as Class B controlled drugs, and the cannabinoid cannabinol and its derivatives (defined as THC and 3-alkyl homologues thereof) as Class A controlled drugs. Offences involving Class A drugs attract harsher penalties. Under the Act it is an offence to import, export, produce, supply or possess controlled drugs (thought it is not an offence to use them); it is also an offence to cultivate cannabis plants, or to permit premises to be used for smoking cannabis. A recent recommendation to reclassify cannabis, contained in a report by the Independent Police Foundation, has been rejected by the current Government.[219]

Reference is often made in this context to "Schedule 1 and Schedule 2". These are Schedules not to the Act itself, but to the *Misuse of Drugs Regulations 1985* made under the Act. Schedules 2-5 list drugs to which the various exemptions from the Act apply; in particular, drugs in Schedule 2 may be administered by, or on the instructions of, a doctor or dentist (r.7), may be produced by a practitioner or pharmacist (r.8), may be supplied (r.8) and possessed (r.10) by various classes of person, including practitioners, pharmacists and heads of laboratories, and may be possessed by patients (r.10). Schedule 1 lists drugs to which the exemptions do not apply; cannabis, cannabis resin, and cannabinol and its derivatives (other than dronabinol) appear in Schedule 1.

The 1985 Regulations also empower the Secretary of State to license anyone to produce, possess or supply any controlled drug, including a Schedule 1 drug (r.5); to license cultivation of cannabis plants (r.12); and to approve premises for smoking cannabis for research purposes (r.13).

The position in practice is therefore that cannabis and most of its derivatives may not be used in medicine, and may be possessed for research only under Home Office licence. There are two psychoactive cannabinoids, nabilone and dronabinol, which may be used for medicine. Two non-psychoactive cannabinoids, cannabidiol and cannabichromene, are not controlled drugs, and could in theory be prescribed as unlicensed medicines, but no one is currently doing so. The Home Office have stated publicly that in the event of a Product licence being granted for a medicine containing a Schedule 1 material, the registered pharmaceutical form of that material will be transferred to Schedule 2.

According to the Home Office, there have been a total of 27 applications for cannabis research licences, of which 25 have been approved and two agreed in principle - no application for a licence has been refused. GWP is one such company to be issued with the necessary licences to conduct research concerning the cultivation of standardised cannabis plants, extracting a variety of potential medical products from these, and developing appropriate delivery systems to optimise therapeutic benefits.

In law, it would be possible to make cannabis and/or additional cannabinoids prescribable by moving them from Schedule 1 to Schedule 2 of the *Misuse of Drugs Regulations*, in advance of any cannabis-based medicine being licensed and reaching the market. However, the Government has not been willing to reschedule cannabis in advance of licensing. Licensing depends on research and clinical trials - and the

[218] House of Lords, Select Committee on Science and Technology Ninth Report, 1998 at 5.2.
[219] http://news.bbc.co.uk/hi/engligh/uk_politics/newsid_693000/693846.stm

degree of difficulty associated with this arrangement remains somewhat controversial. In the mean time, medical use of cannabis remains illegal.

CANADA

In Canada, cannabis is controlled under the *Controlled Drug and Substances Act* and the *Narcotic Control Regulations*. In addition, the *Food and Drugs Act* and the *Food and Drugs Regulations* regulate the sale and distribution of therapeutic drugs in Canada. This legal framework controls the cultivation, importation, exportation, distribution, sale and possession of cannabis in Canada.

According to a recent Health Canada Report,[220] the use of cannabis for medical purposes is regulated in the following ways:

THE CONTROLLED DRUGS AND SUBSTANCES ACT AND ITS REGULATIONS

Cannabis, its preparations, derivatives and similar synthetic preparations are listed under Schedule II of the *Controlled Drugs and Substances Act*.[221] Except as authorized under the *Narcotic Control Regulations*, the possession, possession for trafficking, trafficking, importation, exportation, possession for exporting and production of narcotics, including cannabis, is prohibited under the *Controlled Drugs and Substances Act*. The *Narcotic Control Regulations* authorize various persons or institutions (e.g., licensed dealers, pharmacists, physicians and hospitals) to carry out certain activities which are otherwise illegal under the *Controlled Drugs and Substances Act* by creating a legal chain of distribution for controlled substances, including cannabis, to permit, among other things, their use for research purposes.

