HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Cannabis for Medical Use -
A Scientific Review

31 JANUARY 2017

CONTENTS

1 EXECUTIVE SUMMARY

The Health Products Regulatory Authority (HPRA) convened an expert working group to assist with its review of the potential medical use of cannabis, as requested by the Minister for Health. The key findings of the working group are:

1. To date there is an absence of scientific data demonstrating the effectiveness (efficacy) of cannabis products. The safety of cannabis as a medical treatment is not well characterised. In particular, there is insufficient information on its safety during long-term use for the treatment of chronic medical conditions, such as those for which there is a public interest. For these reasons, and because most cannabis products available under international access schemes do not meet pharmaceutical quality requirements, they are not capable of being authorised as medicinal products (medicines). There appears to be a significant gap between the public perception of effectiveness and safety, and the regulatory requirement for scientific data which is mandatory to determine the role of cannabis as a medicine. Any proposal to circumvent the medicines regulatory system, established by law, would require careful consideration, so as to avoid unintended consequences, and lower standards of patient protection.

2. The best outcome for patients is the development of authorised (or capable of being authorised) cannabis-based medicines where the safety, efficacy and quality can be assured, and understood by the patient and healthcare professionals.

3. A distinction can be drawn between cannabis products containing tetrahydrocannabinol (THC) and those, such as certain cannabidiol (CBD) oils, which contain no THC. The latter are not subject to the Misuse of Drugs legislation, and do not contain the psychotogenic (capable of causing symptoms associated with psychosis, including delusions, delirium and hallucinations) element of cannabis. As such, products containing only CBD are not considered 'controlled drugs', and can be provided under existing legislation. While the research is still limited, there are reports that a CBD oil is capable of being authorised as a medicinal product and an application for the first authorisation is expected in the USA and Europe in 2017.

4. The decision to permit access to cannabis for medical use is a societal and policy decision due to the paucity of scientific research, the recreational use of the product and the strong public and patient demand. If cannabis products that are not capable of being authorised as medicines, are made available through an access programme, patients and healthcare professionals must recognise the limitations of the programme in assuring the safety, quality and effectiveness, as compared with what would be expected for an authorised medicine.

5. If the policy decision is to make cannabis available for medical purposes, the HPRA advises that it should recognise patient need, but be evidence based. Therefore, it is

advised, that treatment with cannabis is only permitted under a controlled access programme for the treatment of patients with;

a. Spasticity associated with multiple sclerosis resistant to all standard therapies and interventions whilst under expert medical supervision;
b. Intractable nausea and vomiting associated with chemotherapy, despite the use of standard anti-emetic regimes whilst under expert medical supervision;
c. Severe, refractory (treatment-resistant) epilepsy that has failed to respond to standard anticonvulsant medications whilst under expert medical supervision.

Patients accessing cannabis through the programme should be under the care of a medical consultant and medical information and utilisation data should be kept on a central register. This will ensure accountability and will inform the future direction of access to cannabis for medical purposes. Clinical (patient) research should be facilitated. Primary legislation will be required to address these points.

2 OVERVIEW OF HPRA REVIEW

There is considerable public and political interest in the use of cannabis for medical purposes. In November 2016, the Minster for Health requested the HPRA to provide scientific advice on this topic. As the regulator of medicines in Ireland, with a primary role in the protection of public health, the HPRA evaluates the benefits and risks of medicines on the basis of their scientific evidence, prior to granting a marketing authorisation. As the evidence for the use of many cannabis products is insufficient to permit a conventional benefit risk evaluation, or authorisation as medicines, the HPRA sought the advice of relevant clinical experts and patient representatives to facilitate this scientific review.

At the outset, it is important to draw a clear distinction between medical and recreational use. This document is concerned solely with the medical use of cannabis products in a controlled, regulated medical context.

In the limited time available, the expert working group convened by the HPRA has considered the main scientific reviews and relevant publications available on cannabis for medical use, the products available, and the international approach on access to treatment with cannabis.

The public interest in cannabis for medical use is acknowledged, and anecdotal reports of effectiveness in individual patients are compelling. Comments in the media refer to a growing body of evidence regarding the effectiveness of cannabis. However, it should be understood that this evidence finds, at best, a moderate benefit for cannabis in a small number of conditions and conflicting evidence, or no evidence at all, in a large number of other medical conditions. The effectiveness and safety of cannabis in large number of

medical conditions is simply not proven. Cannabis has potential therapeutic benefits but these need to be better defined through peer-reviewed clinical research.

The safety of cannabis as a medical treatment is not well characterised. In particular, there is insufficient information on its safety during long-term use for the treatment of chronic medical conditions, such as those for which there is a public interest. The scientific evidence in respect of potential harm is better documented for recreational use. Side effects associated with recreational use include: impaired short-term memory and coordination, psychiatric features of psychosis (including schizophrenia and paranoia), addiction, and altered brain development. The medical treatment of children and adolescents with cannabis requires careful consideration of the benefits, due to the potential risks to the developing brain. In addition, there is compelling evidence linking cannabis use in adolescence with the development of psychosis in later life.

A distinction can be drawn between cannabis products containing THC and those, such as certain CBD oils, which contain no THC. The latter are not subject to the Misuse of Drugs legislation, and do not contain the psychotogenic element of cannabis, THC. As such, products containing only CBD, are not considered 'controlled drugs', and can be provided under existing legislation. While the research is still limited, there are reports that CBD oil is capable of being authorised as a medicinal product and an application for the first authorisation is expected in Europe and the USA, in 2017. Currently, CBD oils may be available in Member States without medical indications as a food supplement and while emerging evidence suggests that the product may be more correctly classified as a medicine, particularly when used for serious illnesses, access as a food supplement remains. The HPRA are reviewing this, and in taking any decision will balance the need for access with the regulation of the market.

As part of its review, the HPRA examined the access programmes for cannabis for medical use in other countries. There have been recent changes in this area, much of it led by patient demand, rather than requests from healthcare professionals. In many cases, countries determined their supply needs prior to developing access programmes, and this is in line with the requirements of the 1961 UN Convention on Narcotic Drugs. Most of the programmes introduced to date include well-defined patient access and dispensing controls and place an emphasis on supply chain integrity and quality control of the product supplied. Authorised cannabis medicines are prescribed in many cases and use of cannabis products that meet defined quality controls is also permitted. The monitoring of side effects associated with use appears to be limited or non-existent. Despite the increasing development of access programmes in many countries, medical organisations worldwide are cautious about the medical use of cannabis because of insufficient evidence on benefits and risks. This puts healthcare professionals in countries with access programmes in a difficult position, as they may be under pressure to prescribe a treatment which they consider is not in the best interests of the patient, and is not supported by robust clinical evidence.

It is a requirement to demonstrate that the benefits of a new medicine outweigh its risks prior to authorisation. To date, few cannabis-based medicines have met this criteria. In the absence of scientific data demonstrating effectiveness (efficacy) and safety, and given the wide range in the composition of cannabis products, many healthcare professionals are cautious of recommending cannabis for medical use. There appears to be a significant gap between the public perception of effectiveness and safety, and the position of many medical experts that further scientific research is required to determine the role of cannabis as a medical treatment. A recent survey of Irish general practitioners (GPs) reported that a majority (58.6%) supported the legalisation of cannabis for medical use for certain medical conditions, however, many GPs cited the need for regulation of cannabis products, the requirement for an enhanced evidence-base to support decisions on treatment, and expressed concern about the mental health consequences of cannabis use, and the potential for misuse and abuse.

The wider availability of cannabis for medical use will result in increased overall use. Without further characterisation of the benefits and risks, the possibility of unintended consequences exists, some of which could have significant individual and societal impact.

The decision to allow cannabis for medical use is as much a societal and policy decision as a scientific one due to the paucity of robust clinical evidence, the recreational use of the product and the strong public and patient led demand.

In this context, if access to cannabis is to be permitted for medical purposes, the HPRA advises that cannabis should only be made available for the treatment of patients with specified medical conditions which have failed to respond to all other previous treatments, and where there is at least modest evidence that cannabis may be effective. Such patients should be under the direct supervision of an appropriately trained and experienced medical consultant. The specified medical conditions (medical indications) are:

1. Spasticity associated with multiple sclerosis resistant to all standard therapies and interventions whilst under expert medical supervision;
2. Intractable nausea and vomiting associated with chemotherapy, despite the use of standard anti-emetic regimes whilst under expert medical supervision;
3. Severe, refractory (treatment-resistant) epilepsy that has failed to respond to standard anticonvulsant medications whilst under expert medical supervision.

The selection of these medical conditions is based on:

- a possible unmet medical need for individual patients;
- the ability for the medical consultant to monitor the effectiveness of treatment using objective endpoints; and

- the existence of authorised cannabis-based medicines or medicines undergoing clinical trials, consequently there is clinical evidence and some research in relation to cannabis and these conditions.

It is important to note that the HPRA is not recommending treatment with cannabis or stating that cannabis is capable of being authorised as a treatment for these medical conditions (with the exception of Sativex which is authorised in Ireland for the treatment of spasticity associated with multiple sclerosis). This is because, in many cases, the data are not available to permit a benefit to risk evaluation to be performed in these patient populations. In addition, the HPRA has no information on the quality or composition of many of the cannabis products used in clinical research, and cannot verify their quality.

The HPRA does not consider that the available evidence supports the use of cannabis in other medical conditions. While the evidence for cannabis in the treatment of chronic pain is acknowledged, the HPRA does not support its inclusion as a specified medical condition for the following reasons:

- the causes of chronic pain are diverse and a suitable patient population or clinical indication for treatment with cannabis cannot be defined, due to the complexity and variety of chronic pain syndromes;
- physical, emotional, social, spiritual and other subjective factors inform the individual pain experience, making it difficult for a doctor to objectively assess the effectiveness of treatment;
- there are a large number of authorised medicines that are of proven effectiveness, and other non-pharmacological treatments available to treat the many factors involved in chronic pain; and
- chronic pain is common, and the potential use of cannabis-based medicines by a large number of patients, raises concerns about misuse and diversion into the wider community.

In respect of the possible use of cannabis for the three specified medical conditions, the HPRA recommends the introduction of a monitored cannabis treatment programme. Such a programme is necessary, both to maximise the safe and effective use of cannabis as a medical therapy for an individual patient, and to minimise the potential negative impact of wider access on society. It is proposed that the programme should run for a period of five years, with a centralised data collection point and regular reports to the Department of Health. This information will provide data on the medical use of cannabis and the supply needs in Ireland. Misuse and diversion of cannabis intended for medical use should also be monitored.

The cannabis treatment programme should involve the following elements:-

- Patients treated with cannabis should be under the care of a medical consultant who has expertise and experience in the treatment of the specified condition, and who is responsible for the monitoring and follow-up of the patient.

- Doctors, pharmacists and patients should be registered, and data collected on the use of cannabis in these patients.
- Authorised cannabis-based medicines should, be considered for treatment in the first instance. Cannabis products subject to quality control requirements in other countries, should only be used if a suitable medicine is not available, in Ireland.
- Patients should be educated on the correct use of the cannabis for medical purposes, the benefits and risks involved, how to report side-effects, and the care and safe disposal of cannabis products.
- Doctors and pharmacists should be supported to facilitate prescribing and dispensing.

The medicines regulations are in place so that patients can access safe and effective medicines. These regulations should not be viewed as a barrier to cannabis access for medical use, as the main barrier is in fact the absence of rigorous evidence-based information on the safety and effectiveness of cannabis as a treatment. As this information is vital in determining the role of cannabis, scientific research into the pharmacology and mechanism of action of cannabis and cannabinoids, and clinical research into cannabis for medical use should be encouraged through facilitated access, and targeted funding.

The HPRA will continue to support the conduct of research to allow a comprehensive evaluation of the risks and benefits of cannabis, with a view to the authorisation of cannabis medicines. The imperative for researchers to actively undertake collaborative clinical research in intractable pain syndromes is particularly emphasised.

In conclusion, if a policy decision is taken to permit access to cannabis for medical use, the HPRA advises that its use should only be initiated as part of a structured process of formal on-going clinical evaluation in a limited number of clearly defined medical conditions. This position is based on current scientific evidence and will be kept under review.

The HPRA wishes to thank the members of the working group, and the many others who kindly assisted us in compiling this review.

3 BACKGROUND

In November 2016, the Minister for Health, Simon Harris, TD, requested the HPRA's views on the recent developments in the use of cannabis for medical purposes including products available, research, indications and evidence of effectiveness, an overview of the different regulatory regimes in place in countries which allow cannabis to be used for medical purposes and legislative changes that would be required to allow use of cannabis for medical purposes in Ireland. The Minister requested that the response be received by mid-January 2017 (the Minister's request is set out in Appendix 1).

The HPRA convened a working group of relevant clinical experts and patient representatives to assist in the review given the complex nature of the issues under consideration. The clinical experts included consultant neurologists, a consultant in palliative medicine, a consultant psychiatrist with speciality in addiction, a consultant anaesthetist/pain specialist, and a palliative care pharmacist (see Appendix 2 for details of the members of the HPRA expert working group).

4 MEDICINES AUTHORISATION IN IRELAND

It is the role of the HPRA to ensure that medicines on the Irish market are safe, effective, and of an appropriate quality, based on clinical and scientific data. The HPRA also approves and monitors clinical trials, reviews data submitted for the authorisation of medicines, inspects and licenses manufacturing sites and wholesalers, and monitors medicines throughout their full life cycle.

Products which make medical claims or which contain substances likely to produce medical effects in the body are considered to be medicines. Under Irish and EU law, medicines are required to be authorised before they are placed on the market. These requirements were introduced in the 1960s in response to birth defects associated with the medicine, thalidomide.

A company seeking to market a medicine is required to make an application for a marketing authorisation, to a regulatory authority, such as the HPRA. The application must include data which demonstrate the effectiveness and safety, along with details of the medicine's quality. A typical development programme for a medicine will include rigorous characterisation of the quality of the medicine, non-clinical (animal) studies to characterise the toxicological effects, and clinical trials, approved by regulatory authorities, in hundreds or thousands of patients to determine its effectiveness and safety. The company may obtain scientific advice from regulatory authorities to guide the development of the medicine. The development programme may take many years. If the benefit-risk balance of a medicine is considered positive by the regulatory authority, that medicine will receive a marketing authorisation. This authorisation details the medical indication (or the condition the medicine treats), the dose and duration of use, any precautions regarding use, and the side effects (for more information on the authorisation of medicines see Appendix 3).

The medicines regulations are in place to ensure that patients have access to high-quality, safe and effective medicines.

5 CANNABIS AND ITS REGULATION IN IRELAND

The definition of cannabis, according to the Misuse of Drugs Acts 1977 to 2016 ('the Acts') is 'cannabis' (except in 'cannabis resin') means any plant of the genus Cannabis or any part of any such plant (by whatever name designated) but includes neither cannabis resin nor any of the following products after separation from the rest of any such plant, namely -

(a) mature stalk of any such plant,

(b) fibre produced from such mature stalk, or

(c) seed of any such plant;

Cannabis resin while excluded from the above definition is separately addressed in the Misuse of Drugs Act and for the purposes of this document references to cannabis include cannabis resin and other derivatives from the plant such as oils and other processed plant parts.

The current legal position in Ireland is that cannabis, and products or preparations extracted from the plant which are psychotogenic (capable of causing symptoms associated with psychosis, including delusions, delirium and hallucinations), are controlled under the Misuse of Drugs legislation. Cannabis is listed in Schedule 1 of the Misuse of Drugs Regulations 1988, as amended ('the Regulations'). This means that it is subject to the strictest level of control and medical use is not permitted. This is due to the absence of sufficient scientific data to demonstrate a clear medical benefit. The Misuse of Drugs (Designation) Order 1988, as amended ('the Order'), provides for the prohibition of the manufacture, production, preparation, sale, supply, distribution and possession of cannabis, except for limited purposes including research or forensic analysis. Current legislation does not allow for any such use unless a specific licence has been granted by the Minister for Health. The Order also has the effect of prohibiting a doctor or a pharmacist from performing certain activities relating to cannabis. For example, a pharmacist is prohibited from manufacturing, compounding or supplying cannabis. A doctor is prohibited from prescribing and administering cannabis, in addition to the restrictions placed on a pharmacist. However, the Order provides for a mechanism whereby the Minister can issue a licence to enable a doctor or a pharmacist to perform any of the activities. There is an exception for an authorised cannabis-based medicine (see Section 5).

The cannabis plant is considered to be a narcotic substance under the 1961 UN Convention on Narcotic Drugs ('the Convention'), to which Ireland is a party (for further information, see Appendix 4). The aim of the Convention is to limit the production, manufacturing, possession, and trade of controlled drugs, so that they are used exclusively for medical and scientific purposes. Under the Convention, the production and distribution of controlled substances must be licensed and supervised. Therefore, governments are obliged to provide estimates and statistical returns to the International Narcotics Control Board (INCB) on the quantities of controlled substances that are required, manufactured, and utilised. Each country has been granted a set amount of the narcotic drug that can be imported and/or

produced on an annual basis, but allowances can be increased, subject to justification of the medical need. The INCB can request information on the planned medical purposes, including information on the numbers of patients treated, along with the method of administration of the cannabis (e.g. smoked or inhaled). The measures put in place by the INCB seek to ensure that the supply of cannabis for medical and scientific purposes meets, but does not exceed the demand.

Cannabis for Medical Use Regulation Bill (2016)

It is not the remit of this review to consider the recent Bill. However, it is noted that it is proposed to regulate cannabis outside of the existing medicines' and Misuse of Drugs legislative systems. This proposal allows for greater access than recommended in the conclusions of this report and therefore is a matter of concern.

6 MEDICAL USE OF CANNABIS

Definition

In the context of this report, the term medical use of cannabis is taken to mean a situation where a doctor prescribes or recommends the use of cannabis for treatment of a medical condition in a patient under his/her care. As the regulator of medicines, the HPRA has not been asked to consider the personal use of cannabis for medical or other purposes. Therefore, this matter is not addressed within this review.

The movement to use cannabis as a therapy is driven by multiple factors. These include perceived inadequacies in current medications to treat specific symptoms or diseases, along with anecdotal reports of benefits derived from cannabis. Additional factors include a desire by those using cannabis for medical purposes to have medical oversight of their use of cannabis, access to a cannabis product that is of a standardised quality, the avoidance of criminality, and concerns regarding the cost of cannabis products.

Cannabis and cannabinoids

Cannabis contains more than 100 plant cannabinoids. These are the biologically active constituents of the cannabis plant that bind to receptors throughout the body to produce wide-ranging effects. The mechanism of action of cannabinoids is not yet fully understood, and it is likely that these work by 'mimicking' the effects of the body's own cannabinoids, or endocannabinoids. Endocannabinoid receptors are located in the brain and throughout the central and peripheral nervous systems; they play pivotal roles in the body's health and some disease processes. In recent years, there has been considerable interest in cannabis and cannabinoids for the treatment of human diseases, through modulation of the endocannabinoid system, and potentially other systems, though the mechanism of action is

not fully understood. The majority of this research has not involved formal clinical trials in human subjects.

Cannabis can be administered orally, sublingually, or topically; it can be smoked, inhaled, mixed with food, or made into tea. Cannabis can be taken in herbal form, extracted naturally from the plant, or manufactured synthetically (examples of cannabis products are provided in Appendix 5). Smoking cannabis for medical purposes is not generally recommended due to the risks associated with smoking.

The cannabis plant is not authorised as a medicine, as formal clinical trials in human subjects have not been performed to determine the benefits and risks of its possible medical use. Cannabinoids derived from the cannabis plant or synthetic cannabinoids are authorised as medicines, and other cannabinoids are under scientific investigation for the treatment of a number of medical conditions.

The main cannabinoids studied, and thought to be the most important in terms of clinical effects, are tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is the main psychotogenic component of cannabis. Cannabis products are often referred to by their composition of THC and CBD, or by the ratio of these components.

Prescribing of cannabis products

Under the Misuse of Drugs legislation, if the Minister for Health considers it is in the public interest, products containing THC can be prescribed by doctors, subject to licence (see Section 4). CBD lacks psychotogenic effects and for this reason, products containing only CBD do not fall under the Misuse of Drugs legislation and its restrictions.

