HERBAL CANNABIS FOR MEDICAL USE: A SPECTRUM OF REGULATORY APPROACHES
In recent decades, several political, legislative and judicial processes have advanced efforts to allow the use of the cannabis plant and its derivative products for medicinal purposes. The cannabis products that are currently being used medicinally can take different forms. These range from pharmaceutical preparations that have marketing authorization to cannabis plant extracts and magistral preparations. Pharmaceutical preparations are typically regulated by long-existing frameworks that govern pharmaceutical products, while cannabis plant extracts and magistral preparations and other cannabis-based products have started to be regulated more recently. Approaches to regulating medical cannabis differ widely between countries, leading to substantial variations in terms of products available, patient accessibility and supply mechanisms, with potentially different impacts on the non-medical market for cannabis.

### Cannabis-based products

The term “cannabis-based products” refers to a broad range of products and may include any of the following:

- Herbal cannabis, that is, harvested and dried female flowering tops, which contain the highest concentrations of cannabinoids, THC, CBD, CBG (cannabigerol), etc.
- Herbal cannabis is also a generic term used to denote cannabis products that are not pharmaceutical products with marketing authorization, such as nabiximols.
- Cannabis plant extract refers to the extract made from the resinous flowers and small leaves of the cannabis plant.
- A medical-grade cannabis product is medicinal cannabis that has been certified for biocompatibility through a range of tests and standards and meets the standards of good agricultural and collection practices (GAP), good manufacturing practices (GMP) and active pharmaceutical ingredients (API).

Different batches of a medical-grade cannabis product will have the same composition and ratio of the main cannabinoids. However, a medical-grade cannabis product may not have marketing authorization.

In the present chapter, the term “cannabis-based products” is used to describe the medical use of any of the above.

Additionally, a “pharmaceutical product with marketing authorization” has gone through clinical trials for safety and efficacy, complies with quality guidelines for production (e.g. good manufacturing practices) and has a marketing authorization issued by a drug regulatory authority.
This chapter provides an overview of the heterogeneity of the regulatory approaches in place for cannabis-based products, based on a few country examples. The aim is to provide the reader with some key elements that define the different regulatory approaches to the medicinal market for herbal cannabis products by looking at access by patients (the “who”) to particular products (the “what”) through various supply mechanisms (the “how”), with the aim of identifying the regulatory factors that determine the degree to which medical approaches to cannabis-based products differ in terms of limitations in accessing medical cannabis-based products or enabling conditions that could facilitate spillover into non-medical markets. The rationale for different approaches to regulating cannabis-based products may arise from various “push” and “pull” factors, including from advocacy groups and the industry, that shape the overall permissibility of access to cannabis-based products and the levels of control over their production, contents and quality.

What is presented in this chapter is not an exhaustive or a comprehensive review of regulatory approaches to medical cannabis-based products. It is based on a limited number of countries to illustrate the range of approaches taken.

One of the challenges of regulating the medical use of cannabis-based products, as for any medical product, is to ensure the right balance between guaranteeing the supervised use of approved products for recognized conditions and promoting the rational use of such products and preventing their diversion and non-medical use. Similar to the typical medical practice, this would entail ensuring a regulatory mechanism by which the approval of the medical products is based on evidence of their safety and efficacy in treating specific conditions, and that they adhere to quality control measures and are made affordable and accessible to patients in need, with the necessary safeguards in place.

The regulation of cannabis for medical purposes in the Single Convention on Narcotics Drugs of 1961 as amended by the 1972 Protocol

- Establishing a national cannabis agency (in line with articles 28 and 23 of the 1961 Convention as amended). The duties of such an agency include, in particular, the designation of the specific areas and plots of land where cultivation will be permitted and the establishment of a licensing system for the cultivation and production of cannabis-based products.
- Ensuring that the agency purchases and takes physical possession of cannabis crops and has the exclusive right of importing, exporting, wholesale trading and maintaining stocks of the cannabis products (article 23).
- Estimating the anticipated consumption of cannabis for medicinal purposes and submitting annually to the Board the estimates, along with statistical reports on the consumption, stocks and production of cannabis for such purposes (articles 19 and 20).
- Ensuring that the prescription of cannabis for medical use is performed with competent medical knowledge and supervision.
- Ensuring that the labelling under which cannabis for medicinal purposes is offered for sale shows the exact contents by weight or percentage (article 30).
- Ensuring that the provision of medical cannabis and its practice is based on available scientific evidence and consideration of potential side effects.