It is important to note that even if a new therapeutic drug can legally be sold or distributed under the *Food and Drugs Act* and the *Food and Drugs Regulations*, it does not mean that its sale, distribution or possession is legal under the *Controlled Drugs and Substances Act*. Conversely, even if a manufacturer is licensed under the *Controlled Drugs and Substances Act* and the *Narcotic Control Regulations*, it does not mean that the drug is approved for sale and distribution as a therapeutic product in Canada. The requirements under both statutes and underlying regulations need to be met to legally authorize cannabis to be used for medical purposes.

The sale and distribution of cannabis is subject to the same regulations as those that apply to morphine. However, in the case of morphine - unlike that of cannabis, its safety and efficacy has been established for specific medical conditions. In addition, medical-quality morphine is produced and distributed by properly licensed manufacturers in accordance with Good Manufacturing Practices.

The Food and Drugs Act and Regulations

Since the safety and efficacy of cannabis as a therapeutic product has yet to be demonstrated conclusively in any country of the world, the first step under the *Food and Drugs Act* is to gather scientific information and in particular, to conduct clinical trials to this end. Prior to initiating a clinical trial,

[220] Health Canada, *Research Plan for marijuana for* Medical *Purposes: A Status Report*, Therapeutic Products Programme, June 9, 1999.
http://www.hcsc.gc.ca/hpbdgps/therapeut/zfiles/english/cds/marijuana/resear_e.html
[221] The *Controlled Drugs and Substances Act* came into force on May 14, 1997.

sponsors are required to submit a research proposal in the form of an Investigational New Drug Submission.

An Investigational New Drug Submission includes, but is not limited to, the following information: the names of the clinical investigators, the rationale for the study, a complete study protocol (defining the study objectives, design, number of patients to be studied, treatment plan, dosage regimen, patient inclusion and exclusion criteria, safety monitoring, efficacy parameters, statistical plan, etc.), as well as information on the chemistry and manufacturing of the drug (including the specific dosage form(s) and strength(s)). This information is reviewed by the Therapeutic Products Programme within Health Canada to ensure that the design of the study is appropriate to test the hypothesis and that participants are not exposed to undue risk. The assessment also ensures that the clinical trial adheres to Canadian and international ethical and scientific standards and that the product is manufactured to ensure purity and concentration.

Research Plan for the Medical Use of Cannabis

Health Canada's research plan has been developed with advice from the Therapeutic Products Programme's external Expert Advisory Committee on New Active Substances.[222] The following information is a continuation of the Status Report prepared at the request of the Minister for Health to provide details of the work-in-progress of this set of initiatives.[223]

The proposed research plan consists of three projects:

Research using smoked cannabis: the Community Research Initiative of Toronto[224] and the Canadian HIV Trials Network[225]

The Canadian HIV Trials Network is a partnership committed to developing treatments, vaccines and a cure for HIV/AIDS, through the conduct of scientifically sound and ethical clinical trials. The Community Research Initiative of Toronto with the Canadian Trial Network partners will coordinate these activities. It is envisaged that a multi-centre research design would permit eligible Canadians outside of Toronto to participate in the clinical trials. The details of the protocol, such as the inclusion criteria and number of subjects required, are currently being developed. Health Canada has committed funding for short-term clinical trials using smoked cannabis.

Currently, the US National Institute of Drug Abuse[226] is the only supplier of research-grade cannabis cigarettes available for researchers. The National Institute of Drug Abuse has established a drug supply system through which US and foreign researchers may gain access to certain drugs including cannabis cigarettes and cannabinoids. Officials within the Therapeutic Products Programme will be assisting researchers to obtain access to a source of research-grade cannabis for use in clinical research conducted in Canada. Researchers will not be required to contact the National Institute of Drug Abuse directly; Health Canada will be the only authorised contact and will manage the distribution system. Shortly after