Authorised medicines

An exception to the legislation relates to a cannabis-based medicine Sativex hereafter referred to under its US adopted name (USAN), nabiximols. This prescription-only medicine is authorised by the HPRA as a treatment for symptom improvement in adult patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity-related symptoms during an initial trial of therapy. Nabiximols can be prescribed, supplied and possessed for the treatment of patients. This exception was specific to nabiximols and was facilitated based on evidence from scientific studies conducted by the marketing authorisation holder and submitted to the HPRA which demonstrate the quality, safety and effectiveness of this specific product and its ability to provide a clear medical benefit.

Two medicines based on the structure of THC are authorised in other countries. Nabilone, a synthetic analogue of THC, is approved for controlling nausea and vomiting associated with

chemotherapy, in patients who have failed to respond adequately to conventional antiemetic therapies. Nabilone is listed in Schedule 2 of the Regulations and is therefore not subject to the same prohibitions as the cannabis plant. It can be prescribed without Ministerial license. Schedule 2 of the Regulations also includes other regularly prescribed controlled drugs which are medicines such as morphine and fentanyl. Dronabinol, a synthetic version of THC, is approved for stimulating appetite in patients with AIDS-related wasting and for nausea and vomiting associated with chemotherapy, it can be prescribed, subject to Ministerial license.

Cannabis products outside of formal medicines regulatory system

While authorised medicines have met the legally-required quality control standards, this is not the case for many cannabis products available and proposed for medical use (authorised cannabis-based medicines are outlined in Appendix 5). The expectation is that the production of cannabis products or extracts thereof (such as cannabis oils) will comply with Good Manufacturing Practice (GMP) and adhere to the European Medicines Agency's guidelines on quality. In particular, it is necessary to ensure acceptable levels of impurities which may be harmful (such as heavy metals, pesticides, mycotoxins and pathogenic micro-organisms), and to ensure accurate labelling of the relevant cannabinoid content.

Cannabis products that have met quality-control criteria are available to patients from producers based in countries with cannabis access programmes. In many cases, these products refer to the dried flower tips of the cannabis plant. Such products are required to have a standardised THC and CBD content.

A company based in the Netherlands produces cannabis that ranges in terms of the THC to CBD ratio. To illustrate the variety of products that the company produces, one product contains 22% THC and less than 1% CBD, whereas another of the company's product contains less than 1% THC and 9% CBD (both products are dried flower tips). This company has recently been issued with a certificate of compliance with GMP standards from the Dutch medicines regulator. Whilst this does not mean that the product is an authorised medicine, it does indicate that the plant was cultivated, harvested and packaged in a quality-controlled manner. The Dutch Office of Medicinal Cannabis, based in the Ministry of Health, facilitates the export of these products, subject to the agreement of the importing country. This is in alignment with established protocols under the UN Conventions relating to controlled drugs. In accordance with a doctor's prescription, a compounding pharmacy in the Netherlands, will formulates an oil from the dried flower tips produced by the company. The HPRA understands that cannabis oil is only available to Dutch citizens, and the Office of Medicinal Cannabis does not facilitate its export.

A Canadian-based company, has recently received a certificate of compliance with GMP standards from a European medicines regulator. This company also produces a variety of cannabis products containing different concentrations of THC and CBD. The company produces dried flower tip cannabis products in concentrations of THC (11% to 25.6%) and

CBD (0% to 15%). The company also produces cannabis products extracted from the flowering tips in the form of drops with a range of THC and CBD concentrations (0.3% to 1.5% THC and 0% to 1.2% CBD). In the European context, the company supplies two different liquid capsule products to the Croatian market. One of the liquid capsule cannabis products contains 5mg each of THC and CBD, whereas the other liquid capsule cannabis product contains 2.5mg THC and 2mg CBD.

In Israel, a company produces oils and capsules with a variety of THC and CBD content. The oils contain concentrations of THC from 0.5% to 15% and CBD from 0.5% to 30%. The company produces three different capsules, each with different concentrations of THC and CBD (10% THC and 1% CBD; 1% THC and 12% CBD; 8% THC and 10% CBD).

In Switzerland, a company produces a variety of different cannabis products including dried flowers, liquid extracts and powders. The dried flower products range in THC concentration from 0.6% to 0.9% with the CBD component ranging from 7% to 17%. The powders contain THC concentrations of 0.2% to 0.5% and CBD concentrations from 7% to 10%. The company produces three different types of liquid formulations. Its liquid extract formulation contains less than 0.9% THC and 16% CBD. The two other liquid formulations are tinctures developed separately in sesame oil or propylene glycol and ethanol combinations. The sesame oil product contains less than 0.2% THC and 4% CBD whereas the propylene glycol and ethanol product contains a similar level of THC and 5.25% CBD.

The regulatory authority in the Czech Republic has recently (March 2016) purchased its first batch of cannabis products from producers that it licences. The dried flower products range in THC (0.3% to 21%) and CBD (0.1% to 19%) concentrations.

For comparison, the authorised medicine based on extracts of cannabis, nabiximols, contains 2.7% THC and 2.5% CBD in an oromucosal spray. A medicine based on extracts from the cannabis plant containing 10% CBD in a liquid formulation, but no THC, is currently undergoing clinical trials. It is understood that this medicine has met quality standards for investigational medicines in clinical trials.

Quality of cannabis for medical use products

Data from the US on commercially available edible cannabis for medical use reports that more than 50% products were mislabelled in terms of their CBD and THC content. An FDA analysis of cannabis products making medical claims found that 6 of 18 products tested contained no cannabinoid. Such products may not produce the desired medical benefit, or may place patients at risk of experiencing side effects.

7 SUMMARY OF SCIENTIFIC DATA ON EFFECTIVENESS

Cannabis and cannabinoids have been studied in a wide variety of medical conditions over many years (for further information, see Appendix 6). While the therapeutic potential of cannabis is clearly of interest and potentially promising, the quality of the evidence reported thus far is limited for many indications, and researchers consistently cite the need for formal clinical trials to evaluate the benefits and risks of treatment. In some cases, authors differ on their views on the quality of the evidence.

A major limitation of previous cannabis studies is that a number of different formulations of cannabis have been used. Most studies use the cannabis products that are commercially available. However, some studies have used 'natural' smoked cannabis or a cannabis extract. Evidence of potential effectiveness is likely to be specific to a particular cannabis formulation and will depend on many variables, particularly the THC to CBD ratio. Effectiveness in one medical condition will not necessarily imply that cannabis is effective in another medical condition.

As the potential benefits and risks of cannabis products are dependent on the product, dose and duration of use, and the patient population, it is challenging to draw conclusions regarding the effectiveness of treatment.

Spasticity associated with multiple sclerosis

There is evidence of effectiveness of cannabinoids in spasticity associated with multiple sclerosis. The benefits and risks of nabiximols have been demonstrated in controlled clinical trials, and it is authorised as a medicine for patients with this condition that have failed other treatments. Oral cannabis extract has also been reported to be effective. It is likely that the effectiveness will depend on the relative ratio of cannabinoids, therefore, evidence for one formulation, does not mean that any cannabis product would have the same effect on spasticity.

The scientific evidence, and the availability of an authorised medicine, support the use of cannabis in the treatment of spasticity associated with multiple sclerosis, where other treatments have failed.

Nausea and vomiting associated with chemotherapy

Cannabinoids are reported to be a useful adjunctive treatment for patients on chemotherapy who are not responding to other treatments for and nausea and vomiting. Nabilone is authorised for this medical condition in some countries.

The scientific evidence, and the availability of an authorised medicine, support the use of cannabis in the treatment of intractable nausea and vomiting associated with chemotherapy, where other treatments have failed.

Chronic pain

Chronic pain is regarded as a disease of the nervous system and is defined as pain without apparent biological value that has persisted beyond normal tissue healing time (usually taken to be 3 -6 months). It is prevalent, affecting 1 in 5 people worldwide. Chronic pain is subjective, and is a multifactorial experience encompassing physical, emotional, social, spiritual and other factors. A large number of authorised medicines are available, and pain specialists recognise that pharmacological treatment is only one element of a multi-faceted approach to chronic pain management, that includes physical and psychological interventions.

There are a number of types of chronic pain, for example cancer, pain, postsurgical or post-traumatic pain, and an individual patient may experience more than one type of chronic pain. The published literature on chronic pain (in respect of cannabis and other treatments) is confusing and conflicting, as in many cases the specific type of pain being investigated is not adequately defined, or the clinical trial does not describe the underlying causes of the pain in sufficient detail.

The clinical trials of cannabis in chronic pain involved patients with a wide range of causes including neuropathic pain, cancer pain and fibromyalgia. The cannabis products evaluated included authorised medicines, and smoked cannabis. The data generally suggested an improvement in pain associated with cannabis products. When these clinical trials are combined, the overall estimate of benefit is moderate and there is no effect on patient's self-reported quality of life. The symptoms of pain are subjective, and the majority of clinical trials that have been conducted have been shown to be subject to a moderate risk of bias (where repeated errors in data collection have led to incorrect estimates). These biases mean that the treatment effects that have been reported in clinical trials of cannabis for chronic pain should be viewed with caution, and that the evidence-base in terms of benefit remains uncertain. In addition, cannabis products were associated with a greater risk of side effects, including serious side effects, when compared to other pain medicines. No studies have evaluated the long term safety of treatment with cannabis products. Current evidence suggests that larger more definitive clinical trials are needed. This approach is consistent with the views of pain specialists and medical professional bodies who have cited concern about the use of cannabis and cannabinoids in the management of chronic pain, in the absence of proven benefit to risk data.

The use of cannabis in chronic pain merits further research, in particular, formal clinical trials comparing the effectiveness of cannabis-based medicines with authorised medicines are required. It is recommended that researchers conduct long-term, randomised, double-blind

clinical trials to more completely characterise the effectiveness and safety profiles of cannabis-based medicines. This work will most usefully be progressed in a collaborative, international programme.

Severe, refractory (treatment-resistant) epilepsies

The main cannabinoid with anticonvulsant properties is CBD, although the mechanism of action in epilepsy is unknown. The situation is complex, with THC appearing to act as an anticonvulsant in some circumstances but as a pro-convulsant in others. There are initial reports of effectiveness for a medicine containing only CBD, in the treatment of severe, refractory epilepsies including Dravet Syndrome and Lennox-Gastaut Syndrome, as an add-on treatment. However, placebo-controlled clinical trials have not been subject to peer review, and the medicine has not undergone a benefit-risk evaluation. It is understood that an application for the authorisation of this medicine will be made in Europe and the USA, during 2017. If this medicine is assessed to be safe and effective in this medical condition, and if it meets quality requirements, it will be authorised and will be available to Irish patients.

Other medical conditions/medical indications

In many cases information on the effectiveness of cannabis in other medical conditions is insufficient and of low quality. There is evidence for appetite stimulation in AIDS, but this treatment may have been surpassed by newer treatments. There may be some effectiveness in Parkinson's disease, sleep disorders, and post-traumatic sleep disorder but further clinical research is required to characterise these findings. The evidence is weak for the use of cannabis in inflammatory disorders such as rheumatoid arthritis, ulcerative colitis or Crohn's Disease. In addition, the side effects are considered to be significant. Cannabis has not been shown to be effective in anxiety, depression, or in the treatment of agitation associated with dementia. There is currently no evidence for a benefit in the treatment of cancer, despite anecdotal reports to the contrary.

Treatment with cannabis

The effectiveness of cannabis as a medical treatment varies with the formulation used and the individual or patient population studied. In addition, the patients concerned often have complex health needs, are being treated with other medicines that may interact with cannabis, and require careful medical supervision.

Medical professional bodies emphasise the importance of rigorous scientific data to guide treatment with cannabis, and highlight the importance of using a product that has been well-characterised, chemically, pharmacologically and toxicologically. Such data forms the basis of a product authorisation for medicines granted by regulatory bodies, such as the HPRA.

There are only three authorised cannabinoid-based medicines available worldwide, namely nabiximols, nabilone and dronabinol. Clinical trials are being conducted with a pure CBD

medicine in epilepsy, and researchers are continuing to explore the possible uses of THC, CBD, and other cannabinoids for medical treatment (see Appendix 7 for details of clinical trials). In time, information may become available on the appropriate doses, duration of treatment, potential interactions, and side-effects associated with the use of cannabis products.

In summary, the HPRA considers that there is some scientific evidence to support the use of cannabis or cannabinoids as a medical treatment in patients who have failed available treatments, for the following medical conditions:

- Spasticity associated with multiple sclerosis;
- Intractable nausea and vomiting associated with the use of chemotherapy; and
- Severe, refractory (treatment-resistant) epilepsy.

The scientific evidence is currently insufficient to recommend use in other medical conditions.

8 SUMMARY OF SCIENTIFIC DATA ON SAFETY

The safety concerns related to cannabis use can be viewed in terms of immediate short term effects and effects related to longer term, repeated use (see Appendix 6). In terms of short term effects, the side effect profile is reasonably well understood. The most common short term side effects relate to the psychiatric and nervous system and include euphoria, hallucinations, paranoia, sedation, confusion, and short term memory effects. This is in addition to the effects on the gastrointestinal system which include nausea, vomiting, and diarrhoea.

The effects related to long term, repeated use of cannabis are where the greatest concerns, and main uncertainties lie. Cannabis dependence is estimated to occur in 9% of users with even higher estimates reported in those who start using cannabis as teenagers (17%). In addition to increasing the duration of regular use, the development of dependence may also increase the risk of other long term health risks associated with cannabis. In particular, chronic cannabis use has been associated with the development of psychosis and schizophrenia, with the impairment of cognitive function and with an increased risk of suicidality.

A number of large longitudinal studies have found that exposure to cannabis, particularly during adolescence, is associated with an increased risk of development of psychosis in later life. There is also evidence emerging that there is an association between the amount of cannabis used and the risk of psychosis. The continued use of cannabis after the onset of psychosis has also been linked to poorer disease prognosis and an increased risk for relapse and hospital admission. In terms of other psychiatric disorders, whilst the risk of depression and suicidality have not been investigated to the same extent as the risk of psychosis and

schizophrenia, the literature is generally supportive of the view that cannabis increases the risk of suicidal ideation and attempt.

An area which has been investigated in some depth is the effect of cannabis use on cognition. The major cognitive domains including memory, attention, psychomotor function, executive function and decision-making, all seem to be affected by cannabis use. While it remains unclear as to whether cognitive function fully recovers after cessation of use, many studies indicate that the effects are persistent even after long periods of abstinence. The age of onset of use appears to be a critical factor with many studies identifying adolescents as being a particularly vulnerable population. Following on from this, cannabis use during adolescence has been linked to a reduced educational capacity and has been identified as a predictor of early school leaving.

Importantly, the limitations of the research base need to be considered in determining whether the associations described between cannabis use and the development of these risks are truly causal. Much of the evidence to date arises from epidemiological studies which have been conducted in a setting of recreational drug use. The information on exposure to cannabis and the form of cannabis used is limited in many of these studies and therefore accurately determining the amount of drug used can be problematic. Notably, in the majority of studies there is little information on the content of the cannabinoids, THC and CBD. This is a significant limitation given the different pharmacological properties of these cannabinoids. There is evidence, for example, that suggests that both the psychotic effects and the negative neurocognitive effects of cannabis are predominantly linked to the THC component. Other non-causal explanations for associations arising from epidemiological studies include reverse causation (where associations reflect the condition under investigation increasing the likelihood of cannabis use itself), bias (where repeated errors, with measurements, for example, have led to incorrect estimates) and confounding (where other factors that increase the risk of cannabis use and the condition of interest have led to spurious associations, such as concomitant drug use).

In spite of these limitations, the literature suggests cannabis can contribute to the development of significant side effects. Whilst risk factors have been difficult to determine, a consistently emerging theme is that adolescents may be particularly susceptible to the psychiatric and neurocognitive effects. Researchers have suggested that this may be because adolescence represents a critical neurodevelopmental period and consumption of cannabis during adolescence could disrupt normal brain development.

9 CANNABIS MISUSE

Cannabis is widely used as a recreational drug and is acknowledged to be associated with problem drug use. A 2016 report from the National Advisory Committee on Drugs and Alcohol (NACDA) indicates that cannabis is the most commonly used illegal drug across all age groups in Ireland. Lifetime usage of cannabis (24.0%) is considerably higher than any other illegal drug and significant increases in lifetime prevalence have been observed (25.3% in 2010/2011 increasing to 27.9% in 2014/2015).

In Europe, the prevalence of cannabis use is about five times that of other substances, and cannabis has now overtaken heroin as the most widely reported illegal drug used amongst people entering addiction services (EMCDDA. European Drug Report, 2015).

Cannabis abuse in the United States is on the increase, including among high school students, for which annual prevalence rates rose from 24.7% in 2012 to 25.8 % in 2013. In states that have medical cannabis programmes, diversion of cannabis from the programmes has been reported as a major source for illicit use, particularly among young people. Prevalence surveys cited by the Drug Enforcement Administration indicate that 34% of twelfth grade students (aged 17-18 years) who had used cannabis in the past 12 months and who lived in states that have medical cannabis schemes, identified medical cannabis prescribed to another person as one of their sources for the drug.

The prescribing of cannabis for medical purposes has come under scrutiny in Canada following requests from medical licensing bodies for increased information on how doctors are authorising cannabis use. The regulations require licensed producers of cannabis for medical purposes to provide quarterly reports to health-care licensing bodies upon request, thus allowing them to more effectively monitor the professional practice of their members.

10 INTERNATIONAL PROGRAMMES FOR CANNABIS ACCESS

Overview

The HPRA conducted a survey of our regulatory counterparts based in Europe, through the European Medicines Agencies Co-operation of Legal and Legislative Issues (EMACOLEX) working group, and globally through members of the International Coalition of Medicines Regulatory Authorities (ICMRA) to determine policies on access to cannabis for medical use (see Appendix 8). In total 40 countries were contacted, from which 28 responses from EU Member Countries and 7 outside the EU were received. Israel was included as a supplementary country which does not participate in either of the two groups mentioned above but which does have a large medical cannabis programme.

Survey
40 countries were surveyed: 35 responses were received as follows:

- No access: 18
- Exceptional access: 10
- Access programme: 6
- Mixed access (USA): 1

35 (total)

Although a number of countries in both the EU and international context are moving towards establishing schemes or evolving existing schemes for medical access to cannabis, it remains the case that many countries that do not permit access.

The key findings are summarised below:

- Prescribing of cannabis in some form for medical use is increasing.
- Authorised medicines which are primarily prescribed are nabiximols or dronabinol. Herbal preparations made by pharmacists are also prescribed.
- Medical doctors are the only healthcare professionals permitted to prescribe cannabis. Canada also permits nurse prescribing. Specialised training or an authorisation to prescribe cannabis is required, monitoring and follow-up of patients is expected.
- Some countries specify the medical conditions suitable for treatment with cannabis. In other countries, prescribing is at the doctor's discretion but clinical justification for treatment is expected, for example, a condition which is not amenable to other treatments, where cannabis is considered to provide benefit.
- There is very limited prescribing in paediatric patients.
- In terms of the legal framework, countries have usually initiated access by permitting importation often under compassionate use programmes. When the medical needs are determined, growing is permitted, if necessary for supply.
    - Importing countries have specific provisions for exemptions of the use of controlled drugs or unlicensed medicines for medical purposes.
    - Growing countries allow for the cultivation and manufacture of cannabis for medical purposes by granting licenses and permits for growers and manufacturers.
- The side effects of authorised cannabis based medicines are monitored, however side effects deriving from unauthorised cannabis products are not monitored as stringently, if at all.

Countries without access programmes
Of the 40 countries surveyed, 18 responded to indicate they do not have any legal conditions under which cannabis can be used for medical purposes. The 18 countries are listed in the Table 1 below.