Evidence of the effectiveness of cannabis to treat medical conditions

Renewed interest in the therapeutic potential of cannabis and cannabis extracts followed the discovery of the endocannabinoid system in the mid-1980s and growing understanding of that system throughout the 1990s. Nevertheless, evidence of the effectiveness of cannabinoids in treating certain conditions remains limited, and cannabinoids are typically recommended for use after a patient has failed to respond to conventional treatment for those conditions or as an adjunctive therapy. There is conclusive or at least substantial evidence that cannabis and cannabinoids are effective for the treatment of chronic pain in adults, in the treatment of chemotherapy-induced nausea and vomiting, and for mitigating patient-reported multiple sclerosis spasticity symptoms and epilepsy. Evidence of the effectiveness of cannabis in the treatment of other conditions is, however, moderate, insufficient or inconclusive.

In the scientific literature, researchers have hypothesized an “entourage effect”, whereby the combination of phytocannabinoids, terpenes and other constituents of the whole cannabis plant has a greater medicinal effect than an isolated cannabinoid extract present in a pharmaceutical product; such an effect also lead patients in some jurisdictions to indicate their preference for herbal cannabis, as opposed to specific cannabinoid or cannabis extracts.
### PHARMACEUTICAL AND CANNABIS-BASED PRODUCTS

<table>
<thead>
<tr>
<th>Medical products</th>
<th>Many countries have regulated and allowed the medical use of cannabinoid pharmaceutical as any other pharmaceutical product with marketing authorization with clearly determined conditions and recommendations on dosage and conditions for use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nabilone: Oral capsule containing synthetic cannabinoid similar to THC</td>
<td></td>
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<tr>
<td>Dronabinol: Oral capsule or solution containing synthetic THC</td>
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<tr>
<td>Nabiximols: Containing balanced quantities of THC and CBD</td>
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</tr>
<tr>
<td>Epidiolex: (cannabidiol) Plant-derived CBD oral solution</td>
<td></td>
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</tbody>
</table>

### Cannabis-based products

<table>
<thead>
<tr>
<th>Standardized cannabis-based medical products</th>
<th>Magistral preparations</th>
<th>Cannabis-based products with unspecified composition</th>
<th>Raw cannabis</th>
<th>Approaches to regulating cannabis-based products for medical use vary widely between countries</th>
</tr>
</thead>
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<tr>
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</tbody>
</table>

### Variable THC/CBD composition

Source: Adapted from EMCDDA “Medical use of cannabis and cannabinoids: questions and answers for policymaking” (Luxembourg, 2018); and UNODC, responses to the annual report questionnaire.

### COUNTRIES THAT HAVE PROVISIONS FOR MEDICAL USE OF CANNABIS, 2021

As of 2021, 64 countries had provisions in their national legislation, or had developed guidelines, allowing the medical use of cannabinoid pharmaceutical preparations and/or cannabis-based products for a range of medical conditions.

Out of the 64 countries, 34 countries allow the use of cannabis-based products for the treatment of a range of medical conditions.

#### Number of countries having provisions for medical use of cannabis, 2021:

<table>
<thead>
<tr>
<th>Region</th>
<th>Yes</th>
<th>No (Low confidence)</th>
<th>No (High confidence)</th>
<th>No data available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>9</td>
<td>42</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Americas</td>
<td>15</td>
<td>2</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Asia</td>
<td>6</td>
<td>4</td>
<td>30</td>
<td>8</td>
</tr>
<tr>
<td>Europe</td>
<td>32</td>
<td>5</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Oceania</td>
<td>2</td>
<td>13</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Is regulating medical cannabis-based products similar to regulating traditional herbal medicines?

The countries that allow the medical use of cannabis-based products face a range of options and issues in relation to the regulation of such products that are similar to those that may affect the regulation of any of the traditional herbal medicines and products.

The approaches to regulating the medical use of cannabis can range from those used in regulating pharmaceutical products to those used in regulating herbal medicines. Even within the regulatory options for herbal medicines, there is a range of options that countries have chosen and apply to varying degrees.

Apart from those herbal products that are exempted from regulatory control, most of the herbal products for medicinal use are regulated in a manner that does not differ considerably from the regulation of pharmaceutical products. However, the regulatory control of herbal products may differ among countries, and not all of the regulatory requirements for traditional herbal medicines may be applied for a particular herbal product.