[222] Terms of Reference, membership and minutes from the EAC/NAS meetings are on the TPP website at http://www.hc-sc.gc.ca/hpb-dgps/therapeut.htmleng/advcomm_eacnas.html
[223] http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/cds/marijuana/resear_e.html
[224] Information on CRIT is available at http://www.web.net/~crit/index.html
[225] Information on the Canadian HIV Trials Network is on the web at http://www.hivnet.ubc.ca/ctn.html.
[226] NIDA is one of the U.S. National Institutes of Health (http://www.nida.nih.gov/). In 1999, NIDA issued a guidance document on the provision of cannabis forn medical research. It can be accessed via the Internet at http://www,nih.gov/grants/guide/notice-files/not99-091.html

the study protocol has been finalised and authorised, and research-grade cannabis has been obtained, research will begin.

Research using other cannabis extracts and components: Medical Research Council of Canada

The Medical Research Council of Canada is the major federal agency responsible for funding biomedical research in Canada. The Medical Research Council of Canada does not operate laboratories of its own. Rather, the research it supports is carried out by scientists in universities, hospitals and research institutes across the country.

Health Canada has committed funds so that the Medical Research Council of Canada can sponsor clinical trials as well as other basic and applied research activities, pertaining to cannabis, extracts and related products, subject to approval by the Council.

Research using non-smoked cannabis: GW Pharmaceuticals (U.K.)

The Therapeutic Products Programme is considering a proposal from GW Pharmaceuticals to conduct clinical trials on inhaled cannabinoids with the following objectives:

- to make available legal, cannabis-based medicines to Canadian patients by establishing a clinical research programme and long term safety monitoring;

- to allow a research programme to proceed in the Canadian public's interest by replicating the legal, regulatory and ethical framework that has been established in the UK. This will be in accordance with Canadian law, the Single Convention on Narcotic Drugs (1961) and the domestic regulatory and ethical framework;

- to evaluate delivery methods other than smoking and to generate data on quality, safety and efficacy of a scope and standard satisfactory for peer review publication; and

- to establish a pilot programme (100 patients) which can be expanded if required to a full programme eventually leading to a licensed prescription medicine.

GW Pharmaceuticals is a British company that currently holds a license from the UK Home Office to cultivate research-grade cannabis plants for use in research studies in the UK, under specific conditions established by the Home Office. GW Pharmaceuticals has already initiated the cultivation of research-grade cannabis. The company is developing various cannabis extracts to be delivered through an inhalation device. The company believes that its product would offer the advantage of an inhaled (non-smoked) form of drug without the harmful by-products of the smoked form. Pending the outcome of the review of GW Pharmaceutical's proposal, there will be an announcement providing details about the research protocol with contact information.

Other Mechanisms for Access Outside of Research Projects

Access is also available to therapeutic cannabis other than through clinical trials. These mechanisms include the Special Access Programme and the Exemption for Medical Purposes under section 56 of the *Controlled Drugs and Substances Act*.

Special Access Programme[227]

The *Food and Drug Regulations* enable the Canadian regulator to enable substances which have not yet been approved for marketing in Canada accessible to physicians for compassionate use. The Special Access Programme, as managed by the Therapeutic Products Programme, allows physicians to gain access to drug products on a patient-by-patient basis, if the physician believes that conventional therapies have failed, are unavailable in Canada, or are unsuitable.

The Special Access Programme routinely authorizes access to controlled and narcotic substances. In each of these cases the authorization is for a drug product, in dosage form, and manufactured by a credible, licensed establishment that adheres to national and international drug manufacturing standards. These standards guarantee that drug substances are available in known and consistent concentrations. The Therapeutic Products Programme's role, as a federal institution, is to ensure that physicians' requests and patients' needs are legitimate in each case and that the substance is generally safe and of a high quality. A physician's decision that alternative therapies are not appropriate is considered to be a part of the practice of medicine, thereby falling under provincial jurisdiction.

Currently, there is no licit, licensed, non-governmental supplier anywhere from whom research-grade cannabis can be obtained under the Special Access Programme. In some countries, including the USA and the UK, cannabis is legally cultivated in limited quantity and under strict government controls but its availability is restricted to research purposes. In addition, any importation or production of cannabis must comply with Canada's international obligations under the United Nations Single Convention on Narcotic Drugs, 1961.