Table 1: Surveyed countries who do not have legal provisions allowing cannabis use for medical purposes

EU COUNTRIES	INTERNATIONAL COUNTRIES
Austria	China
Cyprus	Singapore
Bulgaria	
Greece	
France	
Hungary	
Iceland	
Latvia	
Lithuania	
Luxembourg	
Portugal	
Romania	
Slovakia	
Slovenia	
Spain	
United Kingdom	

Countries with programmes for exceptional use

Nine of the countries who responded have an exceptional/compassionate use programme to allow for access to cannabis for the treatment of a narrow range of medical conditions. The common features of these types of access programmes include a specialised prescriber who has obtained a specific license to prescribe non-authorised cannabis products. The patient generally must also have one of a defined list of medical conditions and must have exhausted all authorised treatment options prior to be granted use of cannabis products. These products are imported and pharmacies who wish to supply them must also obtain a specific license to import and also to prepare 'magistral' preparations in accordance with patient´s prescription dosage. Based on our survey, countries which currently have programmes for exceptional use include: Croatia; Denmark; Estonia; Finland; Germany; Malta; Norway; Poland; Sweden; Switzerland; Brazil. In the case of both Denmark and Germany further changes to legislation to expand access are pending. Further details on these schemes are set out in Appendix 8 – Part 2.

Countries with expanding/established access programmes

Of the countries surveyed and those reviewed separately by the HPRA, there are a number that have established access programmes for cannabis for medical use. In Europe, these include the Netherlands, Italy, and the Czech Republic. Internationally Canada, Israel, Australia and a number of US States (outside the federal system) have programmes in place over a number of years. Canada's access programme has been dictated by court cases and the rights

of the individual under Canadian law. Australia and Israel have more recently introduced legislation to permit more expanded access following compassionate use or exceptional use programmes.

Common to all approaches is the involvement of a healthcare professional in the identification of the need and use of cannabis for the patient. The approaches vary from conventional prescribing to the system within US states where it is 'practitioner recommended' rather than prescribed. In most of the European countries that have such systems, cannabis is dispensed to patients through pharmacies. In Canada, the patient engages directly with the producer without having the cannabis to be dispensed. In addition, the patient can grow their own cannabis for medical use.

The systems for supply of cannabis include measures to control and secure the growing, processing and supply chain. This is achieved through licensing of the growers and producers involved or similar measures. Measures are also put in place to provide quality control for the cultivated cannabis and products produced from this. These include the cannabinoid contents (namely THC and CBD), and ensuring the absence of pesticides and microbial contaminants. In many cases, growing, processing and supply are controlled and operated under government tenders co-ordinated through the Ministry of Health. (A more detailed analysis of the systems in place in these countries is provided in Appendix 8 – part 3).

11 CONCLUSIONS

The HPRA, in consultation with a specially convened working group, has reviewed the scientific research available on cannabis for medical use, the cannabis products available, and the international approaches to access to cannabis for medical use.

The scientific evidence supporting the effectiveness of cannabis across a large range of medical conditions is in general poor, and often conflicting. Cannabis has potential therapeutic benefits but these need to be better defined through clinical research.

The safety of cannabis as a medical treatment is not well characterised and, in particular, there is insufficient information on its safety during long-term use for treatment of chronic medical conditions, such as those for which there is a public interest. The scientific evidence in respect of potential harm is better characterised for recreational use. Side effects associated with recreational use include: impaired short-term memory and coordination, psychiatric features of psychosis (including schizophrenia and paranoia), addiction, and altered brain development. The medical treatment of children and adolescents with cannabis requires careful consideration due to the potential impact on the developing brain. In addition, there is compelling evidence linking cannabis use in adolescence with the development of psychosis in later life.

As part of its review, the HPRA examined the access programmes for cannabis for medical use in other countries. There have been recent changes in this area, much of it led by patient demand rather than requests from healthcare professionals. Authorised cannabis medicines are prescribed in many cases, while cannabis products that meet defined quality controls are also permitted. The monitoring of side effects appears to be limited or non-existent in many countries. Despite the increasing development of access programmes in many countries, medical organisations worldwide are generally cautious about the medical use of cannabis because of insufficient evidence on benefits and risks. This can put healthcare professionals in countries with access programmes in a difficult position, as they may be under pressure to prescribe a treatment which they consider is not in best interests of the patient.

The public interest in cannabis for medical use is acknowledged, and anecdotal reports of effectiveness in individual patients are compelling. Comments in the media refer to a growing body of evidence regarding the effectiveness of cannabis, however the limitations of the scientific data should be understood. The effectiveness and safety of cannabis in a large number of medical conditions is simply not proven. Prior to being made available to patients, a medicine is required to demonstrate that the benefits of treatment outweigh the risks, but few cannabis products have met this criteria. There appears to be a significant gap between the public perception of effectiveness and safety, and the position of many medical experts that further scientific research is required to determine the role of cannabis as a medical treatment.

Increasing access to cannabis may benefit individual patients that have an unmet medical need. However, gaps in scientific knowledge regarding the safety and effectiveness may result in unintended consequences including the impact on vulnerable populations, increased use of cannabis for recreational purposes, normalisation of use, and increased prevalence of cannabis use disorders or other side effects (cognitive deficits, lack of motivation, psychosis) resulting in a negative impact on public health. The benefit/risk to the individual patient and the risk to society in general must both be considered in the formation of public health policy on access to cannabis for medical purposes.

In order to maximise the potential benefits to patients with an unmet medical need and to minimise the potential harm to those patients and society as a whole, medical use of cannabis should be considered with caution. Based on current evidence the HPRA advises that medical use of cannabis should be only be initiated as part of a structured process of formal on-going clinical evaluation by a medical consultant, in a limited number of clearly defined medical conditions.

The HPRA, having considered the expert views of its working group, is of the following opinion:

1. Treatment of medical conditions should be informed by scientific evidence on effectiveness and safety from high quality randomised controlled trials. In the first

instance, products intended for therapeutic purposes should be fully characterised chemically, pharmacologically, and toxicologically. These are the conditions under which medicines are authorised worldwide, and ideally cannabis intended for medical use should be subject to these conditions, to ensure that patients have access to safe and effective treatment. In the longer term, the development of authorised cannabis-based medicines demonstrating safety, efficacy and quality, best meets patient needs.

2. A distinction should be drawn between cannabis products containing THC and those, such as certain CBD oils, which contain no THC. The latter are not controlled under the Misuse of Drugs legislation and do not contain the psychotogenic element of cannabis. Pure CBD products are not considered 'controlled drugs' and can be provided under existing legislation. While the research is still emerging, there are indications that CBD oil is capable of being authorised as a medicinal product and an application for the first authorisation is expected in the USA and Europe in 2017. The existence of an authorised CBD oil would provide a regulated source of this medicine for critically ill patients. In the meantime, the HPRA would be supportive of measures to facilitate access to this unauthorised medicine.

3. In relation to other cannabis products (THC containing) the data available are not sufficient, in many cases, to support their authorisation as medicines. Any proposal to circumvent the medicines regulatory system, established by law, would require careful consideration, so as to avoid unintended consequences, and lower standards of patient protection.

4. It is not clear that cannabis is the answer to a variety of unmet medical needs, and the medical need for cannabis has not been determined in Ireland.

5. The potential benefits and risks of cannabis products are dependent on the formulation, dose and duration of use, and the patient population, which makes it challenging to draw general conclusions.

6. The medical conditions which cannabis is proposed to treat are chronic conditions, and there is a paucity of data and numerous uncertainties with regard to the long-term safety of the use of cannabis as a medical therapy.

7. If a policy decision is taken to permit access, the circumstances under which cannabis could be prescribed to a patient are:
   - Where a patient is under the care of a medical consultant with expertise in the relevant medical condition, who will be responsible for monitoring the patient, and for follow-up; and
   - In a situation where there is a defined medical condition with an unmet medical need, where prior treatments are ineffective or unsuitable and where scientific data suggests cannabis may be effective.

8. On the basis of scientific evidence, patients with the following medical conditions, who have failed treatment with other therapies, and where the medical consultant responsible for the care of the patient considers that cannabis products may be effective, could be considered for treatment:
   a. Spasticity associated with multiple sclerosis resistant to all standard therapies and interventions whilst under expert medical supervision;
   b. Intractable nausea and vomiting associated with chemotherapy, despite the use of standard anti-emetic regimes under expert medical supervision;
   c. Severe, refractory (treatment-resistant) epilepsy that has failed to respond to standard anticonvulsant medications under expert medical supervision.

   This does not imply that the use of cannabis products is safe in these patient populations, as it is not possible to carry out a benefit risk evaluation (with the exception of Sativex, which is authorised for the treatment of spasticity associated with multiple sclerosis).

9. Subject to a policy decision, access to cannabis for medical purposes under the current legislation should be fully explored, or primary legislation introduced, as necessary. The pathways for legal access should be clarified for patients and doctors.

10. If is considered that access to cannabis for medical use should be permitted, and cannabis products that are not capable of being authorised as medicines, are made available through an access programme, patients and healthcare professionals must recognise the limitations of the programme in assuring the safety, quality and effectiveness, as compared with what would be expected for an authorised medicine.

11. Authorised cannabis-based medicines should be used in the first instance, as these meet medicines' quality control requirements. Unauthorised cannabis-based medicines or quality-controlled cannabis products could be considered by the doctor for an unmet medical need, when other treatment options are exhausted. The HPRA can provide information on sources of quality controlled cannabis products through our interaction with other agencies internationally.

12. The role of the doctor and the pharmacist in prescribing and dispensing cannabis is integral to its safe and effective use. It is important that healthcare professionals have access to information on cannabis for medical purposes. This will allow them to support their patients, for example, in the explanation of side effects such as sedation and cognitive impairment which may impact on work, driving, operating machinery, or other activities.

13. Patients prescribed cannabis for medical use require information to facilitate the safe and effective treatment. Education on safe storage and disposal of cannabis for medical use may limit diversion and unintentional exposure. Education on reporting side-effects may facilitate appropriate treatment.

14. Increased access will result in increased use and the possibility of misuse.

15. The benefit to the individual patient should be balanced against the risk to society.

16. Cannabis products that are psychotogenic should continue to be controlled under Schedule 1 of the Misuse of Drugs Regulations, 1988, unless authorised as a medicine, or made available under a monitored treatment programme.

17. While outside the remit of the HPRA, the cost of access to cannabis for medical use will need to be considered. It is noted that medicines considered for reimbursement through public health schemes are usually authorised. Such medicines have proven benefit versus risk, and in many cases have proven cost-benefit.

If a policy decision is made to facilitate access to cannabis for medical use, the following recommendations could be considered:

1. A five-year pilot programme that permits patients with the defined medical conditions (outlined above) to be treated with cannabis or cannabinoids prescribed by their doctors, under current legislation, should be conducted. Under the cannabis treatment programme:

    - A registry of patients, prescribers, and pharmacists should be established (a registry may be necessary to provide legal protection for possession).
    - Information on the product prescribed, the medical condition treated, adverse events and the outcome of treatment should be collected.
    - The registry should be subject to medical oversight, and report provided to the Department of Health on the numbers of patients, patterns of prescribing, and supply needs. A report at the end of the period would permit decisions to be made on future direction of access to cannabis for medical purposes.
    - The annual national reports to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) will facilitate the tracking of problem drug use.

2. The pilot programme would allow patients to be treated legally with cannabis products within the healthcare system, and avoid the use of cannabis products that are subject to no regulation.

3. Legislation to support the cannabis treatment programme should specify the medical conditions identified above where cannabis can be used as a medical treatment, the doctors that can prescribe treatment (consultants with expertise in the relevant medical condition), and the permissions necessary to allow doctors to prescribe, pharmacists dispense, and patient possession. The legislation should identify the routes of supply and the required quality controls. It should also address labelling requirements and

appropriate categorisation of cannabis products. It should outline the records that are required to be kept and the necessity for a patient register.

4. Dronabinol is an authorised medicine in other countries and is currently controlled in Ireland by the provisions of Schedule 1 of the Misuse of Drugs Regulations. To facilitate patient access, it is recommended that dronabinol is included in Schedule 2, this would place the medicine in a similar category to other authorised medicines including nabiximols and nabilone.

5. The defined medical conditions that could be treated with cannabis should be presented to the medical professional bodies, such as the Royal College of Physicians (RCPI) or societies, for review. The development of prescribing guidelines or training could be considered by the professional bodies. These guidelines could address the patient population suitable for treatment, taking into account:
   - the age of the patient and their medical history (including active substance use, concomitant medical or psychotic disorder, cardiovascular or respiratory disease, whether they are pregnant or breast-feeding); and
   - the type of cannabis product suitable for treatment (THC and CBD content).

   The elements to be included in an education programme for patients could also be considered, such as the correct use of the cannabis for medical purposes, the benefits and risks involved, how to report side-effects, and the care and safe disposal of cannabis products.

6. A confidential survey should be conducted across patient's organisations to determine the use of cannabis-based medicines with this information providing an estimate of the supplies required.

7. Clinical research into the safety, in particular the long-term safety and the effectiveness of cannabis for medical use, should be encouraged through facilitated access under the legislation, and targeted funding. The HPRA fully endorses clinical research with cannabis products to characterise their therapeutic promise, and will provide the necessary supports.

8. The HPRA working group should continue to review scientific developments in this area, and report to the Minister, as required.

APPENDIX 1 Minister of Health's Letter to the HPRA

An Roinn Sláinte
DEPARTMENT OF HEALTH

Oifig an Aire
Office of the Minister

RECEIVED
08 NOV 2016
BY:

4 November 2016

Dr. Lorraine Nolan,
Chief Executive,
Health Products Regulatory Authority,
Kevin O'Malley House,
Earlsfort Centre,
Earlsfort Terrace,
Dublin 2

Re: Review of policy on use of cannabis for medicinal purposes.

Dear Lorraine,

Further to our recent discussion on the use of cannabis for medicinal purposes I have decided to review Ireland's policy in this area.

I would very much appreciate the assistance of the HPRA in providing expert advice to my Department on this matter.

In particular, I would welcome your views on the following aspects of this subject:

- recent developments in the use of cannabis for medical purposes; in particular this should include: an overview of products that have been authorised in other jurisdictions; overview of the wider on-going and emerging clinical research in new indications and evidence of efficacy;
- an overview of the different regulatory regimes in place in countries which allow cannabis to be used for medicinal purposes;
- legislative changes that would be required to allow use of cannabis for medicinal purposes in Ireland.

I would be grateful if this work would be concluded by mid January.

Kind regards,

Simon Harris, TD
Minister for Health.

Tús Áite do Shábháilteacht Othar
Patient Safety First

hi Healthy Ireland

Cuirfear fáilte roimh chomhfhreagras i nGaeilge
An Roinn Sláinte Teach Haicin Baile Átha Cliath D02 VW90
Department of Health Hawkins House Dublin D02 VW90
Fón/Tel (01) 635 4148
R-phost/Email ministersoffice@health.gov.ie
Suíomh Gréasáin/Web www.health.gov.ie
Páipéar Athchúrsáilte/Printed on Recycled Paper

APPENDIX 2 HPRA Expert Working Group on Cannabis for Medical Use

- Professor Tony O'Brien, Consultant in Palliative Medicine
- Dr Colin Doherty, Consultant Neurologist and National Clinical Lead for the Epilepsy Programme
- Dr Jennifer Westrup, Consultant Medical Oncologist
- Ms Marie Wright, Palliative Care Pharmacist, Milford Care Centre
- Dr Camillus Power, Consultant Anaesthetist, Pain Specialist
- Professor Desmond Corrigan, Adjunct Associate Professor, School of Pharmacy & Pharmaceutical Sciences, TCD
- Dr Bryan Lynch, Consultant Paediatric Neurologist, Temple Street Children's University Hospital
- Dr Mike Scully, Consultant Psychiatrist, HSE Addictions Service , CHO 7 and Chair, Addictions Faculty, College of Psychiatrists of Ireland
- Aileen Tierney PhD, Patient Representative, Reg. FTAI , ICP, EAP
- Joan Jordan, Patient Representative, EUPATI Graduate

APPENDIX 3 Medicines Authorisation in Ireland

The role of the HPRA is to protect and enhance public and animal health by regulating medicines, medical devices and other health products. The aim of the HPRA is to make sure that health products are as safe as possible and do what they are intended to do.

A medicine (medicinal product) is defined as:

- Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or
- Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

Therefore, products can be medicines by virtue of the claims they make or their composition and function.

The regulation and authorisation of medicines in Ireland is underpinned by EU and Irish legislation. All medicines placed on the Irish market must be authorised by the HPRA or by the European Commission. An Irish authorisation for a human medicine is called a product authorisation.

Pharmaceutical companies wishing to obtain a product authorisation to place a medicine on the Irish market must first submit an application. Before a product authorisation can be granted, a thorough review of the application is carried out by scientific and clinical experts. The following issues are carefully considered during the review of an application:

(i) The safety, quality and effectiveness of the medicine, based on clinical trial data.

(ii) The benefit/risk profile of the medicine.

In order to determine if the safety, quality and effectiveness of a new medicine is sufficient, human clinical trials using the new medicine must be conducted before an application is submitted to the HPRA. Clinical trials begin with small studies in a controlled population of volunteers or patients and, as data are gathered, expand to large scale studies in patients. These large scale studies will often compare the new medicine with a currently used treatment. As information is obtained, larger numbers of patients are exposed to the new product and data are collected showing the safety of the product in the intended patient population. Information on the quality of the product and its non-clinical safety (use in animal studies) will have been obtained before the clinical trial programme commences.

In addition to reviewing safety, quality and effectiveness data, an evaluation of the benefit to risk profile is carried out by the HPRA. While all medicines have some risks (side effects)

associated with their use, the benefits of using a medicine should always outweigh the potential risks.

If the HPRA determines that a new medicine meets the stringent requirements for safety, quality and effectiveness, and the overall benefits outweigh the known risks, a product authorisation is granted. At that point, the new medicine can be placed on the Irish market.

The benefit versus risk balance should be acceptable to the patient for their individual circumstances following consultation with their healthcare professional (e.g. doctor, nurse prescriber or pharmacist).

Although the importance of clinical trials cannot be understated, it is recognised that not all safety issues relating to a medicine will be identified during the clinical trials carried out before it comes on the market. In real life, a medicine may be used in larger numbers of patients, in different types of patients (such as older patients, younger patients, patients with more severe or even milder disease, patients on other medications which could interact) and for longer periods of time. The challenge for regulators like the HPRA is to find the right balance between making an effective new medicine available to the patients who would benefit and the fact that knowledge on the safety profile may be limited at the time of marketing authorisation. This is why following authorisation of a medicine, the HPRA continues to monitor the risks of the medicine throughout its lifecycle. This ensures that the balance between benefit and risk remains positive for the patients taking the medicine.

APPENDIX 4 Misuse of Drugs Framework relating to Cannabis

National Legislation

The current legal position in Ireland is that *Cannabis*, defined as a naturally occurring plant material, is controlled under the Misuse of Drugs Acts 1977 to 2016 ('the Acts') and the various Orders and Regulations made thereunder. *Cannabis* is listed in Schedule 1 of the Misuse of Drugs Regulations 1988, as amended ('the Regulations'). This means that it is subject to the strictest level of control.

The key distinction of controlled substances listed in Schedule 1 is that medical use is not permitted. This is due to the absence of sufficient scientific data to demonstrate a clear medical benefit. The Misuse of Drugs (Designation) Order 1988, as amended, ('the Order') provides for the prohibition of the manufacture, production, preparation, sale, supply, distribution and possession of *Cannabis* except for:

- Research, forensic analysis, use as an essential intermediate or starting material in an industrial manufacturing process and
- Cultivation of hemp.

Current legislation does not allow for any such use unless a specific licence has been granted. To date such licences have been granted in limited and controlled circumstances relating to academic research, forensic analysis and as a starting material for use in the production of a non-controlled medicine.

The Order also has the effect of prohibiting a doctor and a pharmacist from performing certain activities relating to *Cannabis*. For example a pharmacist is prohibited from manufacturing, compounding or supplying *Cannabis*. A doctor is prohibited from prescribing and administering *Cannabis* in addition to the same restrictions placed on a pharmacist. However, the Order provides for a mechanism whereby the Minister can issue a licence to enable a doctor or a pharmacist to perform any of the activities. One such licence has been granted to a prescriber for this purpose.

Derogation for Sativex (nabiximols)

The exception to above situation relates to a medicine, nabiximols (US adopted name, USAN). This medicine contains an extract from the *Cannabis* plant and was authorised in Ireland in July 2014. It contains delta-9- tetrahydrocannabinol (THC) and cannabidiol (CBD). It has been authorised by the HPRA as a prescription only medicine as treatment for symptomatic improvement in adult patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication.

