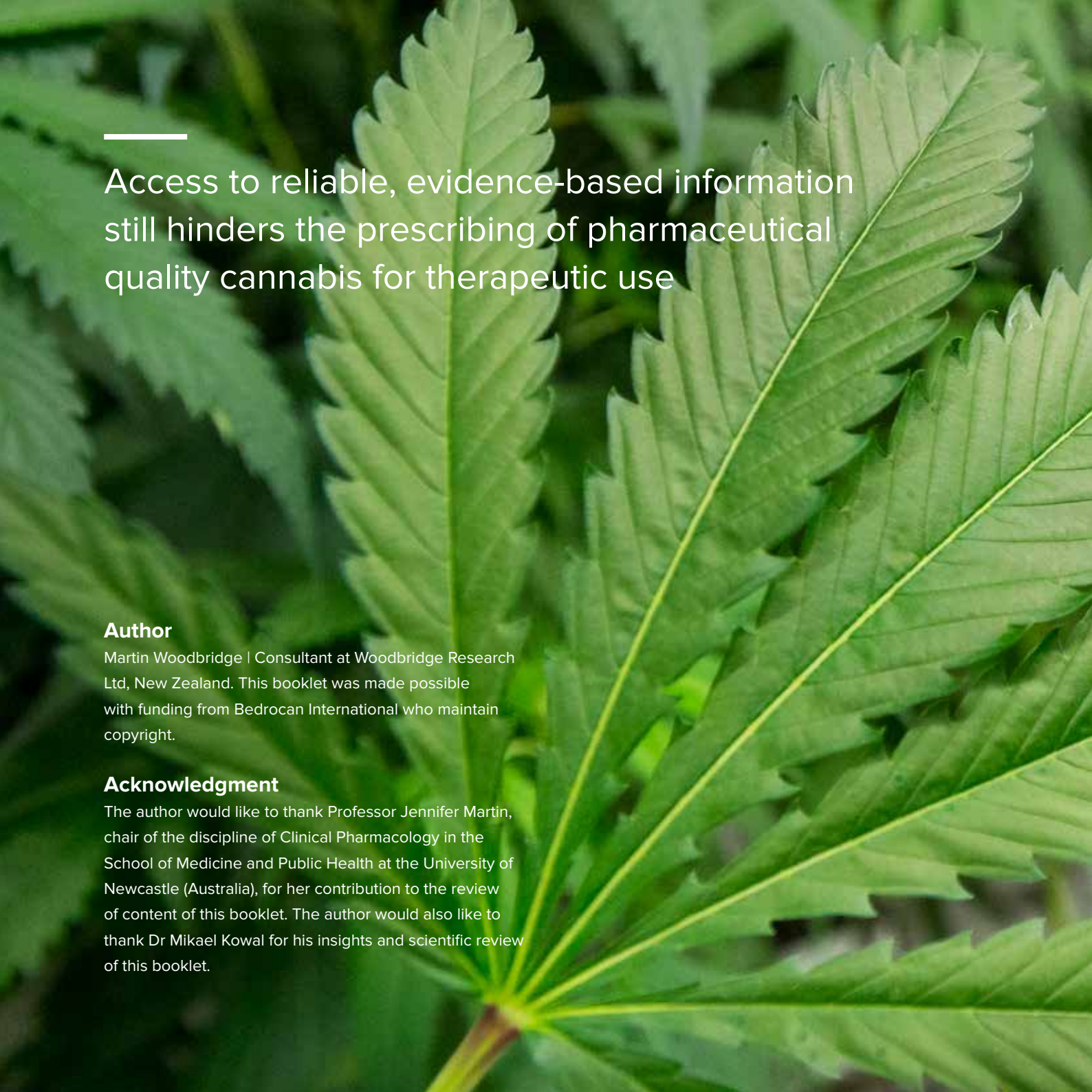
A primer to medicinal cannabis

An introductory text to the therapeutic use of cannabis



Access to reliable, evidence-based information still hinders the prescribing of pharmaceutical quality cannabis for therapeutic use

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A primer to medicinal cannabis

This booklet discusses the therapeutic use of cannabis. That means we are not talking about pot, marijuana, grass, or dope for recreational use to get 'high'. It focusses strictly on medicinal cannabis. It is meant to give health care professionals, regulators and patients insights into the medical and scientific aspects of *Cannabis sativa* L. and how this plant fits in the chain of therapeutic options.

Cannabis is a complex plant. There are over 500 chemical components identified; the chemical content of each cannabis variety is different to the next. Globally, and for generations, it has been used recreationally and associated with criminal activity - this has tainted its image as a legitimate medicine. International treaties also make its medical use complicated. However, despite illegality, vast numbers of patients across the globe use cannabis in its crude form for symptom relief, while a smaller number access pharmaceutical-quality products via their doctors and pharmacists. Access to reliable, evidence-based information still hinders the prescribing of pharmaceutical-quality cannabis for therapeutic use. Medicine regulators often do not permit cannabinoids, the active substances in cannabis, to be used as a mainstream medicine.

As early as the 1960s, the major biologically active cannabinoids THC and CBD were identified in the plant. By the late 1980s to early 1990s the cannabinoid receptors had been discovered. Both are critical time points for identifying the key therapeutic components of the cannabis plant and confirming the biological pathway for its action. Since that time clinical research demonstrates medicinal cannabis has potential therapeutic applications in certain conditions.

With the development and availability of pharmaceutical-quality products, reliable clinical data are now being generated. This knowledge will help determine the place of medicinal cannabis in the therapeutic toolbox and to separate therapeutic use from recreational.

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1 What a medicine is and where cannabis fits in

Medicines are central to modern and traditional medical practice. Medicines are tools. They are used to treat or prevent disease, and to promote health. If misused they can also cause harm.

Doctors must have access to quality, safe, and effective medicines. They must also use them rationally. Every time the doctor has to make decisions around whether it is appropriate to a patient's needs, at the correct dose, for the right length of time, and at an acceptable cost.

Doctors also need choice. For patients who do not respond well to one medicine, having an alternative therapeutic option is helpful. Medicine choice allows doctors to find the most appropriate treatment for the patient under their care.

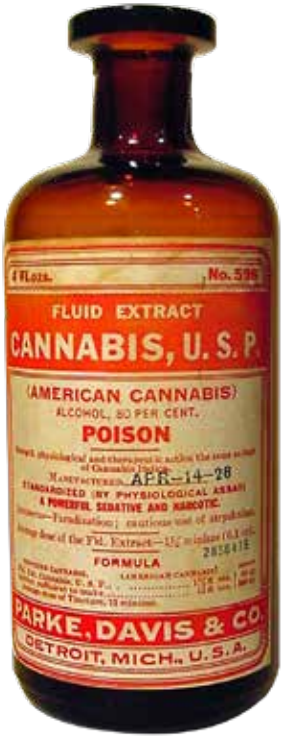
Over the last decade the number of patients exposed to medicinal cannabis (the cannabinoids THC and CBD) has increased alongside a variety of conditions where patients have reported symptomatic benefit. These include, but are not limited to, chronic pain; multiple sclerosis; nausea, vomiting and appetite stimulation; epilepsy; and anxiety. Others include sleep disorders; fibromyalgia; Gilles de la tourette syndrome; therapy-resistant glaucoma; Crohn's disease and ulcerative colitis; Parkinson's disease; rheumatoid arthritis; attention-deficit disorder (ADD); and posttraumatic stress disorder (PTSD). Each has shown varying degrees of response, and many still require being confirmed by good clinical science.

Medicinal cannabis is a novel class of medicine. It is not a panacea or a cure for disease. Currently, in most parts of the world, it is also not a first line treatment. Rather, eligible patients have not responded well to other medicines, or experience unacceptable side effects. While only few are officially registered medicines, cannabis products for medical use are still required to meet certain quality standards. As a result, government medicine regulators often are managing a patient and doctor demand for medicinal cannabis alongside the requirements of product safety, quality and efficacy. So, as much as there is a need for clinical data and prescribing guidance, robust information to support policy development and decision making by government officials is just as essential.

Medicinal cannabis is a novel class of medicine

A potted history

Cannabis is one of the oldest known medicinal plants. It is described in ancient handbooks on plant medicine. Archaeological evidence indicates the plant spread from Asia to Africa and on to the Middle-East. Eventually it arrived in Europe around 500 BC. It was later used widely for industrial purposes and was integral to early shipping as hemp fibre. History states that the therapeutic use of cannabis was introduced to Europe in around 1840 by an Irish doctor called William O'Shaughnessy. While in India he observed its widespread therapeutic use. In the following decades cannabis gained a short period of popularity in Europe and the United States. Dozens of different cannabis preparations were available. These products were recommended for conditions including menstrual cramps, asthma, cough, insomnia, labour pains during birth, migraine, throat infection and withdrawal from opium use. At the time no tools existed for quality control and standardised preparations. Patients often received a dose that was either too low having no effect, or too high resulting in unwanted side effects. These drawbacks meant the therapeutic use of cannabis was largely taken over by standardised opium-based drugs such as codeine and morphine. Cannabis gradually disappeared from all Western pharmacopoeias. In the late fifties the World Health Organisation (WHO) claimed that cannabis and its preparations no longer served any useful medical purpose.



A cannabis extract produced by the pharmaceutical company Parke Davis & Co.

The therapeutic use of cannabis was introduced to Europe in around 1840 by an Irish doctor called William O'Shaughnessy

2 The cannabis plant, its makeup and chemistry

Like other plants, cannabis is made up of hundreds of chemical compounds. It also comes in many different types. Some people refer to *indica, sativa,* or *ruderalis* types. But all of these belong to the same species: *Cannabis sativa* L. – a member of the *Cannabaceae* family. Many people are familiar with cannabis by the name hemp. Another of its close relatives is *Humulus lupulus* L., better known as hops, a key ingredient of beer.

Cannabis is said to originate in the arid climates of Central Asia (Eurasian steppe), most likely the Hindu-Kush region. Straddling the borders of Pakistan and Afghanistan, the 800-kilometre-long mountain range was an integral part of the ancient Silk Road. The Silk Road provided a network of trade routes connecting Eurasia. The road and maritime trading routes moved various goods, including cannabis, in its various forms (hemp fibers, oil-rich seeds, intoxicants, and medicines), to the east beyond the Korean peninsula and west beyond the Mediterranean Sea. Nowadays, cannabis can be found growing in places all around the world, except in humid, tropical rain forests.

There are male and female cannabis plants, each with a distinct way of blooming. The cannabis plant has a lifespan of one year. The plant typically reaches a height of two to three meters (seven to 10 feet), after which it blooms and the growth ceases. After fertilisation, the seeds mature and the plant dies.

A female cannabis plant

Cannabis by any other name

More than 700 cultivated varieties (cultivars) of cannabis are thought to exist. The difference between distinct cannabis varieties is not solely determined by the cannabinoid content, but also the specific terpene content. These chemical constituents act as distinct biochemical markers, and can be used to 'map the current chemical diversity of cannabis'. By analysing the concentrations of these compounds, researchers can identify specific cannabis plants with defined chemical profiles. For the purposes of medicine development, these particular plants can be used in clinical trials to determine their specific biological actions, and later introduced as new varieties to the existing product range.

Such analytical insights have led to a better understanding of cannabis taxonomy (scientific classification of plants). In the past, the distinction between *sativa* and *indica* has presented much debate. The classification was based upon differences in chemical composition, especially the differences in terpene content. However, to date there is no conclusive research displaying distinct ancestral lines for *Cannabis indica* or *sativa.* So, although cannabis plants can significantly differ from one another, the scientific emphasis has shifted to a hypothesis that all cannabis falls under *Cannabis sativa.*

The cannabinoids

Over 500 chemical compounds are produced by the cannabis plant. Of these, at least 100 are unique to the cannabis plant – the cannabinoids. The plant-derived cannabinoids are termed phytocannabinoids. The major phytocannabinoids, and those we know most about, are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC possesses psychoactive effects, while CBD is non-psychoactive (i.e. it does not alter perception or consciousness).

The cannabinoids are biologically active chemicals. The concentration of cannabinoids varies throughout the plant (excluding seeds and roots). The highest concentration is found in the unfertilised female flower.

The biological activity is mainly linked to the major cannabinoids THC and CBD. Although THC and CBD have unique activities, it is becoming clear that a wider range of cannabinoids and other constituents of the cannabis plant may be involved in its various therapeutic effects. These include the cannabinoids tetrahydrocannabivarin (THCV), cannabichromene (CBC), and cannabigerol (CBG). These minor cannabinoids are thought to subtly modulate or enhance biological effects when taken therapeutically. This effect may be the result of them working on their own, or working together with THC and CBD.

The terpenes

The other main compounds in cannabis are the terpenes. These are aromatic compounds which give cannabis varieties distinctive smells and tastes. Terpenes may have additive therapeutic action, meaning they may work together with cannabinoids to modify or enhance medicinal effects. To date more than 120 different terpenes have been identified in cannabis. Unlike cannabinoids, all major terpenes present in cannabis (e.g. myrcene, alpha-pinene, and beta-caryophyllene) can be found abundantly in nature.

It is thought that the terpenes work together with cannabinoids to modify or enhance their effects. This is known as the 'entourage effect'.

The glandular trichomes

The cannabinoids and terpenes are produced in the plant's resin glands. These are called glandular trichomes. The trichomes are located on the surface of the entire plant. The largest concentration of the glands are found in the flowering heads of the female plant.

The cannabinoids exist mainly in an inactive acid form. The pharmacologically active cannabinoids (e.g., THC/CBD) are formed when cannabis is heated to a temperature of at least 180°C resulting in 'decarboxylation'. With the use of a vaporizer, the active cannabinoids are released from the glandular trichomes in a vapour at 230°C which can then be inhaled into the lungs.

Close up: The glandular trichomes containing cannabinoids and terpenes are found over the entire surface of the cannabis plant.

3 Our endocannabinoid system

Like in the case of the opioid system reacting to opioids (morphine, codeine), humans have a distinct receptor system for cannabinoids. The endocannabinoid system (ECS) contains cannabinoid (CB) receptors and influences the activity of many other body systems. The phytocannabinoids of the cannabis plant work in a similar way to our naturally produced endocannabinoids.

The human brain and other organs contain naturally occurring cannabinoid (CB) receptors and the chemicals that bind to them. This is called the human endocannabinoid system (ECS). The ECS role is to maintain our body's ability to function normally by influencing the functioning of other systems. It plays a critical role in our nervous system, and regulates multiple physiological processes. This includes the adjustment of our response to pain, appetite, digestion, sleep, mood, inflammation, and memory. The ECS also influences seizure thresholds (i.e. in epilepsy), coordination, and other processes such as the immune system, heart function, sensory integration (touch, balance, sense of space), fertility, bone physiology, the central stress response system (the HPAA), neural development, and eye pressure.

Humans produce their own cannabinoids, the endocannabinoids. These endocannabinoids act on, or stimulate, the cannabinoid receptors. These compounds act in a similar way to phytocannabinoids which also bind to the receptors.

The plant cannabinoids are called phytocannabinoids. They are the unique constituents of the cannabis plant. Tetrahydrocannabinol (THC) and cannabidiol (CBD) are the main constituents. There are other cannabinoids, but currently far less is known about them.

How cannabinoids work

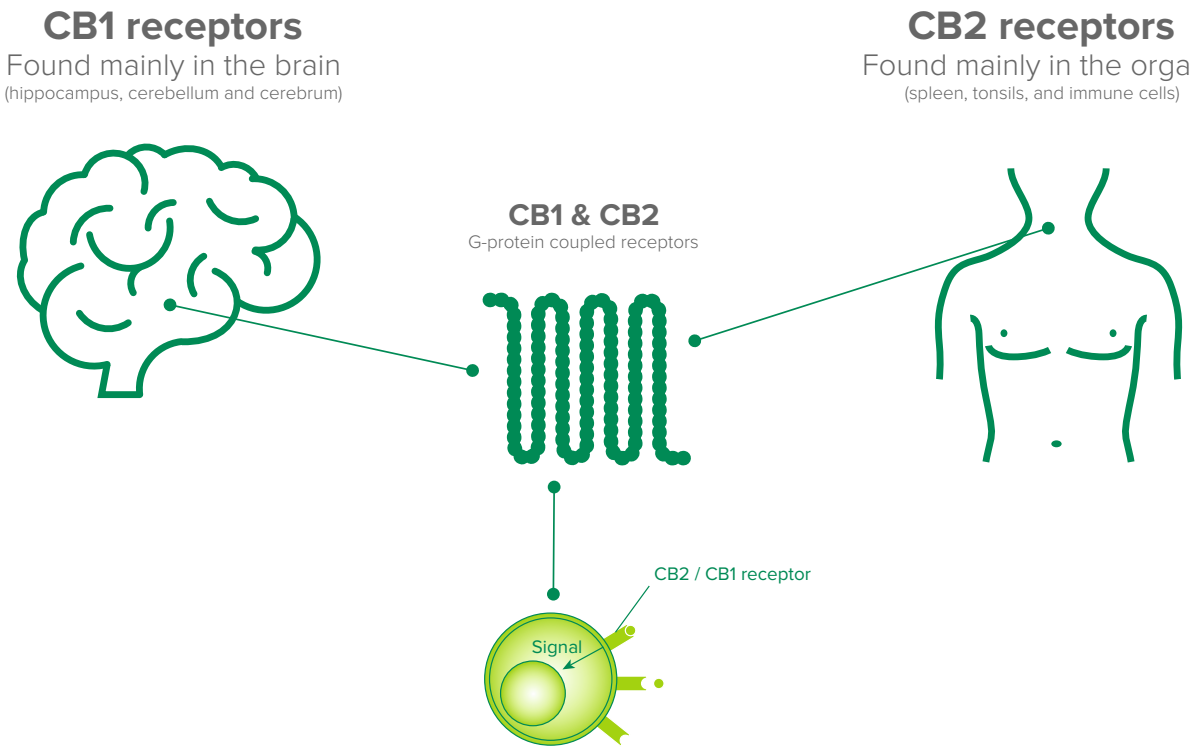
Cannabinoids produce their effects by binding to specific CB receptors. Cannabinoid receptors are one of the superfamily of G-protein-coupled receptors (see illustration). So far, two types of cannabinoid receptors (CB1 and CB2) have been identified with certainty.

The CB1 receptor is found mainly in the brain and central nervous system. CB1 is also found in certain tissues and organs, such as the lungs, liver and kidneys.

The CB2 receptors are mainly found on certain cells of the immune system, the gastrointestinal tract, and in immune-related organs such as the spleen and tonsils.

The phytocannabinoid THC activates both CB1 and CB2 receptors, which in turn influences the activity of various physiological systems. CBD, by comparison to THC, has less affinity for the CB receptors, and works to partly block receptor activity.