Exemption Under s.56 (CDSA) for Medical Purposes

Section 56 of the *Controlled Drugs and Substances Act* gives the Minister of Health the discretionary power to grant, in specific cases, an exemption from the application of any or all parts of the *Controlled Drugs and Substances Act* or its regulations if, in the opinion of the Minister, the exemption is necessary for medical or scientific purposes or is otherwise in the public interest.

An Interim Guidance Document was published in early May 1999, to assist individuals who want to apply for an exemption for medical purposes.[228] This document details the information that should be furnished in such an application to enable a fair and complete review of each request. As of June 3, 1999, just over thirty requests have been made under section 56 of the *Controlled Drugs and Substances Act* for medical purposes. After all of the required information has been submitted, the Department endeavours to review a request within 15 working days. The Minister's decision to exercise his or her discretion in each case is made in the context of the recommendation formulated as part of the review and the circumstances of each individual applicant.

Special Considerations

Under both the *Controlled Drugs and Substances Act* and the *Food and Drugs Act* there are already processes and controls in place that apply to cannabis distribution and possession for medical purposes. The

[227] For further information concerning the Special Access Scheme see: http://www.hc-sc.gc.ca/hpb-dgps/thrapeut/htmleng/edrp.html

[228] The Interim Guidance Document is posted on the Health Canada web site at http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/cds/guides/interim_e.html

Narcotic Control Regulations allow certain persons to distribute narcotics. For instance, subject to certain conditions, licensed dealers may supply narcotics to pharmacists or practitioners who may in turn supply those same drugs pursuant to a prescription to patients. The *Narcotic Control Regulations* do not permit any further distribution of the drugs by patients. The aim of the distribution processes contained in the *Narcotic Control Regulations* is to provide an adequate control over the drugs to prevent misuse and illicit trafficking. These schemes would also apply to cannabis from a licit licensed dealer.

The *Food and Drug Regulations* also provide various avenues through which drugs intended for therapeutic purposes may be distributed (i.e., general marketing, clinical trial and the Special Access Programme). The *Regulations* make provisions for specific distribution paths, which aim to ensure that the drugs distributed are safe, effective and of a high quality.

Although the existing processes and controls applicable to the possession and distribution of controlled substances are generally adequate, cannabis, because of its unique nature (i.e., a smoked product, psychoactive, with a high street value) may require the imposition of additional terms and conditions. Health Canada will determine, on a case-by-case basis, the necessity of imposing other terms and conditions, particularly for use within a research context. By way of example, the Status Report states that following conditions may apply:

- participants in research studies and possessing cannabis (in a smoked form) will be strongly encouraged to consent to the release of their name, date of birth and address to Health Canada and law enforcement agencies. This will assist in avoiding police intervention where the substance is lawfully possessed. This personal information will be held in confidence;

- participants in research studies should be informed by the clinical investigators to take appropriate measures to ensure that others will not be exposed to second-hand smoke;

- the quantity of cannabis that participants might be allowed to possess within the research studies should be limited; and/or

- participants in research studies should be instructed by clinical investigators to keep cannabis in a secure area and be reminded that they cannot distribute cannabis to others.

Canadian Source of Research-Grade Cannabis

In keeping with Canada's obligations under the Single Convention on Narcotic Drugs and the views of the International Narcotics Control Board, the use of confiscated cannabis is not deemed a viable option. Given that a dependable source of research-grade cannabis is necessary for the purpose of clinical trials and given that the National Institute of Drug Addiction may not be able to meet Canada's demand, Health Canada has taken steps to establish a government-controlled growing operation in Canada.

In addition, the two commercially available drugs related to cannabis, namely, Marinol (which contains chemically synthesised THC) and Cesamet (a synthetic cannabinoid) have been approved in Canada and may be prescribed by medical practitioners. Other natural and synthetic cannabinoids (e.g., cannabinol, levonantradol) are also available to researchers.

UNITED STATES[229]

The Marijuana Tax Act of 1937 established the federal prohibition of cannabis. The introduction of the Act was the start of the general move to discourage all uses of cannabis, including any medical application, and was followed by other laws that defined cannabis as a narcotic, thereby further restricting its general availability in the US. Cannabis was eventually removed from the US Pharmacopoeia in 1941.