Traditionally, countries have taken different approaches to regulating medical herbal products, based on how they may be defined as products. Some traditional herbal medicines, like any other pharmaceutical product, require strict monitoring and controls, including allowing access only through prescriptions, while others, such as supplements, are available over the counter. One challenge in the regulation of herbal medical products is the natural variability that occurs within a plant’s constituents. A plant – or a herb-based product derived from a plant – may contain one or more active ingredients, and different batches of the

## Comparison of broad guidelines for herbal and pharmaceutical products

<table>
<thead>
<tr>
<th></th>
<th>Herbal products</th>
<th>Pharmaceutical or medical-grade products</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agency</strong></td>
<td>National law, policy or regulation on traditional medicines</td>
<td>National pharmaceutical regulatory body</td>
</tr>
<tr>
<td><strong>Pharmacopoeia and monograph</strong></td>
<td>Description of pharmacopoeia and monograph defining qualifying conditions and dosage</td>
<td>Pharmacopoeia or monograph defining qualifying conditions and dosage</td>
</tr>
<tr>
<td><strong>Evidence of efficacy and safety</strong></td>
<td>Evidence of therapeutic effects and benefits based on established traditional herbal medical practices, as well as evaluation of quality, safety and efficacy of herbal medicines. For dietary supplements, any claim can be accepted</td>
<td>Evidence-based laboratory and clinical trials among humans, with evaluation of quality, safety and efficacy of pharmaceutical products, with identification of active pharmaceutical ingredient</td>
</tr>
<tr>
<td><strong>Designation</strong></td>
<td>Either as:</td>
<td>Either as:</td>
</tr>
<tr>
<td></td>
<td>• Prescription herbal medicines</td>
<td>• Prescription medicines</td>
</tr>
<tr>
<td></td>
<td>• Over-the-counter herbal medicines</td>
<td>• Over-the-counter medicines</td>
</tr>
<tr>
<td></td>
<td>• Dietary supplements</td>
<td>• Dietary supplements</td>
</tr>
<tr>
<td></td>
<td>• Health food</td>
<td></td>
</tr>
<tr>
<td><strong>Manufacturing</strong></td>
<td>Quality assurance through:</td>
<td>Quality assurance (national laboratories) through:</td>
</tr>
<tr>
<td></td>
<td>• Application of good manufacturing practices (GMP)</td>
<td>• Application of good manufacturing practices (GMP)</td>
</tr>
<tr>
<td></td>
<td>• Good laboratory practices</td>
<td>• Active pharmaceutical ingredients (API)</td>
</tr>
<tr>
<td></td>
<td>• Active p ingredients (API)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Good agricultural and collection practices (GAP or GACP)</td>
<td></td>
</tr>
<tr>
<td><strong>Marketing</strong></td>
<td>Marketing authorization</td>
<td>Marketing authorization</td>
</tr>
<tr>
<td><strong>Pharmacovigilance</strong></td>
<td>Post-marketing surveillance of herbal medicines for adverse effects</td>
<td>Pharmacovigilance based on reporting of adverse effects</td>
</tr>
<tr>
<td><strong>Essential medicines list</strong></td>
<td>National law, policy or regulation on traditional medicines</td>
<td>National essential medicines list</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Registration requirements to establish interchangeability (bioequivalence)</td>
</tr>
</tbody>
</table>

same plant or herb may vary in their content of active ingredients. In addition, variations in the cultivation environment (e.g. soil, water, sunlight, humidity, pesticides, fungi and other contaminants) can affect the quality of any herbal medicine. For these reasons, there are recommended quality control practices for plant-based pharmaceutical preparations that may also be applied to cannabis-based products for medical use, with the aim of protecting consumer health by ensuring that medicines are effective, safe and of high quality.

**Approaches to patient access to medical cannabis-based products: from restricted access for only few predetermined conditions to limited oversight for unspecified conditions**

A range of regulatory approaches provide patients with access to medical cannabis-based products. At one end of the spectrum is the regulatory approach, where patients with very specific conditions only can access medical cannabis products. For example, in the United Kingdom, medical cannabis products for medical use can be prescribed only by a specialist based in a hospital for specific conditions, such as...

| Recommended quality control practices for plant-based medicinal preparations |
|---|---|---|
| **Quality control practice** | **Description** | **Result or purpose** |
| **GAP – good agricultural practices or GACP – good agricultural and collection practices** | Quality assurance mechanism ensuring homogeneity of concentrations of herbal preparations (e.g. cannabinoid concentrations in the case of cannabis-based productions) applied to medical plants in order to obtain standardized products | Control of batch-to-batch variation (e.g. cannabinoid profile in the case of cannabis-based products); limitation of microbiological and chemical contamination (e.g. pesticides, heavy metals) of the herbal material; and guaranteeing that the plant material is free from microbiological contamination (e.g. bacteria and fungi) |
| **GMP – good manufacturing practices** | Quality assurance for industrial-scale production of herbal products (in the context of cannabis-based products, assuring quality control measures in production, including of the contents and composition of cannabinoids) | Certification of the production site evaluation of basic quality parameters, including the fulfilment of criteria established in pharmacopeial monographs |
| **API – active pharmaceutical ingredients** | Quality assurance for each herbal pharmaceutical product (in the cannabis-based products context, it would include those that are cannabis extracts) | Homogeneity of chemical composition and content (in the cannabis-based products context, it would be to ensure the homogeneity of the cannabinoids) |

chemotherapy-induced nausea and vomiting, spasticity associated with multiple sclerosis and treatment-resistant epilepsies. In Germany, every physician can prescribe medicinal cannabis products. The physician has the responsibility for every single prescription of a medical cannabis product; however, for the first prescription, the physician is required to get the approval of the patient’s health insurance company. In the Kingdom of the Netherlands, a general practitioner can prescribe medical cannabis-based products, and their prescription is allowed only when conventional treatments (using authorized medicines) have failed or cause adverse effects. In Israel, the cannabis guidelines lay down the conditions for which medical cannabis-based products can be prescribed. The attending physician is required to determine the appropriate product type and adjust the potency, route of administration, monthly quantity, daily dosage and consumption according to those guidelines.

A few countries, for example Australia and Brazil, make cannabis-based products available to a limited set of patients with specific conditions through existing therapeutic special access schemes. These existing national programmes, typically known as “compassionate access schemes”, “compassionate use schemes” or “authorized prescriber schemes”, allow the use of cannabis-based products. In the case of Australia, the “Special Access Scheme” authorizes lawful access to certain medical practitioners and nurse practitioners who may prescribe unapproved medicinal cannabis products to clinically appropriate patients under their care. As a condition of approval to use unapproved medicinal cannabis products via these schemes, the prescribing health practitioner is required to have considered all clinically appropriate treatment options before applying to access an unapproved medicinal cannabis product for their patient and report adverse events and defects associated with the unapproved medicine to the Therapeutic Goods Administration. In the case of Brazil, cannabis-based products are made available on a controlled basis and under controlled conditions. Access to cannabis-based products is subject to prescription by a qualified health professional, who is responsible for defining the indications and appropriate dosage of the cannabis-based product on the basis of a clinical assessment of the patient.

In some jurisdictions in the United States, a compassionate use programme allows the use of low-THC cannabis-based products for patients with a limited set of medical conditions.
At the other end of the spectrum are regulatory approaches like that of Canada and several states in the United States, where patients with qualifying medical conditions, such as “chronic pain”, “anxiety” and “muscle spasms”, can obtain a recommendation from a licensed health care practitioner for cannabis.\textsuperscript{20, 21, 22} Similarly, in South Africa medical cannabis-based products can be prescribed for any health condition if the physician with whom the patient is registered determines that it could help the treatment of that health condition.\textsuperscript{23, 24}

Guidance or guidelines are available in many countries to inform the medical use of cannabis-based products, including in Australia, Canada, the United Kingdom, Israel, the Kingdom of the Netherlands, and some states in the United States.\textsuperscript{25} For example, the Israeli Medical Cannabis Agency has a medical-grade cannabis “Cannacopoeia” – a manual for prescribing physicians as a good clinical practice guideline – as well as guidelines for high-quality practice for all supply chain segments. Notably, the clinical guidance on the qualifying conditions and on prescribing specific cannabis-based products for those conditions may vary by country or even within a country.\textsuperscript{26}

Medical cannabis products in the Kingdom of the Netherlands

<table>
<thead>
<tr>
<th>Category</th>
<th>Product</th>
<th>THC</th>
<th>CBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>High THC, low CBD</td>
<td>Bedrocan&lt;sup&gt;®&lt;/sup&gt;</td>
<td>$\geq 22$</td>
<td>$&lt;1$</td>
</tr>
<tr>
<td></td>
<td>Bedica&lt;sup&gt;®&lt;/sup&gt;</td>
<td>$\geq 14$</td>
<td>$&lt;1$</td>
</tr>
<tr>
<td></td>
<td>Bedrobinol&lt;sup&gt;®&lt;/sup&gt;</td>
<td>$\geq 13.5$</td>
<td>$&lt;1$</td>
</tr>
<tr>
<td>THC and CBD balanced</td>
<td>Bediol&lt;sup&gt;®&lt;/sup&gt;</td>
<td>6.3</td>
<td>8</td>
</tr>
<tr>
<td>Low THC, high CBD</td>
<td>Bedrolite&lt;sup&gt;®&lt;/sup&gt;</td>
<td>$&lt;1$</td>
<td>9</td>
</tr>
</tbody>
</table>

cannabis leaf, inflorescence and extracts, are available as herbal medicinal preparations.\textsuperscript{31, 32, 33} These products have not been approved by the federal Food and Drug Administration, however, and their marketing and use is illegal under federal law throughout the United States.

Some jurisdictions, such as Israel and the Kingdom of the Netherlands, require producers of cannabis-based products to provide evidence of product quality and consistency to a central regulatory authority and to ensure that patients receive standardized doses of cannabis-based products that are free of contaminants and adulterants.\textsuperscript{34} In the Kingdom of the Netherlands, the Office for Medicinal Cannabis Research, for instance, makes available five types of medical cannabis-based products with different cannabinoid compositions and content to be used for specific qualifying conditions. The quality of the herbal cannabis in each of the products is guaranteed by constant supervision to ensure compliance with good agricultural practices and good manufacturing practices and by batch-to-batch quality control analysis performed by a certified laboratory.\textsuperscript{35}

In Germany, several hundred pharmaceutical-grade cannabis herbal products, which are imported from more than a dozen different countries, are available on the market.\textsuperscript{36} The concentrations of the specific medical products range from less than 1 per cent to 30 per cent THC and from less than 1 per cent to 17 per cent CBD.\textsuperscript{37} Some of these products, similar to those in the Kingdom of the Netherlands, include preparations with high THC and low CBD (e.g. Tilray THC 25\textsuperscript{®} contains 25 per cent THC and less than 1 per cent CBD), THC and CBD balanced (e.g. Tilray THC 10\textsuperscript{®} contains 10 per cent of both THC and CBD), and high CBD and low THC (e.g. Bedrolite\textsuperscript{®}, contains less than 1 per cent THC and 8.1 per cent CBD).\textsuperscript{38}

The Israeli Medical Cannabis Agency makes available two forms of medical cannabis-based products – inflorescence and cannabis extract diluted in oil. Each of these forms is manufactured in the three groups of products, i.e. high-CBD products with 20 per cent or higher CBD and 1 per cent or lower THC; high-THC products, which contain between 10 and 20 per cent THC and 2 to 4 per cent CBD; and CBD-THC balanced products, which contain nearly equal quantities of the two cannabinoids (5 per cent THC and CBD or 10 per cent CBD and THC).\textsuperscript{39} Each medical cannabis-based product that is approved for medical marketing and is of a quality suitable for medical use, is marked as “IMC-Medical Grade”.\textsuperscript{40} However, unlike in the
Kingdom of the Netherlands, although all aspects of the supply chain are standardized, the production or manufacturing of those medical cannabis-based products is not centralized.

In other jurisdictions, the cannabis-based products made available for medical use may be neither limited nor highly regulated. While the Government of Australia makes cannabis-based products available for medical use through its special access scheme, the specific products used by patients are all unapproved by the federal medicines regulator, the Therapeutic Goods Administration, although the Administration does require companies or individuals that produce or grow a medical cannabis-based product to follow good manufacturing practice for medicines. More than 40 companies were registered in 2022, and several dozen more imported products have been approved, offering patients in Australia a wide range of medical cannabis-based product options with varying cannabinoid compositions, including CBD-only or CBD-predominant, CBD-THC balanced, and THC-only or THC-predominant products.

Canada and some jurisdictions in the United States have allowed a much wider array of producers and cannabis-based products in their medical markets; in the case of United States, these include products that are not approved by the federal Food and Drug Administration and are therefore illegal under federal law throughout the country. In Canada, people can access cannabis-based products for medical purposes by registering with licensed cannabis producers, they can register with Health Canada to produce a limited amount for their own medical purposes, or they can designate someone else to produce cannabis for them. The cannabis-based products available for medical (and equally for non-medical) purposes include products ranging from plants or seeds to dried and fresh cannabis plant, extracts, edibles and topical ointments.

There are risks associated with self-cultivation or home cultivation of cannabis for medicinal use. The extracts from cannabis plants may contain pesticides or herbicides as well as other contaminants. The THC potency may vary from one plant to another, making it difficult to determine the precise dosage for the consumption of cannabis, and rather than providing therapeutic benefits, such use may actually harm the person. In addition, if cannabis-based products are not stored safely in a dwelling, it may even lead to their diversion. Different studies that have reviewed the cannabis-based products available in medical cannabis dispensaries in jurisdictions in the United States have reported a variety of products available; several studies have also noted that these products are similar to the cannabis-based products offered for non-medical use. Another issue noted in studies of the medical cannabis market in the United States is that the contents of the cannabis-based products do not always match what is indicated on the labels. For instance, in one study some products contained negligible amounts of CBD and others contained significantly more THC than indicated on the label; the median THC-to-CBD ratio of the products that were tested was 36:1, placing patients at risk of experiencing adverse effects. In another study, the THC content observed in the samples that were tested were considered to be high enough to produce intoxication or impairment, especially among children, thereby negating any potential clinical response. The level of THC and CBD and their ratio are important factors in the therapeutical effects of the products. In a study, for instance, it was shown that the exposure of patients with chronic pain to high THC concentrations, i.e. higher than 10 to 15 per cent THC, puts them at risk of experiencing side effects or adverse events without any further beneficial effect of pain relief. Similarly, a THC-CBD balanced product is considered appropriate for pain management, and cannabis-based products with other THC-to-CBD ratios or with a THC content higher than 15 per cent may not provide the desired therapeutic benefit.

Supply of medical cannabis-based products: from centralized systems to unlicensed or unregulated supply

Regulatory control of the supply of medical cannabis may vary, with limits placed on the number of producers, distributors and retailers supplying medical cannabis products and limits on the actual products allowed. Regulations may also relate to the practice of cultivation and production of cannabis-based
medical products, requiring that suppliers follow good agricultural practices, good manufacturing practices or ensure the consistency of the active pharmaceutical ingredients. Furthermore, regulatory approaches can range from a centralized and closed cultivation and production system to decentralized approaches and ultimately approaches with limited to no oversight over the production or the quality of cannabis-based products for medical use. The standards of good agricultural practice and good manufacturing practice may be applied within any of these approaches, but oversight of the application of those standards may be easier in a more centralized and closed system.

Centralized systems for the supply of medical cannabis products are in place in countries such as the Kingdom of the Netherlands, Italy, Israel and Germany. In the Kingdom of the Netherlands, the Office of Medicinal Cannabis purchases cannabis from all licensed producers and maintains a monopoly over the supply of medical cannabis-based products to pharmacies and general practitioners. The Cannabis Agency of Germany controls cultivation of medicinal cannabis in Germany and its distribution. The cultivators of medicinal cannabis in Germany and the company commissioned with its distribution were selected in a Europe-wide tendering process. Another example of centralized production is Italy, where only two standardized cannabis-based products of pharmaceutical grade (FM2, containing 5–8 per cent THC and 7–12 per cent CBD, and FM1, containing 13–20 per cent THC and less than 1 per cent CBD) are made available through the Military Pharmaceutical Chemical Works of Florence. The Israeli Medical Cannabis Agency also has guidelines for the production of standardized medical cannabis-based products, which are equivalent to the guidelines for good manufacturing practices applied in the European Union, and internalizes the entire supply chain through a centralized system.

Examples of less regulated approaches are those observed in South Africa and Brazil. The South African Health Products Regulatory Authority allows patients to access unregistered cannabis-based products by applying for individual authorization. The Authority issues licences for cannabis cultivation and the manufacture of cannabis-based products. Such licences are subject to broader regulations on good agricultural practices and good manufacturing practices and strict controls to ensure security to prevent the diversion of cannabis-based products. In Brazil, the national agency responsible for the medical cannabis programme (Agência Nacional de Vigilância Sanitária) issues individual import authorizations as well as broader authorizations for cannabis-based products to be marketed in Brazil for a specified period. However, applicants seeking authorization have been exempted from the obligation to present proof of safety and efficacy of the products since many of the imported products are not subject to regulatory approval as medicines in their countries of origin.

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**SPECTRUM OF APPROACHES FOR REGULATING THE SUPPLY OF MEDICAL CANNABIS AND CANNABIS-BASED PRODUCTS**

- **Centralized**
  - Centralized and closed cultivation and production scheme

- **Decentralized**
  - Decentralized cultivation and production, including import of products
  - Loosely regulated with decentralized cultivation and production of cannabis products

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Other examples of less or minimally regulated supply chains are some state jurisdictions in the United States, where patients or their caregivers are allowed to grow their own cannabis for medicinal purposes without the need for a formal licence or the requirement to follow good agricultural practices or good manufacturing practices for the plants and other medical cannabis products that are produced, with inherent risks of product variation and contamination, e.g., with pesticides and heavy metals. Medical cannabis dispensaries also operate in many of these jurisdictions, with varying legal requirements across states on the products and the contents that are allowed to be sold, the companies allowed to manufacture those products and the practices that they may follow.62, 63

Other issues and considerations for regulating cannabis-based products for medical purposes

Besides the main areas of medical cannabis regulation reviewed above, there are other issues that could influence the evolution of regulatory approaches to medical cannabis-based products. The evidence on the conditions for which medical cannabis-based products can be effective is continuously evolving, and the use of cannabis-based products for conditions for which there is a perceived benefit may also evolve. Other factors that may also have an influence on regulatory approaches to medical cannabis-based products include changes in the perception of risk and harms of non-medical cannabis use, as well as product innovation and diversification led by commercial interests, which may also open the market for the recreational or non-medical use of cannabis.

Dosage of cannabis-based products

There remains limited research on cannabis-based products for therapeutic use. Given the costs and time involved in developing a new medical product, especially for a plant-based or herbal product such as cannabis, in an environment of developments to legalize the non-medical use of cannabis, there is less incentive for pharmaceutical companies to finance clinical trials that generate evidence using the “gold standard” of randomized clinical trials for qualifying medical conditions on the basis of the exact concentration and dosage at which medical-grade cannabis-based products can be effective. For that reason, the pharmaceutical industry has not gone beyond the development of pharmaceutical products such as nabiximols, nabilone and dronabinol. As a result, for cannabis-based products, standards for effective dosages, typologies and medical conditions for which they would exhibit proven efficacy are not as well established as for pharmaceutical products. There are advocates who, instead of pursuing this “gold standard”, favour relying on the real-world or lived experiences of people, using information similar to pharmacovigilance data on adverse events from patients who use a range of cannabis-based products for medical purposes.64 These are issues that have emerged and also may have an influence on the regulation of traditional herbal medicine.65

A false perception of health and safety

It has been argued that in the absence of clinical guidelines on specific medical conditions that can be treated with cannabis-based products or on the dosing of cannabinoids that could be prescribed, health practitioners are often uncomfortable speaking to patients about these products. Patients may then turn to their friends or family, social media, cannabis dispensaries and cannabis advocacy groups to learn about dosage and self-administration of cannabis for medical purposes.66

The perception or belief, backed by cannabis advocacy groups and the industry, that herbal cannabis and cannabis-based products are a natural remedy and that people need to accept the “natural origin” of cannabis plant with no “safety concerns”, has reduced perceptions of harm for a wide array of health conditions in addition to the non-medical use of cannabis.67 The marketing of CBD-based products as health and wellness products, often labelled as cannabis, has amplified this perception. While there are conditions for which the science does support therapeutic benefits from cannabis-based medications,68, 69 there is also growing evidence documenting adverse events associated with high-CBD products,70 high-THC products and drug interactions with other drugs that may be used in the treatment of a condition.71, 72, 73, 74
Moreover, medical cannabis markets that are minimally regulated and exposed to competing commercial interests, such as those in jurisdictions in the United States, have been shown in various studies to give a degree of credibility to the use of cannabis-based products in general (not only medically). They have led to a shift in public opinion, encouraging voter initiatives for the legalization of the non-medical use of cannabis in several states\textsuperscript{75,76,77} and to an increase in the non-medical use of cannabis by adults\textsuperscript{78,79} as well as an increase in emergency room visits and hospitalizations related to adverse effects, such as cannabis hyperemesis syndrome, after cannabis consumption\textsuperscript{80,81}.

**Commercial interests**

Lastly, in jurisdictions with competing commercial interests, there has also been an industry-led diversification of products, some of which may contain a specific cannabinoid or a combination of either THC or CBD, or both, at levels that may not be safe for the conditions for which the products are advertised\textsuperscript{82,83}. There are reports from patients in the United States who are unable to find products containing their desired ratios of THC and CBD since the cannabis industry is instead producing products that appeal to non-medical users\textsuperscript{84,85,86}.

The examples of regulatory approaches presented above highlight the range of choices that regulators need to consider when defining a medical market for cannabis-based products. These choices determine the permeability of the market. There are key factors that ensure limited product availability, with proven safety and efficacy, that can address legitimate medical needs, making medical products available for the conditions where scientific evidence is available. Such factors may also limit potential spillover into a non-medical or recreational use market. In jurisdictions with minimal or no regulation of the market for medical cannabis-based products, there are concerns regarding quality assurance for the products as well as the diffusion of new products containing ingredients that are not well suited for medical conditions, and regarding changes in the perception of harm associated with the non-medical use of cannabis. Regulatory approaches that centralize the supply of medical cannabis are also likely to limit the influence of private sector entities with commercial interests that advocate for increasing the acceptability of cannabis use and the portrayal of cannabis as a healthy choice.

The regulation of medical cannabis programmes also depends on the expansion of clinical research to obtain the needed evidence base regarding qualifying conditions for medical cannabis, stakeholders’ involvement in the development of supply and regulatory frameworks and clinical guidelines that outline the potential benefits and risks of medical cannabis, and broader strategies to promote safe and equitable access to medical cannabis products that meet the required quality standards\textsuperscript{87}.
Notes and references

1. A magistral preparation is prepared by or under the supervision of a pharmacist, specifically according to a detailed medical prescription for the medicinal substances that it contains, applying the technical and scientific standards of the pharmacies.


7. Ibid.


17. de Souza, Henriques, and Limberger, ‘Medical Cannabis Regulation’.


For instance with regard to exceptions made in the provisions for herbal medicinal products with a long tradition of safe use in the EU, the European Medicines Agency requires that “Herbal medicinal products that have been used for more than 30 years (including at least 15 years in the EU), and that are intended to be used without the supervision of a medical practitioner and that are not administered by injection, can be authorised in accordance with the requirements laid down in the Traditional Herbal Medicinal Products Directive (Directive 2004/24/EC), that amends Directive 2001/83/EC (Article 16a)”. Source: European Medicines Agency, EMA/ HMPC/176770/2022 Committee on Herbal Medicinal Products (HMPC), 25 January 2023


Some of the commonly reported adverse effects of CBD include somnolence, diarrhea and decreased appetite. Other less frequent adverse effects include vomiting, fatigue, weight loss, pyrexia, and upper respiratory tract infections. (Anciones and Gil-Nigel, ‘Adverse Effects of Cannabinoids’)


Jacob Felson, Amy Adamczyk, and Christopher Thomas, ‘How and Why Have Attitudes about Cannabis Legalization Changed so Much?’, Social Science Research 78 (February 2019): 12–27.

Hall et al., ‘Public Health Implications of Legalising the Production and Sale of Cannabis for Medicinal and Recreational Use’.

Magdalena Cerdá et al., ‘Association Between Recreational Marijuana Legalization in the United States and Changes in Marijuana Use and Cannabis Use Disorder From 2008 to 2016’, JAMA Psychiatry 77, no. 2 (1 February 2020): 165.
79 Nicole V. Tolan et al., ‘Impact of Marijuana Legalization on Cannabis-Related Visits to the Emergency Department’, *Clinical Toxicology* 60, no. 5 (4 May 2022): 585–95.

80 Daniel Thomas Myran et al., ‘Changes in Emergency Department Visits for Cannabis Hyperemesis Syndrome Following Recreational Cannabis Legalization and Subsequent Commercialization in Ontario, Canada’, *JAMA Network Open* 5, no. 9 (16 September 2022): e2231937. but it is unclear how cannabis commercialization (i.e., greater retail store access as well as increased variety and potency of cannabis products)


83 Pennypacker et al., ‘Potency and Therapeutic THC and CBD Ratios’.


85 Pennypacker et al., ‘Potency and Therapeutic THC and CBD Ratios’.

86 Kritikos and Pacula, ‘Characterization of Cannabis Products Purchased for Medical Use in New York State’.