The Regulations and Order were amended to permit nabiximols to be prescribed, supplied and possessed for the treatment of patients. This derogation was very specific to nabiximols and was facilitated based on evidence from scientific studies conducted by the marketing authorisation holder to demonstrate the quality, safety and effectiveness of this specific product and its ability to provide a clear medical benefit. As such, other cannabis-derived medicines in other member states could not be supplied to patients under the current legislation without Ministerial licence as described above.

The HPRA understands that prescribers are entitled however, under their own responsibility, to use nabiximols for the treatment of medical conditions other than those for which it has been approved (i.e. 'off-label' use of this product).

International Legal Considerations

Cannabis is considered a narcotic substance under the 1961 UN Convention on Narcotic Drugs ('the Convention'), to which Ireland is a party. The aim of the Convention is to limit the production, manufacture, possession and trade of controlled drugs so that they are used exclusively for medical and scientific purposes. Under the Convention, the production and distribution of controlled substances must be licensed and supervised. Governments must provide estimates and statistical returns to the International Narcotics Control Board (INCB) on the quantities of drugs required, manufactured and utilised.

The practical implication for this in relation to *Cannabis* is that each country has been granted an amount of the narcotic drug that can be imported on an annual basis. The estimate allowance for *Cannabis* in Ireland is 10g per annum (THC is given a separate threshold of 50g per annum). An estimate allowance increase can be requested by a country with supporting substantiation. Each importation of *Cannabis* would require an export authorisation from the exporting country's authority and an associated import authorisation from the Department of Health.

Considerations around Cultivation

Pursuant to Articles 23 and 28 of the Convention, States wishing to establish programmes for the use of *Cannabis* for medical purposes that are consistent with the requirements of the Convention must establish a national cannabis agency to control, supervise and license the cultivation of *Cannabis* crops. Additional obligations incumbent upon national *Cannabis* agencies include the designation of the areas in which cultivation is permitted, the licensing of cultivators, and the purchase and taking of physical possession of crops; they also have the exclusive right of wholesale trading and maintaining stocks.

Of potential importance, the INCB has previously stated that it has reviewed the issue of cultivation of *Cannabis* for personal medical use and has determined that, in the light of the heightened risk of diversion it represents, such cultivation does not meet the minimum

control requirements set out in the Convention. Accordingly, the INCB has consistently maintained the position that a State which allows individuals to cultivate *Cannabis* for personal use would not be in compliance with its legal obligations under the Convention. In addition, the INCB states that allowing private individuals to produce *Cannabis* for personal medical consumption may present health risks, in that dosages and levels of THC consumed may be different from those medically prescribed.

APPENDIX 5 Forms of Cannabis and Cannabinoids and Authorisation Status

Cannabis: Any product of the *Cannabis sativa* plant that is used for its psychoactive effects.

- **Cannabis or Marijuana:** consists of the dried plant product, leaves stems and flowers, typically smoked or vaporised.
- **Hash:** a concentrated resin cake that can be smoked or ingested.
- Other preparations include tinctures, oils (obtained by solvent extraction), and infusions.

Regulated under Schedule I of the Misuse of Drugs Regulations, 1988, as amended.

- **Cannabinoids:** This term usually refers to a group of different chemical compounds that activate cannabinoid receptors in the body, including cannabis or marijuana, endogenous neurotransmitters, and synthetic compounds e.g.
- Medical extracts from the cannabis plant, such as nabiximols (Sativex) approved for muscle spasticity in multiple sclerosis (Ireland, EU and US)
- Synthetic drugs that act on cannabinoid receptors, such as
    - Dronabinol (Marinol) approved for stimulating appetite in patients with AIDS related wasting and for nausea and vomiting associated with chemotherapy (US and Germany).
    - Nabilone (Cesamet) approved for controlling nausea and vomiting in cancer chemotherapy (UK, Austria, US, and Mexico). Nabilone is listed in Schedule 2 of the Regulations.
- **Tetrahydrocannabinol (THC):** The constituent of cannabis that by acting as an agonist on cannabinoid receptors is responsible for many of its psychoactive (capable of affecting the mind) or psychotogenic (capable of causing symptoms associated with psychosis, including delusions, delirium and hallucinations) effects. Present in regulated amounts in nabiximols, dronabinol, and nabilone.

  THCs, with the exception of nabiximols are regulated under Schedule I of the Misuse of Drugs Regulations, 1988, as amended. Nabiximols is regulated under Schedule 2, and can be prescribed.
- **Cannabinoid agonists:** Cannabinoids that produce psychological effects similar to those produced by THC
- **Cannabidiol (CBD):** Non-psychotogenic constituent of cannabis, sedative and anti-convulsant properties. CBD does not act via the endocannabinoid system. CBD is not controlled under the Regulations.

  A purified CBD medicine is under investigation for the treatment of genetic epilepsies.

APPENDIX 6 Review of Effectiveness and Safety

1. Introduction

a. Description of Cannabis and Products

Cannabis is a generic term used for medicines or products produced from plants belonging to the genus *Cannabis*. Cannabis is a controlled drug under the UN Single Convention on Narcotic Drugs, and its use is illegal in many countries. Cannabis contains more than a 100 plant cannabinoids (phytocannabinoids).

Medical use of cannabis is a broad term where part of the dried cannabis plant material, or products which have been manufactured from chemicals, known as cannabinoids, extracted from the cannabis plant, are used in medical treatment.

The use of cannabis for medical purposes is plausible. The human brain and other organs contain naturally occurring cannabinoid receptors as well chemicals that bind to those receptors. This is called the endocannabinoid system, and it appears to be responsible for the modulation of the nervous system, including effects on pain, control of movement, protection of nerve cells and a role in natural brain adaptability (plasticity), as well as having a role in various metabolic, immune and inflammatory processes and a possible role in the control of tumour growth.

Plant cannabis probably works by "mimicking" the effects of the human endocannabinoid system. The effect that cannabinoid compounds have on the cannabinoid receptors found in the brain can create varying pharmacologic responses based on formulation and patient characteristics. The main phytocannabinoids studied, and thought to be the most important in terms of effectiveness, are tetrahydrocannabinol (THC) and cannabidiol (CBD), although many others exist. THC is an agonist at endocannabinoid receptors and is the main psychoactive or psychotogenic part of cannabis. CBD is an antagonist and its pharmacological effects are different to THC in that it lacks psychotogenic effects.

Cannabinoids can be administered orally, sublingually, or topically; they can be smoked, inhaled, mixed with food, or made into tea. They can be taken in herbal form, extracted naturally from the plant, gained by isomerisation of cannabidiol, or manufactured synthetically (examples of cannabis products are given in Appendix 5).

The movement to revive cannabis as a medicine is driven by multiple factors. These include inadequacies in current medication to treat specific symptoms or diseases, along with self-reported benefits derived from cannabis (WHO, 2015).

b. UK Consumer Survey

The UK All Party Parliamentary Group (APPG) for Drug Policy Reform recently commissioned an online survey of medical cannabis use in the UK. This revealed cannabis use for a considerable range of conditions: for example, chronic and severe pain (24% of respondents); arthritis (12%); insomnia (21%); fibromyalgia (9%); post-traumatic stress disorder (PTSD) (7%); depression (30%); and anxiety (26%).

A majority of respondents (63%) had discussed using a cannabis-based treatment with their GP or consultant, but 72% of patients had obtained their cannabis on the street, directly or indirectly. Some respondents reported stress and anxiety associated with obtaining cannabis illegally.

The APPG is not a statutory committee of the UK Houses of Parliament, but appears to be a lobby group established by representatives with interests in drug policy reform.

c. Information on Evidence

The purpose of this review is to highlight the scientific evidence for the effectiveness of medical cannabinoids in a number of indications. It is not a comprehensive review of the data on cannabis for medical use.

A major problem with cannabis studies is that a number of different formulations of cannabis are available. A few studies have used 'natural' smoked cannabis or a cannabis extract. However, most studies use the cannabis products that are commercially available. Effectiveness is likely to be specific, in evidential terms, to a particular cannabis formulation and will depend on many variables, particularly the THC to CBD ratio. Effectiveness in one indication will not necessarily imply that a cannabinoid is effective in another indication.

Due to time-limits, it is not possible to conduct an evaluation of all published studies on the medical use of cannabis. The main documents reviewed include the Barnes & Barnes report (2016) commissioned by the UK APPG, hereafter referred to as 'the Barnes report', a recent meta-analyses published in the Journal of the American Medical Association (JAMA) (Whiting et al, 2016) and a review published recently in JAMA (Hill, 2015). These publications are referenced in the Barnes report. The Barnes report also cites Cochrane database systematic reviews, and a review representing the American Academy of Neurology position on medical marijuana/cannabis (Koppel et al, 2014). Where relevant, additional references not cited in the Barnes report, for example the recently published report from the Health and Medicine Division of the US National Academies of Sciences, Engineering, Medicine (2017), have been included.

2. Grading of Evidence

a. The Barnes report (2016) is based on a literature search of over 20,000 references. The evidence was graded according to the system used by the AAN, based on the robustness of the research methodology (Koppel et al, 2014). For example, a Class I study represents the highest quality evidence such as is available from a randomised, controlled clinical trial with masked or objective outcome assessment in a representative population, other classes of evidence are of lesser quality. The evidence for particular medical applications of cannabis was then grouped into three categories: "good', "moderate" and "some", where 'good' is based on the availability of at least two Class I studies for the medical condition or indication, backed up by a theoretical basis and other Class II/III/IV evidence. The Barnes report has been published on the APPG website, but it is does not appear that the report has been subject to peer-review, or is intended to be published in the medical literature.

b. The JAMA meta-analysis (Whiting et al, 2015) reviewed much of the same data as Barnes, but used a more widely recognised and adopted system that grades the quality of individual clinical trials (GRADE, Grading of Recommendations Assessment, Development and Evaluation) and this may account for the differences in conclusions on the quality of the evidence.

c. The National Academies report (2017) is based on an expert committee's recommendations on a comprehensive review of the published scientific evidence. Evidence was weighted and categorised as conclusive, substantial, moderate, limited or none.

3. Medical Conditions/Indications Reviewed

a. Spasticity

Muscle spasticity is a common disabling symptom of many neurological disorders. There are a number of available treatments (pharmacological, surgical and physiotherapy) but none are entirely satisfactory, so there is an unmet medical need for many patients.

Spasticity is the second most researched indication for cannabinoids. Most of the work has been done in the context of multiple sclerosis. Nabiximols is authorised for symptomatic relief of spasticity in patients with multiple sclerosis who have not responded to other treatments, and who respond to an initial trial of nabiximols. The authorised product information details the effectiveness and the side effects of nabiximols in this indication.

Regarding nabiximols, the Barnes report reviewed three studies (Class I) and a number of long term studies (Class IV). The report concluded that the evidence in support of reducing patient-reported spasticity symptoms was good, although there was not firm evidence for improvement in objective measures. The question of un-blinding of treatment due to the 'high' associated with the THC content was addressed in a number of publications and

considered not to be an issue as the CBD content counteracts the THC effects. This counteracting effect was noted only to be relevant to products with a high CBD to THC ratio.

The Barnes report examined three studies using an oral cannabis extract (two x Class I, one x Class II), and one study of smoked marijuana (Class III). The report concluded that there was moderate evidence of effectiveness for oral cannabis extract for reducing patient-reported spasticity scores.

The JAMA meta-analysis examined 14 studies, and concluded that concluded that there was no statistically significant improvement in spasticity in most studies. The quality of the evidence was considered to be moderate for spasticity due to multiple sclerosis. The relevant products were nabiximols, nabilone, THC/CBD capsules and dronabinol.

The AAN found strong evidence that oral cannabis extract reduces patient-reported scores as adjunctive therapy, but moderate evidence that cannabis extract was effective in reducing objective measures at 12 and 15 weeks.

The National Academies found substantial evidence that oral cannabinoids are an effective treatment for improving patient-reported multiple sclerosis spasticity symptoms, but limited evidence for an effect on clinician-measured spasticity. There is insufficient evidence to support or refute the conclusion that cannabinoids are an effective treatment for spasticity in patients with paralysis due to spinal cord injury.

The Barnes report notes that there is no difference in management of spasticity whatever the underlying neurological aetiology and if cannabis is deemed to be effective in spasticity in multiple sclerosis then there is no reason why it should not be effective in other neurological disorders that give rise to spasticity, such as spinal cord injury, traumatic brain injury and stroke.

The HPRA considers that there is evidence that oral cannabinoids are an effective treatment for spasticity associated with multiple sclerosis, where other treatments have failed.

b. Nausea and Vomiting in the Context of Chemotherapy

The Barnes report considered a Cochrane review, the JAMA meta-analysis, a literature review and two trials with Class I evidence and one trial with Class II evidence.

A Cochrane review (Smith et al, 2015) of 23 randomised controlled trials concluded that cannabinoids may be a useful therapeutic option for adult patients who have not responded to other anti-emetics. The synthetic cannabinoids nabilone and dronabinol were used either as monotherapy or as adjunct to conventional dopamine antagonists. The quality of the

evidence was judged to be low to moderate, and did not reflect current chemotherapy and anti-emetic regimens, further research is required.

A Cochrane review, not referenced in the Barnes report, examined 4 studies using cannabinoids (THC or nabilone) in children (Phillips et al, 2010). The heterogeneity of the studies meant no outcomes could be pooled.

The JAMA meta-analysis examined 28 studies, 14 were for nabilone, three for dronabinol, one for nabiximols and, four for levonantradol, and six for THC. The most common active comparators included prochlorperazine, chlopromazine, and domperidone. All studies suggested a greater benefit of cannabinoids compared with both active comparators and placebo, but these did not reach statistical significance.

The Barnes report concluded that medical cannabis could be a useful adjunctive treatment to consider for patients on moderately or highly emetic chemotherapy who are not responding to other anti-emetic treatments. They consider that that there is good evidence for this indication.

The JAMA meta-analysis considered the evidence to be of low quality, the relevant products were dronabinol and nabiximols.

A BMJ review concludes that there are now newer, much more effective, anti-nausea drugs, such as ondansetron (Farrell et al, 2014). These drugs have not been directly compared with cannabinoids, but indirect comparisons suggest that the newer drugs control nausea in a larger proportion of patients than THC does. Cannabinoids are thus not recommended as first line treatment for nausea in patients with cancer, although cannabinoids may have a role as adjunctive treatments.

The New England Journal of Medicine review concludes that THC is an effective antiemetic agent in patients undergoing chemotherapy, but patients often state that marijuana is more effective in suppressing nausea. Other, unidentified compounds in marijuana may enhance the effect of THC (as appears to be the case with THC and cannabidiol, which operate through different antiemetic mechanisms). Paradoxically, increased vomiting (hyperemesis) has been reported with repeated marijuana use.

The National Academies report finds conclusive evidence that oral cannabinoids are effective anti-emetics in the treatment of chemotherapy-induced nausea and vomiting.

The HPRA considers that there is evidence to support the effectiveness of cannabinoids in the treatment of chemotherapy-induced nausea and vomiting, where other treatments have failed.

c. Epilepsy

The unmet need in refractory epilepsies, in particular the severe childhood epilepsies, such as Dravet Syndrome and Lennox-Gastaut Syndrome, is acknowledged in the literature. The substantial psychological and social burden of moderate or severe epilepsy may lead patients and carers to seek alternative treatments. Retrospective case reports and individual experiences gain wide media attention. Professional associations such as the AAN and the American Epilepsy Society have called for higher quality research and advised caution in the interpretation of the information.

The main cannabinoid with anticonvulsant properties is CBD, although the mechanism of action is unknown. The Barnes report acknowledges that the situation is complex, with THC appearing to act as an anticonvulsant in some circumstances but as a pro-convulsant in other circumstances. Crippa and colleagues (2016) describe the cases of two children with treatment-resistant epilepsy, who received CBD enriched extract with 4.03%, and 3.1% THC, respectively, and experienced THC intoxication and increased seizures. The CBD/THC extract was replaced with the same dose of purified CBD with no THC (BSPG-Pharm, Sandwich, UK) which led to improvement in intoxication signs and seizure remission. The authors express concern regarding the potential toxic effects of THC in younger patients, including cognitive impairment and chronic psychiatric disturbances, and highlight the need for randomised, clinical trials using high-quality and reliable cannabis-derived substances.

The Barnes report examines the press releases published by GW Pharmaceuticals on its purified plant-derived CBD extract publications on the use of this extract, and CBD oil (CBD and THC in a ratio of 20:1) in treatment-resistant epilepsy (Class III), and makes reference to initial data on cannabidavarin (GWP42006), a cannabinoid that may also have anticonvulsant properties.

An online survey of parents who had had administered CBD-enriched cannabis reported a reduction in seizure frequency of 85% and 14% reported complete seizure freedom. The authors wrote that the study did not represent compelling evidence of effectiveness or safety, and highlighted the methodological weaknesses, including participation bias and lack of blinded outcome assessment.

The Barnes report concludes that there is a theoretical basis for effectiveness and initial human studies are promising, however, there is insufficient evidence for effectiveness at the moment, and further studies are required.

GW Pharmaceuticals press releases report significant reductions in seizures with their pure CBD extract, compared with placebo in patients with Dravet Syndrome (March, 2016), and as adjunctive treatment in Lennox-Gastaut Syndrome (September, 2016). Caregivers reported an improvement in overall condition and the medicine was well tolerated. An open-label clinical trial of pure CBD as adjunctive treatment for patients with treatment-resistant epilepsy suggests a reduction in seizure frequency (Devinsky et al, 2015). GW Pharmaceuticals have indicated that they intent to submit an application for authorisation to the FDA in mid-2017, an application to European countries is also planned.

A Cochrane systematic review (2014) examined four trials of 48 patients, each of which used cannabidiol as an adjunctive treatment to anti-epileptic medicines. No reliable conclusions could be drawn regarding the effectiveness of cannabinoids.

The National Academies conclude that there is insufficient evidence to support or refute the conclusion that cannabinoids are an effective treatment in epilepsy.

The HPRA considers that there is not currently evidence that cannabinoids are an effective treatment in epilepsy. Randomised controlled clinical trials have yet to be published. However, the management of severe, intractable epilepsies that are resistant to multiple anti-epileptic medicines is an acknowledged unmet medical need, and subject to a policy decision, patients with these conditions, could be facilitated in accessing cannabinoids as a medical treatment.

d. Chronic pain

Chronic pain is the most researched indication for cannabinoids.

The Barnes report reviewed 22 studies in chronic pain including cancer pain and rheumatoid arthritis and neuropathic pain. The pain was usually resistant to other analgesics, including opioids.

Nine studies evaluated nabilone, seven were for nabiximols (Sativex), two were for dronabinol, and four were for smoked cannabis (THC). The majority of trials were placebo-controlled. Nabilone was compared to dihydrocodeine, or ibuprofen, or gabapentin in separate trials. In most cases, cannabinoids were used as adjunctive treatment to other analgesics.

Nine studies met the criteria for Class I, six studies met the criteria for Class II, five studies met Class III/IV criteria and one study was unclassified. Studies generally reported improvements in pain measures associated with cannabinoids but these did not reach statistical significance in most studies.

No significant differences in effectiveness were noted between chronic pain (of various causes) and neuropathic pain.

The Barnes report concludes that there is good evidence for effectiveness for pain relief in various formulations and in a number of settings.

The JAMA meta-analysis included 28 studies in pain indications, and using the GRADE approach found that there was moderate-quality evidence to suggest that cannabinoids may be beneficial for the treatment of chronic neuropathic pain or cancer pain, specifically smoked THC or nabiximols.

The American Academy of Neurology (Koppel et al, 2014) systematic review found strong evidence for oral cannabis extract for reducing central pain or painful spasms in patients with multiple sclerosis. The review found moderate evidence for the effectiveness of THC or nabiximols. The effectiveness of smoked marijuana for reducing pain was unclear.

However, it is noted that nabiximols was not been found to be better than placebo in three clinical trials in cancer pain (GW Pharmaceuticals, 2015).

Farrell et al (2014) concluded that the effectiveness of cannabinoids for the treatment of muscle spasticity or neuropathic pain in multiple sclerosis is unclear and any benefit is likely to be modest, while mild to moderate adverse events are common and long term safety has not been established.

A New England Journal of Medicine review (Volkow et al, 2014), not cited in the Barnes report, concluded that both marijuana and dronabinol, decrease pain, but dronabinol may lead to longer-lasting reductions in pain sensitivity and lower ratings of rewarding effects.

The National Academies report concludes that there is substantial evidence that cannabis is an effective treatment for chronic pain in adults. The report relies mainly on the JAMA meta-analysis mentioned above.

The Australian government recently passed legislation allowing the prescription of suitable medical cannabis products for painful and chronic conditions, however, the Australian Rheumatology Association (ARA) considers that there is currently not enough supportive evidence to recommend medical cannabis as a clinical intervention for chronic musculoskeletal pain outside of a clinical trial setting (ARA, 2016).

The Faculty of Pain Medicine (FPM), Australian and New Zealand College of Anaesthetists does not endorse the use of cannabinoids in chronic non-cancer pain until such time as a

clear therapeutic role for them is identified in the scientific literature, patients in palliative care are excluded from this statement (FPM, 2015).

Chronic pain is regarded as a disease of the nervous system and is defined as pain without apparent biological value that has persisted beyond normal tissue healing time (usually taken to be 3 - 6 months). It is prevalent, affecting 1 in 5 people worldwide (Moore et al, 2013). Chronic pain is subjective, and is a multifactorial experience encompassing physical, emotional, social, spiritual and other factors. A large number of authorised medicines are available, and pain specialists recognise that pharmacological treatment is only one element of a multi-faceted approach to chronic pain management, that includes physical and psychological interventions.

There are a number of types of chronic pain, for example cancer, pain, postsurgical or post-traumatic pain, and an individual patient may experience more than one type of chronic pain. The published literature on chronic pain (in respect of cannabis and other therapies) is confusing and conflicting as in many cases the specific type of pain being investigated is not adequately defined, or the clinical trial does not describe the underlying causes of the pain in sufficient detail.

The symptoms of pain are subjective, and clinical trials can be subject to biases that compromise the results. In addition, patients suffering chronic pain may already be taking medications with addictive potential, and their care is complex.

The clinical trials of chronic pain involved patients with a wide range of causes including neuropathic pain, cancer pain and fibromyalgia. The cannabis products evaluated included authorised medicines, and smoked cannabis. The data generally suggested an improvement in pain measures associated with cannabis products, but when these clinical trials are combined, the overall estimate of benefit is moderate and there is no effect on patient's self-reported quality of life. The symptoms of chronic pain are subjective, and the clinical trials that have been conducted have been shown to be subject to a moderate risk of bias, for all but one clinical trial. These biases mean that the treatment effects that have been reported in clinical trials of cannabis for chronic pain have to be viewed with caution, and that the evidence-base in terms of the benefit to patients suffering pain remains uncertain, In addition, cannabis products were associated with a greater risk of side effects including serious side effects when compared to other pain medicines. No studies have evaluated the long term safety of treatment with cannabis products.

Current evidence suggests that larger more definitive clinical trials are needed. This approach is consistent with the views of pain specialists and medical professional bodies who have cited concern about the use of cannabis and cannabinoids in the management of chronic pain. In particular, studies comparing the effectiveness of cannabis and the cannabinoids with authorised medicines are necessary to determine the place for cannabis in pain management.

For example, it has been reported that cannabinoids are no more effective than codeine in controlling pain (Campbell et al, 2001).

It is recommended that researchers should be encouraged and supported in the conduct of long-term, randomised, double-blind clinical studies to more completely characterise the effectiveness and safety profiles of cannabis-based medicines. This will most usefully be progressed in a collaborative, international programme.

The HPRA considers that current evidence does not support the use of cannabis in the treatment of chronic pain. The HPRA does not consider that there is an unmet medical need as a large number of authorised medicines, and other treatments are available to treat the many factors involved in chronic pain.

e. Anxiety

Cannabis use can both increase and decrease anxiety in humans. CBD has been shown to reduce anxiety whereas THC usually has the converse effect. The mechanism by which CBD exerts its anxiety-reducing effects is not well established.

The Barnes report examined three studies with Class I evidence, one study with Class III evidence, and one unclassified study. CBD was found to reduce anxiety, and the evidence was considered to be of good quality.

One of these studies reported effectiveness for CBD in patients with generalised social anxiety disorder subjected to a simulated public-speaking test. Of interest, the JAMA meta-analysis considered the evidence from this study to be of very-low quality. The National Academies consider the evidence to be limited.

The HPRA considers that there is insufficient evidence to support the use of cannabis or cannabinoids in the treatment of anxiety.

f. Other Medical Conditions/Indications

Cannabis and cannabinoids have been proposed for the treatment of a large number of other medical conditions. The HPRA considers that there is insufficient evidence to support the use of cannabis or cannabinoids in the treatment of these conditions.

Some of the information available is summarised in Table 2.

Table 2: Information on other medical conditions/indications

	Barnes Report – quality of evidence	JAMA Meta-analysis – quality of evidence	Cochrane Systematic Reviews	NEJM (Volkow et al, 2014)	AAN (Koppel et al, 2014)	National Academies, 2017	Other
Parkinson's Disease	Moderate	Not addressed			Oral cannabis extract: probably ineffective	Insufficient evidence	
Sleep disorders	Moderate	Low quality				Moderate evidence	
Fibromyalgia	Moderate		No evidence for effectiveness (nabilone)				
Post-traumatic stress disorder	Moderate					Limited evidence	
Appetite stimulation - AIDS	Moderate	Low quality	No evidence for effectiveness	No long-term or rigorous evidence of a sustained effect		Limited evidence	
HIV/AIDS – reduction of morbidity and mortality			Limited evidence				
Inflammation			Weak evidence, significant side effect profile	Potential for treatment of rheumatoid arthritis, ulcerative colitis and Crohn's disease based on animal data			
Bladder dysfunction, in the context of neurological disorders, e.g. multiple sclerosis	Some				Nabiximols: probably effective		
Glaucoma	Some			Other standard treatments are currently more effective		Limited evidence	
Control of agitation in dementia	Some		No evidence for effectiveness			Limited evidence	

	Barnes Report – quality of evidence	JAMA Meta-analysis – quality of evidence	Cochrane Systematic Reviews	NEJM (Volkow et al, 2014)	AAN (Koppel et al, 2014)	National Academies, 2017	Other
Tourette's syndrome	Some	Low quality			Effectiveness unknown	Limited evidence (THC)	
Depression	No recommendation	Very low quality				Limited evidence that treatments are ineffective	
Cancer	Very limited evidence						CBD may have potential, further studies required (Fraguas-Sanchex et al, 2016; Javid et al, 2016)
Tremor					Probably ineffective		

4. Review of Safety

When considering the side effect profile of cannabis and cannabinoid formulations it is appropriate to distinguish between effects from short-term use and effects related to longer term repeated use. An overview of these is provided in the table below.

Table 3: Adverse Effects of Short term Use and Long-term or Heavy Use of Cannabis (Adapted from Volkow et al, 2014)

EFFECTS OF SHORT-TERM USE
• Euphoria, hallucinations, anxiety, paranoia and psychosis
• Impaired short-term memory and confusion, making it difficult to learn and retain information
• Impaired motor co-ordination, interfering with driving skills and increasing the risk of injuries
• Altered judgement, increasing the risk of sexual behaviours that facilitate the transmission of sexually transmitted diseases

EFFECTS OF LONG-TERM OR HEAVY USE
• Addiction (in 9% of users overall, 17% of those who begin use in adolescence, and 25 to 50% of those who are daily users)
• Increased risk of chronic psychosis disorders (including schizophrenia) particularly in adolescents and persons with a predisposition to such disorders
• Cognitive impairment, with lower IQ among those who were frequent users during adolescence
• Altered brain development
• Poor educational outcome, with increased likelihood of dropping out of schools
• Diminished life satisfaction and achievement (determined on the basis of subjective and objective measures as compared with such ratings in the general populations)
• Increased risk of suicidal ideation and attempt
• Symptoms of chronic bronchitis

There is a clear paucity of studies evaluating the long-term adverse events of cannabis. The studies evaluating longer term effects which have been conducted are mostly in a setting of recreational drug use and therefore the user profile and their baseline risks are likely to be quite different to the patient populations seeking to use cannabinoids for the aforementioned therapeutic purposes. This is further discussed below.

It is also important to consider the different pharmacological effects of different cannabinoids and the importance of the THC to CBD ratio. The cannabis formulation used in a setting of recreational drug use is likely to contain a high content of THC and may contain impurities. In recent years there has been an increase in potency of recreational cannabis due to increased cultivation of high THC containing strains. As alluded to earlier, the majority of psychoactive side effects are associated with THC which can be counteracted to a certain extent by CBD.

Therefore, whilst the following discussion provides a general overview of the adverse events associated with cannabinoids reported in the literature, extrapolation of data is not always appropriate as formulation and population-specific issues need to be considered.

a. Short Term Side Effects

In terms of the short term side effects the Barnes report refers to two main meta-analyses. The first of these conducted by Koppel et al, found a relatively low discontinuation rate of 6.9% (95% CI 5.7%-8.2%) due to adverse events versus 2.2% (95% CI 1.6%-3.5%) for placebo patients. This overall analysis included 1619 patients across 34 studies who were treated with different formulations of cannabinoids for less than 6 months. The Koppel analysis highlighted adverse events (AEs) which were reported in 2 or more studies including *nausea,*

increased weakness, behavioural or mood changes, suicidal ideation or hallucinations, dizziness or vasovagal symptoms, fatigue, feelings of intoxication (Koppel et al, 2014).

Following on from the Koppel review a more recent meta-analysis was conducted by Whiting et al which reported on adverse events reported in 1710 patients across 62 studies. As outlined in the table below, cannabinoids were associated with an increased risk of experiencing "Any Adverse Event", "A Serious AE" and "Withdrawals due to an AE" when compared to controls (placebo or active comparator) (Whiting et al, 2015). Unsurprisingly given the differences in formulations combined with different outcome measures and broad indication groupings, there was high heterogeneity in the study set included. Nevertheless, it is of note that the nature of adverse events reported in these studies are generally in keeping with the safety profile of nabiximols (see Sativex: Summary of Products Characteristics, SmPC, www.hpra.ie) authorised in Ireland and also with that of nabilone which is currently authorised in the UK for the treatment of nausea and vomiting. The most commonly reported adverse events relate to psychiatric and nervous system effects including euphoria, hallucinations, anxiety and paranoia. Cannabis acutely impairs several components of cognitive function leading to confusion and effects on episodic and working memory. It also acutely impairs psychomotor co-ordination.

The risk of a fatal cannabis overdose is small in comparison to the risks of opioid and stimulant drug overdoses. The lack of respiratory depression is consistent with the absence of cannabinoid receptors in brain stem areas that control respiration. Whilst the risk of a fatal cannabis overdose is small, acute exposure to cannabis increases heart rate and blood pressure (both listed in the Sativex SmPC) and there is some epidemiological evidence that suggests an increased risk of myocardial infarction during acute intoxication. Mittleman et al, reported that the risk of myocardial infarction (MI) was four times higher in patients with a recent myocardial infarction in the hour after smoking cannabis (Mittleman et al, 2001).

Table 4: Summary Estimates from Meta-Analyses for Each Adverse Event (Adapted from Whiting et al, 2015)

	NO. OF STUDIES (NO. OF PATIENTS)	SUMMARY OR (95% CI)	I^2, %
General AE Categories			
Any	29 (3714)	3.03 (2.42-3.80)	31
Serious	34 (3248)	1.41 (1.04-1.92)	0
Withdrawal due to AE	23 (2755)	2.94 (2.18-3.96)	2
Individual AEs			
Nervous System Disorders SOC			
Dizziness	41 (4243)	5.09 (4.10-6.32)	18
Somnolence	26 (3168)	2.83 (2.05-3.91)	27
Drowsiness	18 (1272)	3.68 (2.24-6.01)	44
Balance Disorder	6 (920)	2.62 (1.12-6.13)	0
Seizures	2 (42)	0.91 (0.05-15.66)	0
Gastrointestinal Disorders SOC			
Dry Mouth	36 (4181)	3.50 (2.58-4.75)	28
Nausea	30 (3579)	2.08 (1.63-2.65)	0
Vomiting	17 (2191)	1.67 (1.13-2.47)	0
Diarrhoea	17 (2077)	1.65 (1.04-2.62)	15
General disorders and administration site conditions SOC			
Fatigue	20 (2717)	2.00 (1.54-2.62)	0
Asthenia	15 (1717)	2.03 (1.35-3.06)	0
Psychiatric Disorders SOC			
Euphoria	27 (2420)	4.08 (2.18-7.64)	49
Depression	15 (2353)	1.32 (0.87-2.01)	0
Disorientation	12 (1736)	5.41 (2.61-11.19)	0

	NO. OF STUDIES (NO. OF PATIENTS)	SUMMARY OR (95% CI)	I^2, %
Anxiety	12 (1242)	1.98 (0.73-5.35)	54
Confusion	13 (1160)	4.03 (2.05-7.97)	0
Hallucination	10 (898)	2.19 (1.02-4.68)	0
Paranoia	4 (492)	2.05 (0.42-10.10)	0
Psychosis	2 (37)	1.09 (0.07-16.35)	25
Respiratory, thoracic and Mediastinal Disorders SOC			
Dyspnoea	4 (375)	0.83 (0.26-2.63)	0

OR (Odds Ratio); 95% CI (95% Confidence Interval) Odds of Participants Experiencing AE With Cannabinoid Vs Placebo or Active Comparison. The Individual AEs are grouped according to System Organ Class (ref MedDRA version 18).

Potential for drug-drug interactions

The therapeutic areas in which the role of cannabis and cannabinoids are currently being investigated are predominantly chronic conditions for which patients are likely to be on multiple medications. Hence, polypharmacy and an understanding of the potential for drug-drug interactions needs to be considered. Stout et al, in a recent review investigating exogenous cannabinoids as substrates, inhibitors and inducers of human drug metabolising enzymes highlight a number of in vitro studies which have identified metabolic pathways via the cytochrome P450 (CYP450) system. Specifically CYP2C9 and CYP3A4 contribute to the metabolism of THC and CBD is likely metabolised via CYP2C19 and CYP3A4 (Stout et al, 2014).

The Sativex summary of product characteristics (SmPC) states that concomitant treatment with other CYP3A4 inhibitors (for example, itraconazole, ritonavir, clarithromycin) may require titration of the Sativex dosing schedule as the CYP3A4 inhibitor ketoconazole increased the Cmax (maximum plasma concentration) of both THC and CBD by 1.2- and 2 fold respectively. Similarly treatment with the CYP3A4 inducer, rifampicin, resulted in a 40% and 50% reduction in the maximum plasma concentrations of THC and CBD respectively. Based on this data, the Sativex SmPC recommends that concomitant administration with strong enzyme inducers should be avoided when possible. Many anti-epileptic drugs including carbamazepine and phenytoin are CYP3A4 inducers (Sativex SmPC).

Other potential pharmacokinetic interactions include CYP2C9 mediated interactions with tricyclic antidepressants and selective serotonin reuptake inhibitors. A case series reports on

development of tachycardia and development of increased delirium in four patients treated with tricyclic anti-depressants and THC. There are also reports of manic symptoms after smoking cannabis and taking fluoxetine. Potential interactions with warfarin through inhibition of metabolism and displacement from protein binding sites have also been reported (Lindsey et al, 2012).

The potential for pharmacodynamic interactions also needs to be considered. As THC is a central nervous system (CNS) depressant, there is potential for exacerbation of depressant effects with concomitant use of other CNS agents. Although studies investigating the effects of THC with alcohol, barbiturates, benzodiazepines, antihistamines and narcotics are lacking, given the potential for additive effects caution with concomitant use is warranted. This is highlighted in the Sativex SmPC.

Overall, however the full spectrum of potential interactions and the clinical significance of these remains to be fully characterised. Furthermore Stout et al note that interactions involving cannabinoids are expected to vary considerably in their clinical significance given the wide variability in products, doses, routes of administration, population using cannabinoids and other factors (Stout et al, 2014).

b. Long Term Side Effects

The number of studies investigating the side effects of long-term or heavy cannabis use are limited in terms of numbers and quality. The key areas of concern are highlighted below.

i. Psychosis and Schizophrenia

The majority of the population studies reviewed in the Barnes report and by the WHO in their update on "The health and social effects of nonmedical cannabis use" (2016) show that cannabis use is associated with long-term psychotic disorders, including schizophrenia. Other important reviews of note include a meta-analysis conducted by Moore et al (2007) and a more recent systematic review by Gage et al which reported increased odds ratios for psychotic disorders in regular cannabis users versus non-users. Some of the key studies are further discussed below (Gage et al, 2016; Moore et al, 2007).

A 15 year follow up study of schizophrenia among 50, 465 Swedish male conscripts (WHO, 2016) found that those conscripts who had tried cannabis by the age of 18 years were 2.4 times more likely to be diagnosed with schizophrenia over the next 15 years than those who had not. This study adjusted for a personal history of psychiatric disorder by age 18 and number of other psychosocial confounders and found that those who had used cannabis 10 or more times by age 18 were 2.3 times more likely to be diagnosed with schizophrenia than those who had not used cannabis. A 27-year follow-up to this Swedish cohort (WHO, 2016) study found a dose-response relationship between frequency of cannabis use at the age of 18 years and the risk of schizophrenia during the follow up period which persisted after

controlling for confounding factors. The California Hospital Study (Gage et al, 2016) reported a large association between hospital admission diagnosis of cannabis use disorder and risk of later hospitalisation for schizophrenia compared with a cohort of subjects who were hospitalised for appendicitis (0R 8.16, 95% CI 5.08, 13.12). These findings have also been reported in smaller longitudinal studies. In the Dunedin birth cohort study (WHO, 2016), cannabis use by age 15 was associated with an increase in schizophrenia disorder at age 26 (OR 11.4, 95% CI 1.8, 70.5) with a weaker association reported in the older age group of 15 and 18 (OR 2.0, 95% CI 0.8, 5.0). In the Dutch Netherlands Mental Health Survey and Incidence Study (NEMESIS), cumulative cannabis (Gage et al, 2016) use was associated with incident psychotic symptoms measured 3 years later (OR 1.89, 95% CI 1.25, 2.85). On the other hand the Zurich study followed a sample of participants for 30 years and found weak evidence that cannabis use was associated with schizophrenia nuclear symptoms before but not after adjustment. Similarly in the Avon Longitudinal Study of Parents and Children birth cohort cumulative cannabis use at age 16 was associated with psychotic experiences at age 18 after adjustment for pre-birth and childhood confounders however this no longer remained following further adjustment for cigarette use and other illicit drug (Gage et al, 2010; Moore et al, 2007; WHO, 2016).

The 2007 meta-analysis conducted by Moore et al, which included the above studies reported a 40% increase in risk of any psychotic outcome in cannabis users compared with never users and a stronger association with heavier or more regular cannabis users (OR 2.1, 95% CI 1.5, 2.8) (Moore et al, 2007). Updating the estimate from this study to also include more recently conducted studies (Table 4 below) resulted in a similar pooled odds ratio for any outcome as reported by Gage et al (OR 1.46, 95% CI 1.24, 1.72) (Gage et al, 2016). Findings of a recent meta-analysis by Schloer et al, also suggested that continued cannabis use after the onset of psychosis predicts poor disease outcome as shown by a high number of relapses, admittance to hospital and more severe positive symptomology (Schloer et al, 2016).

Overall, whilst risk factors remain difficult to determine, early usage in terms of age and a genetic predisposition to psychosis have been identified as increasing the risk for development of psychotic disorders. The association between cannabis use and chronic psychosis (including a schizophrenia diagnosis) is stronger in those individuals who have had heavy or frequent cannabis use during adolescence. In terms of genetic factors the DRD2 genotype has been identified as influencing the likelihood of a psychotic disorder in individuals who used cannabis. The COMT Val-158 polymorphism has also been reported to moderate the effect of adolescent cannabis use on adult psychosis, such that carriers of this allele were more likely to develop schizophreniform disorder if they used cannabis than non-carriers of the allele. In terms of genetic risk however alternative explanations suggested in the literature are that individuals at genetic high risk for schizophrenia may be more likely to use cannabis through a common genetic risk for schizophrenia and cannabis use disorder. Overall, however as noted by Volkow et al, the influence of genetic variants requires further research in larger studies (Volkow et al, 2016).

Table 5: Studies investigating association of Cannabis with Psychosis and Schizophrenia, Adapted from Gage et al, 2016

COHORT	SAMPLE SIZE	EXPOSURE	OUTCOME	RESULTS OR (95% CI)	STRENGTHS	LIMITATIONS
ECA	2295	Daily use of Cannabis	Psychotic experiences	2.0 (1.25, 3.12)	Large sample size, interview based psychotic experiences measure	No attempt to account for intoxication
NEMESIS	4045	Ever use and frequency of use	Psychosis symptoms	2.76 (1.18, 6.47)	Legality of cannabis use in Netherlands; attempt to remove intoxication effect; repeated measures for exposure and outcome	Sample size too small to examine psychotic disorders robustly
Swedish Cohort	50087	Cumulative cannabis use	Schizophrenia diagnosis	Linear trend 1.2 (1.2, 1.4)	Large sample size, attempt to remove intoxication effect, schizophrenia measure	Only males included; large temporal gap between exposure and outcome, could miss variation in cannabis use; low levels of cannabis use at baseline
Dunedin	759	Ever use of cannabis by age 15/18	Schizophreniform diagnosis	2.91 (1.20, 7.04)	Strong cohort retention, minimising possibility of attrition bias; schizophreniform disorder measure	Small sample size, exacerbated by dividing sample into cannabis before/after 15; limited adjustment for confounding
Christchurch	1265	Cannabis use; dependence	Psychotic experiences	1.8 (1.2, 2.6)	Through consideration of confounders; use of fixed	Lack of clinical measure of psychosis; small sample size

COHORT	SAMPLE SIZE	EXPOSURE	OUTCOME	RESULTS OR (95% CI)	STRENGTHS	LIMITATIONS
					effects regression to minimise confounding by time invariant confounders	
EDSP	2437	Used at least five times	Psychotic symptoms	1.2 (1.1, 1.3)	Investigation of reverse causation hypothesis	Sample size too small to examine psychotic disorders robustly
NPMS	1795	Dependence (three level measure)	Self-reported psychotic symptoms	1.5 (0.6, 3.9)	Thorough consideration of confounders	Few cannabis users; sample selected due to pre-existing mental health problems so may not be generalisable
Zurich Study	591	Heaviness of use (three level measure)	Schizophrenia nuclear symptoms (self-report)	1.77 (0.96, 3.24)	Many repeated measures over long follow up	Small sample size; limited consideration of confounders
California	41,670	Hospitalisation for cannabis abuse	Hospitalisation for schizophrenia	8.2 (5.1, 13.1)	Large sample size	Extreme exposure measure
ALSPAC	1756	Cumulative use (four-level)	Psychotic experiences severity (four-level)	1.12 (0.76, 1.65)	Thorough consideration of confounders	Small sample size; young age of participants; lack of clinical measure of psychosis.

ALSPAC, Avon Longitudinal Study of Parents and Children; ECA, Epidemiologic Catchment Area; EDSP, Early Developmental Stages of Psychopathology; NEMESIS, Netherlands Mental Health Survey and Incidence Study; NPS, National Psychiatric Morbidity Survey

Despite the overall trend in the literature which consistently reports an association between cannabis and psychotic disorders determining whether these associations are truly causal

does remain difficult due to the limitations in the research base. No randomised control trials of note have been conducted and the majority of evidence arises from epidemiological observational studies as described above. The Barnes report classifies this as Class III and Class IV research. Non-causal explanations for associations arising from observational studies including reverse causation (where associations reflect psychosis increasing the risk of cannabis use), bias (where problems with measurement and sample selection have led to incorrect estimates), and confounding (where other variables that increase risk of both cannabis use and psychosis lead to spurious associations for example underlying diseases or concomitant drug use) (Gage et al, 2016). Several of the larger studies have made attempts to account for these limitations in their design and analysis however uncertainties do remain.

Another limitation is that the definitions used for Psychosis or Schizophrenia are not consistent across the literature and are often not defined in individual studies. Therefore, it is often not clear if the negative symptoms of schizophrenia (apathy, social withdrawal, memory impairment) have been evaluated in addition to the positive symptoms of hallucinations, delusional thinking, paranoia etc. In many of the studies the focus is on psychotic symptoms and it is not clear if the clinical diagnosis of schizophrenia has been properly evaluated. It is also important to highlight that as the majority of studies in the area have also been conducted in a setting of recreational drug use. Information on exposure is limited in many studies and based on self-reported usage. Therefore, accurately defining the amount of drug used is difficult and in the majority of studies there is no information on the balance of the cannabinoids, THC and CBD. Another concern is the appropriateness of extrapolating results from studies conducted in a setting of recreational drug use to the aforementioned clinical populations of interest.

Overall, whilst the literature remains broadly supportive of a causal role for cannabis in the development of schizophrenia, uncertainty remains with regard to the magnitude of this effect, the effect of different cannabinoids on the risk and the key risk factors including identification of the high-risk groups who would be particularly susceptible.

ii. Cognitive Impairment

Cannabis use has been associated with impaired cognition during acute intoxication as well as in the non-intoxicated state in long-term users. There is much literature investigating the effects of cannabis use across the different cognitive domains. Deficits have been noted amongst cannabis users in terms of reduced episodic memory and reduced attention and concentration. Cannabis has also been shown to impact planning and decision making, response speed, accuracy and latency. The effects on cognitive impairment have been correlated with the duration and frequency of cannabis use, the age of initiation and the estimated cumulative dose of THC (WHO, 2016). Longer term cumulative effects however remain unclear and it is also unclear whether cognitive function fully recovers after cessation of cannabis use.

Broyd et al have recently conducted a systematic review on the acute and chronic effects of cannabinoids on human cognition and have summarised their findings across the major cognitive domains investigated, namely *Memory* (verbal learning and memory; working memory), *Attention*, *Psychomotor Function, Executive Function (*Planning, reasoning, interference control and problem solving; Inhibition; Verbal Fluency; Time estimation) and *Decision Making, Reward Processing and Delay Discounting*. Their key findings are summarised in the Table 5 below (Broyd et al, 2016).

Table 6: Key Findings for Cognitive Impairment in Cannabis Users (Taken from Broyd et al, 2016)

ACUTE EFFECTS OF CANNABIS ON COGNITION
• Impaired verbal learning and memory
• Impaired working memory and other memory functions
• Impaired attention, take and dose dependent
• Impaired inhibition, less for other executive functions
• Impaired psychomotor function
CHRONIC EFFECTS OF CANNABIS ON COGNITION
• Impaired verbal learning and memory
• Impaired attention and attentional bias
• Possible impaired psychomotor function
• Mixed evidence for executive function and decision making ➢ Most associated with cannabis use parameters, particularly frequency of use and age of onset
RECOVERY OF FUNCTION WITH ABSTINENCE
• Likely persistent effects on attention and psychomotor function
• Possible persistent effects on verbal learning and memory
• Evidence insufficient and mixed

Broyd et al, additionally reviewed the literature evaluating whether impairment persists or recovers with abstinence and concluded that the literature remains divided regarding this issue. A longitudinal study from the Dunedin birth cohort suggested that sustained heavy cannabis use over several decades produced substantial declines in cognitive performance that may not be wholly reversible. This study assessed changes in IQ between age 13 and at age 38 in 1037 New Zealanders born in 1972 or 1973. Early and persistent cannabis users showed an average decline of eight IQ points compared with peers who had not used

cannabis, and cannabis-using peers who had not used cannabis in this sustained way. Similar results have been reported in other studies. Poor performance was associated with lifetime cannabis exposure or an earlier age of onset of use in adolescents with 30 days of abstinence and predicted relapse to cannabis use during a 1-year follow up. Even after 53 days of abstinence, adolescents showed impaired working memory and risk taking. In another study young adults abstinent for up to 4 weeks showed poorer verbal fluency relative to control subjects and poorer performance on a gambling task, associated with prior quantity of weekly cannabis use. On the other hand an adult sample showed improvements in critical tracking and divided attention with increasing abstinence periods of 8-23 days but sample subjects nevertheless remained impaired relative to controls. In a large prospective study collecting data over a 4 year period, former heavy users who were abstinent for ≥ 12months improved relative to ongoing heavy users regarding verbal memory and did not differ from non-users on any cognitive measure. The evidence generally tends to suggest that the magnitude of neuropsychological impairment and the extent to which it persists after abstinence may depend on multiple factors including the frequency and duration of cannabis use, the length of abstinence, and age at onset of use (Broyd et al, 2016; Volkow et al, 2016; WHO, 2016).

Morphological and connectivity changes on brain structures have also been investigated. The Barnes report highlights some studies which have shown that cannabis use may lead to a reduction in brain volume particularly in the hippocampus and para-hippocampal regions with the largest structural changes reported in those who had used cannabis longest. Volkow et al, report that adolescent use of cannabis has been linked to impaired neural connectivity in specific brain regions including the fimbria which is a key area of the hippocampus that is important in learning and memory (Volkow et al, 2014). There is also evidence that suggests that THC produces complex, diverse and potentially long-term effects on the dopamine system and furthermore that gestational exposure to THC was associated with dysregulated dopamine synthesis in adult life (Bloomfield et al, 2016). Such pre-clinical studies may provide some support and a biological plausibility for the epidemiological findings reported above however the literature remains conflicted and the clinical significance of this and the potential link to cognitive impairment has not been fully elucidated. Volkow et al, comment that there is a need for longitudinal studies that follow up adolescents from before to after initiation of cannabis use and combine neuropsychological testing with neuroimaging (Volkow et al, 2016).

A point to consider in terms of therapeutic use in children is that there is evidence that suggests that neurocognitive deficits have a greater impact on exposure of cannabis to a developing brain, for example during adolescence. Volkow et al, highlight that adolescence represents a critical neurodevelopmental period and that the endocannabinoid system is a key regulator in these developmental processes. Therefore, introduction of exogenous cannabinoids during adolescence could disrupt normal brain development. Many studies have shown that earlier age of onset of use of cannabis is associated with greater cognitive impairment. Research has also shown that children exposed to cannabis prenatally have higher rates of neurobehavioural and cognitive impairments that may be related to the

impaired formation of axonal connections between neurons during foetal development as alluded to above (Volkow et al, 2016; WHO 2016).

Heavy cannabis use has also been associated with apathy and reduced motivation for goal directed behaviour. This is often referred to as cannabis amotivational syndrome in the literature and in addition to apathy it is characterised as diminished ability to concentrate, follow routines and master new material. Volkow et al, highlight the societal impact of such effects particularly in adolescence as failure to learn at school even for short or sporadic periods will interfere with the subsequent capacity to achieve educational goals. Longitudinal studies since the 1990's have found that cannabis use before the age of 15 years predicts early school leaving and this persists after adjustment for confounders. A meta-analysis of three Australian and New Zealand longitudinal studies confirmed this finding. Indeed early marijuana use has been associated with impaired school performance and an increased risk of dropping out of school and longer time to graduate from college although the role of other environmental factors cannot be excluded (Volkow et al, 2014; Volkow et al, 2016; WHO 2016).

Other populations who may be particularly vulnerable include those with pre-existing cognitive dysfunction. This concern is highlighted by the American Academy of Neurology (AAN) who consider that cognitive impairment is likely to be one of the key safety issues associated with cannabis use outside the setting of clinical trials. They cite a study of patients with multiple sclerosis (MS) who used cannabis and were found to be twice as likely to be classified as globally cognitively impaired in comparison to non-users (AAN, 2014).

As with the investigations into the schizophrenia risk, the difficulty in excluding the possibility of reverse causation in the epidemiological studies is important to acknowledge as younger persons with poorer cognitive performance may be more likely to become regular cannabis users. Also similar limitations apply in terms of the means used to assess cognitive function, difficulties in accounting for important confounders and the heterogeneity across studies in the extent of cannabis exposure. In this latter context the pharmacological effects of the individual cannabinoids also needs to be further considered. There is evidence that the THC component in cannabis has more negative neurocognitive effects than cannabis formulations which are higher in CBD for example. Broyd et al, for example, report some studies which have shown that pre-dosing with CBD or greater CBD content in cannabis may protect against some THC-induced verbal learning and memory deficits (Broyd et al, 2016). There is a similar suggestion in the preliminary findings reported by Gruber et al, from an ongoing longitudinal study (n=24) assessing the impact of medical cannabis (as opposed to recreational cannabis) on executive function in patients being treated in the USA for different conditions including anxiety, depression and chronic pain. Following three months of treatment preliminary results of the study suggested an improvement in measures of executive functioning including increased speed in completing tasks without loss of accuracy. The authors suggest that these contrasting results may reflect the different composition of the medical cannabis being used which may contain a higher amount of CBD in comparison

to recreational strains in which the THC potency is rising. The composition of the medical cannabis used has not been reported in this study although this is to be reported in future publications. The particularly modest sample size of the study however and the short duration warrant particularly cautious interpretation (Gruber et al, 2016).

iii. Dependence, Abuse and Cannabis Use Disorder (CUD)

Cannabis is the most widely used illicit substance in the world and the WHO state that there is strong scientific support for concluding that it has high potential for abuse and is addictive. Cannabis dependence is now seen as part of a broader concept of Cannabis Use Disorder (CUD) within the fifth edition of the Diagnostic and Statistical Manual of Mental Health Disorders. CUD consists of behavioural, cognitive and physiological symptoms that develop after repeated cannabis use and includes loss of control over use, tolerance, hazardous use, social/interpersonal problems related to use, user of larger amounts or for longer than planned, repeated attempts to quit and craving. Cannabis dependence leads to increased duration of regular use and therefore may also increase the risk of other long-term health risks associated with cannabis use (WHO, 2016).

The currently accepted figure for development of cannabis use disorder is 9% however there is an increased risk in those who start using cannabis as teenagers (17%) and rates as high as 25 to 50% have been reported in those who smoke cannabis daily. Approximately, 13.1 million people are cannabis dependent globally according to the WHO (2015). Cannabis withdrawal is reported in up to one-third of regular users in the general population and by 50-95% of heavy users in treatment or research studies. It is characterised by psychological symptoms during the initial abstinent phase including irritability, anger or aggression, nervousness or anxiety, sleep difficulty or insomnia, decreased appetite, weight loss, restlessness, depressed mood and can also be accompanied by physical symptoms such as stomach pain, shakiness, tremors, sweating, fever, chills and headache.

The Barnes report notes that a dependency rate of 9% for Cannabis compares to dependence rates of 15% with alcohol, 23% with heroin and 32% with tobacco. Whilst this may be the case epidemiological literature and preclinical data also indicate that cannabis can be regarded as a gateway drug as early and regular cannabis use can influence other addictive behaviours in later life and increase the risk of the use of other illicit drugs of abuse. Epidemiological studies in Australia, New Zealand and the USA in the 1970s and 1980s have found that regular cannabis users were more likely to use heroin and cocaine and that the younger they were when they first used cannabis the more likely they were to use other drugs. Explanations offered for these patterns included that cannabis users had more opportunities to use other illicit drugs because these were supplied by the same black market as cannabis. Other explanations include that the pharmacological effects of Cannabis increased interest in using other illicit drugs (WHO, 2016).

iv. Other Mental Health Disorders

In longitudinal studies, the relationship between regular cannabis use and depression has been weaker than for the relationship between cannabis and psychosis. However many large-scale cross-sectional studies and mental health surveys have found high prevalence of comorbid cannabis use and depression. Meta-analysis of the longitudinal studies (Moore et al, 2007 OR 1.49; 95% CI 1.15-1.94) that have been conducted have found modest associations between regular cannabis use and depressive disorders however a lack of adjustment for confounding variables is a noted limitation of many of these studies (Moore et al, 2007)

In terms of suicide risk, the USA's Drug Abuse Warning Network (DAWN) estimated rates of cannabis use among drug related visits to hospital emergency departments for suicide in 2011 and found that Cannabis was involved in an estimated 6.5% of drug related suicide attempts, and in 46% of attempts alcohol was also concomitantly used. In terms of suicide mortality the WHO comment on a large case-control study of 1463 suicides and 7392 natural deaths which found an association between any cannabis use and suicide risk after adjusting for depression, alcohol and mental health services (WHO, 2016). A similar finding was reported in a four year follow up study of cannabis users conducted in Denmark which found an increased risk of suicide amongst those with cannabis use disorders (Males OR 2.28, 95% CI 1.54-3.37; Females OR 4.82, 95% CI 2.47-9.39) (WHO, 2016). The literature remains conflicted and many studies have not reported associations or have reported significantly reduced associations following adjustment for confounders or the increased risk has been confined to subgroups only, for example, in some studies associations have varied with age. It is of note that the newer and larger longitudinal studies have reported positive associations.

A meta-analysis of cannabis use and suicidality has recently been conducted by Borges et al, in which they attempt to investigate the risk by separation of suicidality outcomes (suicidal ideation, suicidal attempt and death). They found 4 studies providing estimates for any chronic cannabis use and death by suicide and reported an increased risk (OR=2.56 (1.25-5.27)). After deleting duplicates they included 6 studies on any cannabis use and suicide ideation (OR=1.43 (1.13-1.83)), 5 studies on heavy cannabis use and suicide ideation (OR=2.53 (1.00-6.39)), 6 studies on any cannabis use and suicide attempt (OR=2.23 (1.24-4.00)) and 6 studies on heavy cannabis use and suicide attempt (OR=3.20 (1.72-5.94)). The authors conclude that whilst evidence is currently lacking that acute cannabis use increases the risk of suicidality the evidence tends to support that chronic cannabis use can predict suicidality. However they do highlight that the lack of homogeneity in the measurement of cannabis exposure, the small number of cases of suicidality included in the studies, the concentration of research to a few geographical areas and the lack of measurement of other key confounding variables hinder the conclusions that can be drawn (Borges et al, 2016).

v. Risk of Cancer

Literature investigating associations between cannabis use and cancers are confined to those involving smoking the natural product in recreational users. In these users the impact of long-term use of smoking cannabis on the overall cancer risk including lung cancer remain unclear. A major limitation of epidemiological research in this area is that the results are confounded by the fact that many recreational users of cannabis also smoke tobacco. It is of note that cannabis smoke contains many of the same carcinogens as tobacco smoke, at up to 5% higher concentrations and with three times the tar per cigarette. Other cancers which have been potentially associated with cannabis use include head and neck squamous cell cancer (not supported by the majority of studies), prostate cancer (3-fold risk) and cervical cancer (1.4 fold risk). Smaller studies have also implicated cannabis use in the development of bladder cancer and testicular germ cell cancer. Cannabis smoking during pregnancy has been associated with development of cancers among children in three case-control studies however these results have not been replicated in other studies (WHO, 2016). Overall, it is difficult to draw definitive conclusions based on the current data however it appears that smoked cannabis may be associated with a slightly elevated risk for certain cancers.

vi. Respiratory Diseases

Cannabis smoking has also been associated with inflammation of the large airways and increased airway resistance. This is based on endoscopic and microscopic evidence of injury and inflammation involving the central airways of habitual smokers of cannabis. Considerable epidemiological and clinical research has assessed whether cannabis smoking is a risk factor for COPD. In most of these studies cannabis only smokers have been more likely to have reported cough, sputum and wheezing but no more likely to report shortness of breath than controls who do not smoke cannabis. A reduction in ciliated cells, and subsequent increased mucus secretion from the larger number of mucus secreting cells probably explain the increased symptoms of chronic bronchitis in regular cannabis smokers. In terms of COPD although cannabis users do not appear to be at greater risk of COPD they do appear to lose lung function more quickly than non-smokers although the rate of decline is slower than that of tobacco smokers (WHO, 2016).

vii. Cardiovascular Diseases

Volkow et al, also note that intoxication with cannabis has been associated with vascular conditions that increase the risk of myocardial infarction (MI), stroke and transient ischaemic attacks although the actual mechanisms underlying the specific effects on the cardiovascular and cerebrovascular system have not been elucidated (Volkow et al, 2014). There are a limited number of epidemiological studies of CVD in cannabis smokers. The study by Mittleman et al, which found an increased risk of MI in those who had recently had an MI during acute intoxication with cannabis has been previously discussed. Recent case reports and case series also suggest that cannabis smoking may increase the risk of CVD in younger cannabis smokers who are otherwise at relatively low risk (WHO 2016).

Some case-control studies also suggested that cannabis smoking was risk factor for stroke in young adults and there are numerous case reports in the literature of ischaemic stroke being reported in cannabis smokers and patient using synthetic cannabinoids. Much of the research in this area has been carried out by Wolff et al who have noted increased incidence of stroke in young adults in parallel with increased cannabis use. Wolff et al report that cannabis associated stroke usually occurs in chronic or current cannabis users who smoke tobacco (Wolf et al, 2015). The stroke often occurs while the drug is being smoked or minutes afterwards. The CV effects of cannabis provide possible mechanisms for these strokes-namely, orthostatic hypotension, altered cerebral vasomotor function, supine hypertension and swings in blood pressure, cardioembolism, vasculopathy, vasospasm and reversible cerebral vasoconstriction syndrome (RCVS).

c. Cannabis and Societal Impacts

In addition to the pharmacological impact of cannabis at an individual patient level the societal impact of cannabis use is also of paramount consideration.

Cannabis is the most commonly used illicit drug and therefore the risk for abuse and diversion of any form of medical cannabis is a significant issue. It is of note that in the United States the decriminalisation of medical cannabis and the legalisation of recreational use in certain states has been accompanied by an increase in the usage of the drug which the WHO have noted is likely due to a change in the perception of risk particularly amongst the youth. This is highlighted in a recent survey based study by Compton et al, which in an attempt to understand trends in patterns of cannabis use. analysed results of annual cross-sectional surveys conducted in the USA between 2002-2014, Prevalence of marijuana use increased in adults during this period (10·4% (95% CI 9·97–10·82) to 13·3% (12·84–13·70) which coincided with a decrease in the perception of harm (50·4% (49·60–51·25) to 33·3% (32·64–33·96) (Compton et al, 2016). In this context, Volkow et al draw a pertinent comparison with alcohol and tobacco highlighting that these drugs account for the greatest burden of disease associated with drugs not as a result of increased toxicities but rather due to easier access and widespread availability (Volkow et al, 2014).

Cannabis use has been associated with a higher risk for motor vehicle accidents due to impaired driving ability. Cannabis is the most frequently reported illicit drug in connection with driving and accidents, including fatal accidents. Serum THC concentrations of 3.8ng/ml have been found to be as impairing as blood alcohol concentrations of 0.5g/L and Hartman et al report that recent smoking and/or blood THC concentrations of 2-5ng/ml are associated with substantial driving impairment. This same study reports that the overall risk of involvement in an accident increases by a factor of about 2 when a person drives soon after using cannabis. Other epidemiological studies have reported similar findings (Hartman et al, 2013). A meta-analysis of nine case-control and culpability studies found that recent cannabis use increased the risk of a car crash (OR=1.92 95% CI: 1.35, 2.73). The Driving Under the Influence of Drugs, Alcohol and Medicines (DRUID) study was a large population based study

of accident risks related to the use of cannabis and other drugs in nine EU countries which found that drivers who tested positive for THC were 1-3 times more likely to be in an accident than sober drivers. Furthermore, the use of cannabis in combination with alcohol significantly impacts reaction times and increases the risk of impaired driving ability more than use with either drug alone as the effects are additive. Overall, the WHO (2016) conclude that traffic injury may be the most important adverse public health outcome for cannabis in terms of mortality in high-income countries.

The impact of cannabis use on cognitive impairment and the detrimental effects on school performance have been briefly discussed above. Several studies have shown that cannabis use can adversely affect academic achievement among adolescents. Although more limited in number, studies have also been done examining the detrimental impacts of cannabis use in the work place with reports of reduced performance and mood and increased human errors. During an economic downturn, cannabis use was also shown to increase unemployment among users.

5. Experience of Use and Misuse

Ireland

Cannabis is widely used as a recreational drug and is acknowledged to be associated with problem drug use. A 2016 report from the National Advisory Committee on Drugs and Alcohol (NACDA) indicates that cannabis is the most commonly used illegal drug across all age groups, in Ireland. Lifetime usage of cannabis (24.0%) is considerably higher than any other form of illegal drug and significant increases in lifetime prevalence have been observed (25.3% in 2010/2011 to 27.9% in 2014/2015).

A recent survey of Irish general practitioners (GPs) reported that a majority (58.6%) supported the legalisation of cannabis for medical use for certain medical conditions (Crowley et al., 2017). The response rate to the survey was low at 15% (n=565). Many GPs cited the need for regulation of cannabis products, the requirement for an enhanced evidence-base to support decisions on treatment, and expressed concern about the mental health consequences of cannabis use, and the potential for misuse and abuse (Van Hout et al., 2016).

EU

In Europe, the prevalence of cannabis use is about five times than that of other illicit substances, and cannabis has now overtaken heroin as the most widely reported illegal drug used amongst people entering addiction services (EMCDDA. European Drug Report, 2015).

USA

Cannabis abuse in the United States is on the increase, including among high school students, for which annual prevalence rates rose from 24.7 per cent in 2012 to 25.8 per cent in 2013. In

states of the United States that have medical cannabis programmes, the diversion of cannabis from the programmes has been reported as a major source for the drug's illicit use, particularly among young people. Prevalence surveys cited by the Drug Enforcement Administration indicate that 34 per cent of the twelfth grade students (aged 17-18 years) who had used cannabis in the past 12 months and who lived in states that have medical cannabis schemes, identified medical cannabis prescribed to another person as one of their sources for the drug. This is of particular concern due to emerging evidence which suggests that adolescents may be particularly vulnerable to the adverse effects of cannabis use, due to a disruption in normal brain development (Volkow et al, 2016. Murray et al. 2016).

Medical marijuana laws are now in place in 28 US states and Washington DC to facilitate access as a treatment for a variety of 'approved conditions'. The approved conditions include those for which there is reasonable evidence of effectiveness (as outlined above) but also conditions for which there are only preliminary data e.g. glaucoma. Other conditions can be included subject to the approval of the state department of health. There are also legal limits on the amount of medical marijuana that can be held by a patient, for example the 60 day supply is 10 oz (283 g), in Massachusetts.

Patients being treated with marijuana are required to have a medical marijuana certificate. In practice, physicians in the relevant states can write a medical marijuana certificate for any medical condition, provided the physician has completed requisite training. It is important to note that cannabis and cannabinoids, other than those authorised by the FDA, are not considered to be medicines and therefore cannot be prescribed, but only recommended, by physicians in the US.

Hill (2015) has proposed practical considerations for physicians to consider when evaluating a patient for a medical marijuana certificate, including:

- A debilitating medical condition that data from randomised clinical trials suggest would respond to medical marijuana pharmacotherapy.
- Multiple failed uses of first and second line pharmacotherapies for these conditions.
- No active substance use disorder or psychotic disorder or no unstable mood disorder or anxiety disorder.

Hill advises that once the patient begins medical marijuana pharmacotherapy, close follow up with a physician is imperative, as it would be with any medications having significant adverse effects and abuse potential.

The quality of cannabis for medical use has come under scrutiny in the US. A review of edible medical cannabis products from three major metropolitan areas found that greater than 50% of the products had significantly less CBD than labelled, with some products containing negligible amounts of THC (Vandrey et al., 2015). Such products may not produce the desired medical benefit. Other products contained significantly more THC than labelled,

placing patients at risk of experiencing side effects. An FDA analysis of cannabis products making medical claims found that six of 18 products tested contained no cannabinoid (FDA, 2015).

Canada

The prescribing of cannabis for medical purposes has come under scrutiny in Canada following requests from medical licensing bodies for increased information on how doctors are authorising cannabis use. The regulations require licensed producers of cannabis for medical purposes to provide quarterly reports to health-care licensing bodies on how healthcare practitioners are authorising the use of cannabis, which will be provided to provincial and territorial medical and nurse licensing bodies upon request, allowing them to more effectively monitor the professional practice of their members.

American Academy of Neurology (AAN) and World Health Organisation (WHO) perspective

The AAN states that the risks and benefits of medical marijuana should be weighed carefully. It notes that the risk of serious adverse psychopathologic effects was nearly 1%, and highlights that the comparative effectiveness of medical marijuana versus other therapies is unknown for neurological indications.

The WHO (2015) states 'Especially for psychoactive drugs such as cannabis, rigorous criteria for its approval as a safe and effective medicine need to be fulfilled, along with a meticulous cost-benefit analysis to weigh its therapeutic potential alongside its detrimental effects to society and individuals'.

6. Summary of Effectiveness and Safety of Cannabis for Medical Use

Cannabis and cannabinoids have been studied in a wide variety of medical conditions over many years. The quality of the evidence is limited, for many medical conditions. It is clear that the effectiveness of cannabis and cannabinoids varies with the formulation used and the individual or patient population studied. Cannabis and cannabinoids may offer a useful adjunct for patients who have exhausted available treatments.

The side effect profile of cannabis can be considered in terms of short term immediate effects and longer term effects associated with repeated use. In particular the key areas of concern include development of psychosis and schizophrenia and effects on cognitive function. Hence, particular care is required when treating young patients, or patients with psychiatric disorders. Increased access will result in increased use and wider availability with the possibility of diversion, this raises societal issues.

Subject to a policy decision to permit access to cannabis for medical use, the HPRA advises that cannabis should only be made available for the treatment of patients with specified medical conditions which have failed to respond to all other previous treatments, and where

there is at least modest evidence that cannabis may be effective. Such patients should be under the direct supervision of an appropriately trained and experienced medical consultant. The specified medical conditions are:

1. Spasticity associated with multiple sclerosis resistant to all standard therapies and interventions whilst under expert medical supervision;
2. Intractable nausea and vomiting associated with chemotherapy, despite the use of standard anti-emetic regimes whilst under expert medical supervision;
3. Severe, refractory (treatment-resistant) epilepsy that has failed to respond to standard anticonvulsant medications whilst under expert medical supervision.

The selection of these medical conditions is based on:

- a possible unmet medical need for individual patients;
- the ability for the medical consultant to monitor the effectiveness of treatment using objective endpoints; and
- the existence of authorised cannabis-based medicines or medicines undergoing clinical trials, consequently there is clinical evidence and some research in relation to cannabis and these conditions.

The evidence supporting treatment does not comprehensively address the safety of use of cannabis by patients with these medical conditions. Information on the short-term use of cannabis is available and the side effects may be acceptable to patients with an unmet medical need. The side-effects of long-term treatment are not clear.

Patients with the medical conditions outlined above have complex medical needs, in many cases. They are under specialist, usually medical consultant care and if cannabis products are used, they would be adjunctive to other medicines. In the absence of information on prescribing, side effects, and interactions, such patients may be best treated under the care of a medical consultant, with regular review.

It is important to note that the HPRA is not recommending treatment with cannabis or stating that cannabis is capable of being authorised as a treatment for these medical conditions. This is because the data are not available to permit a benefit to risk evaluation to be performed.

The need for rigorous evidence of benefit and safety from clinical trials is emphasised in the literature and in statements from medical professional associations.

APPENDIX 7 Clinical Trials

Clinical trials being conducted in the European Union (EU) and worldwide with cannabidiols (excluding Phase 1 and First in Man) - (updated December 2016, as per EU Clinical Trials Register Public Website: www.clinicaltrialsregister.eu).

1. Cannabis Trials

In relation to current research, there are a number of clinical trials evaluating cannabis products being conducted within Europe. In each case, cannabis is considered to be a medical product and the clinical trial is approved under EU clinical trials legislation. Authorised clinical trials, with the exception of Phase I/first in man trials, are required to be included on the EU clinical trials register, which is publicly accessible.

There are currently thirty eight clinical trials listed on the EU clinical trials register as being conducted with cannabidiols. These clinical trials are being conducted to investigate the use of cannabidiols in the treatment of a range of conditions including chronic pain, psychiatric disorders and neurological conditions, including epilepsy. The majority of these clinical trials are being conducted in adults. However some of the clinical trials involve children and are investigating the use of products containing only non-psychotogenic cannabidiol (CBD) for the treatment of epilepsy, including severe forms of this condition, which have failed other treatments.

2. Participating EU Member States

For information, an approximate breakdown of the number of clinical trials with cannabidiols conducted in each EU member state is listed in table 7 below. None of these clinical trials are being conducted in Ireland.

Table 7: Number of clinical trials with cannabidiols conducted or ongoing in each EU member state

PARTICIPATING COUNTRIES	*NO. OF CLINICAL TRIALS COMPLETED OR ONGOING IN EACH COUNTRY
UK	37
Czech Republic	16
Belgium	5
Germany	17

PARTICIPATING COUNTRIES	*NO. OF CLINICAL TRIALS COMPLETED OR ONGOING IN EACH COUNTRY
Spain	14
France	7
Poland	11
Finland	1
Romania	4
Latvia	2
Estonia	2
Lithuania	3
Bulgaria	4
Hungary	6
Sweden	1
Italy	3
Denmark	1
The Netherlands	11
Slovakia	2

*In most instances the clinical trials are conducted in more than one Member State.

3. Sativex (nabiximols)

The investigational medicine in a number of these clinical trials is Sativex oromucosal spray. Sativex was authorised in Ireland in July 2014 for symptom improvement in adult patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy. Each 100 microlitre of Sativex oromucosal spray contains: 2.7 mg delta-9-tetrahydrocannabinol (THC) and 2.5 mg cannabidiol (CBD).

The clinical trials which are ongoing specifically with Sativex in the EU are being conducted in medical conditions including those of neuropathic pain, spasticity in multiple sclerosis, chemotherapy induced nausea and vomiting, lymphoma/chronic lymphocytic leukaemia and

other advanced cancers, post-herpetic neuralgia, pain associated with allodynia and diabetic neuropathy.

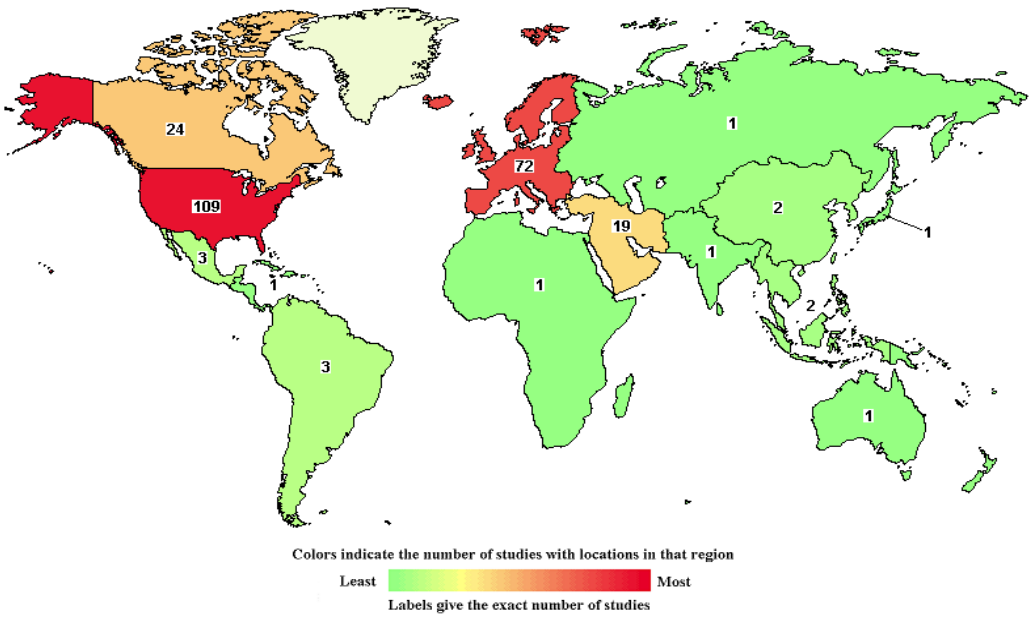
4. Clinical trials approved in the EU with the investigative product GWP42003 (pure plant-derived cannabidiol, CBD)

A number of clinical trials are being conducted in the EU with a product which contains only non-psychoactive cannabidiol (CBD). In most instances each clinical trial is being conducted in more than one European Member State (MS). These clinical trials are being conducted in a number of conditions including ulcerative colitis, schizophrenia and Dravet syndrome.

In addition to the clinical trials being conducted with GWP42003, it is understood that GW Pharmaceuticals also commenced a phase II clinical trial in 2015 with the non-psychoactive cannabinoid cannabidavarin (CBDV), GWP42006, in adult patients with epilepsy. The company has stated that it has completed significant pre-clinical work on CBDV as well as a phase 1 trial which demonstrated a reassuring safety profile.

5. Clinical trials being conducted worldwide with THC/CBD containing products

Figure 1: Diagram showing clinical trials being conducted worldwide with THC/CBD containing products



Source:https://ClinicalTrials.gov

APPENDIX 8 Survey to Determine Worldwide Status

Appendix 8-Part 1: Survey of EU and International Regulatory Authorities
The use of cannabis for medical purposes

Table 8: List of EU and international countries that responded

EU COUNTRIES CONTACTED	MEDICAL CANNABIS PROGRAMME
Austria	No
Bulgaria	No
Croatia	Exceptional use programme
Cyprus	No
Czech Republic	Access programme
Denmark	Exceptional use programme
Estonia	Exceptional use programme
France	No
Germany	Exceptional use programme
Greece	No
Hungary	No
Iceland	No
Italy	Access programme
Latvia	No
Lithuania	No
Luxembourg	No
Malta	Exceptional use programme
Netherlands	Access programme
Norway	Exceptional use programme
Poland	Exceptional use programme
Portugal	No
Romania	No

EU COUNTRIES CONTACTED	MEDICAL CANNABIS PROGRAMME
Slovakia	No
Slovenia	No
Spain	No
Sweden	Exceptional use programme
Switzerland	Exceptional use programme
United Kingdom	No
INTERNATIONAL COUNTRIES CONTACTED	**MEDICAL CANNABIS PROGRAMME**
Australia	Access programme
Brazil	Exceptional use programme
Canada	Access programme
China	No
Israel	Access programme
Singapore	No
USA	Federally no, by State there are some exceptional use programmes and access programme in 8 states.

Appendix 8-Part 2: Summary overview of countries with programmes for exceptional use

- **Croatia:** Patients can receive a prescription of up to 30 days with a maximum of 0.75g of THC per month.

- **Denmark:** In November 2016, the government agreed to establish a four year pilot project of medical cannabis which will expand on the current restrictive process for application for exception use of cannabis based products.

- **Estonia:** In the written application of the doctor there must be well-founded medical reasons that indicate the medical need and indication for the use of the Cannabis. If the specialist advisory committee at the Ministry approves the application, the State Agency of Medicines will evaluate the proposed medical use.

- **Finland:** The use of herbal medicinal cannabis is also possible under specific conditions with a special permission from Fimea. Permissions are granted individually based on medical need.

- **Germany:** It is expected that in early 2017 that legislation will come into place to establish a "cannabis agency" within the structure of Federal Institute for Drugs and Medical Devices. The new legislation was fostered by high court decisions. It indicates reduced restrictions for prescribers for which conditions they can issue prescriptions**.**

- **Malta:** Specialists registered un the Health Care Professional Act are entitled to prescribe to patients medicinal preparations of the cannabis plant, if he considers that there is no viable alternative to such prescription due account being taken of any protocols which may be in force from time to time in respect of the prescription of medicines, of the interests of the patient and of the costs.

- **Norway:** In November 2016 the Norwegian Medicines Agency and the Directorate of Health published a common "Guidance for doctors" describing the procedure to follow when applying for a permission to prescribe medical cannabis within the existing legal framework.

- **Poland:** In Poland at present the access to medical cannabis is possible under Article 5 of Dir.2001/83 and remains in the remit of the Minister of Health. As of January 2017, the Parliament is in the course of proceedings on a proposal drafted by the representatives of one of the political parties on the legal framework for specific regulation of cannabis for medical purposes.

- **Sweden:** There are no specific rules regarding prescription of medicines containing cannabis. It is the physician's responsibility to prescribe the accurate medicine to his/her patient.

- **Switzerland:** Cannabis, its formulations (oil, resin, extract, tincture), cannabis seeds and Tetrahydrocannabinol are scheduled in schedule D, which covers illegal recreational drugs.

- **Brazil:** The companies can only send those products to patients in Brazil that are registered with Anvisa. The patient's registration is valid for one year and can be renewed, if it is necessary.

Appendix 8- Part 3: Summary overview of countries with expanding/established access programmes for medical cannabis

Czech Republic

There is a national government controlled system for the production and supply of cannabis for the state under the "Cannabis Decree" legislative framework. The State Institute for Drug Control (SUKL) grants a license through public tender for the cultivation and production of cannabis for medical use. Under the license the producer is obliged to transfer all of their GMP certified produce exclusively to SUKL through a purchasing agreement to distribute to pharmacies. The producer must obtain a certificate of quality from a control laboratory for their product before SUKL proceeds with a written purchase agreement. In the conditions of the tender, the State Institute for Drug Control determines the maximum amount of the quotation price.

The SUKL ensures the distribution of the cannabis to pharmacies. Pharmacies must meet the conditions of a framework agreement before ordering cannabis products for the purposes of preparing magistral preparations. A written purchase agreement is concluded by and between the State Institute for Drug Control and the pharmacy operator. The purchase price upon the transfer of the cannabis to the pharmacy operator is non-profit for the State Institute for Drug Control.

The prescriber specialisations and medical indications for medical use are outlined in the "Cannabis Decree" legislative framework. Physicians must be registered in order to issue electronic prescriptions for individually prepared medicine containing cannabis for medical use as medical cannabis can only be prescribed electronically. This allows for a central repository of electronic prescriptions. Medical cannabis may be prescribed only for defined indications, by defined medical specialists, and for patients aged 18 or more years. On the electronic prescription, the doctor is obliged to specify, the posology, amount, and route of administration of medical cannabis, as well as the type and required percentage content of THC and CBD.

Italy

Since 2013, cannabis has been available for medicinal purpose through a government controlled access scheme including license prescribers and state-run pharmacies. Medicinal Cannabis must be prescribed by physicians and supplied by pharmacists in a pharmacy. Cannabis Extemporaneous Preparation should be prescribed under the physician responsibility as a symptomatic treatment where other conventional therapies have failed. The Italian Medicines Regulator (AIFA) and the Italian Ministry of Health reviewed the possibility to produce medicinal Cannabis at a national level. In September 2014, an agreement was reached between the Ministry of Health and the Ministry of Defence to start a 24 months pilot project for the production of medicinal Cannabis. In November 2015, the Ministry of Health approved a technical annex addressed to physicians and pharmacists in order to grant the homogeneous medical use of Cannabis in Italy. The pilot phase of the project expired in September 2016 and the industrial production was initiated. The THC based

product is being cultivated under tight restrictions at the Florence Military Chemical Pharmaceutical Plant (SCFM). The first batch of product was commercialized in December 2016 and distributed by the SCFM. The personal use of Cannabis has been decriminalised in Italy. From January to June 2016, AIFA has received 18 adverse reaction reporting related to medical use of cannabis magistral formula.

Netherlands

The Office of Medicinal Cannabis (OMC) is a government agency that is part of the Dutch Ministry of Health, Welfare and Sports. It is responsible for all cultivation of cannabis for medical and scientific purposes, and has a monopoly on all transactions regarding these products, including import and export. An OMCL also responsible for the validity of the cannabis.

Only one company Bedrocan is contracted as a grower. GMP guidelines apply to all methods of cannabis production. Bedrocan is company licensed by the Dutch Ministry of Health to dry, cut, pick and grind plant material. It produces five types of pharmaceutical grade cannabis varying in THC and CBD strength. The company has a GMP cert and only have dried flowers or granulated plant. Oils are made by a compounding pharmacy and mainly produce oils with CBD with a GMP certified protocol.

Access to quality-controlled product for medical use, licensed growers and registered prescribers, are supervised by the Health Ministry.

In the Netherlands a physician can prescribe. The OMC provides workshops on how you can use cannabis and the therapeutic effects. They only prescribe if regular pharmaceutical products don't work or if they have too many side effects. The Dutch Health authorities made a list of indications based on the outcome of an extensive review of the scientific literature. Medical doctors are allowed to prescribe medical cannabis in other conditions than those listed above, if they think it can have a beneficial effect and regular medicines are not sufficiently effective or have severe side-effects

Israel

Israel's medical cannabis framework is regulated by the Israel Medical Cannabis Agency (IMCA), a department of the Ministry of Health in Israel. For a number of years, patients in Israel have had the opportunity to request a special permission from the state to use medical Cannabis. The request for permission must be submitted by a specialist to IMCA under the Israeli Ministry of Health. In 2016 the Minister of Health launched a new resolution for the expansion of the medical cannabis programme. The key changes to the policy include:

1. Cannabis-based medications will be sold and distributed in pharmacies instead of by growers.
2. Calls to increase the number of physicians able to prescribe medical cannabis, as well as more staff to manage medical cannabis license issuance.

3. Standard physician prescriptions will be used for patients to acquire medical cannabis from a pharmacy. Previously, a special license was issued.
4. Opening up the market of approved grow operations in Israel. Currently, the number of grow operations is limited to eight – with another ten expected to be approved.

As part of the ongoing expansion of the medical marijuana program in Israel, the Ministry of Health has initiated an educational program for doctors to become proficient in the various aspects of endocannabinoid medicine. Once they have completed the programme, doctors will eventually be able to properly prescribe cannabis for the patients based on a predetermined list of conditions, who, in turn, will receive pre-packaged cannabis through the regulated pharmacy system.

Australia

There are mechanisms in place to enable access to medical cannabis products through the Therapeutic Goods Act 1989 which allows for:

- access under clinical trials; and
- individual patients, access under the Special Access and Authorised Prescriber Schemes administered by the Therapeutic Goods Administration (TGA).

Legislation came into effect on 30 October 2016 to allow legal cultivation, production and manufacturing of medical cannabis products in Australia. A detailed regulatory framework has been put in place to enable applications for licences and permits for the cultivation, production and manufacture of medical cannabis products. This scheme is administered by the ODC (Office of Drugs Control).

The Department of Health's Health Product Regulation Group provides the two 'commonwealth arms' of the scheme:

- Cultivation and manufacture through ODC
- Product GMP, product scheduling and patient access through TGA.
- States and territory roles are critical and also evolving

When applying for a permit to manufacture, you must provide evidence that you hold a GMP licence from the TGA. The initial licence will be for 12 months to ensure there is annual review of compliance with the licence. As the system matures, the licence periods may be subsequently increased to 2 or 3 years. Specific guidance have been published on GMP compliance for the manufacture of medical cannabis products for supply under 'approved access' provisions.

The TGA will evaluates applications received from a doctor to access unapproved medical cannabis products. Currently no specific medical conditions for prescribing have been established by the Commonwealth.

The TGA is developing educational materials in conjunction with the states/territories for doctors to support them in prescribing medical cannabis.

The manufacture of medical cannabis products will be determined by reference to patient need, therefore the products authorised to be manufactured will be those supported by clinical evidence.

TGA has a role in oversight of the manufacture of cannabis oils and extracts to GMP standards and in the policing of compositional and identification regulations around raw materials and products.

Canada

Canada's policy on Cannabis for medical use has been largely impacted by court rulings. Since 1999 there have been a number of court driven changes to the law. Over time, changes in the legislation resulting from the court decisions have changed from individuals being able to produce their own cannabis plants for medical purposes to access only through industrial licensed producers only and most recently in 2016, new legislation again has emerged as a results of a Federal Court ruling. The new Access to Cannabis for Medicinal Purposes Regulations (ACMPR) will again allow Canadians who need access to cannabis for medical purposes to produce a limited amount of cannabis for their own medical purposes, or designate someone to produce it for them.

Canada has made a system with three possible permissions for medical cannabis:

1. Possession as a patient
2. Private cultivation for a patient
3. Cultivation for a designated person

As cannabis is not regarded as a medical product a patient instead receives a medical document from the doctor outlining how many grams/day a patient should consume. However this does not indicate any dosage level. It is up to the patient to decide on what concentrations work best for them regarding CBD/THC concentrations.

Authorised physicians or nurse practitioners in provinces and territories where supporting cannabis for medical purposes are permitted to prescribe. No specific training is required. Each state has a physician's body/college of physicians who have developed guidelines on the prescribing of cannabis.

Licensed producers are subject to Good Production Practices that are meant, among other things, to ensure the cleanliness of the premises and equipment.

The industrial manufactures produce strains based on the demand from their market, there are no criteria or restrictions from Health Canada regarding what strains are produced.

A licensed producer must report serious adverse reactions of dried Cannabis to the state within 15 days. A licensed producer must annually prepare a summary report of all adverse reactions, including analyses, and provide the state with a copy.

Patients or caregivers can possess a maximum of 150g dried Cannabis or less if the physician has fixed a lower daily quantity, in that case 30 times the daily quantity. The patient can only apply for Cannabis from one source at a time on the basis of the same medical document. A medical document must indicate the period of use that must not exceed one year, and the daily quantity of dried Cannabis to be used by the patient, expressed in grams.

United States

A number of states have presently legalised the medical use of Cannabis. However, according to US federal law, it is illegal to possess, use, buy, sell or grow Cannabis under the Controlled Substance Act, in which Cannabis is listed as a 'Schedule I drug', meaning that it has a high potential for abuse and has no currently accepted medical use. Since 1996, 29 US states and Washington, DC have passed laws allowing patients in these states to use Cannabis for medical use without being punished. To date, only eight States have introduced access programmes, others have restrictive programmes and others have none. Physicians can recommend the use of Cannabis to a specific patient if they believe that it will have a beneficial effect.

General differences of the programmes across states:

- There are legal differences in relation to regulation, including whether the rules are applicable for the state, for a county or a city. In several places, counties and cities of a specific state can regulate medical use of Cannabis locally.
- Physicians' recommendation to a specific patient for use of Cannabis can be either oral or written. In California the recommendation can be both written and oral whereas in Alaska, a physician must issue a written statement.
- There are different programmes involving Cannabis identification cards. In some places it is voluntary to use identification cards to document that Cannabis is for medical use (e.g. in California where more than 70,000 ID cards have been issued). In other states, an ID card is required to get access to medical Cannabis (e.g. in Alaska). In some instances, a caregiver (defined differently by the states) can also be registered and get an ID card and grow Cannabis on behalf of the patient. It varies how much Cannabis a patient or his/her caregiver is allowed to grow to the patient.
- Different diseases are defined as a debilitating medical condition in different states for which cannabis may be prescribed. In some states it is up to the physician to assess whether Cannabis may be beneficial to the specific patient regardless of their health condition.
- There are differences between the regulation of sales outlets selling Cannabis ('marijuana dispensaries') and where they can be located.
- There are differences between the taxation and fees of medical Cannabis. For example, some counties and cities in California have chosen to tax the sale of medical Cannabis.

APPENDIX 9 References

All-Party Parliamentary Group for Drug Policy Reform. *Access To Medicinal Cannabis: Meeting Patient Needs*. London: Houses of Parliament, 2016. Web. 18 Nov. 2016. Inquiry Report.

Andrew, R., Derry, S., Taylor, R.S., Straube, S. and Phillips, C.J., (2014). The costs and consequences of adequately managed chronic non-cancer pain and chronic neuropathic pain. *Pain Practice*, *14*(1), pp.79-94.

Australian Rheumatology Association (ARA). *Position Statement On The Use Of Medicinal Cannabis For Musculoskeletal Pain.* 2016. Web. 7 Dec. 2016.

Barnes, Michael P and Jennifer C Barnes. *The Evidence For Medical Use*. 2016. Web. 10 Nov. 2016.

Bloomfield, M.A., Ashok, A.H., Volkow, N.D. and Howes, O.D., (2016). The effects of Δ9-tetrahydrocannabinol on the dopamine system. *Nature*, *539*(7629), pp.369-377.

Borges, G., Bagge, C.L. and Orozco, R., (2016). A literature review and meta-analyses of cannabis use and suicidality. *Journal of affective disorders*, *195*, pp.63-74.

Broyd, S.J., van Hell, H.H., Beale, C., Yücel, M. and Solowij, N., (2016). Acute and chronic effects of cannabinoids on human cognition—a systematic review. *Biological psychiatry*, *79*(7), pp.557-567.

Campbell, F.A., Tramèr, M.R., Carroll, D., Reynolds, D.J.M., Moore, R.A. and McQuay, H.J., (2001). Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. *Bmj*, *323*(7303), p.13.

Compton, W.M., Han, B., Jones, C.M., Blanco, C. and Hughes, A., (2016). Marijuana use and use disorders in adults in the USA, 2002–14: analysis of annual cross-sectional surveys. *The Lancet Psychiatry*, *3*(10), pp.954-964.

Crippa, J.A., Crippa, A.C., Hallak, J.E., Martín-Santos, R. and Zuardi, A.W., (2016). Δ9-THC Intoxication by Cannabidiol-Enriched Cannabis Extract in Two Children with Refractory Epilepsy: Full Remission after Switching to Purified Cannabidiol. *Frontiers in Pharmacology*, *7*.

Crowley, D., Collins, C., Delargy, I., Laird, E. and Van Hout, M.C., (2017). Irish general practitioner attitudes toward decriminalisation and medical use of cannabis: results from a national survey. *Harm Reduction Journal*, *14*(1), p.4.

Faculty or Pain Medicine. *Statement On "Medicinal Cannabis" With Particular Reference To Its Use In The Management Of Patients With Chronic Non-Cancer Pain*. Australian and New Zealand College of Anaesthetists, 2015. Web. 16 Nov. 2016.

Farrell, M., Buchbinder, R. and Hall, W., (2014). Should doctors prescribe cannabinoids. *BMj*, *348*(348), p.g2737.

Gage, S.H., Hickman, M. and Zammit, S., (2016). Association between cannabis and psychosis: epidemiologic evidence. *Biological psychiatry*, *79*(7), pp.549-556.

Gloss, D. and Vickrey, B., (2014). Cannabinoids for epilepsy. *The Cochrane Library*.

Gruber, S.A., Sagar, K.A., Dahlgren, M.K., Racine, M.T., Smith, R.T. and Lukas, S.E., (2016). Splendor in the Grass? A Pilot Study Assessing the Impact of Medical Marijuana on Executive Function. *Frontiers in pharmacology*, *7*.

"For Patients. GW's Epidiolex Clinical Program". *GW Pharmaceuticals, plc*. Web. 16 Nov. 2016.

"GW Pharmaceuticals And Otsuka Announce Results From Two Remaining Sativex® Phase 3 Cancer Pain Trials". *GW Pharmaceuticals, plc*. N.p., 2015. Web. 16 Nov. 2016.

Hall, Wayne, Maria Renstrom, and Vladimir Poznyak. *The Health And Social Effects Of Nonmedical Cannabis Use.* Geneva: World Health Organisation, 2016. Web. 17 Nov. 2016.

Hartman, R.L. and Huestis, M.A., (2013). Cannabis effects on driving skills. *Clinical chemistry*, *59*(3), pp.478-492.

Hill, K.P., (2015). Medical marijuana for treatment of chronic pain and other medical and psychiatric problems: a clinical review. *Jama*, *313*(24), pp.2474-2483.

Koppel, B.S., Brust, J.C., Fife, T., Bronstein, J., Youssof, S., Gronseth, G. and Gloss, D., (2014). Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders Report of the Guideline Development Subcommittee of the American Academy of Neurology.*Neurology*, *82*(17), pp.1556-1563.

Krishnan, S., Cairns, R. and Howard, R., (2009). Cannabinoids for the treatment of dementia. *The Cochrane Library*.

Lindsey, W.T., Stewart, D. and Childress, D., (2012). Drug interactions between common illicit drugs and prescription therapies. *The American journal of drug and alcohol abuse*, *38*(4), pp.334-343.

Madras, B.K., (2015). Update of cannabis and its medical use. *Report to the WHO Expert Committee on Drug Dependence (http://www. who. int/medicines/access/controlled-substances/6_2_cannabis_update. pdf*.

"Nabilone 1Mg Capsules - Summary Of Product Characteristics". *Medicines.org.uk*. N.p., 2014. Web. 18 Nov. 2016.

Mittleman, M.A., Lewis, R.A., Maclure, M., Sherwood, J.B. and Muller, J.E., (2001). Triggering myocardial infarction by marijuana. *Circulation*, *103*(23), pp.2805-2809.

Moore, R.A., Derry, S. and Wiffen, P.J., (2013). Challenges in design and interpretation of chronic pain trials. *British journal of anaesthesia*, *111*(1), pp.38-45.

Moore, T.H., Zammit, S., Lingford-Hughes, A., Barnes, T.R., Jones, P.B., Burke, M. and Lewis, G., (2007). Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *The Lancet*, *370*(9584), pp.319-328.

Murray, R.M., Quigley, H., Quattrone, D., Englund, A. and Di Forti, M., (2016). Traditional marijuana, high-potency cannabis and synthetic cannabinoids: increasing risk for psychosis. *World Psychiatry*, *15*(3), pp.195-204.

National Advisory Committee on Drugs and Alcohol (NACDA). *Prevalence Of Drug Use And Gambling In Ireland And Drug Use In Northern Ireland*. Dublin: National Advisory Committee on Drugs and Alcohol (NACDA), 2016. Web. 21 Nov. 2015.

Schoeler, T., Monk, A., Sami, M.B., Klamerus, E., Foglia, E., Brown, R., Camuri, G., Altamura, A.C., Murray, R. and Bhattacharyya, S., (2016). Continued versus discontinued cannabis use in patients with psychosis: a systematic review and meta-analysis. *The Lancet Psychiatry*, *3*(3), pp.215-225.

Stout, S.M. and Cimino, N.M., (2014). Exogenous cannabinoids as substrates, inhibitors, and inducers of human drug metabolizing enzymes: a systematic review. *Drug metabolism reviews*, *46*(1), pp.86-95.

The National Academies of Sciences, Engineering and Medicine. *The Health Effects Of Cannabis And Cannabinoids: The Current State Of Evidence And Recommendations For Research*. National Academies Press, 2017. Web. 25 Jan. 2017.

Throckmorton, Douglas C. "FDA Work On Medical Products Containing Marijuana". 2015. Presentation.

Unimed Pharmaceuticals. *Marionol (Dronabinol) Capsules*. Food and Drug Administration, 2004. Web. 6 Jan. 2017.

Van Hout, M.C., Collins, C., Delargy, I. and Crowley, D., (2016). Irish General Practitioner (GP) Perspectives Toward Decriminalisation, Legalisation and Cannabis for Therapeutic Purposes (CTP). *International Journal of Mental Health and Addiction*, pp.1-14.

Vandrey, R., Raber, J.C., Raber, M.E., Douglass, B., Miller, C. and Bonn-Miller, M.O., (2015). Cannabinoid dose and label accuracy in edible medical cannabis products. *Jama*, *313*(24), pp.2491-2493.

Volkow, N.D., Baler, R.D., Compton, W.M. and Weiss, S.R., (2014). Adverse health effects of marijuana use. *New England Journal of Medicine*, *370*(23), pp.2219-2227.

Volkow, N.D., Swanson, J.M., Evins, A.E., DeLisi, L.E., Meier, M.H., Gonzalez, R., Bloomfield, M.A., Curran, H.V. and Baler, R., (2016). Effects of cannabis use on human behavior, including cognition, motivation, and psychosis: a review. *JAMA psychiatry*, *73*(3), pp.292-297.

Walitt, B., Klose, P., Fitzcharles, M.A., Phillips, T. and Häuser, W., (2016). Cannabinoids for fibromyalgia. *The Cochrane Library*.

Whiting, P.F., Wolff, R.F., Deshpande, S., Di Nisio, M., Duffy, S., Hernandez, A.V., Keurentjes, J.C., Lang, S., Misso, K., Ryder, S. and Schmidlkofer, S., (2015). Cannabinoids for medical use: a systematic review and meta-analysis*Jama*, *313*(24), pp.2456-2473.

Wolff, V., Zinchenko, I., Quenardelle, V., Rouyer, O. and Geny, B., (2015). Characteristics and prognosis of ischemic stroke in young cannabis users compared with non-cannabis users. *Journal of the American College of Cardiology*, *66*(18), pp.2052-2053.