The Federal Controlled Substances Act of 1970 created a series of five schedules establishing varying degrees of control over certain substances. Cannabis and its primary active ingredient - tetrahydrocannabinol (THC) - are presently categorised as a Schedule I drug and, as such, is described as having a high potential for abuse, no currently accepted medical use and no acceptable safe level of use under medical supervision. Consequently, doctors may not prescribe cannabis under any circumstances.

The Drug Enforcement Administration (DEA) has been delegated the authority to determine the schedule into which a controlled substance is placed. The DEA will generally not move a substance into a less restrictive schedule without an official determination of safety and efficacy by the Food and Drug Administration (FDA). This requires a series of controlled scientific studies.

Congress has the power to override the DEA and reschedule a substance through legislation. The Attorney General - the executive branch cabinet official who heads the U.S. Department of Justice - also has the authority to override the DEA. However, at this time both of these courses of action remain unprecedented.

In 1986, the pill "dronabinol", comprised of synthetic THC, was moved from Schedule I into Schedule II - a slightly less restrictive schedule. Doctors can prescribe dronabinol (marketed as "Marinol") under tightly restricted circumstances, as Schedule II substances are defined as having accepted medical use "with severe restrictions" and having a high potential for abuse and dependence. Schedules III, IV and V are progressively less restrictive.

In addition, the DEA applied special restrictions to dronabinol that do not generally apply to Schedule II substances: Doctors may be penalised for prescribing dronabinol for conditions other than those "approved" by the FDA - namely, HIV wasting syndrome and cancer chemotherapy-induced nausea.

Most states mirror the scheduling criteria established by the federal government. However, cannabis has been assigned Schedule II or lower in a few states that have recognised its medical value and/or relative safety. Rescheduling at the state level is mainly symbolic at this time - medical practitioners still may not legally prescribe cannabis because the federal schedules supersede state law. In sum, federal law prohibits the possession, cultivation, and distribution of cannabis for any reason - including medical use. There is only one exception available, namely, federally approved research.

[229] The following overview and analysis of the situation in the United States is from Kyriagis M, "Marijuana - Just What the Doctor Ordered? A Review of the Medico-Legal and Political Debate in the United States of America on Medical Use of Marijuana and Implications for Australia", in (1997) 20(3) *UNSWLJ* 594.

THERAPEUTIC RESEARCH PROGRAM

Medical practitioners who wish to conduct research on Schedule I substances must receive special permission from the federal government, including:

- a special licence from the DEA to handle the substance;
- FDA approval of the research protocol; and
- legal access to a supply of the substance.

An individual doctor may conduct research if all the necessary permissions are granted, or a state may run a large-scale program involving many doctor-patient teams. In the latter case, the state secures the necessary permissions from the federal government for the researchers.

There are four potential legal sources of cannabis for research purposes: (1) receiving it from the National Institute on Drug Abuse (NIDA); (2) getting permission from the DEA to import it (e.g. from the Netherlands); (3) getting permission from the DEA to cultivate it; and (4) using confiscated cannabis supplied by state police.

Since the late 1970s, numerous states have passed legislation creating state-run research programs for cannabis and/or THC. In some states these laws have since expired or been repealed; while in the remaining states no state-run research program is currently operational.

The typical structure of a state-run research program is:

- The program is administered by the state department of health or board of pharmacy;
- Participating patients, physicians, and pharmacies that dispense cannabis must be approved by a patient qualification review board;
- Patients must be suffering from glaucoma or undergoing cancer chemotherapy or radiology - and not responding or having adverse reactions to conventional treatment;
- In some states, patients with other ailments may participate - but only after receiving special approval from the appropriate agencies;
- The research protocols must be approved by the FDA, and the programs must adhere to federal regulations;
- The cannabis and THC must be supplied by the federal government - but in some states, the state department of health or board of pharmacy was permitted to distribute confiscated cannabis to patients in emergency situations;
- Programs administrators must collect and analyse data; and
- Patients' privacy must be protected.

