AN COMHCHOISTE UM SHLÁINTE

Tuarascáil maidir le Cannaibionóideacha Íocshláinte

Eanáir 2017

JOINT COMMITTEE ON HEALTH

Report on Medicinal Cannabinoids

January 2017

32H003

Chair's Foreword

The Joint Committee on Health of the 32nd Dáil made assessment of medicinal cannabinoids an early priority of its Work Programme. The membership of this Committee believes that relieving the suffering of individuals is, ultimately, what healthcare is all about. Elucidating the issues around products which may be able to further that aim and make a real difference to people's lives is therefore of great importance to the Committee.

It is for that reason that, on behalf of the Committee, I wish to extend sincere thanks to Ms. Vera Twomey, mother of Ava, who suffers from a rare form of childhood epilepsy, Dravet Syndrome. Ms. Twomey's evidence to the Committee served to highlight the central place that should always be given to patient experience and outcomes when pursuing health policy. No less gratitude is extended to Dr. Colin Doherty, consultant neurologist, and Ms. Lorraine Nolan and Dr. Elaine Breslin of the Health Products Regulatory Authority, all of whose evidence helped to clarify the key regulatory issues surrounding medicinal cannabinoids in an Irish context. Each witness provided invaluable insight into how we, as a society, can begin to formulate a positive, safe and effective approach to cannabinoids.

I would also like to acknowledge the contribution of the Therapeutic Goods Administration of Australia, whose prompt and thorough response to the Committee's questions helped us to better understand the international context in which the regulation of medicinal cannabinoids is framed. In order to move forward effectively it is vital that we learn from best practice elsewhere and, in that regard, the agency's cooperation has been very helpful.

This report offers background to the status of medicinal cannabis and cannabinoids and highlights both the risks and potential benefits of those products. Although medicinal cannabinoids have the exciting potential to offer relief from a number of illnesses, there are also attendant risks which cannot be ignored. It is the Committee's view that Ireland should pursue a balanced course of action in considering the merits of authorising the use of medicinal cannabinoids, and the recommendations contained within this report are made in that spirit.

I would like to express my appreciation to my fellow members of the Joint Committee for their commitment to producing this report in such a short time-frame.

Dr. Michael Harty TD

_____

Dr. Michael Harty T.D.
Chair
Joint Committee on Health
19th January 2017

Membership of the Joint Committee on Health

Deputies:

Bernard Durkan (Fine Gael)

Dr. Michael Harty (Rural Independent Technical Group)

Billy Kelleher (Fianna Fáil)

Alan Kelly (Labour)

Kate O'Connell (Fine Gael)

Margaret Murphy O'Mahony (Fianna Fáil)

Louise O'Reilly (Sinn Féin)

Senators:

Colm Burke (Fine Gael)

John Dolan (Civil Engagement Technical Group)

Rónán Mullen (Independent)

Dr. Keith Swanick (Fianna Fáil)

Contents

Chair's Foreword 1
Membership of the Joint Committee on Health 2
Stakeholders 4
Transcript 4
Chapter 1: Cannabis, cannabinoids, and the endocannabinoid system 5
Chapter 2: Theoretical bases and evidence for medicinal use of cannabis and cannabinoids 7
Chapter 3: Health and social risks of medicinal cannabis 9
3.1 Health risks 9
3.2 Social risks 11
3.3 Overview 12
Chapter 4: Key Issues: Legal status of THC and medicinal market authorisation 13
4.1 Legal status of THC 13
4.2 Authorisation of cannabinoid products as medicines 13
Chapter 5: Cognisance of contemporary events 14
5.1 HPRA Report 14
5.2 Cannabis for Medicinal Use Regulation Bill 2016 14
Chapter 6: Analysis of stakeholder evidence 16
Chapter 7: International comparison 19
7.1 Australia 19
7.2 Canada 21
7.3 Overview 21
Recommendations 22
Issue 1: Currently legal cannabinoid products and their medicinal status 22
Issue 2: The legality of THC and cannabis for medicinal purposes 23
Other recommendations 23

Stakeholders

The Joint Committee (hereinafter referred to as the "Committee") held a day of hearings on 24 November of 2016 to engage with relevant stakeholders to discuss medicinal cannabinoids.

The Committee engaged with three primary witnesses/witness groups to elucidate the major issues around the potential for making cannabis, and/or cannabis derived products, available for medicinal use in Ireland. These were Ms. Lorraine Nolan and Dr. Elaine Breslin, representatives of the Health Products Regulatory Authority (HPRA), Dr. Colin Doherty, consultant neurologist at St. James' Hospital, and Ms. Vera Twomey, whose child Ava suffers from Dravet syndrome, a rare form of childhood epilepsy.

Further desk research was undertaken into relevant policy and literature background.

Transcript

The transcript of the meeting of 24 November is available online.[1]

[1] http://oireachtasdebates.oireachtas.ie/Debates%20Authoring/DebatesWebPack.nsf/committeetakes/HEJ2016112400002?opendocument

Chapter 1: Cannabis, cannabinoids, and the endocannabinoid system

Since there are a number of different chemical compounds defined as cannabinoids, it is useful to clearly differentiate between cannabis and cannabinoids and to identify the main substances under consideration in this report.

Cannabis is a naturally occurring plant that grows in different strains and medical applications for the plant are recorded throughout history[2]. However, medicinal usage of cannabis and its constituent cannabinoids has until recently not been part of the modern, scientific mainstream, perhaps due, in part, to national and international controls on the substance, such as the 1961 United Nations Single Convention on Narcotic Drugs.

Cannabinoids are some of the constituent elements of cannabis. One of the differential factors in strains of the cannabis plant, as mentioned above, is the potential for varying amounts of different cannabinoids[3]. Even within the same strain, growth factors and genetics can result in differing ratios of cannabinoids.[4]

There are 100+ known cannabinoids.[5] Only Tetrahydrocannabinol (THC) and Cannabidiol (CBD) are mentioned by name in this report, as the majority of indicative medicinal evidence currently in existence primarily concerns these.

THC has been identified as the major psychoactive cannabinoid, and is specifically controlled under Irish law.[6]

CBD exists in high concentrations in oils designed to alleviate epilepsy, especially rare childhood epilepsy, a type of condition which the Committee gave particular attention to in its consideration of medicinal cannabinoids. CBD is not controlled under Irish law.

Cannabinoids can affect cannabinoid receptors in the endocannabinoid system, a natural system[7] in the human body. Therefore, as well as compounds naturally occurring in the cannabis plant, synthetic compounds which mimic natural cannabinoids and affect the endocannabinoid system are also considered cannabinoids.

The endocannabinoid system was discovered in 1990 and, as *The Barnes report* outlines[8], has a role in many different areas of human function, including normal functioning of the brain, pain modulation, and digestion.

---

[2] P. 9, Access to medicinal cannabis: meeting patient needs (Access to medicinal cannabis), Westminster All-Party Parliamentary Group for Drug Policy Reform (2016) https://drive.google.com/file/d/0B0c_8hkDJu0DRnBfdGRDRXBROUU/view

[3] P. 10, Cannabis: The Evidence for Medical Use (The Barnes report), Professor Michael P Barnes MD FRCP and Dr Jennifer C Barnes DPsychol (2016) https://drive.google.com/file/d/0B0c_8hkDJu0DUDZMUzhoY1RqMG8/view

[4] P. 11, Information for Healthcare Professionals: Cannabis (marihuana, marijuana) and the cannabinoids (Information for Healthcare Professionals), Health Canada (2013) http://www.hc-sc.gc.ca/dhp-mps/marihuana/med/infoprof-eng.php

[5] P. 10, The Barnes report

[6] Misuse of Drugs Act 1977

[7] P. 8, The Barnes report

[8] P. 8, The Barnes report

The multiple natural roles of this system provide theoretical bases for the medicinal potentiality of cannabinoids for many different conditions. A report from Westminster's All-Party Parliamentary Group for Drug Reform claims that plant cannabis probably has medicinal effects due to its "mimicking" the effects of the endocannabinoid system[9], and *The Barnes report* posits that:

"The emerging concept of the endocannabinoid deficiency syndrome may provide a partial explanation for the aetiology[10]."

According to the World Health Organisation's 2015 report *Update on cannabis and its medical use*, the discovery of the extent and manifold purposes of endocannabinoids has given a "modern context" to the rationale for medicinal cannabis and cannabinoids.[11]

Awareness of different cannabinoids, and the potential for different medicinal products (including, in some jurisdictions, dried or fresh cannabis herb) to contain differing amounts of cannabinoids is important, as different ratios of cannabinoids are likely to offer relief for different medical products. As *The Barnes report* states:

"We wish to emphasise that efficacy is likely to be specific, in evidential terms, to a particular cannabis formulation. If, for example, nabiximols is efficacious for spasticity this does not necessarily mean that other cannabis formulations will also be useful for spasticity. This will depend on many variables, particularly the THC:CBD ratio." [12]

Therefore, the Committee does not deem it appropriate to make umbrella recommendations encompassing all cannabinoids and strains of cannabis. While the Committee favours an overall approach which endeavours to enable people to access medicinal products which can help them, in order to maintain evidence-based safety standards, blanket encompassing decisions should be treated with caution.

[9] P. 19, Access to medicinal cannabis
[10] P. 77, The Barnes report
[11] P. 26, Update of cannabis and its medical use, World Health Organization, Bertha K. Madras (2015) http://www.who.int/medicines/access/controlled-substances/6_2_cannabis_update.pdf
[12] P. 20, The Barnes report

Chapter 2: Theoretical bases and evidence for medicinal use of cannabis and cannabinoids

As explained in Chapter 1, the discovery of the endocannabinoid system offers fertile ground for theoretical conjecture about potential medicinal usage of cannabis. Due to the variety of bodily processes which feature endocannabinoid involvement, there are many illnesses which could conceivably benefit from cannabis or products containing cannabinoids.

However, it is important to the Committee that evidence of efficacy and safety of medicinal products has primacy over theoretical conjecture. There are varying levels of evidence in existence for the efficacy of cannabis and cannabinoids in treating different types of illness. After an extensive literature review, *The Barnes report* grouped different illness types into 4 different groups based on the strength of evidence available:

Good evidence*: Chronic pain, including neuropathic pain, spasticity, nausea and vomiting, particularly with chemotherapy, anxiety.*

Moderate evidence*: Sleep disorders, appetite stimulation in the context of chemotherapy, fibromyalgia, PTSD, some symptoms of Parkinson's.*

Some limited evidence with further study required*: Management of agitation in dementia, epilepsy especially drug resistant childhood epilepsies, bladder dysfunction, glaucoma, Tourette's.*

Theoretical basis only*: Dystonia, Huntington's disease, headache, brain protection in the context of traumatic brain injury, depression, OCD, gastro-intestinal disorders, anti-psychotic agent (CBD), cancer/tumour control.*[13]

It is important to note that this should not be interpreted as any indication that those illnesses in the groups with less evidence are necessarily ineffective. It merely indicates that there is a lack of strong, positive evidence for efficacy as of yet.

"The medicinal cannabis literature is far from satisfactory in that it contains many small scale studies as well as case reports and anecdotal evidence but very few good quality placebo-controlled double-blind trials."[14]

The World Health Organisation's *Update on cannabis and its medicinal use* highlights CBD as exemplary of the value of looking separately at specific cannabinoids, which can be isolated, and distinguishing them from the use of herbal cannabis.[15]

CBD has not been observed to cause any psychotic effects, unlike THC, and there are even indications that it may mitigate unwanted side effects caused by THC, including psychotic side effects, if ratios between the two cannabinoids are adjusted correctly.[16][17] *The Barnes report* also notes this.[18]

[13] P. 20, The Barnes report
[14] P. 2, The Barnes report
[15] P. 16, Update on cannabis and its medical use
[16] P. 13, Information for healthcare professionals
[17] P. 8, Update of cannabis and its medical use
[18] P. 109, The Barnes report

Particularly in regard to CBD as an anticonvulsant for epilepsy, *The Barnes repor*t concludes that indications are "promising", but that robust trials are lacking in the literature, meaning that evidence is limited.[19] Additionally, *Update on cannabis and its medicinal use* states that preclinical research has suggested that CBD may have "therapeutic applications for treating psychosis, affective and seizure disorders, inflammation, and neurodegenerative disease."[20]

However, the Cochrane review *Cannabinoids for epilepsy* concludes that there is insufficient evidence to recommend using cannabis for epilepsy. This conclusion presumably includes CBD, as it takes issue that "no conclusions can be drawn about the safety of long term cannabidiol treatment" based on available evidence.[21] As the Committee heard in stakeholder evidence (see Chapter 6), in drastic circumstances people may choose to administer based on the limited available evidence, despite a lack of long-term scientific evidence, although conclusions like the Cochrane reviews' present obvious problems for regulators in terms of endorsing a substance as a medicinal product.

The above-mentioned lack of evidence for the long term safety of using cannabis or specific cannabinoids is one of the risks looked at in Chapter 3.

[19] P. 69, The Barnes report
[20] P. 4, Update of cannabis and its medical use
[21] p 7, Cannabinoids for epilepsy, Cochrane review, D. Gloss and B. Vickrey. (2014) http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD009270.pub3/epdf

Chapter 3: Health and social risks of medicinal cannabis

Caution around enabling access to cannabis or cannabinoids for medicinal purposes generally comes from fear of unintended health effects for the patient or of unintended negative social effects for wider society. The Committee has identified a number of risk factors which are worth keeping in mind as medicinal cannabis is explored, and recommends designing policy so that such risks can be mitigated as much as possible.

3.1 Health risks

(a) Lack of evidence for safety of cannabis and cannabinoids, particularly regarding long term effects:

An obvious fear regarding cannabis/cannabinoid usage is that long term health effects may impact on users, since medicinal usage is largely a relative recent phenomenon (notwithstanding historic use before cannabis came under international controls in the early twentieth century). According to *The Barnes report*, there is mixed evidence of residual effects on users of cannabis, with some studies indicating such effects and some indicating none, but THC is likely to be the main driver of any potential long term negative impacts – other cannabinoids have not been implicated.[22]

It is also important to note that most evidence of long term damage from cannabis usage comes from recreational, not medicinal, users of the drug[23] – controlled usage in tandem with medical supervision may not pose the same level of risk.

However, as *Update of Cannabis and its medical use* points out,

"globally, the efficacy, safety and quality of the medical products on the market in countries have benefited enormously from a robust scientific and evidence based process. This should continue to be the central organizing principle in evaluating and approving substances for use as medicine." [24]

Ultimately, the historic shortage of robust evidence may be too much of an impediment for some to accept the mainstreamed medicinal use of cannabis and cannabinoids.

(b) Psychosis and schizophrenia:

One of the greatest stigmas attached to cannabis and an obstacle to approval of usage is the fear of its increasing the likelihood of the onset of schizophrenia, psychosis, or symptoms of same.

[22] P. 121, The Barnes report
[23] P. 9, Update of cannabis and its medical use
[24] P. 16, Update of cannabis and its medical use

The Barnes Report states that a causal link is likely, especially in the case of those with a genetic predisposition towards psychosis, but not proven.[25] Such effects are not likely to occur in the majority of medicinal users. As with any medicine, the decision to use it must be made with risk-benefit analysis. The Barneses also emphasise that THC is likely the main driver of any such causal relationship, and that CBD is actually likely to have anti-psychotic properties.[26]

As this issue, along with some other side effects, is of greater concern in young people (as "cannabis use in adolescence increases the likelihood of schizophrenia like psychoses"[27]), discouragement of medicinal cannabis usage below a certain age can be employed as a mitigating solution. For example, in Canada, usage is not recommended in under 25s.[28]

(c) Cognitive function:

General impairment of cognitive function is another concern around the use of cannabis. According to Health Canada, impairment of cognitive function can be linked to levels of THC after smoking.[29]

According to *Cannabinoids in Health and Disease*, there is mixed evidence of cannabis having negative effects on memory, cognitive function and motivation.[30]

(d) Dependence:

A tendency for people to develop a dependence upon cannabis is often cited as a reason to avoid usage. According to *the Barnes Report*, the generally accepted dependence rate of users of cannabis is 9%, but this is based off recreational usage and is likely to be smaller in medicinal usage.[31]

(e) Variability risk due to dosage and composition inconsistencies:

Unless supply of cannabis is strictly regulated with consistent growth conditions, it is possible that patients could be consuming unknown quantities of cannabinoids, which could present health risks. This risk is a strong incentive for state regulation of supply as highlighted *by Medicinal cannabis in Australia – Framing the regulatory options.*[32] In the Dutch system, three varieties of cannabis are available from pharmacies, each with a set and predictable ratio of THC to CBD.[33]

---

[25] P. 115, The Barnes report
[26] P. 116, The Barnes report
[27] P. 415, Cannabinoids in health and disease, Natalya M. Kogan, MSc and Raphael Mechoulam, PhD (2007) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3202504/pdf/DialoguesClinNeurosci-9-413.pdf
[28] P. 2, Consumer Information – Cannabis, Health Canada (2016) http://www.hc-sc.gc.ca/dhp-mps/marihuana/info/cons-eng.php
[29] P. 14, Information for healthcare professionals
[30] P. 415, Cannabinoids in health and disease
[31] P. 115, The Barnes report
[32] P. 10, Medicinal cannabis in Australia – Framing the regulatory options, Drug Policy Modelling Program, National Drug and Alcohol Research Centre, UNSW Australia (2015) https://ndarc.med.unsw.edu.au/sites/default/files/ndarc/resources/DPMP%20Medicinal%20Cannabis%20Paper%2010th%20March%202015_0.pdf
[33] Medicinal Cannabis – Information for Patients, CIBG, (2011) https://www.cannabisbureau.nl/Media/Default/PDF/5089-A5-BMC-Pat-ENG-web_35842.pdf

(f) Variability risk due to method of administration:

As well as occurring in different dosages, there are numerous methods of administration of cannabis and cannabinoids, which creates a new set of inconsistencies of efficacy. Also, some methods of administration can be dangerous, especially smoking.

"The potential modes of administration of medicinal cannabis include oral administration of pills (for the pharmaceutical preparations), use of oromucosal spray, a tincture or ointment or vaporisation of the herbal product. As a medicinal product, smoking cannabis (joints or bongs) is not recommended given the well-known attendant harms associated with smoking."[34]

"Comparisons between smoking cannabis smoke and tobacco smoke have shown that the former contains many of the same carcinogenic chemicals found in tobacco smoke."[35]

The Barnes Report states that smoking is unlikely to be a recommended route of medicinal usage in the UK, with vaporisation presented as an alternative method for using herbal cannabis.[36] However, *Update of cannabis and its medical use* is less convinced of the safety of vaporisation as a method of use.[37]

Tea and vaporisation are recommended forms of medicinal cannabis consumption in the Netherlands.[38]

3.2 Social risks

(a) The "slippery slope" towards decriminalisation for recreational use:

The slippery slope argument contends that creating access to cannabis especially (though some arguments may also be suspicious of cannabinoid pharmaceuticals which contain THC) is a first step towards liberalisation of the drug in society in general, and will result in greater recreational usage.

However, a DPA review conducted since the medicinal legalisation of cannabis in several US states shows that levels of social use have not increased, and that legalisation may be connected to a reduction in violent crime.[39]

(b) Leakage of supply:

Leakage of medicinal supply into recreational markets is an understandable concern, and the Committee stresses that a properly controlled supply framework should be formulated to mitigate against this. As *Medicinal cannabis in Australia – Framing the regulatory options* acknowledges, prescription systems, in general, have mechanisms which

[34] P. 6, Medicinal cannabis in Australia – Framing the regulatory options
[35] P. 11, Information for healthcare professionals
[36] P. 126, The Barnes report
[37] P. 18, Update of cannabis and its medical use
[38] Medicinal cannabis - Information for patients
[39] P. 14, Access to medicinal cannabis

limit leakage of drugs into recreational markets.[40] This can be seen as a point in favour of mainstreaming medicinal cannabis and cannabinoids into a framework which can experience the full participation of medical professionals.

3.3 Overview

As starkly illustrated in the stakeholder evidence received by the Committee (see Chapter 6), while health risks do exist, they should be analysed in balance with dramatic benefits which could be possible for suffering people.

Many of the indications of health risks which have been documented arise out of recreational usage of cannabis, which is inherently more risky than controlled medicinal usage would be.

Lastly, it is important to compare the risks of medicinal cannabis against the risks of medicines which already exist. On this basis, *the Barnes Report* compared the risks associated with cannabinoids to those of opioids, which are used to treat chronic pain, one of the potential applications for medicinal cannabis. The report concluded that "in general terms there are significantly less risks associated with cannabis and cannabis formulations, particularly with regard to the very severe risk of respiratory depression with risk of death."[41]

[40] P. 12, Medicinal cannabis in Australia – Framing the regulatory options
[41] P. 102, The Barnes report

Chapter 4: Key Issues: Legal status of THC and medicinal market authorisation

As indicated in the above Chapters, there are many potential medicinal products derived from cannabinoids and they cannot be treated uniformly. The Committee has identified two primary issues which need to be addressed separately, and recommend that individual products be subsequently dealt with on a case by case basis.

4.1 Legal status of THC

THC is a controlled substance, and any product (including but not limited to cannabis herb) with greater than trace THC cannot be legally held or consumed in Ireland without special licence[42]. However, there are potential medicinal uses for products with high levels of THC, again inclusive of cannabis herb, which some jurisdictions have allowed for legal, medicinal access. These jurisdictions often focus on controlling supply to (1) prevent criminality, (2) prevent leakage of supply to recreational markets, and (3) ensure predictability of cannabinoid levels within the supply for patients.

4.2 Authorisation of cannabinoid products as medicines

Some cannabinoid products are legal in Ireland, in that they do not contain prohibited levels of THC, and thus can be legally bought and sold. However, they may not have received official approval as medicines (this includes high CBD oil), meaning they are in a medicinal grey area. Doctors may not feel comfortable recommending them as medicines, and patients may face difficult choices about whether to try them. The only cannabinoid product which has received HPRA approval at this juncture is Sativex.

These products receiving endorsement from the HPRA would remove this barrier and, crucially, may help to reduce sometimes prohibitive cost for families if certain products could receive state subsidisation. However, the HPRA understandably has strict evidential standards to maintain. Therefore, many cannabinoid products, though legal, are not medicines, and whether there should be a fast-track pathway for them to be considered as medicines, or receive a similar status (potentially even without HPRA approval), due to a legacy of under-research and potentially life-saving and life-improving qualities, exists as a separate question to the one above regarding THC legality.

[42] Misuse of Drugs Act 1977

Chapter 5: Cognisance of contemporary events

The Committee is aware that at the time of the drafting and publication of this report, there are two contemporaneous processes taking place which may have significant impact on the issues explored here.

5.1 HPRA Report

Firstly, Minister for Health Simon Harris has instructed the HPRA to issue a report, which will:

> - Review the availability of authorised medicines containing cannabis
>
> -Review the status of ongoing clinical research involving cannabis and associated products
>
> -Review the international experience of the medicinal use of cannabis
>
> -On the basis of the above factors, the HPRA is to offer its opinion on its use and, depending on whether they view it positively or negatively, their policy advice
>
> (Ms. Lorraine Nolan, from her evidence to the Committee)

This report may indicate the feasibility and desirability of regulatory approval of cannabinoid products as medicine, or a similar status. It may include an expected timeline for approval for already legal products. If, in its report, the HPRA reaches favourable conclusions for the use of medicinal cannabinoid products as authorised medicinal products and expects a relatively short timeline before that can be achieved, that creates a much different context to a report which is pessimistic about the prudence of authorising such products.

Thus, the Committee considers it appropriate to make different recommendations based on two potential conclusions of the HPRA's report on this issue (see Recommendations).

High THC content products which are currently illegal in Ireland (including herbal cannabis) exist as a separate issue to the above. The HPRA may make conclusions on this issue in its report. Therefore, the Committee has likewise made contingency recommendations in Recommendations on that issue based on the HPRA report.

5.2 Cannabis for Medicinal Use Regulation Bill 2016

The second relevant contemporary issue is the Cannabis for Medicinal Use Regulation Bill 2016, proposed by Deputies Gino Kenny and Bríd Smith, and debated in Dáil Éireann on Thursday, 1 December 2016. That Bill has been referred to the Select Committee on Health and will be considered by them subsequent to the publication of this report. Certain risk

factors of the particular composition of that Bill, such as the potential for leakage of supply or the accidental decriminalisation of cannabis for recreational use, have already been debated. Such risk factors can be intentionally mitigated against, this being touched on in Chapter 7 of this report.

The Committee would welcome amendments to the Bill which would help to enable appropriately controlled access to medicinal cannabinoids and, potentially, cannabis, especially in a manner which demonstrates joined up thinking with the recommendations from this report and the imminent HPRA report.

Chapter 6: Analysis of stakeholder evidence

The witnesses who gave evidence to the Committee each approached the issue from differing but equally important perspectives, with areas of expertise in regulatory, clinical, and patient experience represented. However, each of them expressed their interest in the value of exploring the medical possibilities of cannabis and cannabinoids, whilst also having due regard to the need for a high level of safety and consideration of scientific evidence.

The representatives of the HPRA emphasised that agency's role in verifying that products are safe, effective, and of appropriate quality based on clinical and scientific data before such products can be authorised and supplied as medicines in Ireland. The Committee is aware that the HPRA's market authorisation of a product as a medicine carries a strong endorsement, and provides reassurance that rigorous scientific assessment has been carried out. This status cannot be compromised and no recommendations the Committee makes should be interpreted to seek to do so.

The HPRA clarified to the Committee that products containing THC are controlled under the Misuse of Drugs Acts 1977 - 2016, and can only be prescribed by doctors if a special licence has been granted by the Minister for Health. CBD products do not have market authorisation as medicinal products, leaving them in a "grey area" for medical practitioners and product users, as discussed below in evidence given by Dr. Colin Doherty and Ms. Vera Twomey to the Committee.

There is precedent for a cannabinoid product (containing THC) receiving marketing authorisation from the HPRA and Misuse of Drugs legislation being subsequently amended to allow for it –as was the case with the pain relief spray Sativex. The HPRA told the Committee there are promising indications for Epidiolex, an epilepsy drug discussed further below, to similarly merit authorisation but they don't yet have peer reviewed evidence enabling them to do so.

The HPRA also pointed out that other jurisdictions have made cannabis available while not authorising it as a medicine, instead concentrating on controlling the consistency and quality of supply.

This situation, for enabling access to cannabis, certain cannabinoids, or both, may be appropriate if it is determined that the detriment to some people of not having access to cannabis or certain cannabinoids outweighs the hazards of medicinal use of products which have not been officially authorised by the HPRA for that purpose.

The HPRA told the Committee:

"If on balance, it is considered that a less restrictive approach is appropriate for Ireland, in the absence of clinical data to allow the authorisation of cannabis (and products) as medicines, there are a number of elements that such a framework may potentially cover.

Patients and carers must recognise the limitations of the framework in assuring the safety, quality and effectiveness, as compared with what would be expected from an authorised treatment."

Dr. Colin Doherty's presentation to the Committee included a brief overview of the long history of medical applications of cannabis, and also highlighted the two cannabinoids found in the cannabis plant which are most germane to the Committee's consideration of medical applications: THC and CBD. According to Dr. Doherty, "While the pharmacology of THC is considered to be reasonably straightforward, the pharmacology of CBD is extremely complex; CBD is a multi-target drug whose action is not completely understood."

Dr. Doherty said that over the past few decades, there have been popular indications that cannabis and its constituent cannabinoids can help with a range of conditions, including chemotherapy induced anorexia, chronic pain in cancer, and multiple sclerosis. As well, "there have also been reports of spectacular reversals in epilepsy."

Dr. Doherty explained that Dravet Syndrome is a particularly severe form of childhood epilepsy with a high mortality rate – "20% of people with Dravet Syndrome will be dead by the age of twenty." A well known product used to ameliorate Dravet Syndrome, called Charlotte's Web, was developed in Colorado by growers Stanley Brothers in conjunction with the parents of a Dravet Syndrome sufferer, Charlotte Figi. Charlotte's Web contains a high ratio of CBD to THC (to such an extent that the amount of THC is considered "trace" and the product is not illegal in Ireland, as CBD is not a controlled substance).

Ms. Twomey is using this product to treat her daughter Ava's Dravet Syndrome, and informed the Committee of a dramatic improvement in Ava's condition since they began using it. Dr. Doherty informed the Committee that the popularity of Charlotte's Web has led to open-label trials in the US of a product called Epidiolex (also high in CBD) produced by the pharmaceutical company GW Health. Despite a shortage of peer-reviewed evidence of medicinal applications of cannabis and cannabinoids posing a general problem in the mainstreaming of such substances (as highlighted above in consideration of the HPRA's testimony), Dr. Doherty did call the Committee's attention to the fact that a placebo controlled study on Epidiolex has been accepted for publishing in a peer-reviewed journal and should appear soon.

The cannabis-derived product which seems to work for treatment of epilepsy (high CBD, low THC) cannot be prescribed by Irish physicians in the traditional sense as it is not officially designated as a medicinal product. Dr. Doherty, in the course of his testimony, described a "level of evidence" (a certain level of scientific evidence produced by appropriately large control groups and subsequently peer-reviewed)that would usually be required for prescription of, and access to, products with official medicinal status and that most cannabinoid products (including high CBD products for treating epilepsy) have not reached this typical ceiling.

Although there is some evidence that they can produce positive results, there may not be scientific evidence of efficacy and safety to such a standard which would usually be required to merit the endorsement of the HPRA. As Dr. Doherty told the Committee, "It is very important to distinguish between evidence in the generic colloquial term, where there is evidence that something works for this child or that child, and what we call scientific evidence. Scientific evidence should not be open to interpretation."

However, there is a need to balance that shortage of evidence with the lives such products could save:

“Already, it is possible to state with confidence that this drug will not work for everyone, will cause intolerable, but probably not dangerous, side effects in a few; but for those for whom it will work it may be life-saving.”

Dr. Doherty also pointed out that assessing the safety and efficacy of medicinal products is an ongoing process, and that an adequate level of scientific evidence to initially endorse a drug is only “the start of the journey.” The effects of all medicinal products must be monitored over time.

This issue of balance also arose in Vera Twomey’s evidence to the Committee; while there may not be as large a body of scientific evidence for the efficacy and safety of high-CBD epilepsy treatments as one would desire, when afforded the opportunity to use a product which dramatically reduces the number of severe, potentially fatal seizures a child is experiencing, the difficult decision to use an unregulated product can become a necessary one. Ms. Twomey expressed her wish that cannabinoid products would be authorised as medicinal products so that parents like her could work with the medical establishment, including doctors, to access the best treatment options for their children. The “grey area”, in which such products currently exist, makes the process for parents of accessing and using potentially life-saving products more fraught and less supported.

While the issues around mainstreaming and access to already legal products are considerable and merit consideration in themselves, it is important to point out at this juncture that Ms. Twomey expressed to the Committee that she also seeks access to products with higher levels of THC, in case these could also be of help to her daughter.

Dr. Doherty offered, in conjunction with relevant bodies, to work with the HPRA to determine whether a specific framework for prescribing CBD oil, with particular emphasis on child safety, could be appropriate to help diminish this “grey area”.

Dr. Doherty also asked the Committee to seriously consider the cost factor of cannabinoid based treatments, including CBD oil for epilepsy. As long as such products are outside of HPRA designation as medicinal products, there may not be any framework for State assistance with cost, which can lead to such products being prohibitively expensive. This is a potential cause of obstruction of access to life saving products. It would be especially beneficial to enable access on the long-term illness scheme, which is “the main reimbursement scheme for anti-epileptic drugs”.

He also emphasised the importance of ensuring that medical professionals, including those who would be in a position to prescribe, they will participate in any process that would make cannabinoid medicines more accessible.

Chapter 7: International comparison

7.1 Australia

The report *Medical cannabis in Australia – Framing the regulatory options* (2015) laid out some regulatory issues prior to the country's legislating for medicinal cannabis.

It identifies three principal modes of existence of medicinal cannabis products[43]. The first is a medical grade product which makes use of the isolation of one or more cannabinoids, with standardised content of the active constituents. These have the potential to adhere to the requirements of the Therapeutic Goods Administration (TGA), the Australian equivalent of the Health Products Regulatory Authority. The second is herbal cannabis which is produced and process in controlled and standardised conditions, so that it contains stable and predictable amounts of the cannabinoids THC and CBD. Such products are available in the Netherlands.[44] Unregulated herbal cannabis may also be used illegally (illegal in Australia and most jurisdictions, including Ireland) in the third mode of medicinal application of cannabis, but this poses health risks as stable amounts of cannabinoids cannot be guaranteed, and extra adulterants may be present due to variable growth factors.

As that report outlines, the definition of what includes state-sanctioned legitimate medicinal cannabis can vary. It can stretch from strictly standardised, clinically tested, low-THC cannabinoid products which have received approval from a state-sanctioning body such as the HPRA (as in the case of Sativex), to general usage of non-standardised supplies of herbal cannabis. It is the state-endorsed definition of what is acceptable usage of medicinal cannabis which will dictate which regulatory framework(s) and method(s) of access will exist in any given jurisdiction.

"A policy and regulatory challenge is balancing the extent of access and availability of medicinal cannabis (both pharmaceutical and medical-grade herbal) against the risk of diversion into recreational markets."[45]

"For pharmaceutical preparations such as nabiximols or synthetic cannabinoid pharmaceutical products (B5), standard registration with the Therapeutic Goods Administration is required. This might be a costly and time-consuming process but it adheres to the usual processes for the registration of medicines in Australia. An evidence-base in the form of clinical trials is required for each product that is registered through the TGA" [46]

Subsequent to the publication of that report, the medicinal use of cannabis (extending to mode 2) in Australia was legislated level for. Despite the required ceiling of evidence for registration with the TGA not having been reached, it is possible for doctors to prescribe CBD oil, or other medicinal cannabis products, as unapproved therapeutic goods, through an Authorised Prescriber Scheme.

[43] P. 5, Medical cannabis in Australia - Framing the regulatory options
[44] Medicinal Cannabis – Information for patients
[45] P. 7, Medical cannabis in Australia - Framing the regulatory options
[46] P. 12, Medical cannabis in Australia - Framing the regulatory options

Legal availability of modes of medicinal cannabis and cannabinoids (*as outlined by Medical cannabis in Australia – Framing the regulatory options*) in Australia		
Mode	Legal at Federal Level (availability varying depending on state level decision making)	Not Legally Available in Australia
1. Isolated cannabinoid products	**X** (available, but only Sativex is on the Australian Register of Therapeutic Goods)	
2. Cannabis grown under specific conditions with licence	**X**	
3. Unstable, unregulated cannabis		**X**

On 4th January 2017, the TGA responded to a request from the Committee to confirm the above and informed the Committee of the following:

"Generally, medicines imported into, supplied in, and exported from Australia must be entered in the Australian Register of Therapeutic Goods (ARTG), which is administered by the TGA. Currently, aside from Sativex, there are no medicinal cannabis products entered in the ARTG. Therefore these products are considered unapproved therapeutic goods. However, there are other mechanisms of accessing unapproved therapeutic goods in Australia.

For medicinal cannabis products these include:

· access for individual patients through either:

o Authorised Prescriber Scheme

o Special Access Scheme (Category B)

· access as part of a clinical trial.

These mechanisms maintain the same standards for medicinal cannabis products that apply to any other experimental or emerging medicine. Medicinal cannabis products supplied in Australia will use these alternative supply pathways while evidence to support registration on the ARTG is gathered through clinical trials.

Additionally, in Australia, medicines and poisons are classified into Schedules according to the level of regulatory control over the availability of the medicine or poison, required to protect public health and safety. Legislation came into effect on 1 November 2016 to amend the current Schedule 9 (prohibited substance) entries and create new Schedule 8 (controlled drug) entries for cannabis and tetrahydrocannabinols in certain circumstances... While the scheduling of medicines operates at a federal level, the states and territories have the authority to decide if they want to adopt a scheduling change for a medicine in their relevant legislation.

……

Another aspect of medicinal cannabis supply in Australia of note is that legislation came into effect on 30 October 2016 to allow legal cultivation, production and manufacturing of medicinal cannabis products in Australia. This scheme is administered by the Office of Drug Control (ODC). This legislation is designed to make available medicinal cannabis products and works together with the therapeutic goods legislation and state and territory legislation to make medicinal cannabis products available to certain patients via the exemption schemes outlined above."

Current methods of access to cannabinoid products in Australia		
Traditional prescription through product placement on the Australian Register of Therapeutic Goods	Individual patient access through Authorised Prescriber Scheme or Special Access Scheme	Clinical Trial
NO (excepting Sativex)	**YES**	**YES**

7.2 Canada

Health Canada's Consumer Information Leaflet on medicinal cannabis (which treats cannabis and cannabis derived products as the same) states that cannabis is not an approved therapeutic product)[47], but accessing medicinal cannabis requires the support and endorsement of a healthcare practitioner[48]. A 2015 Supreme Court ruling expanded the definition of medicinal cannabis to include products derived form cannabis.[49]

7.3 Overview

In both of these jurisdictions, while cannabis and cannabinoid products (including CBD oil) have not attained the equivalent of HPRA endorsement, it is permissible for doctors to endorse such substances for a patient's care, and for some products such endorsement is required before a patient can access them.

[47] P. 1, Consumer Information - Cannabis
[48] http://www.hc-sc.gc.ca/dhp-mps/marihuana/info/licencedproducer-producteurautorise/access-usage-eng.php
[49] http://scc-csc.lexum.com/scc-csc/scc-csc/en/item/15403/index.do

Recommendations

Issue 1: Currently legal cannabinoid products and their medicinal status

Recommendation 1: The Committee considers it desirable to diminish the medical "grey area" wherein high content CBD products are legal, but are not medically mainstreamed due to their lack of HPRA medical product authorisation.

The Committee is aware that the HPRA is producing a report which will assess the potential for authorising cannabinoids.

Scenario 1:

If the HPRA report finds that high-CBD anticonvulsive products, such as Charlotte's Web or Epidiolex, can be authorised as medicinal products, the Committee recommends that any practical matters around implementing such authorisation, ensuring supply and ensuring the ability of doctors to prescribe be pursued as speedily as possible, whilst also upholding the HPRA's high standards around authorisation.

In the above case, the Committee also recommends that cost implications for families be looked at, and that efforts to mainstream such products should include making them affordable. This includes the potential to make them free of charge as part of the long-term illness scheme in order to reduce any onerous or prohibitive cost burden on families.

In the above case, the Committee also recommends that consultations with doctor's groups and other relevant medical bodies occur concurrently with the introduction of such products, to ensure medical professional buy-in.

Scenario 2:

If, alternatively, the HPRA report finds that such products have not amassed the requisite levels of scientific evidence for authorisation as medicinal products, the Committee recommends that the possibility for another framework of supply control and access for CBD oil be explored in conjunction with Dr. Colin Doherty and the relevant bodies he cites, as offered by him when appearing before the Committee. Such a framework should also take into account the timeframe, cost, and medical professional buy-in recommendations outlined in Scenario 1.

If the above is not feasible, the Committee recommends continued use of special licensing powers to enable patient access, as has recently occurred.[50]

[50] http://www.thejournal.ie/toddler-medical-cannabis-3158648-Dec2016/?utm_source=shortlink

Issue 2: The legality of THC and cannabis for medicinal purposes

Recommendation 2: More generally, regarding cannabis and cannabinoids other than CBD, including THC, the Committee recommends that the HPRA explores the feasibility and potential benefit of a framework for accessing such products, as experienced internationally and cited by the HPRA in their evidence to the Committee.

Scenario 1:

If the HPRA's policy advice and subsequent decisions by government and legislators conclude that the evidence of efficacy and safety is not strong enough to warrant medicinal access to cannabis and THC, the Committee recommends that that decision be revisited at a later date, due to the possibility of evidence having been advanced in the intervening period.

Scenario 2:

If policy advice and legislative decisions are such that medicinal access to cannabis and THC products is to be legalised, the Committee recommends that a framework of supply be developed which standardises levels of cannabinoids in products insofar as possible, and that a framework of access be developed which mitigates against leakage of supply to recreational markets.

Other recommendations

Recommendation 3: Having noted in the course of its investigation that many of the obstacles to the safe provision of medicinal cannabis and cannabinoids arise from a historical shortage of scientific research in the area, the Committee recommends that Ireland makes a commitment to the long term tracking of the health of users of CBD rich products, and any other cannabis or cannabinoid products which are made accessible, for research purposes, thereby taking advantage of an opportunity to contribute to the global store of medical knowledge of cannabinoids and the endocannabinoid system.

Recommendation 4: The Committee also recommends that methods of usage of medicinal cannabis (for example, vaporising, tea, oil, etc) be designed as part of the access framework with a view to optimising safety and efficacy for each particular condition. Furthermore, the Committee recommends that data on the safety of each method be collected and assessed over time.