Cannabinoid receptors

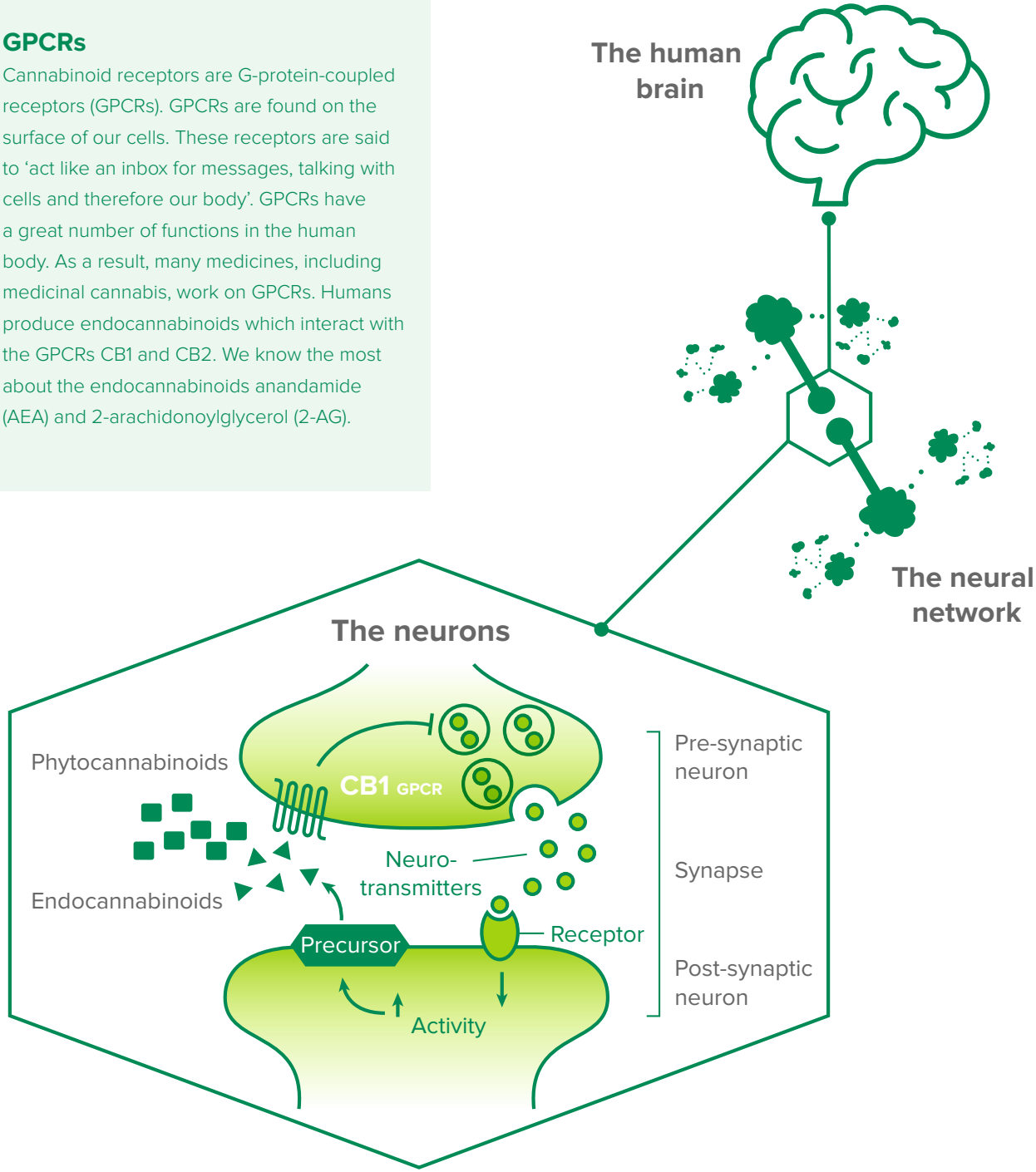


For example, the CB1 receptor is located in a number of regions of the brain which control various physical and behavioural functions. As a result, cannabinoids influence sensory and motor responsiveness (movement), heart rate, emotional reactions, appetite and nausea/vomiting, sensitivity to pain, learning and memory, and high-level decision making.

As our knowledge of the human ECS develops so will our understanding of how the phytocannabinoids, THC, CBD and other cannabinoids work. This understanding will lead to better medicines.

GPCRs

Cannabinoid receptors are G-protein-coupled receptors (GPCRs). GPCRs are found on the surface of our cells. These receptors are said to 'act like an inbox for messages, talking with cells and therefore our body'. GPCRs have a great number of functions in the human body. As a result, many medicines, including medicinal cannabis, work on GPCRs. Humans produce endocannabinoids which interact with the GPCRs CB1 and CB2. We know the most about the endocannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG).



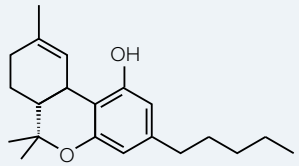
The different types of cannabinoids are briefly described in the schematic below. This includes those derived from the cannabis plant, laboratory made, and made in our bodies.

Types of cannabinoids

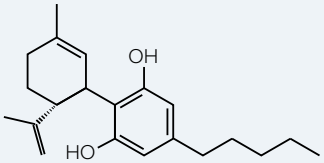
Cannabinoids

***Cannabis sativa* L.**

Phytocannabinoids

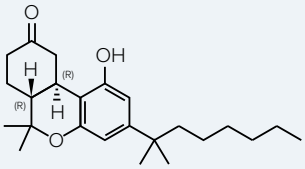


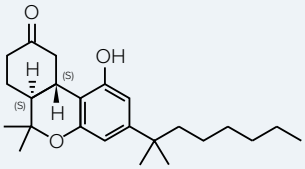
THC:
Delta-9-tetrahydrocannabinol
THC is the primary psychoactive component of cannabis



CBD: Cannabidiol
CBD is the secondary non-psychoactive component of cannabis

Synthetic cannabinoids

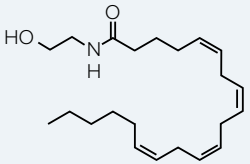




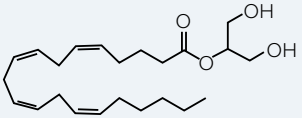
Nabilone
(racemic mixture: cis-trans isomerism)
A synthetic drug that mimics the effect of the natural cannabinoid THC

Endocannabinoids

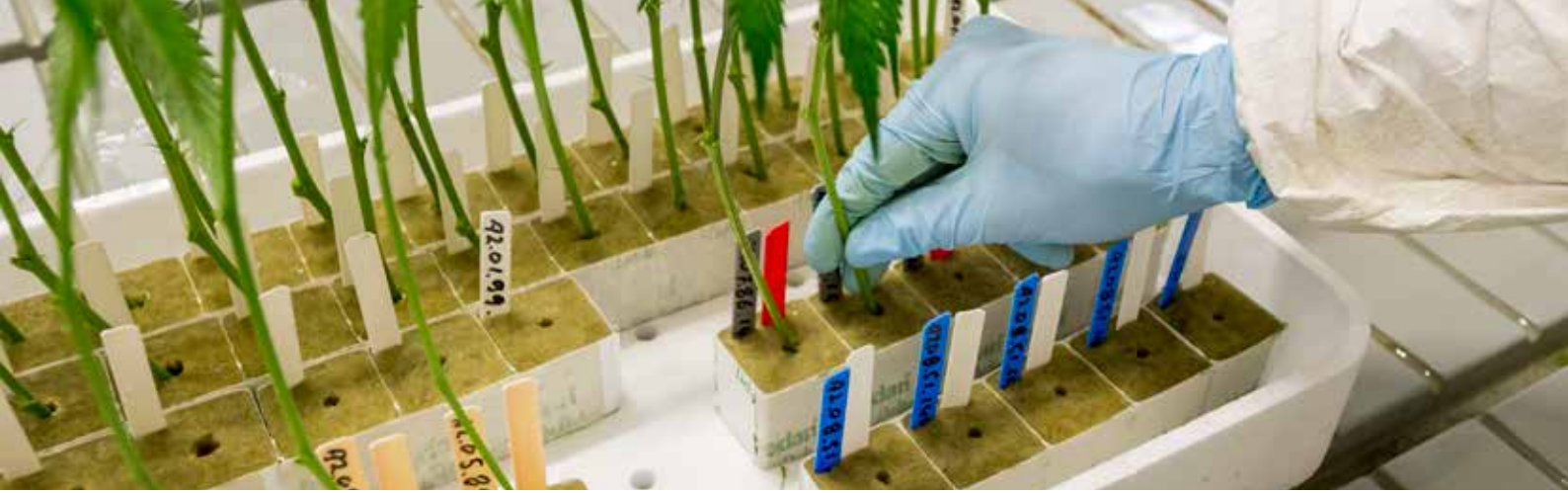
Neurotransmitters produced in the brain that bind to the cannabinoid receptors



Anandamide (AEA)



2-Arachidonoylglycerol (2-AG)



4 Quality and standardisation

The quality of medicinal cannabis can vary greatly. This poses risks and uncertainties to patients and their prescribers. So, why is quality so important?

Cannabis has been used in human clinical studies and found to be relatively safe for most people, compared to other medicines. However, some patients taking cannabis have had worsened symptom control and new side effects such as sleepiness, abnormal liver function and diarrhoea. Absolute safety does not exist for any medicine. All medicines can pose a risk of side effects and possibly adverse effects (resulting in harms). In particular, large doses of THC and potent synthetic cannabinoids have been shown to pose a risk of harm (e.g. postural-hypotension resulting in a fall, or a mild to severe psychotic event).

The safest and most reliable products are of pharmaceutical-quality. These products meet good manufacturing practice (GMP) standards. GMP is the highest standard of medicine manufacture. GMP is an assurance of consistently high-quality products and production processes. For medicinal cannabis, GMP practices should start from the very first step, cultivation, right through the entire production process to the finished product. It is not just about the packaging of cannabis flos, or the production of an oil extract. Under GMP, each part of the medicine production and testing process must be clearly documented. Personnel, premises and materials must meet the highest standards. These processes provide patients and prescribers with the safest and most reliable products.

A pharmaceutical-quality product could be, for example, cannabis flos for inhalation, a capsule for swallowing or a spray for the mouth. Each product type will require a slightly different set of tests for quality. These tests are often published. The pharmacopoeia monographs, for example, are the most reliable published methods for the analysis of medicines. These monographs explain the standards for potency, quality and so on. Medicinal cannabis products are required to be independently tested by specialised laboratories. The tests laboratories undertake often include:

- **The identification of cannabis** – Medicinal cannabis products typically must be derived only from the cannabis plant. An important first step is to test the plant material to confirm it is actually cannabis, and not an adulterant or substitute.
- **The identification of active ingredients** – There are numerous components of the cannabis plant. This test typically requires identifying THC and CBD, and often the terpene content.
- **The absence/presence of microorganisms** – During cultivation the cannabis plant can host harmful microorganisms like fungi and bacteria which can end up in the finished product. This may require decontamination treatment by gamma irradiation to eliminate microorganisms such as *Staphylococcus Aureus* and *Escherichia Coli*. The process must not affect the quality of the finished product.
- **The absence/presence of pesticides** – Many different types of pesticides can be used in cannabis cultivation, but none are approved for use in cannabis. This test ensures the finished product does not contain pesticides which are very harmful to patients' health.
- **The absence/presence of heavy metals** – The cannabis plant can quickly take up heavy metals from soil – termed heavy metal bio-accumulation. Every batch must be checked for the presence of harmful heavy metals such as arsenic, cadmium, lead and mercury.
- **The absence/presence of foreign matter** – It is essential that the final plant material (and the finished product dose form) is free from impurities such as soil, dust, dirt and other contaminations.
- **The total water content** – For cannabis flos which is intended to be inhaled by vaporization, the final water content is important. The right amount of moisture (water content) in dried cannabis flos assures an easy inhalation process during vaporization.

The cornerstone of reliability

Medicines must have a clearly defined composition. GMP-certified, fully standardised medicinal cannabis contains a constant composition active ingredients, batch-to-batch. This means the same dose can be taken each time. Doctors can better monitor dosage, condition progress, and reduce the risk of overdose and side effects. These products are also free of microbial contaminants (moulds, fungi, and bacteria), pesticides, and heavy metals. These are qualities which are especially important for people with weakened immune systems, and which make the products safe for vaporization and inhalation into the lungs. Finally, standardisation allows the comparison of different clinical trials and studies across time. It is a critical factor for building the evidence base of medicinal cannabis.

Batch-to-batch consistency is a challenge. The cannabis plant is chemically complex and can vary greatly from plant-to-plant. Growing standardised cannabis means consistently achieving a balance of all potential active components (specifically the cannabinoids and terpenes). This must be confirmed batch-to-batch by laboratories who issue Certificates of Analysis.

The most common approach standardisation is to select cannabis cultivars with good genetic stability and that originate from one single seed. These plants are then grown by multiplying the original plant material. Copying a fragment of the mother plant helps to prevent 'genetic drift', which can cause major changes and weakness in the plant over time.

To achieve batch-to-batch consistency in the plant is very difficult. Indeed, to date, only one company, Bedrocan in the Netherlands, has been able to achieve fully standardised cannabis flos with GMP certification.

Indoor versus outdoor cultivation

The discussion around standardisation continues with comparing indoor and outdoor cannabis cultivation. This is because the chemical composition of cannabis is determined by the plant's genetics, and the total content is most influenced by the plant's growing conditions.

Indoor, fully controlled cultivation allows for fully standardised cannabis flos (the whole dried female flowers) and whole plant extracts (containing cannabinoids and terpenes) year-round. Controlling all growing conditions and the plant's genetic composition produces a finished product, free of contaminants, and containing an exact content of active components. The production of cannabis flos, in compliance with pharmaceutical standards of GMP, is only possible within fully controlled environments and using plants with stable genetics.

Outdoor cultivation, including in fields or greenhouses, produces genetically undefined, non-standardised cannabis. Outdoor cultivation is suitable for single cannabinoid extraction (i.e. THC or CBD). Outdoor cultivation, from seed, produces plants with a dissimilar genetic composition and inexact content of active components. An uncontrolled growing environment is likely to permit cross-pollination which reduces the quantity and quality of cannabinoids. It also increases the risk of contamination with pesticides, heavy metals, and hazardous moulds, bacteria and fungi.

From cannabis cultivation to cannabis flos

Below is a pictorial illustration of an indoor cultivation growth cycle and production of standardised, GMP-certified pharmaceutical-quality cannabis flos.

A cutting is obtained

Plants are placed into Rockwool

The plants are placed in a growing room

The harvested cannabis plant is dried

The stems and leaves are removed

The cannabis flos is packaged


45mL
40
35
30
25

5 Dosage forms and their administration

Like other medicines, medicinal cannabis is available in different dose forms (e.g., inhalation, oral, transdermal) to meet different patient requirements. How medicinal cannabis is administered or taken depends on its dose form.

In this section we talk about the most common ways medicinal cannabis is taken by patients across the world. In the next section we talk about how cannabis is absorbed, distributed, metabolised and then excreted (removed) from our body.

The dose form is really important. It can influence patient behaviour in different ways, including:

- If patients actually take their medicine, and adhere to their daily regimen
- When they take it (the time of day)
- How often they take it (the frequency of use)
- How much they have to take (total daily dosage)
- The side effects and how these are tolerated

Inhalation – by the lung

Dose form

Using a vaporizer or inhalation medical device, cannabinoids are inhaled (from cannabis flos) as a vapour which then enter the bloodstream from the lungs.

Inhalation has proven to be an efficient administration route. The inhaled vapour is quickly absorbed by the lungs. The immediate onset of action means it is the preferred choice for many patients. The vapour contains cannabinoids and terpenes in consistent, measurable quantities. The speed of onset simplifies titration - the ability to achieve the correct dose without side effects - and achieve fast relief from symptoms. The amount of cannabinoids delivered depends on the depth of inhalation and breath hold. While inhalation results in higher blood levels of cannabinoids, their effects compared to oral administration is shorter in duration.

Medical vaporizer

Given the risks from smoking, patients nowadays seek reliable, affordable and portable vaporizers or inhalation devices. Research dedicated to advancing vaporizer and inhalation technology has seen major developments in device quality.

Medical vaporizers for the administration of cannabis flos - instantly we think of e-cigarettes or vape-pens - are in fact quite different. The vapour does not contain nicotine, liquid propylene glycol, glycerol nor synthetic flavours. There is also no large, socially intrusive, toxic vapour cloud. These vaporizers (or inhalation devices) offer patients an effective, safe, and easy to use delivery system.

Smoking

Ultimately, smoking medicinal cannabis is harmful to patients' health and is therefore not recommended. Toxic pyrolytic compounds are produced when the plant material is smoked (i.e. combustion). Typically cannabis flos is rolled into a 'joint' cigarette, and cannabinoids are inhaled as smoke into the lungs. The medicine enters into the bloodstream from the lungs. Smoking cannabis results a rapid onset of action. The effect is noticed within minutes. While smoking results in higher blood levels of cannabinoids, their effects compared to oral administration is shorter in duration. Furthermore, unless it is fully standardised, the amount of THC and CBD in cannabis flos can vary greatly between batches. The amount of THC delivered also depends on the depth of inhalation, puff volume and duration, and breath hold.

Pharmaceutical quality cannabis flos

For vaporization to deliver consistent therapeutic levels of cannabinoids, the product must be of pharmaceutical quality. This cannabis flos is genetically and chemically standardised according to pharmaceutical standards. From a patient safety perspective, it is free of microbial contaminants, pesticides, impurities and heavy metals. These are qualities that make the vapour safer for inhalation into the lungs.

Oral – by the mouth

Dose form

Cannabinoids (whole plant extracts or individual cannabinoids) taken by mouth and either swallowed (oral), or absorbed from under the tongue (sublingual). When swallowed, the medicine enters into the bloodstream via the stomach, intestines and the liver. When absorbed from under the tongue, the medicine bypasses the liver and enters into the bloodstream directly.

Oral preparations are familiar dose forms. They are similar to other medicines patients already take, and are easy to administer. As a result, concentrated cannabis extracts are becoming increasingly popular.

Oils

An increasing number of patients are using extracts of cannabis flos. Whole plant cannabis extracts contain cannabinoids and terpenes in a concentrated dose form. Often they are called 'oil' because of their dark viscous appearance. The extract is dissolved in an oil (e.g., olive, sunflower, peanut) to act as a carrier and ease administration.

A single dose can be dispensed from a dropper and placed under the tongue. It is absorbed from the lining of the mouth (termed sublingual absorption) where upon it enters the bloodstream.

Sublingual delivery increases total available dose. This means smaller doses are required for the same effect, compared to swallowing capsules or drinking tea.

Sublingual dose forms can provide a reliable uniform dose.

Sprays

Sprays are also administered under the tongue just as oils. An example is Sativex™, a standardised (oromucosal) dose form of a pharmaceutical product, made from two strains of cannabis. One strain produces mainly THC and the other mainly CBD. Exacting proportions of the active compounds THC and CBD are dissolved in an alcohol solution. This is placed in a metered-dose bottle which is sprayed under the tongue.

Capsules

An alternative oral dose form are capsules. These typically contain exacting concentrations of single cannabinoids (i.e. THC and CBD) dissolved in a carrier oil. The capsule is swallowed, breaks open, the drug is released and finally absorbed in the stomach and intestines. The rate (time) of absorption can be unpredictable, and varies depending on, for example, if food is present, and if the patient is mobile (able to exercise/walk freely). Interestingly, THC itself slows the rate of gastric emptying (from the stomach to intestine). Oral administration (by swallowing) results in slower onset of action, lower total blood concentration, and a longer duration of effects compared to inhalation. Total cannabinoid content is affected by liver metabolism and stomach contents. This means oral dosing can be less unreliable and unpredictable.

Tea or infusion

A proportion of patients consume medicinal cannabis as a tea (cannabis flos infused in hot water). Teas are swallowed and the cannabinoids are absorbed in the stomach and small intestine. Similar to oral dosing, the total cannabinoid content is affected by liver metabolism and stomach contents. This means dosing by tea may be unreliable and unpredictable.

Furthermore, tea typically has a low concentration of cannabinoids, the tea composition is effected by boiling time, volume of tea prepared, and the length of time in storage. This means dosing by tea can provide a less certain therapeutic effect.

Edibles

Other whole plant dose forms include edibles such as cookies/brownies. It is difficult to obtain a consistent cannabinoid composition in edibles. Patients can easily overdose, particularly as the time to effect may be 2-3 hours and patients may ingest a second dose if they are awaiting effects.

The therapeutic effect is less certain than standardised oral products and it usually takes longer to achieve. As a result, edibles are not considered a therapeutic product.

The importance of standardisation

There are numerous oil products available on the market. Their quality and reliability relies on the quality of the starting material, cannabis flos. Because most extraction companies don't use fully standardised cannabis flos, the total cannabinoid content of the extract often is different to the medicine label. Some companies' medicine labels show a 'target' cannabinoid concentration. This is because the cannabinoid concentrations in the cannabis starting material varies from batch-to-batch. Unpredictable medicine concentrations are a concern for patient safety. This is because the quality of a medicine is partly determined by 'accuracy of dosing' and 'reproducibility' of the dose.

Transdermal – by the skin

Dose form

Transdermal literally means across the skin. The typical dose forms include creams which are applied to the skin surface or a mucous membrane; and, transdermal patches which are a medicated adhesive patch applied directly on the skin. A specific dose is then administered gradually over a set time.

Transdermal dose forms are being investigated for their clinical use and application. Currently they are being used to treat certain skin conditions and for localised muscular or joint pain.

Given that most cannabinoids dislike water (are highly hydrophobic), it can be difficult to achieve a reliable dose form that is applied to the skin and can achieve appropriate blood concentrations. However, novel nanotechnology may overcome this. Dose forms such as creams are intended for local application and action. These do not require achieving penetration through the skin into the blood stream.

The importance of form

The form in which medicinal cannabis is administered determines the onset, intensity, and duration of effects (how it moves and works in our body). The major factors which determine the selection of dose form include:

- **Accuracy of dosing** – how precise the dosing method is to reach the desired dose, to avoid under-dosing, over-dosing and side effects.
- **Bioavailability** – the fraction of the dose that reaches the bloodstream to provide a therapeutic effect. Typically, intravenous injections have the greatest bioavailability (direct to bloodstream), then inhalation, sublingual, buccal oral mucosal, rectal and oral and transdermal dose forms.
- **Onset of action** – the amount of time before the effects of the medicine are felt.
- **Duration of effect** – the length of time the medicine is active.
- **Reproducibility** – the degree to which the medicine can be given to achieve repeated effects, preferably with good precision.
- **Safety** – the dose form is easy to use, is of good quality and does not cause harm or intolerable side effects.

6 How cannabinoids move through the body

Determining how a medicine is going to work for an individual patient is very important to medicine safety and efficacy. The way the cannabinoids THC and CBD move through the body (pharmacokinetics) varies depending upon how it is taken. The duration of their action is influenced by dose size, dose form, and the route of administration - the lungs, mouth, gut or the skin.

Absorption and distribution

THC and CBD are mainly found in cannabis in their inactive acid form. To activate THC and CBD a carboxyl group must be removed by heat. In practice, this so called 'decarboxylation' occurs by heating cannabis flos in a vaporizer, or heating the cannabis flos extracts before being placed into a solution.

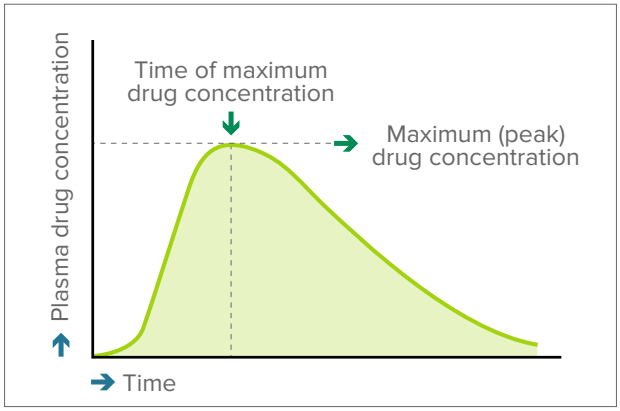
The absorption of inhaled cannabinoids results in a maximum (peak) blood concentration within minutes (see figure). Effects in the brain start within seconds to a few minutes, and reach a maximum after 15-30 minutes. They taper off within 2-3 hours.

Absorption is slower when cannabinoids are ingested. Lower, more-delayed peak concentrations occur with oral ingestion. The effects in the brain are delayed for 30-90 minutes, and reach their maximum after 2-3 hours. They last for about 4-12 hours.

Bioavailability describes the proportion of a medicine entering blood circulation after administration. The bioavailability of oral THC and CBD is low. By comparison, the inhalation of cannabinoids has been shown to be more effective and reliable compared to oral administration.

Pharmacokinetics

Pharmacokinetics is abbreviated as PK. It is the study of the movement of medicine within the body. The acronym ADME is used to describe a medicine's Absorption, its Distribution, Metabolism, and final Excretion from our body.



The pharmacokinetic profile of a medicine is described as the medicines blood plasma concentration over a period of time.

THC and CBD are fat soluble (highly lipophilic) compounds which are rapidly absorbed by the lungs. As a result, inhalation is a convenient and fast-acting method of administration, allowing easier titration to the desired dosage and biological effect. About 25% of inhaled THC enters the blood circulation.

The distribution of cannabinoids in the body are ruled by their lipophilicity (their fat solubility) and binding to blood proteins. THC is distributed widely throughout the body, particularly to fatty tissues. The body storage of THC increases with increasing frequency and duration of use.

Metabolism and elimination

The cannabinoids are mainly metabolised by a collection of liver enzymes called cytochrome P450 (CYP450). The same as many other medicines, these enzymes chemically alter the cannabinoids to remove them from our body (excretion). Besides the liver, other tissues like the heart and lungs are also able to metabolise cannabinoids, albeit to a lesser degree. THC and CBD metabolism follows a similar metabolic route.

Elimination of medicines means their complete removal from our body. Metabolism is the major route for the removal of THC. Unlike THC, a large proportion of CBD is excreted unchanged. Within 5 days of taking a single dose, a total of 80–90% of THC is excreted. The elimination of THC and its metabolites occurs via the faeces and urine. After inhalation, about 25% of the absorbed dose is excreted in the urine; about 65% is eliminated via faeces. Only very small amounts of THC are excreted unchanged. Less than 5% of an oral dose is found unchanged in the faeces. THC metabolites can be found in the urine and faeces for several weeks.

The slow elimination of cannabinoids and their metabolites is due to their slow movement out of our body fat and other tissues back into the bloodstream.

First-pass metabolism and THC

A metabolite is a substance formed during metabolism – a breakdown product. After swallowing a medicine it is then absorbed in the small intestine and carried to the liver and metabolised. This is called first-pass metabolism. First-pass metabolism greatly reduces the medicine concentration, meaning only a proportion of the original medicine reaches the blood circulation. In some cases, the metabolite can be potent and long acting. For THC, the metabolite 11-hydroxy-THC (11-OH-THC) is about twice as psychoactive as THC itself. When THC is inhaled, it avoids first-pass metabolism and its rapid conversion to 11-OH-THC.

7 Prescribing medicinal cannabis

When used rationally and correctly, medicines can be effective in treating or preventing disease. If misused, they can cause harm. This includes medicinal cannabis. In this section we discuss the prescribing of medicinal cannabis.

Medicinal cannabis is a rapidly changing field of medicine, with new products, scientific and clinical data emerging. In the last decade, clinical research has mainly focused on the therapeutic effects of cannabinoids as an analgesic in chronic neuropathic pain, as an appetite stimulant in cancer, and in the treatment of spasticity in multiple sclerosis. Other indications include for example in anxiety, psychosis, and fibromyalgia. More recently, cannabidiol (CBD) has emerged as a single cannabinoid with plausible therapeutic action in childhood epilepsy. Clinical trial reviews provide insight to relevant conditions and dosing, while newly published supporting information on plant chemistry, cultivation, quality analysis, and administration adds value to knowledge of product safety and prescribing practice.

Conditions which show promise

There is clinical research supporting the use of medicinal cannabis in certain conditions including:

- Chronic pain, particularly pain associated with the nervous system, caused for example by a damaged nerve, phantom pain and facial neuralgia
- Nausea, loss of appetite, weight loss, and vomiting associated with chemotherapy or radiotherapy used in the treatment of cancer, and anorexia and cachexia in HIV/AIDS
- Pain and muscle spasms or cramps associated with multiple sclerosis or spinal cord damage

For other conditions there is less available or negative clinical data. These include, epilepsy (particularly the drug resistant childhood epilepsies), Gilles de la Tourette syndrome, therapy-resistant glaucoma, fibromyalgia; post-traumatic stress disorder, sleep disorders, bladder dysfunction, some symptoms of Parkinson's disease, and depression. While existing scientific evidence does not fully support a specific condition, a paucity of clinical research does not necessarily reflect the potential of medicinal cannabis in a given disease for a particular patient.

The next summary covers clinical insights for areas of interest to most readers. These include chronic pain; nausea, vomiting and appetite; multiple sclerosis; and epilepsy.

Chronic pain

Severe chronic pain seems to be the major reason for which patients use medicinal cannabis. There are many types of pain, and cannabinoids do not influence each pain type identically. To date, the therapeutic benefit of medicinal cannabis has only been seen in neuropathic pain studies – the pain originating from injury or disease that affects the sensory nerves. By comparison, studies measuring the effects on acute pain (e.g. postoperative pain) often show no beneficial effects. Most likely, this difference is related to the role endocannabinoids play in both types of pain. However, the mechanism behind this difference is not yet fully understood.

Chronic neuropathic pain is common, difficult to treat, and has limited treatment options. Consequently, even the modest effects of cannabinoids may be important for patients. Patient preference studies show the side effects from cannabinoids are better tolerated than strong opioid medications. Indeed, medicinal cannabis has often been studied in combination with other medicines, including for example morphine. It has been found that cannabinoids and opioids work together with a strong combined effect.

Nausea, vomiting and appetite

Cannabinoids can have strong effects on nausea and vomiting resulting from cancer chemotherapy or radiotherapy, hepatitis C and HIV/AIDS treatments. A synthetic THC dose form (as Marinol®) has been widely used as an antiemetic for cancer patients undergoing chemotherapy. Supporting studies suggest that the addition of THC directly before and after chemotherapy offer more benefit than using older antiemetic medications. However these have not been compared against the latest antiemetic medications which are significantly more effective in this setting than the older ones.

Cannabinoids have been shown to stimulate appetite, described as a strong desire for foods with high fat or sugar content. For example, since the 1980's, Marinol® has been used as an appetite stimulant for weight loss in patients with HIV/AIDS. For patients experiencing loss of appetite, a high caloric intake may contribute to weight gain and to the absorption of nutrients. Often this is crucial in managing medical conditions such as wasting syndrome (cachexia).

Although other drugs are available to treat nausea, vomiting, or reduced appetite, the combined effect of cannabinoids on all these symptoms at once makes it a unique option for contributing to improving a patient's quality of life.

Multiple sclerosis

Together with chronic pain, multiple sclerosis (MS) is the other medical condition in which long-term effects of cannabinoids have been extensively studied. The research show patients do not develop a tolerance for the medicinal effects, nor increase their doses over time to achieve the same therapeutic result. Although the medical evidence supporting cannabis use for MS is still limited, it is important to note the same is true for most conventional MS medications.

As a result, patients suffering from MS have historically experimented with alternative therapies, including cannabis, to improve their quality of life. Standard therapies often provide inadequate relief and can be limited by medication side effects. Existing scientific evidence supports the use of medicinal cannabis to treat disease-related pain, bladder symptoms, tremor, and spasticity. Additionally, for many patients cannabinoids improves sleep, resulting in both deeper and longer sleep.

Epilepsy

Epilepsy is typically well-controlled by existing medications. However, a significant number of people with epilepsy do not have adequate control of their seizures. As early as in 1979, laboratory studies confirmed the anticonvulsant effects of (pure) CBD. In various subsequent animal and (small-scale) human studies, CBD was able to reduce the frequency and severity of seizures. Combined with an absence of psychoactive effects, these results show the potential of CBD as a treatment for human epilepsy.

Unfortunately, the low quality of most the reported scientific data does not allow for making definite conclusions on the potential of cannabinoids as a treatment for epilepsy. In addition, the safety and tolerability of cannabinoid preparations in a paediatric population is not fully clear. Although CBD appears to be effective in reducing seizures in epilepsy patients, more controlled research is needed to understand the full clinical value of these types of products.

Dose, dosage and titration

Like with other medicines, individual patients will respond differently to medicinal cannabis. Their response depends on the cannabis product used, the condition being treated, the duration of treatment, how it is administered, and genetic predispositions. Certain ratios of cannabinoids have so far emerged to be the basis of specific effects; and appear to be better tolerated than single compounds (especially high doses of THC).

A patient's doctor generally provides advice regarding dose titration (dose adjustments to a desired effect) to achieve an optimal daily dosage. This helps patients to obtain the desired therapeutic effects and to minimise undesired effects.

A treatment protocol provides patients with advice on:

- An appropriate starting dose
- How to increase their dose (minimum and maximum dose)
- How to find an optimal daily dosage based the severity of the patient's condition, and changes in their other medication
- How to maintain their daily dosage
- Medicine and food interactions
- Ways to reduce the risk of side effects or adverse reactions occurring
- A plan to stop treatment if there is a poor response

Safety

Potential medicine interactions

Medicines can interact with each other. The risk increases if a patient is taking lots of medicines at once. Indeed, patients' who are prescribed medicinal cannabis often have complex conditions and take multiple medicines.

There are a number of medicines medicinal cannabis may interact with. Care should be taken when co-prescribing medicines with sedating effects, which also includes drinking alcohol. The combination of cannabinoids and sedatives can affect response time, co-ordination, and concentration. Cannabinoids may also interact with heart and circulation medicines (e.g. adrenaline, beta-blockers, and diuretics). Also, THC appears to enhance the action of opioids (e.g. codeine, morphine).

The above list is not exhaustive. A full review should be undertaken before co-prescribing, including those medicines which interact with the CYP-450 metabolic enzymes.

Potential side effects

In general, patients seem to tolerate medicinal cannabis well. Typical side effects last a short time, are mostly benign, and resolve as tolerance builds. Side effects mainly occur after taking high doses, or when used in combination with other substances. These tend to occur quickly after use. Signs of side effects include:

- Dry mouth
- Redness of the eyes
- Heightened appetite (which may be desirable)
- Mild euphoria
- Reduction of alertness of the user, especially in the few hours directly after consumption
- Increased heart rate
- Lowering of blood pressure and dizziness

In general, all side effects will slowly decrease and then disappear within a few hours. This depends upon the dose taken and mode of administration.

Overdosing

Overdose can usually be prevented by preparing a treatment protocol. When using too large doses containing THC, a patient may experience intoxication. This is often described as a mild euphoria or results in sedation and somnolence. In some cases, this can be experienced as a distortion of reality, mild anxiety, changes in heart rate and blood pressure. In these cases, most often, it is sufficient for patients to sit or lay down in a calm and comfortable location, preferably with someone familiar to talk to. Overdosing with very high doses may result in a psychotic state or other psychiatric conditions, particularly in those with a pre-existing genetic vulnerability (see below).

Risks

Like any other medicine, medicinal cannabis is certainly not without risks. The known risk factors and precautions are briefly described in the non-exhaustive list below.

Prescribing for the elderly

Elderly patients are more sensitive to the neurological, psychoactive and postural-hypotensive (feeling dizzy or lightheaded) effects of medicinal cannabis (particularly THC). This is especially so for elderly patients who are prone to falls and those with dementia. If considered appropriate, elderly patients should start at the low end of the dosing range.

> Cannabinoids can have a significant effect on heart rate and blood pressure

Psychosis or other psychiatric conditions

Medicinal cannabis should not be used in patients with a family history or previous episode of psychosis, psychiatric conditions or major depression because THC may bring on psychotic symptoms.

Heart disease cardiac/coronary conditions

Cannabinoids can have a significant effect on heart rate (hypertension, tachycardia) and blood pressure (vascular constriction) which can cause cardiac ischaemia. Patients with a history of heart disease or receiving heart medication should avoid use, or only use medicinal cannabis under careful supervision by their doctor.

Pregnancy and lactation

The use of medicinal cannabis during pregnancy is likely to affect the development of the fetus and should not be prescribed. Because certain cannabinoids – including THC – are excreted in breast milk, use is also not advised while breastfeeding.

Liver disease

After administration, the liver is the main organ involved in chemically altering the cannabinoids to remove them from our body (metabolism). Patients with liver disease should be monitored to make sure the dosage does not exceed the liver's ability to remove it (metabolic capacity).

Addiction and aberrant prescribing

The evidence suggests that the risk of developing an addiction to cannabis when taken as a medicine is not common. Nonetheless, particular care should be taken if patients have prior problematic substance use. High doses of medicinal cannabis, taken over long periods, could lead to dose escalation, misuse and harm. Abrupt ending of treatment may cause withdrawal symptoms, such as restlessness, irritability, insomnia, vivid dreams and decreased appetite.

Diversion and misuse

Cannabinoid therapeutic products containing THC are often considered desirable psychoactive substances. Like other controlled drugs, medicinal cannabis requires the same guidance and considerations by doctors and pharmacists to limit diversion and misuse.

Driving and operating machinery

At therapeutic doses, cannabis may produce undesirable effects such as dizziness and drowsiness which may impair judgement and performance. Patients should not drive, operate machinery or engage in any potentially hazardous activity under the influence of medicinal cannabis or cannabinoid therapeutic products that contain THC.

What is pharmacovigilance?

Pharmacovigilance is the collection and evaluation of information from healthcare providers and patients on the adverse effects of medicines. Monitoring the use of medicines in everyday use helps to identify previously unrecognised adverse effects or changes in the patterns of adverse effects.

Medicine quality and safety relies on patients, their carers, and healthcare professionals to report problems with medicines and administration devices (droppers, syringes, vaporizers, transdermal patches). Pharmaceutical companies and regulatory agencies can then investigate reports, identify the specific cause, and determine any necessary regulatory action to resolve the problem.

Most importantly, understanding why a medicine is causing harm can lead to improvements. This is for the benefit of patients.

8 Health professional perspectives

Who can prescribe and dispense medicinal cannabis depends on country specific policy. Most often health professionals are the gatekeepers to patient access. In particular, prescribers and pharmacists have an important role to play. In a prescriber-pharmacy model, patients are offered more objective communication of risks and benefits, and the safety of health professional guidance.

However, many health professionals do not know how medicinal cannabis should be prescribed and dispensed. This is not surprising given that medicinal cannabis is a new class of medicine. The traditional approach to drug discovery and development, including clinical trials, have not been undertaken on most products. Clinicians are now rapidly trying to understand how they work.

We have talked about the potential place of medicinal cannabis in the medical toolbox. So how should it be prescribed and dispensed? This section presents two case studies: one from the perspective of a pain specialist, and the other from a community pharmacist. They highlight prescribing and dispensing realities, and strategies to improve patient safety. The information shared in these case studies are context-specific and not intended to support decision making by prescribers and pharmacists.

This section focuses on the Netherlands. It has the longest running medicinal cannabis programme (since 2003) and provides fully standardised medicines under the guidance of prescribers and pharmacists. This is the same guidance patients receive with traditional medicines. The insights below are drawn from two professionals with extensive experience working with standardised oral an inhalation dose forms.

Many health professionals do not know how medicinal cannabis should be prescribed

Prescribing medicinal cannabis

Trained as an anaesthesiologist in Germany, **Dr Jürgen Fleisch** then undertook a fellowship in pain medicine (Portland, Oregon). He now practices anaesthesiology and pain therapy in the Netherlands at the Leiden University Medical Centre. For the last decade, his close cooperation with the Department of Oncology means he regularly treats symptoms in cancer patients using medicinal cannabis. In both settings, he typically encounters two types of patients. Those with advanced cancer experiencing loss of appetite and possibly nausea and vomiting, and often many other medications have been tried before. And, those that experience central neuropathic pain after unsuccessful trials of more common medications.

With a focus on safe prescribing practices, prescribers play a pivotal role in managing patient therapy. This is especially important when patients take multiple medicines.

Prescribing

Do you have any advice for doctors starting out prescribing?

"My advice for clinicians who are starting to prescribe medicinal cannabis is to stick to specific indications where there is a solid foundation of evidence for its use. This allows us to gain experience with the effects of this medication in a specific adult patient population.

Recreational cannabis users are, in my opinion, not a good patient category to start with. They may put considerable pressure on the clinician to prescribe for dubious indications."

How is prescribing medicinal cannabis different to prescribing other medicines?

"They are like any other medicine. However, many patients will have an opinion about cannabis. For some it has a rather negative connotation as being a substance of abuse."

What are the key benefits of cannabinoids as a therapeutic product?

"There are three main advantages of medicinal cannabis in general over other medicines used in my field of pain medicine, as follows:

- *There are analgesic effects on neuropathic pain syndromes and, depending on the medicine type, anti-emetic and appetite stimulating effects. This is especially important for cancer patients with pain.*
- *There are no known organ damaging side effects in the adult patient, aside from the potential risk to mental health. As compared to, for example, those linked with using NSAIDs when used inappropriately.*
- *Some cannabis flos variants have a soothing effect, which some patients greatly appreciate."*

What do you think are prescribing practices that improve patient outcomes?

"For patients with no experience using cannabis products, the possible psychological side effects can be distressing. In order to avoid this we advise patients to start with low dosage and use the medicine in a quiet and relaxing environment.

In our experience, it is advantageous to prescribe cannabis flos as an inhalational agent, administered by vaporization, as it creates more rapid analgesic effects and has a more reliable absorption profile.

With cannabis flos, the prescribing clinician needs to be aware that in many countries the standards are different with respect to "regular" medicines: concerning the quality control of the active ingredient, and toxicological contamination. Using cannabis flos originating from controlled producers means patients are assured there is no biological or toxicological contamination."

Aside from eliminating the harms from smoking, what are the benefits of administration by vaporization?

"Using vaporized cannabis flos is the preferred means of use by most patients, especially when compared with an oral application. This is due to the more rapid effect by inhalation.

With vaporization cannabis flos is heated to a specific temperature without burning it. Cannabinoids and terpenes are released in a vapour which is directly inhaled.

There are three main advantages of administration by vaporization is that it:

- *Allows for exact dosing,*
- *Leads to a rapid effect, and*
- *Avoids the disadvantages of smoking (i.e., no tar, ammonia, carbon monoxide)."*

Patient considerations

Thinking about a first consultation with a patient, how do you start a conversation about medicinal cannabis?

"There are two types of discussion around the use of medicinal cannabis:

The elderly, cannabis naive patient:

An elderly cancer patient may be hesitant to use cannabis as a medication. This likely is related to prejudices about cannabis being a product for 'recreational' use. With these patients, I rarely discuss the use of these medicines during a first consult. If the patient is eligible and several other therapies did not provide sufficient pain relief, I then mention medicinal cannabis as a possible option. This allows the patient and his/her family to contemplate that treatment option until the next appointment.

The experienced patient:

There may be patients who have extensive experience using cannabis recreationally. They may be actively looking into medicinal cannabis as a potential adjunct to their pain therapy. These patients emphasise the ineffectiveness or side effects of other therapies, and may push clinicians towards prescribing a cannabis product. With these patients the topic must be discussed fully during a first consult. The main question during this consult is 'are they at all eligible to receive medicinal cannabis?'."

Are you aware of patients experiencing interactions with medicinal cannabis and other medicines?

"Indeed, we do see patients who experience drug interactions using cannabinoid therapeutics alongside other CNS depressant medications (e.g. opioids).

Sedative effects can be enhanced especially in the geriatric population. Severe drowsiness and hallucinations can also be provoked.

Aside from drug interactions, the smoking of cannabis is related to an increased risk of myocardial infarction and stroke. Cannabis as a trigger of myocardial infarction is plausible, given its cardio-stimulatory effects, which may cause ischemia in susceptible hearts. Carboxy-hemoglobinemia from the smoking of cannabis may also contribute to ischemia. Smoking is never recommended."

Do you encounter diversion for misuse or the abuse of medicinal cannabis? How do you identify this issue in your practice?

"During the period when Dutch health insurers widely reimbursed medicinal cannabis, we had frequent discussions with patients, best described as 'recreational users', about their eligibility.

Patients of this group, who were already using large amounts of cannabis, were requesting access for rather dubious indications. Some patients were seeing medicinal cannabis as a cheap way to get a 'recreational drug' which they were already abusing."

How do you deal with diversion for misuse or abuse in your practice?

"This patient group can be quite challenging. They may put pressure on clinicians to prescribe medicinal cannabis as the only means to relieve their pain. Mentioning misuse and abuse can provoke abrupt reactions.

Clinicians should be coherent in prescribing medicinal cannabis only for indications with enough evidence for beneficial effects (e.g. analgesic for neuropathic pain, appetite stimulation). Misuse and abuse should be discussed openly if they become apparent."

Smoking is never recommended

Dispensing medicinal cannabis

As a pharmacist at Transvaal Apotheek, **Salma Boudhan** dispenses cannabis flos, and oil extracts for named patients throughout the Netherlands. Based in The Hague, Transvaal Apotheek has been meeting patient needs since the late 1800's. A patient recently said she had been coming there for more than 70 years. Transvaal has dispensed medicinal cannabis (flos) since it was legalised in 2003, and high quality whole cannabis oil extracts for sublingual use since 2015. A typical patient arriving at Transvaal are those suffering from cancer pain, nausea and vomiting; neuropathic pain; or epilepsy.

The role of pharmacists is just as important as prescribers. Pharmacists support prescribers with patient medicine reviews, and talk with patients about a medicine's risks and benefits. They help to minimise medicine misuse and harm, and seek feedback on safety, effectiveness and adverse reactions.

Administration

Oral dose forms (oil extracts) are an increasingly popular, what advice do you give patients on safe use?

"In accordance with their doctor's prescription, we suggest that patients start low and go slow. As a starting dose for oil, we recommend to use 2 drops (0,05ml) under the tongue, 3 times a day and increase the dose until the desired effect is achieved. The maximum dosage is 10 drops (0,25ml), 3 times a day.

The 'steady state' concentration of THC/CBD and the active metabolite is reached after 1-2 weeks. This time span should be taken into account for the assessment of the medicines effectiveness for the patient."

Vaporization is a popular mode of administration, what advice do you give patients on safe use?

"We recommend patients inhale 1-2 times a day until the desired effect is achieved or until (psychotropic) side effects occur. This means they have had too much. Per inhalation, we recommend patients wait at least 5 minutes between the inhalations.

Patients should take into account that inhaling cannabis results in a higher uptake than when using other administration routes. Patients have to dose carefully when changing to a different variety, especially if they have previously used cannabis with a lower content of THC/CBD.

The 'steady state' concentration of THC/CBD and the active metabolite is reached after one to two weeks. Like oral dosing, this time span should be taken into account for the assessment of the medicines effectiveness for the patient."

Safety

What do you tell patients about the safe and effective use of medicinal cannabis?

"First we ask the patient what they already know about medicinal cannabis. Then we inform them about the mechanism of action, how to use it, the dosage regimen, possible side-effects, how to safely store it. Finally we make sure that the patient takes notice of possible interactions with other medicines or contra-indications (certain conditions where medicinal cannabis should not be used).

In a follow-up discussion we ask the patient about their experience with the use of medicinal cannabis, with extra attention to side-effects and effectiveness."

What are the key risks of using cannabis as a therapeutic product?

"The only known contra-indications include schizophrenia, arrhythmia and other heart conditions. We work closely with prescribing doctors and also provide adequate instructions to patients about the benefits and risk of their medicines."

Are you aware of any patients that have experienced cannabis interactions with other medicines?

"We know that cannabis is metabolised by CYP450 enzymes. When taken together with other medicines metabolised by the same enzymes, there may be the potential for drug-drug interactions. We discuss with patients about the risk of using such medicines concurrently, or recommend alternative medications."

From a pharmacist's point of view, what are the actual and potential complications with medicinal cannabis?

"The biggest risk is getting high and triggering psychoses (especially with psychiatric patients) or worsening current depression. There are risks in prescribing in the elderly, and the potential long-term effects on children are still unknown."

What is the role of the pharmacy profession in ensuring patient safety with the use of these medicines?

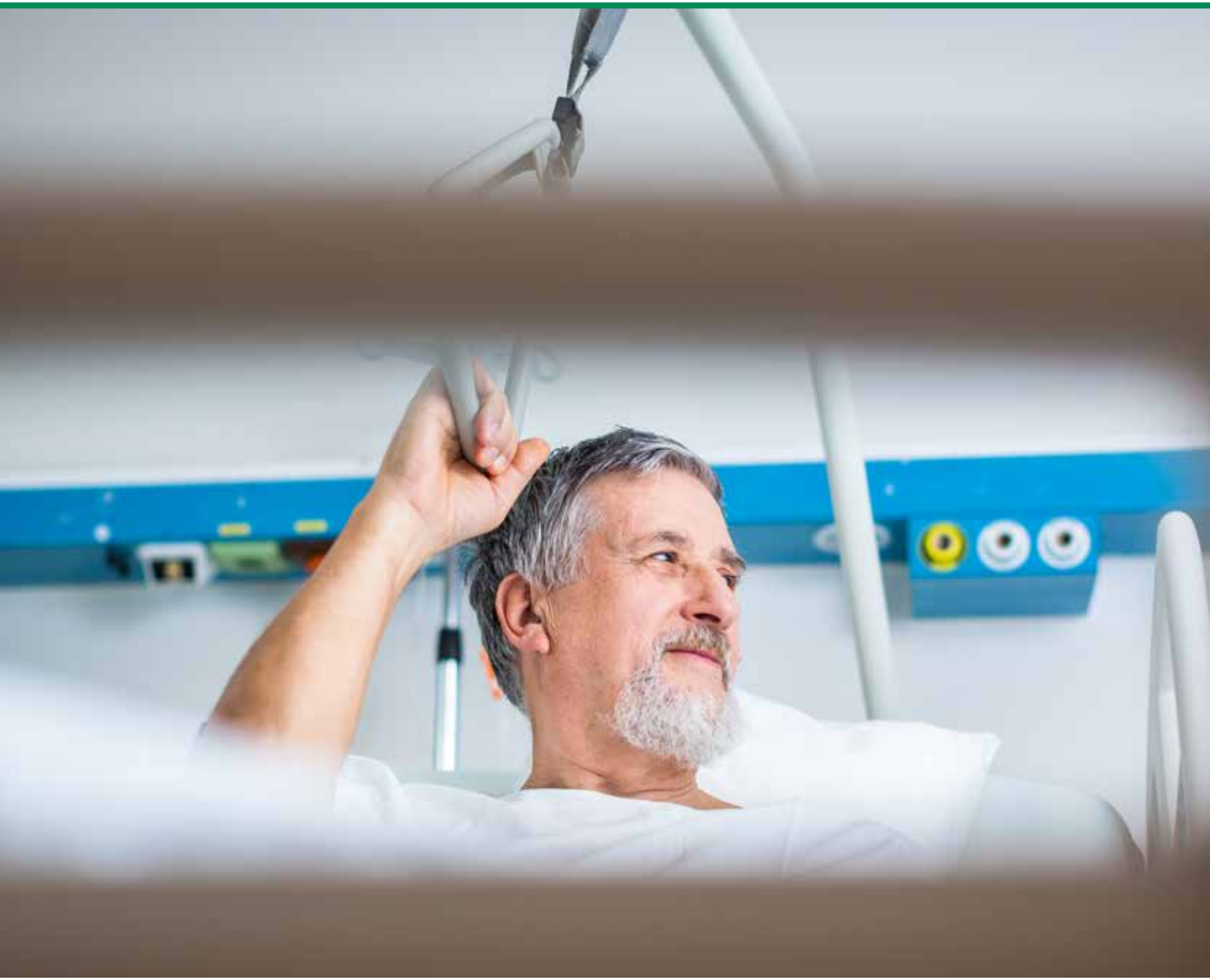
"Pharmacovigilance is an important role of a pharmacist. We seek feedback from patients on the safety, effectiveness and adverse reactions they experience from their medicine use. We are also required to provide adequate instructions and honest information to patients about the benefits and risk of their medicines."

Do you encounter diversion for misuse, or the abuse of medicinal cannabis?

"Not often. We identify this issue by monitoring the quantities dispensed and the frequency of dispensing. We make an agreement with the patient to avoid further misuse. If this doesn't help, we consult the prescribing doctor and find solutions to the problem."

Do you have any good advice (tips) for pharmacists starting out?

"Get training or read a lot into the subject, because patients are generally quite well informed but also misinformed."



9 Patient perspectives

The future of healthcare is in understanding and responding to patients' needs and wants. This is called patient centred healthcare. For medicines, this means gaining patient perspectives throughout the medicine's life cycle. In particular, patient satisfaction with their medicine is very important. This might include understanding if the dose form is acceptable, if the treatment is adhered to, and if there are real improvements in quality of life.

We have talked about all aspects of medicinal cannabis. So, what does this all mean from a patient perspective? This section talks about who uses medicinal cannabis, for what conditions, how they used it, and their relationship with health professionals.

Insights from patients

A Belgian-based social researcher, Frederique Bawin looks at medicinal cannabis from the patients' perspective. Bawin explores the legal and illegal use of medicinal cannabis among self-reported patients. While not the experience of every patient, findings from this cohort provides new insights into uses, behaviours, relationships and risks surrounding medicinal cannabis.

Reasons for use

Why do patients use medicinal cannabis? Patients use medicinal cannabis for multiple reasons, including the following:

- It is perceived to be more effective than other medicines or it was the only effective drug for certain symptoms (e.g. cramps, pain, inflammations, chemotherapy induced nausea and vomiting).
- It is considered healthier than other medication as it is 'natural', and as a 'herbal' medicine is perceived to be less harmful than other 'chemical' medications.
- Patients are often searching for alternatives for their usual medicines due to unbearable side effects (e.g. gastrointestinal problems, drowsiness, numbness, allergic reactions).
- Conventional medicine side effects are considered problematic – patients become emotionless, depressed or apathetic. Patients had experienced significant adverse events caused by conventional medicines.

Most patients found that medicinal cannabis was an effective treatment for their conditions, often mentioning that other people noticed improvements.

Patients used it for symptom management, to relieve symptom complaints. Patient state it suppresses symptoms but it did not cause them to disappear. It is not seen as providing a solution to everything, and generally is not regarded as a cure. Indeed, some patients reported medicating with medicinal cannabis to cope with certain symptoms for which it turned out to be unsuccessful or only partially successful (e.g. bladder problems due to MS, acute headache).

Medicinal cannabis was mainly used as a treatment for pain. While their pain had not completely disappeared, it had lessened and became bearable as a result of their medicinal cannabis use. While higher doses were seen to be more effective in relieving pain, patients balanced this against possible side effects including mild intoxication. Similarly, while typical medicines were more effective in alleviating pain, patients preferred medicinal cannabis because of the adverse effects associated with conventional pain medications.

Treatment response

How did they respond to treatment?

Overall, patients report very few or no side effects from medicinal cannabis. Most adverse effects were perceived to be less severe than their conventional medicines. The side effects that were not considered highly problematic or negative include: dry mouth, laughing, feeling happy, increased appetite, increased heart rate, dizziness and being easily distracted. Some patients, however, did report experiencing negative side effects such as dry mouth, feeling high, increased appetite, memory problems, bad taste, blackouts, multitasking problems and increased heart rate.

Side effects from medicine use are subjective. A side effect reported by one person is not necessarily considered a side effect by another. For example, several patients dealing with insomnia did not regard drowsiness as an adverse effect. While a craving for 'sweets' was a complication for patients who are attentive to maintaining their weight, it was viewed by others as important given their condition meant they were dealing with weight loss.

Health professional relationships

Are their doctor and pharmacist actively involved in their treatment?

Sativex® is the only registered product in Belgium, however, doctors are allowed to prescribe unlicensed medicines* which are available in Dutch pharmacies. This puts doctors in a difficult position. Most doctors' response to patient requests were that they did not want themselves or their patient to face legal problems because of illegal cannabis, they were not allowed to prescribe by the National Medical Association and so on. Patients therefore searched for doctors who were willing to prescribe medicinal cannabis.

Medical support for medicinal cannabis use was very diverse among patients. Some patients reported that their doctors accepted their use and were supportive, whereas others had negative experiences. Numerous patients indicated their doctors were sceptical, disapproved, not interested, or silent about this subject.

For patients who were provided medical guidance, it differed significantly from instructions and advice they received for their other medicines. Most of the time their doctor wrote a prescription and provided very general advice. Patients had to experiment with their patterns of use. Typically those doctors were not willing to supervise use because of a lack of expertise, and the possible harms and legal consequences arising from using medicinal cannabis.

* *In Belgium, physicians are allowed to prescribe unlicensed medicines because of the so-called 'therapy freedom'. As written in law, practitioners cannot be subject to regulatory limitations in the choice of the medicines being used, either for making a diagnosis, for setting up a treatment and its execution, or for the execution of magisterial preparations.*

Most patients sourced their own medicinal cannabis and did not discuss this with their general practitioner (family doctor) because of a lack of interest or a lack of knowledge. As a result, these patients are not supervised by a doctor. Patients therefore self-selected the cannabis product, the dosage, the method of administration, and when they took it.

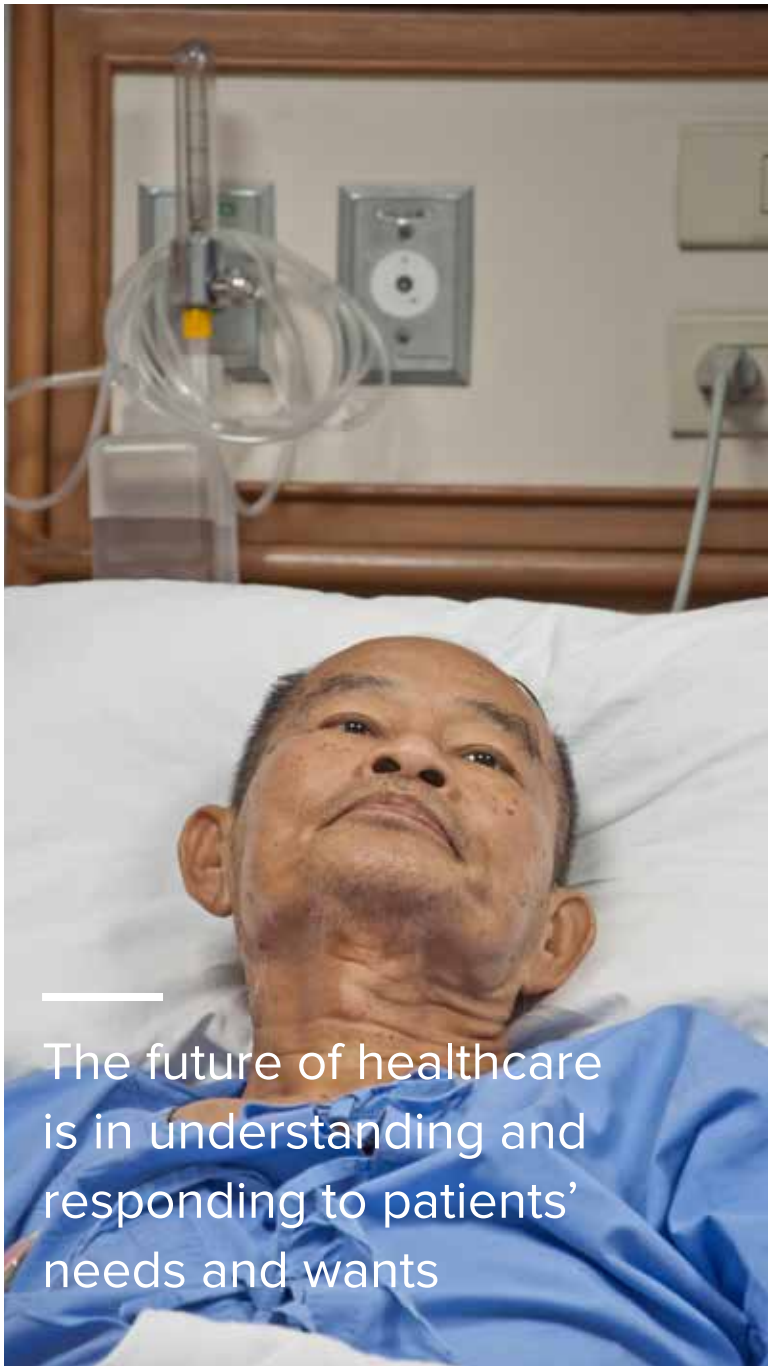
Patients prefer to be supervised by a doctor however, and regretted that few doctors had experience or knowledge in medicinal cannabis. Often, it was the patient providing insights and advice, turning the doctor-patient relationship upside down.

Social cultural issues

What did their family or caregivers think?

For most patients, their use of medicinal cannabis was accepted and supported by family and caregivers. They noticed the difference medicinal cannabis made and were glad the cannabis product appeared to relieve their symptoms. Patients often explained the purpose of using medicinal cannabis in order to gain acceptance.

Although most experience social support, some had to deal with teasing comments, or stereotypical or negative reactions because others were not pleased about a patient's 'cannabis use'. Some patients deal with serious consequences including conflicts in the home and at work. Most patients believe disapproval of medicinal cannabis is because people are ill-informed and have a wrong image of medicinal cannabis.



Insights from surveys

The table below compares findings from patient use surveys drawing on a global and Dutch perspective. The purposes of both surveys were slightly different, but still provide useful insights.

A global perspective	A Dutch perspective
General	
In 2010, The International Association for Cannabinoid Medicines (IACM) surveyed patients from 31 countries. It is a large study of 953 participants. These findings likely reflect the diversity of the current global patient population.	In 2016, a Dutch patient survey provided a snap shot of a group of patients. It is a large study of 582 participants (17% on prescription). These findings likely reflect the total Dutch patient population receiving a prescription for cannabis.
Patients and the conditions being treated	
Few patients had sourced their medication from a pharmacy (10%) or received a pharmaceutical product. This is not surprising, considering in most countries the medical use of cannabis is illegal. The results therefore tend to reflect the use of herbal cannabis.	Patients were prescribed medicinal cannabis for the treatment of conditions from pain through to severe mental illness. The top ten indications are spread across physical and psychological disease states. These included pain, insomnia/ sleeping disorder, nerve pain, spasms, stress, MS, depression, anxiety, appetite, nausea and cancer.
Patients used medicinal cannabis to treat various conditions. The most common conditions were back pain, sleeping disorders, depression, pain resulting from injury or accident, and multiple sclerosis.	The average daily dose was reported to be 0.67 grams/day for cannabis flos and 0.3 mL/day for oil.
An average daily dose of 3.0 grams was reported for vaporizing and smoking (median dose was 2.0 g/day and 1.5, respectively).	At these doses, the majority (80+ %) patients reported some to substantial improvements in their quality of life and a reduction in complaints resulting from their illness.

A global perspective	A Dutch perspective
The mode of administration	
The advantages and disadvantages of different administration forms were identified. Patients described their experience using different modes of delivery by the: dose needed, onset of effect, duration of effect, ease of dose finding, ease of exact dosing, ease of preparation and intake, irritation of lungs, side-effects and cost.	There are various routes of administration for medicinal cannabis. Cannabis oil was the most commonly prescribed, followed by vaporization and tea as popular modes of administration.
Patients reported high satisfaction (approval) scores with the inhalation route. In general, whole plant cannabis based medicines received higher appreciation scores than products containing isolated or single cannabinoids.	While smoking was also popular, it is evident that, like in other countries, patients look for alternatives to smoking. Patient use of oil, or a move to administration by vaporization is evident. The duration of effects and ease of dosing reported by study respondents by the mode of administration were approximately equivalent.
Study limitations	
Most survey participants had experience with herbal cannabis and the results may be biased towards the use of herbal cannabis.	The quasi-legal status of cannabis in the Netherlands means some cannabis may have been sourced outside of the pharmacy by patients also receiving prescriptions.

10 Legal perspectives

We have talked about the place of medicinal cannabis in the medical toolbox. This section discusses why cannabis is treated differently from other medicines.

Marijuana or medicinal cannabis

The idea of what medicinal cannabis is varies across the globe. The number of patients with access to or having used pharmaceutical products is low, compared with illegal cannabis.

Cannabis is the most commonly used illegal or quasi-legal recreational drug worldwide. The recreational cannabis economy is enormous. It supplies a large group of patients who otherwise do not have access to pharmaceutical-quality cannabis products. However the quality of recreational cannabis is often unreliable and unpredictable. Cannabis from this market has varying potency and is at risk of adulteration (for example, the addition of synthetic cannabinoids, or other illegal drug substances). It likely also contains fungi, bacteria and other microbial content, heavy metals and foreign particles. The risk to patients is high, especially patients with weakened immune systems as we see with cancer.

Today, across the globe, there are various ways in which cannabis is supplied to patients. Put simply, two distinct sources exist: the informal illegal/quasi-legal market, and the formal medical market under the control of medicine regulators. Under a formal model, medicinal cannabis is often a last-resort medication, prescribed when other options have failed.

From medicinal cannabis to cannabinoid therapeutics

Medicinal cannabis is an old term used to describe the use of cannabis to treat or manage illness. In recent years there have been major developments in cultivation techniques, product quality and controls. Today, government regulators seek the use of standardised products (e.g., Sativex®, Marinol®, Bedrocan®) and safer modes of administration (sublingual, oral and inhalation by vaporization).

This change in focus from ‘medicinal cannabis’ to ‘cannabinoid therapeutics’ reflects our knowledge and understanding of the endocannabinoid system, the cannabinoid receptors, endogenous (human) cannabinoids, and exogenous (plant) phytocannabinoids. The future appears to be about the therapeutic use of cannabinoids. The class of medicines containing cannabinoids (e.g., THC and CBD) and other chemical compounds secreted by cannabis plant (e.g., terpenes) intended to be used for a therapeutic purpose.

A prescriber-pharmacy model

Government regulators have to make tough calls on managing patient and health professional demand for products, alongside the need to ensure safety and efficacy of products on the market. This is ruled by country specific regulations on controlled drugs and medicines.

Two approaches exist. One is often described as an office of medicinal cannabis, controlling access to cannabis products separate to other medicines. The other is a medicine regulatory pathway, which treats medicinal cannabis the same as any other medicine. Both approaches expect high levels of product quality, safety and efficacy.

Who can prescribe and dispense medicinal cannabis depends on country specific policies and regulations. Most often, health professionals are the gatekeepers to patient access. In particular, doctors are allowed to prescribe medicinal cannabis to treat a defined set of conditions and pharmacists can store and dispense reliable and safe products for patients.

Typically, a prescriber-pharmacy model offers patients better communication of risks and benefits, and the safety of health professional guidance. In some countries the therapeutic use of cannabis is well advanced. However, in other countries medicinal cannabis is a new class of medicines. In both situations health professionals will have variable knowledge, skills, abilities and attitudes. This is because, it is a topic which is not often talked about in their medical training. And often practical, evidence-based guidance and evaluation tools are not available to support decision making by health professionals.

The objectives of the UN Conventions

The United Nations International Drug Control Conventions are the pinnacle international agreement on the control of narcotic drugs, such as cannabis. The Conventions require a global shared responsibility to control manufacture, trade and use of controlled drugs.

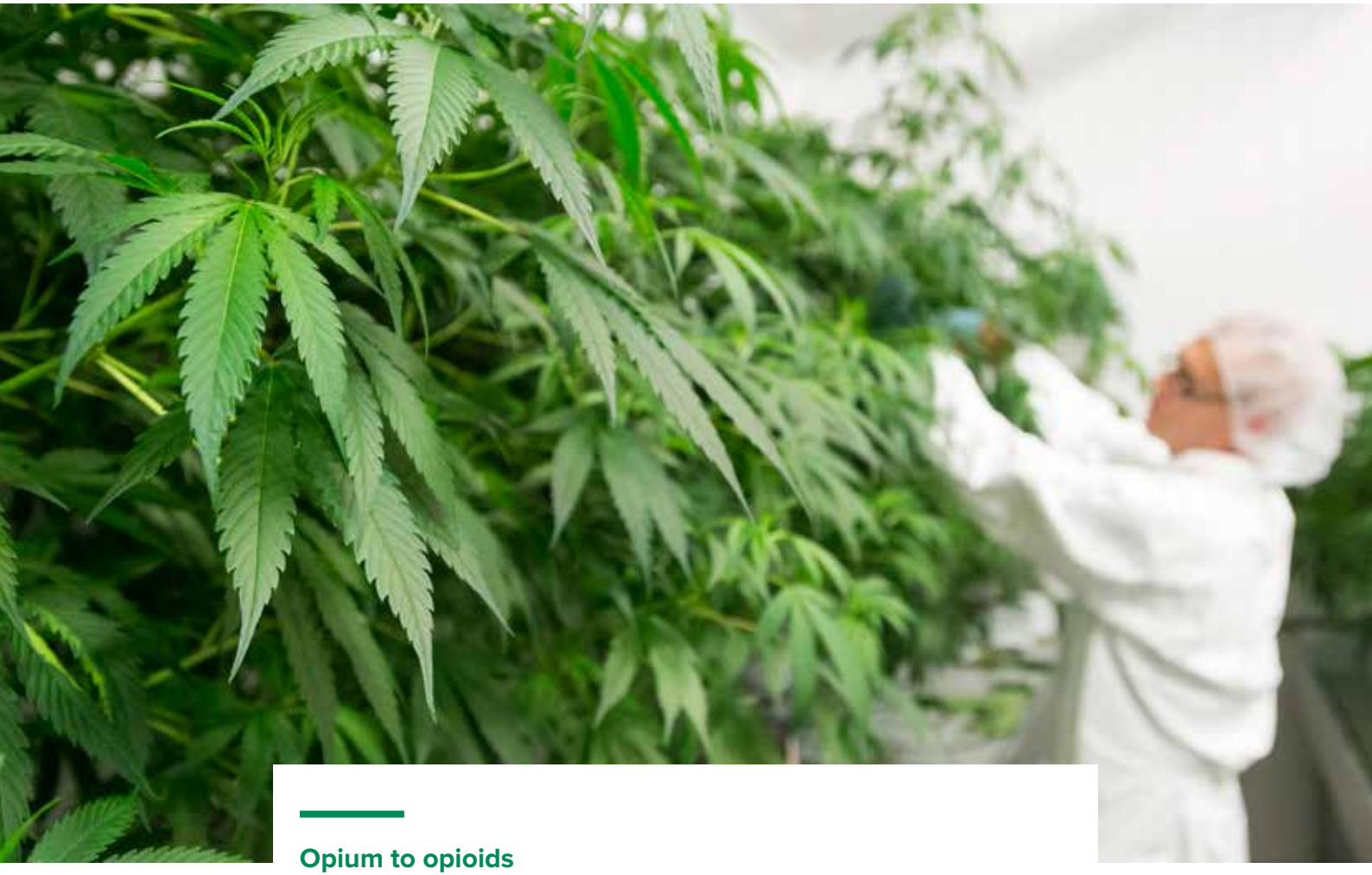
Typically, individual countries develop drug laws which interact with medicines legislation and regulations. For medicinal cannabis, a country's regulatory and other control measures aim to:

- Control legal access and use of medicinal cannabis
- Allow access to adequate supplies of pharmaceutically derived cannabis for medical purposes, in certain cases
- Permit the cultivation and manufacture of cannabis for that purpose

Signatory nations are obliged to carefully control the import, export, and wholesale of cannabis and its preparations. This is most often the responsibility of a country's Ministry of Health who work closely with the International Narcotics Control Board (INCB) in Vienna.

All nations are required to facilitate a working relationship with the INCB. The INCB controls the global flow of cannabis and other controlled drugs intended for medical use. Individual countries provide an annual estimate of the national requirements for medicinal cannabis. These estimates limit the amount of cannabis able to be accessed each year. This is to ensure that the legal manufacture of, trade in and use of cannabis is adequate for national medical and scientific requirements, with negligible diversion to the 'black market'.

These are binding requirements. The idea is that limiting access to controlled drugs makes them difficult to obtain and then be misused. It is the responsibility of the government regulators, health profession and patients to ensure there is no risk of diversion for misuse.



Opium to opioids

The UN Conventions and country specific legislation permits the cultivation of opium in Tasmania Australia, its shipment to global pharmaceutical manufacturing sites, its distribution on the global medicine market, and the ability for a hospital or community pharmacy to fill a patients codeine, morphine, or oxycodone prescription.

The cultivation, manufacture, distribution, and dispensing of opioids is carefully controlled. These are the same requirements for cannabis, when used for therapeutic purposes.

11 Glossary of terms

Cannabis terms

Cannabinoids: naturally occurring or synthetic chemicals that act on the cannabinoid receptors.

Cannabis: *Cannabis sativa* L. – a member of the Cannabaceae family – contains a number of active elements. The main active constituents include THC (delta-9-tetrahydrocannabinol) and CBD (cannabidiol).

Cannabis flos: the whole dried flower of the cannabis plant.

Cannabinoid receptors: cell membrane receptors found in the brain, the peripheral nervous system, and many organs and tissues. These receptors recognise our own endocannabinoids and phytocannabinoids (i.e., THC, CBD) from the cannabis plant. They are typically inclusive of the CB1 and CB2 receptors, but also include other receptors that cannabinoids bind to.

Decarboxylation: the cannabinoids exist mainly in an inactive acid form. The pharmacologically active cannabinoids (e.g., THC/CBD) are formed when cannabis is heated to a temperature of at least 180°C resulting in 'decarboxylation'. Specifically, decarboxylation is a chemical reaction that removes a carboxyl group and releases carbon dioxide (CO2).

Endocannabinoids: the cannabinoids (endogenous neurotransmitters) produced naturally in the bodies of humans and animals that bind to cannabinoid receptors.

Endocannabinoid system: the endocannabinoid system is critical to the bodies overall homeostasis, and influences all of our main organ and tissues systems. This is a unique biological system; its mechanisms are responsive and capable of adaptation and thus allows for a biological response aligned to system demand or environmental conditions.

Endogenous: produced by the body, not delivered from external sources. The endogenous cannabinoids are called endocannabinoids.

Entourage effect: suspected synergistic interactions between cannabinoids and terpenes that lead to modifying or enhancing the therapeutic effects of cannabinoids in different ways. Terpenes are a major component of *Cannabis sativa* L, responsible for the plant's aroma and taste. The therapeutic synergy between cannabinoids and terpenes has not yet been confirmed in clinical research.

Medicinal cannabis: cannabis that is intended for therapeutic use. Is prescribed by a trained medical professional, for a known medical condition or a set of conditions where it has proven to be an effective treatment.

Phytocannabinoids: cannabinoids that occur naturally in cannabis and are derived from the cannabis plant. There a number of known cannabinoids. The most studied phytocannabinoids are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD):

- THC is the most well-known cannabinoid. THC is responsible for many of the medicinal effects of cannabis. These may include, among others, reduction of nausea, vomiting, pain and muscle spasms, and improvement of sleep and appetite.

- CBD is another major cannabinoid. It has medicinal effects, but does not induce a psychotropic state (i.e. its use does not result in feelings of intoxication). CBD may be effective in conditions such as epilepsy, post-traumatic stress disorder (PTSD), and anxiety disorder.

Standardisation: pharmaceutical-quality cannabis flos is the whole, dried flowers of the cannabis plant which is genetically and chemically standardised according to pharmaceutical standards, with a defined cannabinoid composition. Also, it is free of contaminants such as microbial contaminants (moulds, fungi, and bacteria) pesticides (residues), aflatoxins, impurities and heavy metals.

Synthetic cannabinoids: a class of man-made chemicals that bind to cannabinoid receptors, (typically) mimicking the effects of THC.

Terpenes: the aromatic compounds which give cannabis its smell and taste. Each distinct cannabis variety has a unique composition of terpenes. The terpenes are suspected to be involved in different interactions with cannabinoids.

Medical terms

Dose: the specified amount of a medicine taken at one time.

Dosage regimen (therapeutic regimen): the number of doses in a given time period, and the time between doses, that is chosen to reach the therapeutic objective (i.e., to treat the symptoms of a disease). This depends on the drug used, the condition being treated, and the patient's characteristics.

Harm: anything that impairs or negatively affects the safety of patients. Medicine harms include adverse drug reactions, treatment side-effects, and other undesirable consequences from a health intervention. Medicine quality, frequency of use and mode of administration modify the type and severity of drug-related harms.

Illegal: not according to or authorised by law (unlawful and illicit); not permitted.

Ligand: a ligand binds to a specific receptor. The ligands of the cannabinoid receptor are called cannabinoids. The endogenous ligands of the cannabinoid receptor are called endocannabinoids, while exogenous ligands are the phytocannabinoids.

Medicine: the branch of medicine concerned with the nonsurgical treatment of disease, and/or the alternative name for pharmaceuticals.

Misuse (of pharmaceuticals): to use a pharmaceutical incorrectly; taking medication where the dose is increased or used with the intention of achieving an intoxicating effect.

Oral: a medicine is taken by mouth; to be taken orally.

Risk (factor): an aspect of personal behaviour or lifestyle, an environmental exposure, or an inborn or inherited characteristic that is associated with an increased risk of a person developing a disease.

Route (administration of a drug): how a medicine is taken into the body, including the location it is applied. Common examples include oral, inhalation, sublingual, and topical administration.

Sublingual: 'under the tongue'; referring to the route of administration by which a medicine diffuse into the blood through tissues under the tongue.

Therapeutic terms

Active ingredient: the therapeutically active component in a medicine's final formulation that is responsible for its physiological action.

Administration (mode of drug use): describes the way in which a drug is taken or used, includes for example inhalation (vaporisation), ingestion or taking orally, and the injecting of a drug substance.

Batch: a quantity of a product that is (i) uniform in composition, method of manufacture and probability of chemical or microbial contamination; and (ii) made in one cycle of manufacture and, if required, sterilised or freeze dried in one cycle.

Certificate of Analysis (CoA): a document of quality assurance that confirms that a product meets its specifications, and results of quality control test on the individual batch of a product.

Formulation (of a therapeutic product): the different chemical substances, including the active drug substance, which are combined to produce a specific dose form.

Good manufacturing practice (GMP): the acronym GMP is used internationally to describe a set of principles and procedures for the manufacturer of medicines; it helps ensure that the products manufactured are of a certain quality.

Manufacture: the production of medicines or any part of the process of producing medicines or bringing the goods to their final state, including the processing, assembling, packaging, labelling, storage, sterilising, testing or releasing for supply of the goods or of any component or ingredient of the goods as part of that process.

Pharmacokinetics: the branch of pharmacology concerned with the movement of drugs within the body; describing how a medicine is absorbed, distributed, metabolised and excreted from the body.

Pharmacovigilance: the collection and evaluation of information from healthcare providers and patients on the adverse effects of medicines.

Therapeutics: the branch of medicine concerned with the treatment of disease and the action of medicines. A treatment, therapy or drug.

Therapeutic option: the idea that expanding medicine options for a disease provides the prescribing doctor with options to search for a more appropriate treatment for their patient. This may be to reduce the number, frequency or severity of side-effects, and also the total number of medicines taken by the patient in their daily regimen.

12 Suggested reading

Administration and dose forms

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Disclaimer

This booklet reflects published data, information and clinical insights as at June 2018. It mainly considers the use of medicinal cannabis as a therapeutic product within a prescriber-pharmacy model which is governed by traditional medicine frameworks.

This booklet is intended for information purposes only. It is not intended to support decision making by prescribers and pharmacists on the safe and effective use of medicinal cannabis or cannabinoids. It should not be relied upon as a definitive text.

While all efforts have been made to ensure the accuracy and scientific nature of information at the time of its production, the author make no representations, implied or otherwise, as to the safety and efficacy of medicinal cannabis or cannabinoids and the methods of administration, until such time that reliable clinical data is provided, nor to the contents of this booklet as certain information may have become outdated due to rapid scientific and clinical developments in this field.

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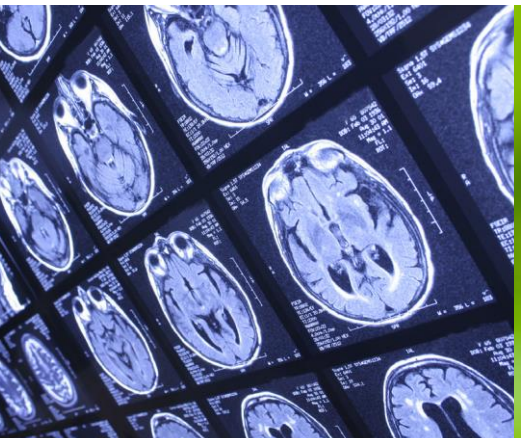
A primer to medicinal cannabis discusses the therapeutic use of cannabis. That means we are not talking about pot, marijuana, grass, or dope for recreational use to get ‘high’. It focusses strictly on medicinal cannabis. It is meant to give health care professionals, regulators and patients insights into the medical and scientific aspects of *Cannabis sativa* L. and how this plant fits in the chain of therapeutic options.

Date of preparation
June 2018

Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

The supply, manufacture, importation and distribution of unlicensed cannabis-based products for medicinal use in humans 'specials'



This document applies to the supply, manufacture, importation and distribution of unlicensed cannabis-based products for medicinal use in humans ‘specials’.

First edition November 2018.
Produced by Regulatory Advice Unit, MHRA

Alternative format versions of this report are available on request from Regulatory Advice Unit.

Contents

Scope

The purpose of this document is to provide specific guidance in relation to unlicensed cannabis-based products for medicinal use in humans following the rescheduling of cannabis under The Misuse of Drugs (Amendments) (Cannabis and Licence Fees) (England, Wales and Scotland) Regulations 2018[1] (the '2018 Regulations), which amend the Misuse of Drugs Regulations 2001 (S.I.2001 / 3998) to allow its use for medical purposes.

The rescheduling of cannabis under the Misuse of Drugs legislation enables unlicensed cannabis-based products for medicinal use in humans to be available under the provisions for ''Specials'' under Regulation 167 of the Human Medicines Regulations 2012.

For ease of reading unlicensed cannabis-based products for medicinal use in humans are referred to hereafter as 'unlicensed CBPMs'. The regulation and licensing of unlicensed CBPMs in the UK are undertaken by the Home Office, DHSC and the MHRA. This guidance is designed to provide information on supply, manufacture, importation and distribution of unlicensed CBPMs which have been specially manufactured or imported to the order of a Specialist doctor for the treatment of his/her individual patients.

Classification and scheduling of cannabis

Cannabis, cannabis resin, cannabinol and cannabinol derivatives are classified as a Class B drugs under the Misuse of Drugs Act 1971, based on a harms assessment. This classification dictates the penalties for committing offences with the drug such as possession and intent to supply and is used to prioritise the law enforcement response. The classification of the drug is entirely separate from its scheduling.

The Misuse of Drugs Regulations 2001 ('the 2001 Regulations') provides the legal framework for access to controlled drugs for legitimate purposes. Cannabis (the plant material, excluding the stalks and seeds), cannabis resin, cannabinol and cannabinol derivatives are listed under Schedule 1 of the 2001 Regulations. These definitions cover, amongst other chemical constituents, the cannabinoid THC[2]. THC is the principal psychoactive constituent of cannabis.

By law, the cultivation, production, supply and possession of cannabis under Schedule 1 is only permitted under a Home Office licence. For more information on Home Office Licensing, see https://www.gov.uk/guidance/controlled-drugs-licences-fees-and-returns.

With effect from the 1 November 2018, Cannabis Based Medicinal Products for Use in Humans ("CBPMs") will be listed in Schedule 2 to the 2001 Regulations. Only forms of cannabis – and the associated controlled products – which meet this definition will fall into Schedule 2.

Cultivation of cannabis, irrespective of THC content and/or medicinal purpose can only be carried out under Home Office licence.

[1] Separate but parallel legislation is being prepared in Northern Ireland.
[2] For the definition of Cannabis see section 37(1) of the Misuse of Drugs Act 1971. For the definition of cannabinol derivatives see Part IV, Schedule 2 to the Misuse of Drugs Act 1971. The 1971 Act can be accessed here: https://www.legislation.gov.uk/ukpga/1971/38

Definition

The definition of unlicensed CBPMs is in the Misuse of Drugs Regulations 2001 ('the 2001 Regulations') as amended by the Misuse of Drugs (Amendments) (Cannabis and Licence Fees) (England, Wales and Scotland) Regulations 2018.[3]

A 'Cannabis-based product for medicinal use in humans' is defined as:

> *""cannabis-based product for medicinal use in humans" means a preparation or other product, other than one to which paragraph 5 of part 1 of Schedule 4 applies, which—*
> *(a) is or contains cannabis, cannabis resin, cannabinol or a cannabinol derivative (not being dronabinol or its stereoisomers);*
> *(b) is produced for medicinal use in humans; and—*
> *(c) is—*
> *(i) a medicinal product, or*
> *(ii) a substance or preparation for use as an ingredient of, or in the production of an ingredient of, a medicinal product;";*

A number of substances are specifically exempted from this definition. This includes the product known as Sativex (the substance controlled in paragraph 5 of part 1 of Schedule 4 of the 2001 Regulations) as well as synthetic dronabinol (separately Scheduled in the 2001 Regulations).

Requirements of the amended 2001 Regulations

The Misuse of Drugs Regulations 2001, as amended by the Misuse of Drugs (Amendments) (Cannabis and Licence Fees) (England, Wales and Scotland) Regulations 2018, provide that the prescriber must be a Specialist doctor registered on the General Medical Council (GMC) Specialist Register to be able to issue prescriptions for unlicensed CBPMs. Once a substance receives Marketing Authorisation this prescribing restriction will no longer apply, and the product is available for patient use as other Schedule 2 drugs. See Regulation 16A of the 2001 Regulations.

As with other Schedule 2 drugs, organisations wishing to possess, supply, produce or manufacture these products will require a Home Office Controlled Drug licence to lawfully undertake these activities unless a limited 'exemption' applies. A Home Office licence will also be required to import or export these controlled drugs.

All information needed to apply for the relevant Home Office licences is available on the website at https://www.gov.uk/guidance/controlled-drugs-licences-fees-and-returns.

The GMC Specialist Register

The GMC Specialist Register is a list of doctors who are eligible to take up appointment in any fixed term, honorary or substantive consultant post in the NHS excluding foundation trusts.[4]

If a doctor is on the GMC Specialist Register it will say so as part of their status on the medical register. The GMC Specialist Register also shows:

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[3] The Misuse of Drugs (Amendments) (Cannabis and Licence Fees) (England, Wales and Scotland) Regulations 2018 http://www.legislation.gov.uk/uksi/2018/1055/regulation/3/made

[4] The Specialist Register – General Medical Council https://www.gmc-uk.org/registration-and-licensing/the-medical-register/a-guide-to-the-medical-register/specialist-registration

- the specialties (and sub-specialties) the doctor is qualified in
- the date the doctor joined the GMC Specialist Register in each specialty.

Checks on the Specialist doctors registered on GMC Specialist Register can be made on the GMC 'List of Registered Medical Practitioners' link:

https://www.gmc-uk.org/registration-and-licensing/the-medical-register/a-guide-to-the-medical-register/specialist-and-gp-application-types

1 Introduction

MHRA is responsible for ensuring that medicines and medical devices work, are safe and of an appropriate quality. MHRA's primary aim is to safeguard public health through a system of regulation. Pharmaceutical manufacturers and distributors operating in the UK marketplace are subject to a system of licensing and inspection, which ensures that licensed medicinal products conform to internationally-agreed standards, and that those medicines are manufactured/imported, stored and distributed in compliance with the required regulatory standards.

The regulation of medicines on the UK market is undertaken by MHRA in accordance with the Human Medicines Regulations 2012 (SI 2012/1916).

Unless exempt, a medicinal product must be the subject of a marketing authorisation (product licence) before being placed on the market. Regulation 167 of the Human Medicines Regulations 2012 provides an exemption from the need for a marketing authorisation for a medicinal product which is supplied under specific conditions:

- in response to an unsolicited order;
- manufactured and assembled in accordance with the specification of a person who is a doctor, dentist, nurse independent prescriber, pharmacist independent prescriber or supplementary prescriber;
- for use by a patient for whose treatment that person is directly responsible in order to fulfil the special needs of that patient; and meets the conditions specified in regulation 167(2)-(8).

In the interest of public health, the exemption is narrowly drawn because these products, unlike licensed medicinal products, may not have been assessed by the Licensing Authority against the criteria of safety, quality and efficacy.

This document provides advice on the supply, manufacture, importation and distribution of unlicensed CBPMs which have been specially manufactured or imported to the order of a Specialist doctor for the treatment of individual patients.

Unlicensed CBPMs

- *Under Regulation 16A of the 2001 Regulations, unlicensed CBPMs must be manufactured and assembled in accordance with the specification of a person who is a registered doctor listed on the GMC's Specialist Register (a 'Specialist doctor').*

- *The unlicensed CBPM is a 'Specials' medicinal product, formulated in accordance with the specifications of a Specialist doctor, and for use by an individual patient under his direct personal responsibility.*
    - ***The prescriber should follow the GMC's guidance on 'Good practice in prescribing and managing medicines and devices'[5] paying special attention to section 'Prescribing unlicensed medicines' as well as provide information for patients about the licence status for their medicines.[6] Additionally, the prescriber should refer to the Flowchart process for prescribing, supplying and importing unlicensed CBPMs (see Appendix 1) as well as the guidance on the hierarchy for the use of unlicensed medicines (see Appendix 2). This hierarchy is provided for guidance only and each case should be considered on its individual merit. The prescriber should satisfy themselves of the following with respect to the product being prescribed: that the product is specified by brand/supplier; cannabis strain and content of THC/CBD (and ratio of THC/CBD where relevant), as appropriate.***
    - ***Route of administration and dosage instructions.***
    - ***That the product is being procured from a manufacturer/importer with a GMP certificate authorised by the Licensing Authority*.***
    - ***That the producer/supplier will provide a certificate of Analysis (CoA) including parameters appropriate to define product quality.***

*The Licensing Authority, for the purposes of the Human Medicines Regulations 2012 and this guidance, refers to the UK Ministers[7] designated by the Regulations, acting either alone or jointly. MHRA is the Government body set up to discharge the responsibilities of the Licensing Authority, under powers delegated by those Ministers.

2 Special clinical needs

Regulation 167 of the Human Medicines Regulations 2012 sets out the exemption from the requirement for a medicinal product, placed on the market in the UK to hold a marketing authorisation. This exemption flows from Article 5(1) of Directive 2001/83/EC, which states:

'A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised healthcare professional and for use by an individual patient under his direct personal responsibility.'

An unlicensed CBPM may only be supplied in order to meet the special needs of an individual patient. This product should not be supplied where a licensed medicinal product can meet the special needs of the patient. Responsibility for deciding whether an individual patient has "special needs" which a licensed product cannot meet should be a matter for the doctor listed on the GMC Specialist Register, responsible for the patient's care.

The requirement for a "special need" relates to the special **clinical** needs of the individual patient. It does not include reasons of cost, convenience or operational needs (see Section 10 of MHRA Guidance Note 14)[8]. Anyone supplying an unlicensed CBPM where an equivalent licensed medicinal product is available must be satisfied as to the existence of a

[5] GMC guidance on Good practice in prescribing and managing medicines and devices - https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/prescribing-and-managing-medicines-and-devices

[6] GMC guidance on Prescribing unlicensed medicines - https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/prescribing-and-managing-medicines-and-devices/prescribing-unlicensed-medicines

[7] The Secretary of State and the Minister for Health, Social Services and Public Safety.

[8] MHRA Guidance Note 14- The supply of unlicensed medicinal products 'specials', Section 10 - European Court cases https://www.gov.uk/government/publications/supply-unlicensed-medicinal-products-specials

special need for the unlicensed CBPM.

MHRA expects that documentary evidence that the requested supply is for clinical need that cannot be met by an unlicensed medicine be obtained by manufacturers, importers or distributors and that this evidence should be made available on request of the Licensing Authority. This may take the form of a prescriber's letter, however an alternative fully documented audit trail through the supply chain confirming special need may be acceptable:

- To include clinical therapeutic use/clinical indications
- Why this product is chosen over licensed medicines
- Confirmation of the clinical indication for what the product will be used
- The decision to prescribe has been made by a doctor on the GMC Specialist Register

The unlicensed CBPM may only be supplied to third parties if ALL of the following apply:

- *there is an unsolicited order from a Specialist doctor;*
- *the Importer must have a Home Office import and Domestic licence. The wholesaler / manufacturer must have a Home Office Domestic Licence and MHRA Wholesaler Dealer's Licence or Manufacturer's (Specials) Licence for possession and supply of unlicensed CBPMs;*
- *the product is manufactured and assembled in accordance with the specification of a person who is a doctor on the GMC Specialist Register, responsible for the patient's care;*
- *the product is for use by a patient for whose treatment that person is directly responsible in order to fulfil the special needs of that patient that cannot be met by existing licensed medicines; and*
- *the product is manufactured and supplied under specific conditions (see Sections 3 to12).*

3 Persons authorised to procure unlicensed CBPMs in the UK

They are:

a) Doctor on the GMC Specialist Register
b) Specialist Importer with a Home Office import and Domestic licence and MHRA licence
c) Registered pharmacies or retail pharmacy businesses (with Home Office Domestic licences, where appropriate)[9];
d) Licensed wholesale dealers for supply to the order of any of the above;

UK licensed manufacturers and wholesale dealers should take reasonable steps to establish that persons supplied satisfy the requirements of regulation 167, and intend to use the product in a way which falls within the specified terms. This could be achieved, for example, by the person ordering the "special" confirming their professional status and the nature of the special need of the individual patient concerned, making clear that where a licensed alternative is available, why that is not clinically appropriate. There is no legal requirement for the individual patient's name to be supplied (see Appendix 2).

All involved in the supply chain should be aware of the unlicensed status of the CBPM. It should be clear from the product's packaging that the product is unlicensed because there will be no marketing authorisation/product licence number on it. However, a prescriber may not have sight of the CBPM, for example, where it is ordered by a hospital pharmacist and

[9] Some pharmacies will NOT need a domestic licence – as pharmacies and retail pharmacy business are able to produce / supply in accordance with their practice. However, if they are wholesale dealing the policy is that they do need a licence.

administered by a nurse. In such cases the pharmacist should ensure before the product is ordered and administered that the prescriber is fully aware of the unlicensed status of the CBPM. Healthcare providers (such as Health Boards, NHS Hospital Trusts, Clinical Commissioning Groups and independent hospitals) will have existing policies on the commissioning and use of unlicensed medicines which should be referred to.

4 Active Substance registration

Active Substances (AS) are responsible for the therapeutic effect of medicinal products and are often referred to as active pharmaceutical ingredients (APIs) or drug substances (DS).

If you manufacture, import or distribute an active substance and you are based in the UK you must register with the Medicines and Healthcare Products Regulatory Agency (MHRA). You can do this through the MHRA Portal.

The MHRA has produced a flowchart on the registration requirements (PDF, 37.9KB, 1 page) requirements to help you decide what kind of registration you need.

Refer to MHRA Guidance on Medicines: register to manufacture, import or distribute active substances https://www.gov.uk/guidance/medicines-register-to-manufacture-import-or-distributor-active-substances for further information on the registration process, changes to registration, annual compliance reports, termination of registration, fees and payments.[10]

5 Manufacture and assembly in the UK

The manufacturer or assembler of "specials" must hold a Manufacturer's (Specials) Licence granted by the Licensing Authority and in most cases, a Home Office Licence. The licence should be applied for in the usual way (subject to the usual application procedures and conditions, see MHRA Guidance Note 5, Notes for applicants and holders of Manufacturer's Licences). The manufacturing/assembly site and its operations will be inspected for compliance with GMP and the conditions of the licence. These require that manufacture or assembly is carried out under the supervision of appropriately qualified staff, including a named quality controller and production manager, who are acceptable to the Licensing Authority. However, a Qualified Person (QP) is not required to be named on a Manufacturer's (Specials) Licence for release of a finished unlicensed product.

Release of "specials" should be by the quality controller or a nominated deputy.

Unlicensed CBPMs

- *Adequate precautions should be taken to ensure that the product is of the quality required for its intended purpose and that it complies with any standards described in relevant pharmacopoeial monographs.*
- *The product should, in particular, comply with the requirements of the British Pharmacopoeia (BP) monographs on Pharmaceutical Preparations and Substances for Pharmaceutical Use.*
- *The BP monograph on Pharmaceutical Preparations encompasses the requirements of the specific monographs concerning active substances, excipients, general monographs (e.g.*

[10] MHRA Guidance on Medicines: register to manufacture, import or distribute active substances – https://www.gov.uk/guidance/medicines-register-to-manufacture-import-or-distributor-active-substances

residual solvents) and the general monographs covering dosage forms, herbal drugs, herbal drug preparations, herbal extracts and herbal medicinal products.

- *Specifications applied to CBPMs and their active substances should take account of all relevant pharmacopoeial monographs and current guidelines on herbal drugs, herbal drug preparations and herbal medicinal products. Suitable validated analytical methods should be applied in line with current guidelines; major cannabinoids, in particular, THC/CBD should be quantitatively determined, as appropriate.*

Written records of manufacture/assembly and supply must be kept for five years and be made available to the Licensing Authority on request.

When inspecting a "specials" manufacturing site, in addition to confirming compliance with GMP and the Human Medicines Regulations 2012, an Inspector will also take account of product specifications, labelling, stability data and justification for expiry dating. Where appropriate, evidence to support compliance with GACP (Good Agricultural and Collection Practice) of the cannabis plant material must be demonstrated; in line with current guidelines.

Decontamination of the cannabis plant material using ethylene oxide is not permitted in accordance with the BP monograph on Herbal Drugs. Use of gamma irradiation to reduce microbial bioburden is permitted provided it does not affect the quality of the material; such treatment should be documented and records should be available for inspection.

The licence holder must demonstrate compliance with the European Commission's 'Notes for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products' and future updates, in accordance with The Unlicensed Medicinal Products for Human Use (Transmissible Spongiform Encephalopathies) (Safety) Regulations 2003 [SI 2003/1680]. See MHRA's guidance: Minimising the risk of Transmission of Transmissible Spongiform Encephalopathies via Unlicensed Medicinal Products for Human Use, available from MHRA's website www.mhra.gov.uk

A holder of a Manufacturer's (Specials) Licence may also be a registered pharmacy supplying unlicensed medicinal products prepared under the exemption provided by regulation 4 of The Human Medicines Regulations 2012. Under these circumstances, the labelling of products prepared under regulation 4, and any documentation associated with them, should not make reference to the Manufacturer's (Specials) Licence or number.

For guidance on labelling of unlicensed medicinal products manufactured by the holder of a Manufacturer's Special Licence, reference should be made to the relevant monographs of the BP.[11]

In addition, labelling should take account of current guidelines on declaration of herbal substances and herbal preparations in herbal medicinal products; content of THC/ CBD (and ratio of THC/CBD where relevant), as appropriate.

[11] British Pharmacopoeia Volume III – Formulated Preparations: General Monographs Unlicensed Medicines
British Pharmacopoeia Volume V – Supplementary Chapters – SC V Unlicensed Medicines SC V Unlicensed Medicines

6 Importation into the UK

The Specialist Importer of an unlicensed CBPM into the UK must hold either a Wholesale Dealer's Licence (WDA (H)) if the product is to be imported from an EEA member state i.e. the EU plus Norway, Iceland and Liechtenstein, or a Manufacturer's (Specials) Licence if the product is to be imported from a third country i.e. a non-EEA country; and,

The Specialist Importer must notify the MHRA at least 28 days before the date of the intended import stating:

(a) The name of the product, which may be the brand name, common name or scientific name under which it is to be sold or supplied.

(b) Any trademark or name of the manufacturer.

(c) The International Non-proprietary Name (INN), British Approved Name (BAN) or other monograph, scientific name or description of the true nature of each of the constituents.

(d) The quantity to be imported which will be the quantity as written on the prescription

(e) The name and address of the manufacturer or assembler of the medical product, or the name and address of the supplier if not the manufacturer or assembler.

Unlicensed CBPMs

For unlicensed CBPMs in addition to the general requirements, MHRA will require evidence that:

1. *The content/ratio of THC/CBD is declared, and appears on the label, as appropriate*
2. *A Certificate of Analysis is available to support the batch specification*
3. *A valid GMP certificate is available for the site of manufacture*

The unlicensed CBPM must not be imported if the MHRA issues an objection to import within 28 days of their acknowledgment of the notification of intent to import.

The MHRA may choose to permit import before 28 days from the date of its acknowledgment. This is usually only used in the case of immediate import of medicines for life threatening or immediately injurious clinical emergencies.

Records required in addition to other provisions of licences are:

(a) The batch number of the product supplied.

(b) Details of any adverse reactions to the product supplied of which the licence holder becomes aware.

Requirements from the Specialist Importer:

- *The Specialist Importer must not import more than the quantity notified to the Licensing Authority.*
- *The Specialist Importer must also apply to the Home Office for an appropriate Home Office licence.*
- *Notifications to MHRA and applications to the Home Office can be submitted in parallel.*
- *The Specialist Importer should send a copy of the Home Office licence to the manufacturer/exporter of unlicensed CBPM in the source country.*

- *UK customs check will be carried out. The product will be placed in quarantine at Specialist Importer's warehouse until routine checks are carried out.*
- *The products will then be supplied to pharmacy/dispensing doctor for dispensing/administering the product to the patient.*
- *The Specialist Importer must inform the MHRA immediately of any matter coming to their attention which may mean that an unlicensed medicine they have imported may not be safe or of adequate quality for administration to humans.*
- *The Specialist Importer must cease import or supply of the unlicensed CBPM from a specified date if so instructed by the MHRA.*
- *The Specialist Importer shall take all reasonable precautions and exercise all due diligence to ensure that any information he provides to the MHRA which is relevant to an evaluation of the safety, quality or efficacy of the unlicensed CBPMs which he imports from a third country, handles, stores or distributes is not false or misleading in a material particular.*

If the product contains substances of animal origin, the Specialist Importer must demonstrate compliance with the European Commission's 'Notes for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products' and future updates, in accordance with, The Unlicensed Medicinal Products for Human Use (Transmissible Spongiform Encephalopathies) (Safety) Regulations 2003 [SI 2003/1680]. See MHRA's guidance: Minimising the risk of Transmission of Transmissible Spongiform Encephalopathies via Unlicensed Medicinal Products for Human Use, available from MHRA's website www.mhra.gov.uk

7 Record keeping

Any person who sells or supplies the unlicensed CBPM in the UK must maintain for at least five years a record showing:

- The name of the product, brand/supplier; cannabis strain and content of THC/CBD (and ratio of THC/CBD where relevant), as appropriate.
- The source from which and the date on which the person obtained the product;
- The person to whom and the date on which the sale or supply was made;
- The quantity of the sale or supply;
- The batch number of the batch of that product from which the sale or supply was made; and
- Details of any suspected adverse reaction to the product so sold or supplied of which the person is aware or subsequently becomes aware. For further guidance on ADR reporting see below.

The person must make the records available for inspection by the MHRA on request. The person must notify the licensing authority of any suspected adverse reaction to the medicinal product which is a serious adverse reaction.

Persons will also need to comply with the record keeping requirements set out in the Misuse of Drugs Regulations 2001.

8 Distribution

Distribution by wholesale dealing must be through licensed wholesale dealers, subject to the usual application procedures and conditions, and appropriate records must be kept.

Directive 2001/83/EC defines wholesale distribution of medicinal products as: 'All activities consisting of procuring, holding, supplying or exporting medicinal products, apart from supplying medicinal products to the public. Such activities are carried out with manufacturers or their depositories, importers, other wholesale distributors or with pharmacists and persons authorized or entitled to supply medicinal products to the public in the Member State concerned.'

The holder of a Wholesale Dealer's Licence (WDA(H)), must only supply unlicensed medicinal products to:

- The holder of a Wholesale Dealer's Licence relating to those products;
- The holder of an authorisation granted by the competent authority of another EEA State authorising the supply of those products by way of wholesale dealing;
- Any person who may lawfully supply medicinal products in circumstances corresponding to retail sale, or
- Any person who may lawfully administer those products.

The holder of a Manufacturer's (Specials) Licence must comply with these requirements in order to distribute the unlicensed medicines that they have manufactured or imported as if they were the holder of a Wholesale Dealer's Licence.

Wholesale dealer's will also require a Home Office licence to lawfully possess and supply these substances.

9 Storage requirements for controlled drugs

The storage requirements for unlicensed CBPM will be the same as for other Schedule 2 controlled drugs (CD).

- They will be subject to the Misuse of Drugs (Safe Custody) Regulations 1973[12] and so should be stored in a locked receptacle, usually in an appropriate CD cabinet or approved safe, which can only be opened by the person in lawful possession of the CD or a person authorised by that person.
- A register must be kept for Schedule 2 CDs and this register must comply with the relevant regulations.
- The destruction of CDs in Schedule 2 must be appropriately authorised and the person witnessing the destruction must be authorised to do so.

10 Labelling

Unlicensed CBPM manufactured in the UK should be labelled in accordance with BP.

[12] The Misuse of Drugs (Safe Custody) Regulations 1973 - http://www.legislation.gov.uk/uksi/1973/798/contents/made

The BP general monograph of “Unlicensed Medicines” contains the following advice for labelling (including warnings). It cross refers to the MHRA guidance:

Labelling

The following requirements are applicable to unlicensed medicines manufactured or prepared in accordance with medicines legislation. They are not intended to apply to repackaging and assembly activities. The requirements were previously included as guidance in Supplementary Chapter V of the British Pharmacopoeia 2007.

Best practice guidance on the labelling and packaging of medicines advises that certain items of information are deemed critical for the safe use of the medicine (see ‘Best Practice Guidance on the Labelling and Packaging of Medicines’, MHRA, 2012).[13] These critical items of information, which should be located together on the pack and appear in the same field of view, are: name, strength, route of administration, dosage and warnings (highlighted in bold).

The following would be considered the minimum information:

1. **The name of the product and declaration of active herbal ingredient, as appropriate for herbal medicinal products.**
2. **A statement of the content/ratio of THC/CBD as appropriate.**
3. **Route of administration.**
4. **Instructions for use, including any special warnings.**
5. The pharmaceutical form.
6. The contents of the container by weight, volume as appropriate.
7. Excipients of known effect. For injectable, topical (including inhalation products) and ophthalmic medicines, all excipients.
8. ‘Keep out of reach and sight of children’. [Note 1]
9. The expiry date expressed in unambiguous terms (dd/mm/yy).
10. Any special storage precautions.
11. The manufacturer’s MS number, where appropriate.
12. The manufacturer’s name and address.
13. The batch number.

Labelling should take account of current guidelines on declaration of herbal substances and herbal preparations in herbal medicinal products; content of THC/CBD (and ratio of THC/CBD where relevant) should be stated, as appropriate.

Specials’ manufacturers and pharmacists ordering unlicensed CBPMs should ensure that the labelling provisions above are complied with as a minimum.

Separately when the product is dispensed the pharmacist should ensure that the usual dispensing label provisions are applied. These are set out in Schedule 25 of Human Medicines Regulations 2012 and apply to any medicine supplied on prescription regardless of legal category. (See Appendix 3).

The products will also need to comply with the marking requirements set out in the Misuse of Drugs Regulations 2001.

[13] BEST PRACTICE GUIDANCE ON THE LABELLING AND PACKAGING OF MEDICINES – https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/474366/Best_practice_guidance_labelling_and_packaging_of_medicines.pdf

Special label warnings for Driving

Unlicensed CBPMs may impair a person's ability to drive safely, and patients should be advised of the risks. The label should include the following information:

- 'WARNING' This medicine may make you feel sleepy. If this happens do not drive or use tools or machinery. Do not drink alcohol
- Do not drive while taking this medicine until you know how it affects you
- Do not drive if you feel sleepy, dizzy, unable to concentrate or make decisions, or if you have blurred or double vision

Further information is available on the Department for Transport website here, which includes information on statutory medical defence.

11 Advertising

A "specials" manufacturer, importer or wholesaler may advertise the service he provides but particular "specials" must not be advertised as provided by condition B of regulation 167 of the Human Medicines Regulations 2012. He may, however, provide factual responses to requests for information on specific "specials" or the range of products he is able to supply.

"Advertisement" is defined in regulation 7 of the Human Medicines Regulations 2012 as "anything designed to promote the prescription, supply, sale or use" of a "special" and includes, in particular, the following activities—

- door-to-door canvassing;
- visits by medical sales representatives to persons qualified to prescribe or supply medicinal products;
- the supply of samples;
- the provision of inducements to prescribe or supply medicinal products by the gift, offer or promise of any benefit or bonus, whether in money or in kind, except where the intrinsic value of such inducements is minimal;
- the sponsorship of promotional meetings attended by persons qualified to prescribe or supply medicinal products; and
- the sponsorship of scientific congresses attended by persons qualified to prescribe or supply medicinal products, including the payment of their travelling and accommodation expenses in that connection.

"Advertisement" does not include reference material and announcements of a factual and informative nature, including—

- material relating to changes to a medicinal product's package or package leaflet,
- adverse reaction warnings,
- trade catalogues, and
- price lists,

provided that no product claim is made.

Paragraphs 22(7) and 40 of Schedule 4 of the Human Medicines Regulations 2012 preclude a "specials" manufacturer, importer or wholesaler from publishing a catalogue or circular. However, provided no product claim is made, a trade catalogue or circular can be sent to an authorised healthcare professional where it is relevant to respond to an unsolicited request for information on the range of products supplied.

Additionally, a “specials” manufacturer, importer or wholesaler may issue a price list to authorised healthcare professionals to whom the price of “specials” may be relevant, such as potential customers and budget managers. Price lists can be sent out at reasonable intervals or in response to an enquiry.

A price list would typically consist of a basic line listing providing the following information:

- reference number;
- drug name (British Approved Name or equivalent);
- dosage form;
- strength;
- pack size; and
- price.

No product claims may be included.

This advice takes into account the decision of the European Court of Justice in *Ref: C-143/06 Ludwigs-Apotheke München Internationale Apotheke v Juers Pharma Import-Export* GmbH (see Section 10 in Guidance note 14).

The advertising of unlicensed medicinal products, including CBPMs, to members of the public is prohibited. For further advice on the prohibition of advertising unlicensed medicines see Section 4.2 of the Blue Guide ‘Advertising and Promotion of Medicines in the UK. This is available at the following link:

http://www.mhra.gov.uk/Howweregulate/Medicines/Advertisingofmedicines/BlueGuide/index.htm.

12 Pharmacovigilance and reporting of Adverse Drug Reactions (ADR)

As for all unlicensed medicines manufacturers should report the suspected ADR immediately and in no case later than 15 calendar days from receipt, stating that the product is unlicensed. It is a mandatory requirement to electronically report suspected ADRs. The ICH-E2B international standard electronic report should be used and the report should be electronically submitted via the EudraVigilance European Gateway (see MHRA or EMA websites for more details).

Prescribers or pharmacists supplying the “special” should report using the electronic Yellow Card (found at http://www.mhra.gov.uk/yellowcard), the Yellow Card app or using a paper form stating the manufacturer and indicating that the product is unlicensed. Wholesalers supplying unlicensed CBPMs are under an obligation to keep records of any adverse reaction of which they become aware and report any serious adverse reaction to the MHRA; this should be done by submission of a ‘Yellow Card’ report.

For CBPMs the MHRA requires reporting of ALL suspected adverse reactions (serious and non-serious, whether the product is licensed or unlicensed), including reports of failure of efficacy. Given the limited safety data that is currently available on the products, the MHRA will be conducting enhanced vigilance activities to support their safe use.

These obligations are placed on any person selling or supplying “specials”, not only manufacturers, importers and distributors but also the Specialist doctor prescribing the unlicensed CBPMs where appropriate. An adverse reaction means a response to a medicinal product which is noxious and unintended.

Pharmacovigilance involves:

- Monitoring the use of medicines in everyday practice to identify previously unrecognised adverse effects or changes in the patterns of adverse effects
- Assessing the risks and benefits of medicines in order to determine what action, if any, is necessary to improve their safe use
- Providing information to healthcare professionals and patients to optimise safe and effective use of medicines
- Monitoring the impact of any action taken

Persons involved in the supply, manufacture, importation and distribution of unlicensed CBPMs should refer to below guidelines[14] to ensure good practice and compliance with the requirements. Further information on reporting procedures can be found on links below:

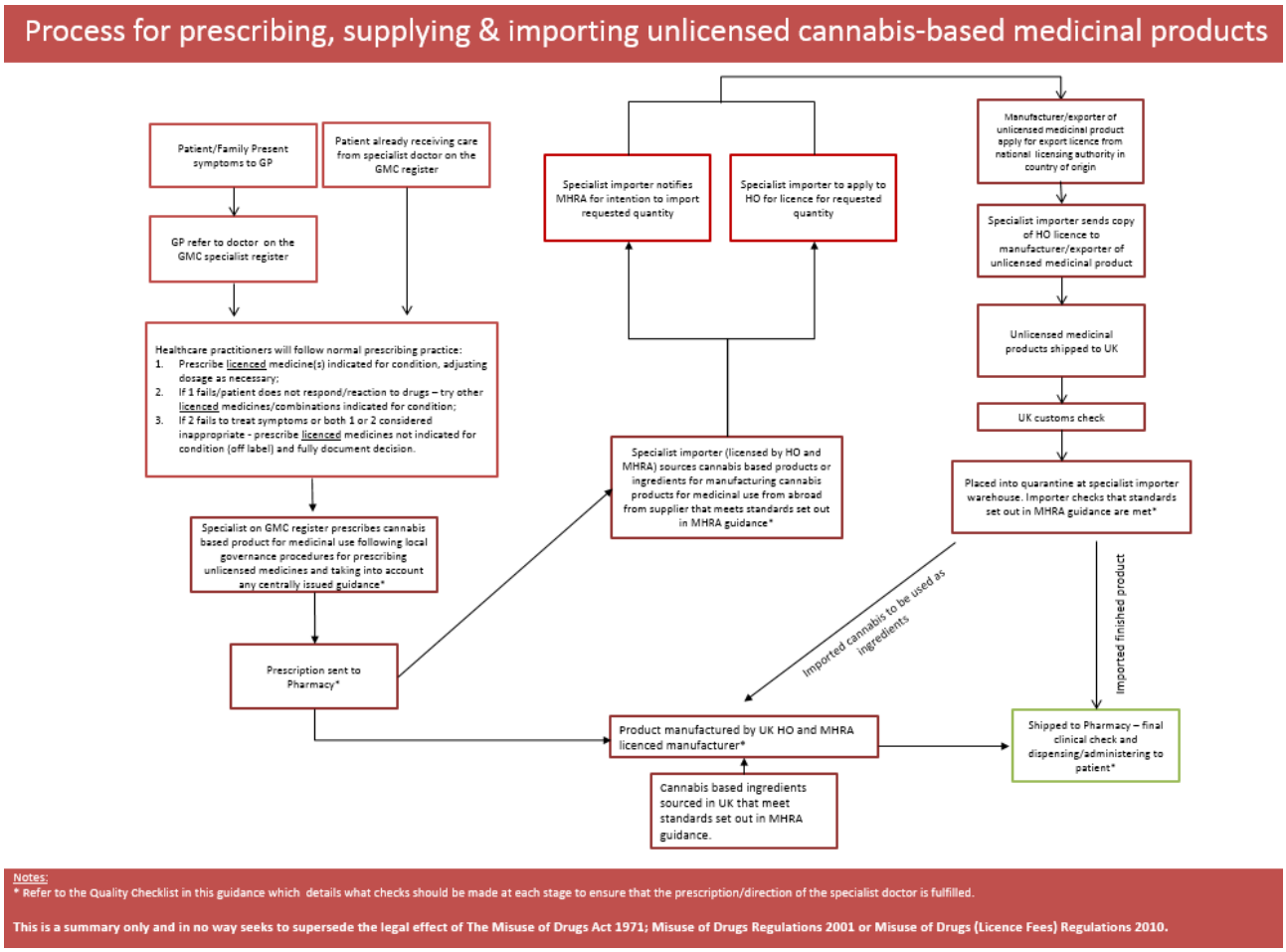
- Guidance on adverse drug reactions
- Contribution of Yellow Cards to identifying safety issues
- Pharmacovigilance – how MHRA monitors the safety of medicines
- What to include in your Yellow Card of an adverse drug reaction
- Specific areas of interest for adverse drug reactions reporting
- Send and receive information on adverse drug reactions (ADRs)

Additional information can be found on NICE guidelines on Clinical Knowledge Summaries- Adverse drug reactions.[15]

[14] The Yellow Card Scheme: guidance for healthcare professionals 2017 - https://www.gov.uk/guidance/the-yellow-card-scheme-guidance-for-healthcare-professionals#what-to-report

[15] NICE – Clinical Knowledge Summaries ADR - https://cks.nice.org.uk/adverse-drug-reactions#!scenario.

APPENDIX 1 – Flowchart



APPENDIX 2 - Guidance on the hierarchy for the use of unlicensed medicines

This hierarchy is provided for guidance only and each case should be considered on its individual merit.

1. An unlicensed product should not be used where a product available and licensed within the UK could be used to meet the patient's special need.

2. Although MHRA does not recommend "off label" (outside of the licensed indications) use of products, if the UK licensed product can meet the special clinical need, even "off-label", it should be used instead of an unlicensed product. Licensed products available in the UK have been assessed for quality, safety and efficacy. If used "off-label" some of this assessment may not apply, but much will still be valid. This is better than the use of an un-assessed, unlicensed product. The fact that the intended use is outside of the licensed indications is therefore not a reason to use an unlicensed product. It should be understood that the prescriber's responsibility and potential liability are increased when prescribing off-label medicines.

3. If the UK product cannot meet the special need, then another (imported) medicinal product should be considered, which is licensed in the country of origin.

4. If none of these options meet the special clinical need, then a completely unlicensed product may have to be used, for example, UK manufactured "specials", which are made in GMP inspected facilities, but which are otherwise un-assessed (GMP inspection of "specials" manufacturers is not product specific). There may also be other products available which are unlicensed in the country of origin.

5. The least acceptable products are those that are unlicensed in the country of origin, and which are not classed as medicines in the country of origin (but are in the UK). For example, the use of products from countries where they are classed as supplements, not pharmaceuticals, and may not be made to expected standards of pharmaceutical GMP. These should be avoided whenever possible.

APPENDIX 3 - Packaging requirements: specific provisions for the dispensing label

SCHEDULE 25 Regulation 258 - Packaging requirements: specific provisions

PART 1: Medicines on prescription

1. Where the product is to be administered to a particular individual, the name of that individual.

2. The name and address of the person who sells or supplies the product.

3. The date on which the product is sold or supplied.

4. Unless paragraph 5, applies, such of the following particulars as the appropriate practitioner

who prescribed the product may specify—

(a) the name of the product or its common name;

(b) directions for use of the product; and

(c) precautions relating to the use of the product.

5. This paragraph applies if the pharmacist, in the exercise of professional skill and judgement, is of the opinion that the inclusion of one or more of the particulars mentioned in paragraph 4 is inappropriate.

6. Where paragraph 5 applies, the pharmacist may include such particulars, of the same kind as those mentioned in paragraph 4, as the pharmacist thinks appropriate.

APPENDIX 4 - Supply Chain Checklist

This checklist is to be used only as guidance for importers and pharmacists carrying out the final clinical check and dispensing/administering the unlicensed CBPMs to the patient.

The pharmacist and importer should satisfy themselves of the following with respect to the product being prescribed/dispensed:

Specialist doctor registration check:

- ✓ there is an unsolicited order from a Specialist doctor;
- ✓ the decision to prescribe is made by a doctor registered on the GMC Specialist Register;

Prescription validation check:

- ✓ the product is specified by brand/supplier; cannabis strain and content of THC/CBD (and ratio of THC/CBD where relevant), as appropriate.
- ✓ route of administration and dosage instructions are stated on the prescription;
- ✓ the quantity is specified;
- ✓ the pharmacist should ensure before the product is ordered and administered that the prescriber is fully aware of the unlicensed status of the product; and
- ✓ the product is for use by a patient for whose treatment that person is directly responsible in order to fulfil the special needs of that patient that cannot be met by existing licensed medicines.

Verification of Importers/Manufacturers

- ✓ the importer has a valid Home Office Licence for the relevant activities which will include possession, supply and possibly production and schedules;
- ✓ the importer has a valid MHRA Wholesaler Dealer's or Manufacturer's (Specials) Licence for possession and supply of unlicensed CBPMs;
- ✓ a valid GMP certificate is available for the site of manufacture/from the importer;
- ✓ a valid Certificate of Analysis (CoA) including parameters appropriate to define product quality and to support batch specification is available from manufacturer/wholesaler;
- ✓ that the product to be imported is labelled with the that the content/ratio of THC/CBD, as appropriate.
- ✓ A holder of a Manufacturer's (Specials) Licence may also be a registered pharmacy supplying unlicensed medicinal products prepared under the exemption provided by regulation 4 of The Human Medicines Regulations 2012. Under these circumstances, the labelling of products prepared under regulation 4, and any documentation associated with them, should not make reference to the Manufacturer's (Specials) Licence or number.

Dispensing label checklist

- ✓ The pharmacist should ensure that the usual dispensing label provisions are applied. These are set out in Schedule 25 of Human Medicines Regulations 2012 and apply to any medicine supplied on prescription regardless of legal category. (See Appendix 3)
- ✓ Special label warnings for Driving should appear on the dispensing label.

Record keeping

Any person who sells or supplies the unlicensed CBPM in the UK must maintain for at least five years a record showing:

- ✓ The name of the product, brand/supplier; cannabis strain and content of THC/CBD (and ratio of THC/CBD where relevant), as appropriate.
- ✓ The source from which, and the date on which, the person obtained the product;
- ✓ The person to whom, and the date on which, the sale or supply was made;
- ✓ The quantity of the sale or supply;

- ✓ The batch number of the batch of that product from which the sale or supply was made; and
- ✓ Details of any suspected adverse reaction to the product sold or supplied of which the person is aware or subsequently becomes aware.
- ✓ Pharmacists and importers should remember these products are classified as Schedule 2 Controlled Drugs and record keeping and storage provisions apply as for any other Schedule 2 CD.

Reporting of ADR and pharmacovigilance checklist

- ✓ For cannabis-based products the MHRA requires reporting of ALL suspected adverse reactions (serious and non-serious, whether the product is licensed or unlicensed), including reports of failure of efficacy. Pharmacists supplying the "special" should report using the electronic Yellow Card (found at http://www.mhra.gov.uk/yellowcard), the Yellow Card app or using a paper form stating the manufacturer and indicating that the product is unlicensed.

FACULTY OF PAIN MEDICINE of the Royal College of Anaesthetists

Faculty Position Statement on the medicinal use of Cannabinoids in Pain Medicine

This statement is focused on the issues relating to cannabis derived medicinal products in relation to Pain Medicine. It does not comment on other areas of medical practice or recreational use, which lie outside our remit.

The issue of cannabis, its extracts, formulations and synthetics has very much been on the radar of pain medicine for many years.

The Cochrane review[1] in March 2018 concluded, "There is a lack of good evidence that any cannabis-derived product works for any chronic neuropathic pain." The authors also concluded that "The potential benefits of cannabis-based medicine in chronic neuropathic pain might be outweighed by their potential harms." The latest review in *Pain*[2] also concluded "It appears unlikely that cannabinoids are highly effective medicines for Chronic non-cancer pain." It is important to note that both papers commented on the poor quality of the existing trials.

National reports form the USA[3], Australia[4] and Ireland[5] all comment on the lack of good quality evidence regarding short and long term outcome for both benefit and harm.

The widespread use of high dose opioids in the absence of good long-term evidence over the last 20 years is already the cause of considerable concern, and it is not difficult to see potential parallels.

With this in mind, the Faculty considers that the issue of cannabinoids needs to be carefully considered and researched in a comprehensive fashion, as would be the case for any new medicinal product reaching the therapeutic market, and that anecdotal positive reporting is not a mechanism to protect public safety. We therefore feel that further high quality research is mandated in view of potential benefit, when considering the numbers of patients with chronic pain and the limited pharmaceutical armoury. If there are specific patient populations that will benefit they should not be denied access when the evidence is available.

The use of unrefined dried plants containing a variety of cannabinoids and other pharmaco-active chemicals of varying quantity cannot be supported and is clearly contrary to the direction of medical science. The potential for exposure to significantly harmful chemicals, in the short or long term, by such an unscientific 'herbal' approach is of considerable concern, as is diversion to non-medical use. Therefore, only products produced to pharmaceutical standards should be considered.

Patients living with chronic pain often have complex comorbidities and a multidisciplinary approach to management that includes physical and psychological therapy rather than reliance on medicines alone is more likely to be effective.

With this in mind:

- The Faculty supports the setting up of robust trials to look at potential benefits in Pain.
- The Faculty is unclear how a committee of "Medical Experts" could advise on the use of any cannabis-related products in the area of Pain Medicine with our current understanding of the science, except in the context of well designed trials or robust databases.
- The Faculty would, with qualifications, support the setting up of a database for the analysis of data from all areas. Such a database would need to be independent, compulsory, fully funded and under the auspices of a suitable organisation (e.g. NICE) to assess the value of treatments of relative rarity.

- Any use of cannabinoids for pain management should only occur after conventional interventions have failed and then only within the confines of a limited number of secondary care multidisciplinary specialist pain services, with all cases being nationally audited.
- The Faculty would wish to be directly involved in the establishment of guidance and data collection which impacts on the management of pain.

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Table of Resources on Medicinal Cannabis

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Research	
	https://www.ncbi.nlm.nih.gov/pubmed/
	https://www.ncbi.nlm.nih.gov/pubmed/29847469
	https://www.ncbi.nlm.nih.gov/pubmed/29513392
	https://www.ncbi.nlm.nih.gov/pubmed/28934780
	https://www.ncbi.nlm.nih.gov/pubmed/28622286
	https://www.ncbi.nlm.nih.gov/pubmed/27428009
	https://www.ncbi.nlm.nih.gov/pubmed/26912385
	https://www.ncbi.nlm.nih.gov/pubmed/26103030
	https://www.ncbi.nlm.nih.gov/pubmed/19732371
	https://www.ncbi.nlm.nih.gov/pubmed/17257464

Medical	
Royal College of Anaesthetists	https://www.rcoa.ac.uk/sites/default/files/FPM%20Cannabis%20Position%20Statement%20Oct18.pdf
NHS England	https://www.england.nhs.uk/wp-content/uploads/2018/10/letter-guidance-on-cannabis-based-products-for-medicinal-use..pdf https://www.nhs.uk/conditions/medical-cannabis/
Canadian Family Physician	http://www.cfp.ca/content/cfp/64/2/111.full.pdf
Canadian Medical Protective Association	https://www.cmpa-acpm.ca/en/advice-publications/browse-articles/2014/medical-marijuana-new-regulations-new-college-guidance-for-canadian-doctors
Guidelines	
	https://www.health.qld.gov.au/__data/assets/pdf_file/0023/634163/med-cannabis-clinical-guide.pdf
Regulatory	
Government	https://www.gov.uk/government/news/cannabis-derived-medicinal-products-to-be-made-available-on-prescription
Government	https://www.gov.uk/government/publications/supply-unlicensed-medicinal-products-specials
Home Office	https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/757786/factsheet-cannabis-cbd-and-cannabinoids-v1-3-2018.pdf
Canadian Government	https://www.canada.ca/en/health-canada/topics/cannabis-for-medical-purposes.html
Australia	https://www.tga.gov.au/access-medicinal-cannabis-products-1

Manufacturers	
	https://bedrocan.com
	https://www.auroramj.com/
	https://www.canopygrowth.com/
	https://www.tilray.com/
	https://www.odc.gov.au/manufacturers-and-suppliers-medicinal-cannabis-products
Products	
	https://www.sahealth.sa.gov.au/wps/wcm/connect/15eb0b8040db6e0ea47ca73ee9bece4b/Fact+Sheet+-+Medicinal+Cannabis+Products+%28Oct+2018%29.pdf?MOD=AJPERES&CACHEID=ROOTWORKSPACE-15eb0b8040db6e0ea47ca73ee9bece4b-msqDVKy
Media	
	https://www.bbc.co.uk/news/health-44968386

Product			Recommended price
SOFT GELS	**concentration per cap**	**caps per bottle**	
Red 2.5	2.5mg THC no CBD	60	£143.75
Red 10	10mg THC no CBD	30	£172.50
Blue 2.5	2.5mg THC 3.75mg CBD	60	£143.75
Blue 10	10mg THC 15mg CBD	30	£172.50
Yellow 20 mg CBD	20mg CBD no THC	30	£115.00
OIL	**concentration per ml**	**mls per bottle**	
Red	26.3mg THC < 1mg CBD	40	£230.00
Blue	10mg THC 15mg CBD	40	£149.50
Yellow	20mg CBD <1mg THC	40	£80.50
FLOWER	**%**	**Grams per pot**	
Red 1	20-23 THC	5	£63.25
Red 2	17- 20THC	5	£63.25
Orange	12-15 THC	5	£63.25
Blue	8-11 THC 8-11 CBD	5	£63.25
Green	5-8 THC 9-12 CBD	5	£63.25
Yellow	14 CBD <1 THC	5	£63.25

Royal College of Physicians

RCR The Royal College of Radiologists

Recommendations on cannabis-based products for medicinal use

These recommendations have been jointly produced by the Royal College of Physicians (RCP), the Royal College of Radiologists (RCR) and in liaison with the Faculty of Pain Medicine of the Royal College of Anaesthetists.

October 2018

1. Background

Professor Dame Sally Davies, the chief medical adviser to the UK government, recently examined evidence of the medicinal benefit of cannabis-based products. She concluded that there is now sufficient evidence of medicinal benefit in some conditions and advised that the whole class of cannabis-based medicinal products should be moved out of Schedule 1 of the Misuse of Drugs Regulations 2001.[1]

The Advisory Council on the Misuse of Drugs agreed that there is now evidence of medicinal benefit for some cannabis-derived products in certain medical conditions for some patients, although they deferred any recommendations on the rescheduling of synthetic cannabinoids for further consideration as part of their longer term review, due in summer 2019. They also advised that clinicians in the UK should have the option to prescribe cannabis-derived medicinal products (hereafter referred to as 'cannabis-based products for medicinal use' (CBPM), which is the term used in legislation) that meet the requirements for medicinal standards to patients with certain medical conditions.[2]

The decisions to prescribe will be restricted to registered medical practitioners on the General Medical Council's specialist register. The National Institute of Health and Care Excellence (NICE) has been commissioned to produce formal guidelines by October 2019 but in view of the need for interim guidance on the use of CBPM the Royal College of Physicians (RCP) was asked to produce such guidance around the management of cancer, palliative and chronic pain, including in multiple sclerosis.

The following guidance has been produced by a collaboration of the RCP Joint Specialty Committee for Palliative Medicine, the Royal College of Radiologists (RCR) and the Faculty of Pain Medicine.

2. CBPM for chemotherapy-induced nausea and vomiting (CINV)

2.1 Summary

There is good evidence that cannabinoids are effective in preventing CINV but they have a high side effect profile and there are more efficacious agents available. Cannabinoids should remain an option for those who have failed standard therapies but not used as a first-line treatment.

2.2 Treatment of CINV

Cannabinoids, most particularly nabilone, a synthetic analogue of Δ9-tetrahydrocannabinol (Δ9-THC),[3] have randomised controlled trial (RCT) evidence of efficacy in prevention of CINV but have high side effect profiles in the form of neurological symptoms.[4] Discontinuation rates for cannabinoid therapy are high in published trials. Most of the data is relatively old and they have not been directly compared against neurokinin-1 receptor antagonists which have emerged as the most effective agents for highly emetogenic agents such as cisplatin.

2.3 Prevention of CINV

There is some potential emerging evidence of the efficacy of cannabinoids in anticipatory CINV.[5] Anticipatory CINV is less common as there are efficacious therapeutic agents managing CINV preventing its development. However, it can be a distressing symptom for which there are limited therapeutic options.

2.4 Adverse effects of CBPM

Anecdotally, cannabinoids are either extremely well liked or significantly disliked by patients (perhaps in both cases because of the euphoria they can sometimes produce).

CBPM have significant adverse effects including psychological, neurological and gastrointestinal. Psychosis is a particular concern.[6,7] Oromucosal preparations such as Sativex® can cause buccal irritation and ulceration.

3. CBPM for pain

3.1 Summary

There is limited research available from which to create guidance on the effect of CBPM on pain in palliative care patients, including those with cancer. Studies show mixed results or statistically significant results of uncertain clinical significance. In view of this and the adverse effects associated with CBPM, their place in the treatment of pain in palliative care patients is unclear and not recommended in routine clinical practice. There is no robust evidence for the use of CBPM in chronic pain and their use is not recommended.

3.2 Pain in palliative care context

A combined formulation of Δ9-THC with cannabidiol (nabiximols, sold under the brand name Sativex®) is the CBPM which has been studied in this population. In patients with multiple sclerosis and refractory spasticity, a meta-analysis found a statistically significant benefit with uncertain clinical significance for the use of Sativex®.[3] In the treatment of cancer pain, Sativex® shows mixed results from five RCTs, with two showing some benefit and three showing no benefit over placebo.[8,9,10,11]

3.3 Chronic neuropathic pain

The Cochrane review[12] in March 2018 concluded, 'There is a lack of good evidence that any cannabis-derived product works for any chronic neuropathic pain.' It also concluded that 'The potential benefits of cannabis-based medicine in chronic neuropathic pain might be outweighed by their potential harms.'

A comprehensive meta-analysis of pharmacotherapy for neuropathic pain was published in *The Lancet Neurology* in 2015.[13] It is important and robust because it accessed the unpublished trials and used the GRADE system to draw conclusions. It recommended against the use of cannabinoids in neuropathic pain, mainly because of negative results, potential misuse, diversion, and long-term mental health risks of cannabis particularly in susceptible individuals. Only two of nine trials of nabiximols in neuropathic pain were positive.

A review and accompanying editorial in *Pain*[14,15] concluded, 'It appears unlikely that cannabinoids are highly effective medicines for chronic non-cancer pain.'

National reports from the USA,[16] Australia[17] and Ireland[18] all comment on the lack of good quality evidence regarding short and long-term outcomes for both benefit and harm. The widespread use of high-dose opioids in the absence of good long-term evidence over the past 20 years is already the cause of considerable concern, and it is not difficult to see potential parallels.

Patients living with chronic pain often have complex comorbidities and a multidisciplinary approach to management that includes physical and psychological therapy rather than reliance on medicines alone is more likely to be effective.

4. Non-CBPM forms of 'cannabis'

The use of unrefined dried plants containing a variety of cannabinoids and other pharmaco-active chemicals of varying quantity cannot be supported due to the variability of preparations and lack of any trial evidence. The potential for exposure to unknown significantly harmful chemicals and potential diversion to non-medical use are also strong arguments against support for their use in patients. Therefore, only pharmaceutical grade products that are licensed by the Medicines and Healthcare products Regulatory Agency (MHRA) or supplied in accordance with MHRA guidance on the supply of unlicensed cannabis-based products for medicinal use should be considered.

5. Other comments

Cannabinoids do present a class of agents with potential benefit in the management of patients with chronic pain, given the limited pharmaceutical armoury. If there are specific patient populations that will benefit they should not be denied access when the evidence is available.

However, the medicinal use of cannabinoids needs to be carefully considered and researched in a comprehensive fashion, as would be the case for any new medicinal product reaching the therapeutic market. Anecdotal positive reporting is not a mechanism to protect public safety.

We recommend that a database is established for the analysis of data from all areas. Such a database would need to be independent, compulsory, fully funded and under the auspices of a suitable organisation (eg NICE) to assess the value of treatments of relative rarity.

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