Medical Necessity Defence

The defence of "medical necessity" was first established in 1975 when a man was arrested for cultivating cannabis for the treatment of severe glaucoma.[230] Defendants must satisfy the following criteria in order to use it:

- That they did not intentionally bring about the circumstances that precipitated the unlawful act;
- That they could not accomplish the same objective using a less offensive alternative available;
- That the evil sought to be avoided was more heinous than the unlawful act perpetrated to avoid it.[231]

Courts in at least three states have allowed, since 1976, the medical necessity defence in medical cannabis cases: Washington, Florida and Idaho. However, courts in the states of New Jersey, Georgia, Massachusetts, Minnesota and Alabama have refused to allow this defence.

"The medical necessity defence does little to allow access to a legal and regulated supply of medical cannabis and the prohibitive court costs involved in arguing the defence may often preclude defendants from using it. In Australia, the defence would apply to situations of imminent peril, but would not normally be applied to cases of therapeutic use of cannabis or other unlawful substances".[232]

Legislative Initiatives

In November 1996, two separate referendums were voted on in California and Arizona, that is, Proposition 215 and Proposition 200 respectively.

Proposition 215

Prior to Proposition 215, two medical cannabis bills were passed by the California Legislature in 1994 and 1995 but were subsequently vetoed by the Governor. After 750 000 registered voters signed a petition supporting a State ballot for legalising medical cannabis use, Proposition 215 became the latest in two decades of reform efforts in California to permit the use of cannabis for medical purposes.

The initiative read in part:

"Patients or defined caregivers, who possess or cultivate marijuana for medical treatment recommended by a physician, are exempt from general provisions of law which otherwise prohibit possession or cultivation of marijuana".

The measure was passed by 54 per cent in favour to 46 per cent opposed on 5 November 1996. It

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230 *United States v Randall,* 104 Daily Wash L Rep, 2249 (DC Sup Ct 1976).

231 Grey MW, "Medical Use of Marijuana: Legal and Ethical Conflicts in the Patient/Physician Relationship" in (1996) 30 *University of Richmond Law Review* 249 at 250.

232 Kyriagis, M, "Marijuana - Just What the Doctor Ordered? A Review of the Medico-Legal and Political Debate in the United States of America on Medical Use of Marijuana and Implications for Australia", in (1997) 20(3) *UNSWLJ* 594 at 617. For further consideration of the question of whether necessity can be a defence in New South Wales courts to the possession or self administration of cannabis for medical purposes see, Heilpern, D and Rayner, G, "Drug Law and Necessity" (1997) 20(4) *Alternative Law Journal* 188.

immediately became law by the addition of the *Compassionate Use Act of 1996* to California's Health and Safety Code. This Act ensures among other things, that:

"… [S]eriously ill Californians have the right to obtain and use marijuana for medical purposes where that medical use is deemed appropriate and has been recommended by a physician who has determined that the person's health would benefit from the use of marijuana in the treatment of cancer, anorexia, HIV, chronic pain, spasticity, glaucoma, arthritis, migraine, or any other illness for which marijuana provides relief".[233]

It also ensures that patients and their primary "caregivers" who obtain and use marijuana for medical purposes upon the recommendation of a physician are not subject to criminal prosecution or sanction.[234] One of the aims of the legislation is to encourage Federal and State governments to provide the safe and affordable distribution of cannabis to all patients in medical need of it.[235] It seeks to circumvent the Federal prohibition of cannabis by preventing State prosecution of patients who grow cannabis, thereby establishing a de facto "legal supply" under State law. However, the danger remains that Federal agents can arrest and prosecute Californians who violate Federal law - however, such action is extremely unlikely.

The Act specifies that it shall not be construed to supersede legislation prohibiting persons from engaging in conduct that endangers others, nor to condone the diversion of cannabis for non-medical purposes. However, patients with a doctor's recommendation will no longer be arrested or prosecuted by State officials and will have a legal defence under State law. The measures will also protect doctors who recommend its use.

Proposition 215 was very broadly worded and differed from previous State measures in that it focused solely on patients and doctors. It did not include any "positive measures" other than for the State to liaise with the Federal Government to implement plans for the safe distribution of cannabis, It avoids either creating new bureaucracies or impacting on California's financial budget, but it fails to provide a guaranteed legal supply of cannabis. Patients will still need to obtain the drug from the black market or to cultivate their own supply, thereby exposing themselves to the potential risk, albeit remote, of Federal charges.

Proposition 200

Proposition 200 was the equivalent Arizona initiative which succeeded by 65 per sent in favour, and 35 per cent opposed on 5 November 1996. The initiative was broader than the Californian proposition and sought to amend local drug statutes by the *Drug Medicalisation, Prevention and Control Act 1996*. The initiative acknowledged that Arizona's current approach to drug control needed to be "medicalised" to recognise drug abuse primarily as a public health problem. The declaration stated:

"Thousands of Arizonans suffer from debilitating diseases such as glaucoma, multiple sclerosis, cancer and HIV, but cannot have access to the necessary drugs they need. Allowing doctors to prescribe Schedule I controlled substances could save victims of these diseases from loss of sight, loss of physical capacity and greatly reduce the pain and suffering of the seriously ill and terminally ill".

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[233] Medical Marijuana Initiative (1996) http://www.marijuana.org/prop.htm at 1. This section will be added at section 11362.5 to the health and Safety Code as (1)(A).
[234] *Ibid.* Added at section 11362.5 to the Health and Safety Code as (1) (B).
[235] *Ibid*. Added at section 11362.5 to the health and Safety Code as (1)(C).

Section 7 paragraph 2 states:

"A medical doctor must document that scientific research exists which supports the use of a controlled substance listed in Schedule I to treat a disease … before prescribing the controlled substance. [A doctor must] obtain the written opinion of a second medical doctor that the prescribing of the controlled substance is appropriate to treat a disease or relieve the pain and suffering of a seriously ill patient or terminally ill patient".

Failure to comply with these provisions may result in an investigation and appropriate disciplinary action by the Board of Medical Examiners. Patients who receive and use a controlled substance prescribed by a doctor will not be subject to (State) criminal penalties. The Arizona initiative is broader than Proposition 215 in allowing doctors to prescribe all Schedule I drugs as well as cannabis (including LSD and heroin). In addition, Proposition 200 went beyond the medical cannabis issue and included broad measures to tackle the overall drug problem in Arizona.

Practical Problems with the Propositions

The laws have created much controversy since their passage. Despite the referendums, medical access to cannabis remains ambiguous. This stems from the difficulty in framing the bills so that they were neither so narrow so as only to assist a small group of patients, nor too broad by allowing "spurious" conditions to be treated. The overriding difficulty remains that a patient will still be in violation of Federal laws, which make it illegal to manufacture, possess or distribute cannabis, even if they follow their doctor's recommendation to use medical cannabis in compliance with State laws.

The Arizona proposition uses the word "prescribe" instead of "recommend" to describe the manner in which doctors can advise their patients. Given that it is still illegal to prescribe cannabis under Federal law, a doctor in Arizona theoretically could be exposed to criminal sanction. In California, the word "recommend" is used to overcome this obstacle. The recommendation may be either written or oral but written advice could be used as evidence in court and oral recommendations would be difficult to substantiate without a doctor's prescription. The purpose of the medical prescription is to provide a valid legal defence against drug use or possession charges, Organisers of the propositions were emphatic that the laws were designed to cover only legitimate and defensible medical use of cannabis. Doctors however, will be cautious to prescribe cannabis or any other Schedule I drug given a certain increase in the scrutiny of their prescribing habits which they may have to justify later before Federal and professional bodies.

Proposition 215 hangover still lingers on. In December 1996, after Barry McCaffrey threatened with prescribing sanctions and/or prosecution of those Californian doctors who counselled or otherwise recommended cannabis use for therapeutic purposes, he was the subject of a class action that is not yet completed. (See web sites: http://www.drugsense.org/CCUA/chrono.html http://www.drugsense.org/CCUA/970114_Conant_v_McCaffrey_index.html etc.). At a recent medical cannabis meeting, many Californian physicians still admitted to being afraid to so provide advice to patients.

The propositions do not to address the problem of patients obtaining a *legal supply* of cannabis or the mechanisms for its sale and distribution given the Federal prohibition. The propositions have also been criticised for failing, among other things, to set age restrictions, to define "medical necessity", to quantify the dose and amounts of cannabis to be used, to set established limits on the amount of cannabis that can be possessed and cultivated, to establish the conditions of use, to establish quality standards for

growing cannabis plants or to determine the period in which cannabis use will be considered "medical".

Many of these issues are matters for discussion between the doctor and the patient in a clinical setting. Indeed, it is questionable whether the laws should expressly deal with these concerns although the lack of guidelines potentially opens the way for the laws to be abused by unscrupulous doctors or healthy persons seeking legal supplies of cannabis. In some ways, the framers of the propositions "overplayed their hand" by not including rigid standards. Had standards been included, the laws could have been tested and later expanded through court litigation with a possible broadening of the definition of medical uses.

FUTURE DEVELOPMENTS

The Clinton Administration has no constitutional legal authority to prevent State governments from changing laws to remove State criminal penalties for medical uses of cannabis. It could decide not to enforce Federal laws in circumstances where the cannabis is strictly used for medical purposes and where the States agree to tighten their cannabis laws to avoid potential abuse. This would avoid any arguments about States' rights and address some of the problems raised by the Propositions. Other States may decide to pass laws which mirror California's initiative but with added restrictions such as parental consent for use by minors, prohibiting use which may affect others (for example, driving while under the influence) and the monitoring of diversion of cannabis for non-medical purposes. Alternately, Congress could simply reschedule cannabis under the *Controlled Substances Act*, thereby enabling doctors to prescribe cannabis and to allow patients to obtain it from a pharmacy.

However, the current anti-drug climate prevailing not just in the US, but across the developed world, suggests that it is unlikely that this issue will be effectively dealt with by the Federal Government.

THE NETHERLANDS

Dutch policy towards small amounts of cannabis for personal use represents a pragmatic compromise between total prohibition and de jure decriminalisation. Under the revised *Opium Act 1976* a distinction is drawn between "drugs presenting unacceptable risks" (mainly heroin, cocaine, LSD and amphetamines) and "cannabis products" (cannabis and hashish). Penalties for drugs with unacceptable risks have been substantially increased with a corresponding reduction for cannabis and cannabis resin. Although acquisition and use of any controlled drugs are not offences, the legislation retains prohibitions on possession, cultivation and supply.

However, under law enforcement and prosecutorial guidelines, possession of up to 30 grams of cannabis for personal use will not result in prosecution. This amount was apparently based on a calculation of a personal supply sufficient for about two weeks' use. The guidelines also tolerate a quasi-legal retail trade in cannabis, mainly in coffee shops where "house dealers" are not prosecuted providing they observe certain conditions such as selling only small quantities, and only to persons over 18.

"One reason the Dutch adopted their self-styled policy of "normalisation" instead of de jure decriminalisation was to avoid any allegation that the Netherlands was in breach of the 1961 and 1988 Conventions. Even though the official Dutch view seems to have been that neither Convention necessarily requires parties to impose criminal sanctions on small-scale cannabis activities, the amendments to the *Opium Act* and the selective moratorium on enforcement were intended to relax controls without appearing to resile from the Netherlands' treaty obligations. So, the absence of any

prohibition on the acquisition or use of cannabis or any other controlled drug is justified on the ground that the 1961 and 1988 Conventions do not require parties to criminalise these acts. At the same time, the formal retention of offences of possession, cultivation and supply satisfies those who take a broad view of the obligations imposed by the Conventions. Furthermore, in deciding not to prosecute small-scale cannabis activities the Dutch can rely on the fact that neither Convention imposes any obligations relating to enforcement. In fact, each expressly recognises that the requirement to criminalise various activities shall not affect the principle that such offences "shall be defined, prosecuted and punished in conformity with the domestic law of a Party" (1961 Convention, art 36(4); 1988 Convention, act 3(11))."[236]

[236] Dawkins K, "International Law and Legalising Cannabis", (1997) NZLJ 281 at 284.

APPENDIX H – CERTIFICATION FORM

I am a medical practitioner accredited to certify patients for medical use of cannabis under the _____ _____ Act.

I certify that _____, born on _____, has one of the conditions specified under this Act.

Signed:

Name:

Date:

Ph number: