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**HERBAL CANNABIS  
FOR MEDICAL USE:  
A SPECTRUM OF  
REGULATORY APPROACHES**



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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.<sup>1</sup> 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.<sup>2</sup> 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.<sup>3,4</sup>

### 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.

Source: Single Convention on Narcotics Drugs of 1961 as amended by the 1972 Protocol, United Nations, 1975.

## Is it medicinal or medical?

The term “medical” refers to the practice of medicine, to medicines, products and devices, and to the broader field of medicine. For instance, the term “medical use of cannabis” refers to the practice of allowing cannabis use for medical purposes or to the use of a cannabis-based product for medical purposes.

The term “medicinal” is mainly used to describe the beneficial effects of a drug or a herb. For a substance used to cure disease or relieve pain, the term may be used in reference to its medicinal properties or its use for medicinal purposes. One example is the medicinal use of cannabis for epilepsy.



In the present chapter, the terms “medical” and “medicinal” have been used with the meanings set out above.

## Evidence of the effectiveness of cannabis to treat medical conditions

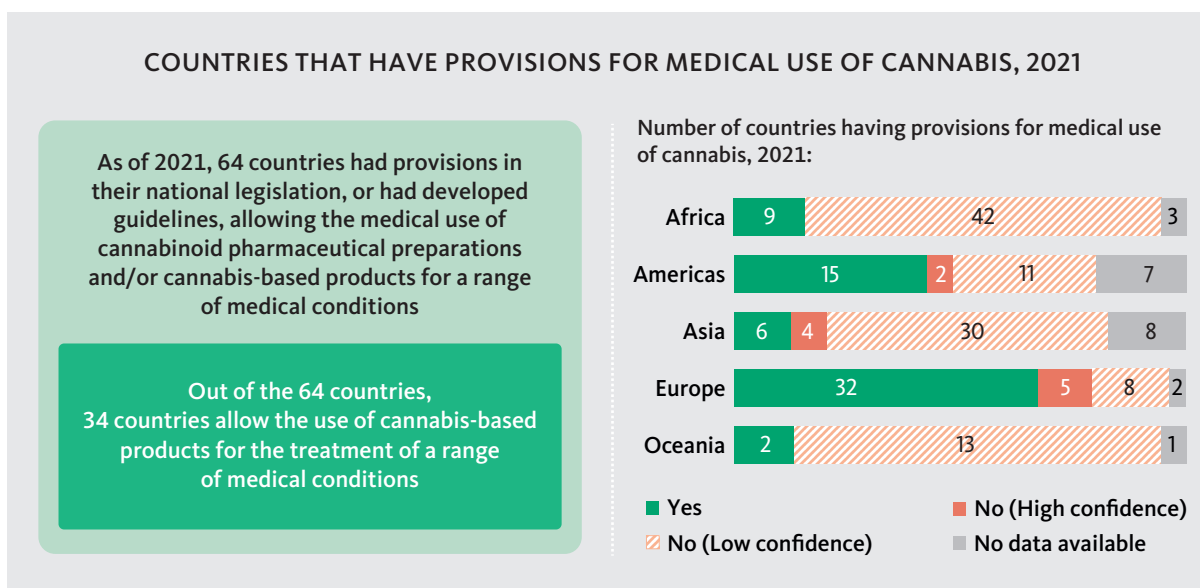
Renewed interest in the therapeutic potential of cannabis and cannabis extracts followed the discovery of the endocannabinoid system in the mid-1980s and growing understanding of that system throughout the 1990s.<sup>a, b</sup> Nevertheless, evidence of the effectiveness of cannabinoids in treating certain 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.<sup>c, d</sup> 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.<sup>e, f</sup> Evidence of the effectiveness of cannabis in the treatment of other conditions is, however, moderate, insufficient or inconclusive.<sup>d</sup>

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;<sup>g</sup> such an effect also lead patients in some jurisdictions to indicate their preference for herbal cannabis, as opposed to specific cannabinoid or cannabis extracts.<sup>d</sup>

- <sup>a</sup> Roger G Pertwee, ‘Cannabinoid Pharmacology: The First 66 Years: Cannabinoid Pharmacology’, *British Journal of Pharmacology* 147, no. S1 (January 2006): S163–71.
- <sup>b</sup> Vincenzo Di Marzo and Stefania Petrosino, ‘Endocannabinoids and the Regulation of Their Levels in Health and Disease’: *Current Opinion in Lipidology* 18, no. 2 (April 2007): 129–40.
- <sup>c</sup> Adjunctive treatment or therapy means that certain medications are added to other medical treatments rather than used on their own.
- <sup>d</sup> European Monitoring Centre for Drugs and Drug Addiction., *Medical Use of Cannabis and Cannabinoids: Questions and Answers for Policymaking* (Luxembourg: Publications Office of the European Union, 2018).
- <sup>e</sup> National Academies of Sciences, Engineering, and Medicine and Board on Population Health and Public Health Practice, *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*, The National Academies Collection: Reports Funded by National Institutes of Health (Washington D.C.: National Academies Press (US), 2017).
- <sup>f</sup> Anne Katrin Schlag, ‘An Evaluation of Regulatory Regimes of Medical Cannabis: What Lessons Can Be Learned for the UK?’, *Medical Cannabis and Cannabinoids* 3, no. 1 (15 January 2020): 76–83.
- <sup>g</sup> Sari Goldstein Ferber et al., ‘The “Entourage Effect”: Terpenes Coupled with Cannabinoids for the Treatment of Mood Disorders and Anxiety Disorders’, *Current Neuropharmacology* 18, no. 2 (23 January 2020): 87–96.

PHARMACEUTICAL AND CANNABIS-BASED PRODUCTS					
 <p>Medical products with marketing authorization</p>	<p><b>Medical products</b></p>				<p>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</p>
	<p><b>Nabilone:</b> Oral capsule containing synthetic cannabinoid similar to THC</p>	<p><b>Dronabinol:</b> Oral capsule or solution containing synthetic THC</p>	<p><b>Nabiximols:</b> Containing balanced quantities of THC and CBD</p>	<p><b>Epidiolex: (cannabidiol)</b> Plant-derived CBD oral solution</p>	
 <p>Cannabis-based products</p>	<p>Standardized cannabis-based medical products</p>	<p>Magistral preparations</p>	<p>Cannabis-based products with unspecified composition</p>	<p>Raw cannabis</p>	<p>Approaches to regulating cannabis-based products for medical use vary widely between countries</p>
	<p>Variable THC/CBD composition</p>				

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.



Source: UNODC, responses to the annual report questionnaire (reproduced from UNODC, *World Drug Report 2022*).

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

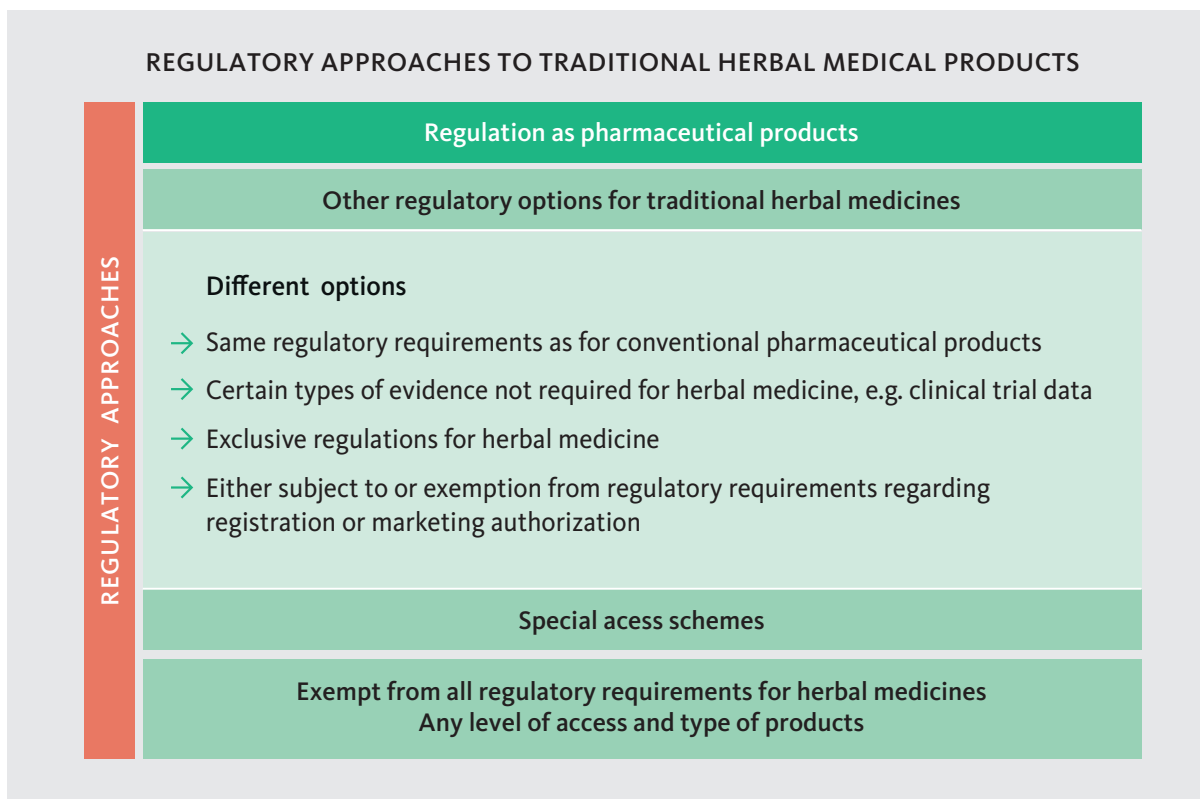
The countries that allow the medical use of cannabis-based products face a range of options and issues in relation to the regulation of such products that are similar to those that may affect the regulation of any of the traditional herbal medicines and products.

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.<sup>5</sup> 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



Source: Based on WHO, "Global report on traditional and complementary medicine 2019", World Health Organization, Geneva, 2019.

Comparison of broad guidelines for herbal and pharmaceutical products		
	Herbal products	Pharmaceutical or medical-grade products
<b>Agency</b>	National law, policy or regulation on traditional medicines	National pharmaceutical regulatory body
<b>Pharmacopoeia and monograph</b>	Description of pharmacopoeia and monograph defining qualifying conditions and dosage	Pharmacopoeia or monograph defining qualifying conditions and dosage
<b>Evidence of efficacy and safety</b>	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	Evidence-based laboratory and clinical trials among humans, with evaluation of quality, safety and efficacy of pharmaceutical products, with identification of active pharmaceutical ingredient
<b>Designation</b>	<b>Either as:</b> <ul style="list-style-type: none"> <li>• Prescription herbal medicines</li> <li>• Over-the-counter herbal medicines</li> <li>• Dietary supplements</li> <li>• Health food</li> </ul>	<b>Either as:</b> <ul style="list-style-type: none"> <li>• Prescription medicines</li> <li>• Over-the-counter medicines</li> <li>• Dietary supplements</li> </ul>
<b>Manufacturing</b>	<b>Quality assurance through:</b> <ul style="list-style-type: none"> <li>• Application of good manufacturing practices (GMP)</li> <li>• Good laboratory practices</li> <li>• Active ingredients (API)</li> <li>• Good agricultural and collection practices (GAP or GACP)</li> </ul>	<b>Quality assurance (national laboratories) through:</b> <ul style="list-style-type: none"> <li>• Application of good manufacturing practices (GMP)</li> <li>• Active pharmaceutical ingredients (API)</li> </ul>
<b>Marketing</b>	Marketing authorization	Marketing authorization
<b>Pharmacovigilance</b>	Post-marketing surveillance of herbal medicines for adverse effects	Pharmacovigilance based on reporting of adverse effects
<b>Essential medicines list</b>	National law, policy or regulation on traditional medicines	National essential medicines list  Registration requirements to establish interchangeability (bioequivalence)

Source: Based on WHO, "Global Report on Traditional and Complementary Medicine 2019." Geneva: World Health Organization, 2019; and WHO, "Expert Committee on Specifications for Pharmaceutical Preparations – Forty-Eighth Report" Technical Report Series, No. 986. Geneva: World Health Organization, 2014.



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.<sup>6</sup> 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.<sup>7</sup>

### 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

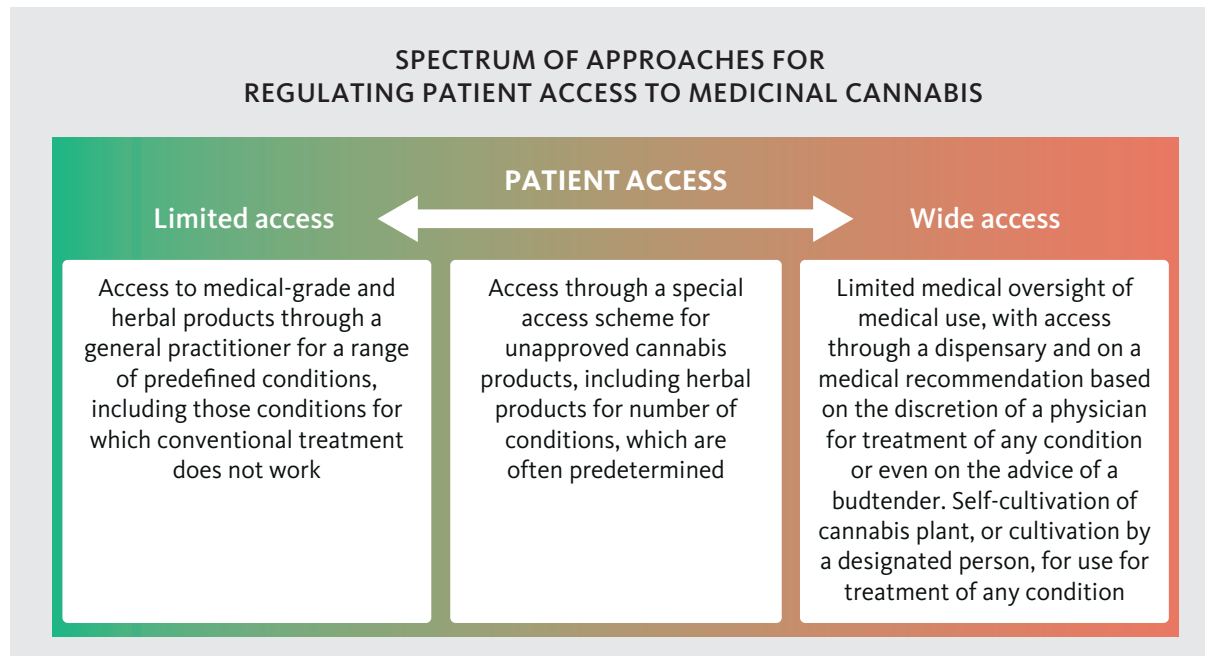
Recommended quality control practices for plant-based medicinal preparations		
Quality control practice	Description	Result or purpose
<b>GAP – good agricultural practices or GACP – good agricultural and collection practices</b>	Quality assurance mechanism ensuring homogeneity of concentrations of herbal 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)
<b>GMP – good manufacturing practices</b>	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
<b>API – active pharmaceutical ingredients</b>	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)

Sources: Souza, Maíra Ribeiro de, Amélia Teresinha Henriques, and Renata Pereira Limberger. "Medical Cannabis Regulation: An Overview of Models around the World with Emphasis on the Brazilian Scenario." *Journal of Cannabis Research* 4, no. 1 (June 16, 2022): 33; WHO. "Expert Committee on Specifications for Pharmaceutical Preparations - Fifty-Fifth Report." Technical Report Series, No. 1033. Geneva: World Health Organization, 2021; WHO. "Guidelines on Good Agricultural and Collection Practices (GACP) for Medicinal Plants." Geneva: World Health Organization, 2003. WHO. "Guidelines for Assessing Quality of Herbal Medicines with Reference to Contaminants and Residues." World Health Organization, 2007.

chemotherapy-induced nausea and vomiting, spasticity associated with multiple sclerosis and treatment-resistant epilepsies.<sup>8,9</sup> 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.<sup>10</sup> 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.<sup>11,12,13</sup> 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.<sup>14</sup>

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.<sup>15</sup> 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.<sup>16</sup> 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.<sup>17</sup> 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.<sup>19</sup>



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.<sup>20, 21, 22</sup> 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.<sup>23, 24</sup>

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.<sup>25</sup> 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.<sup>26</sup>

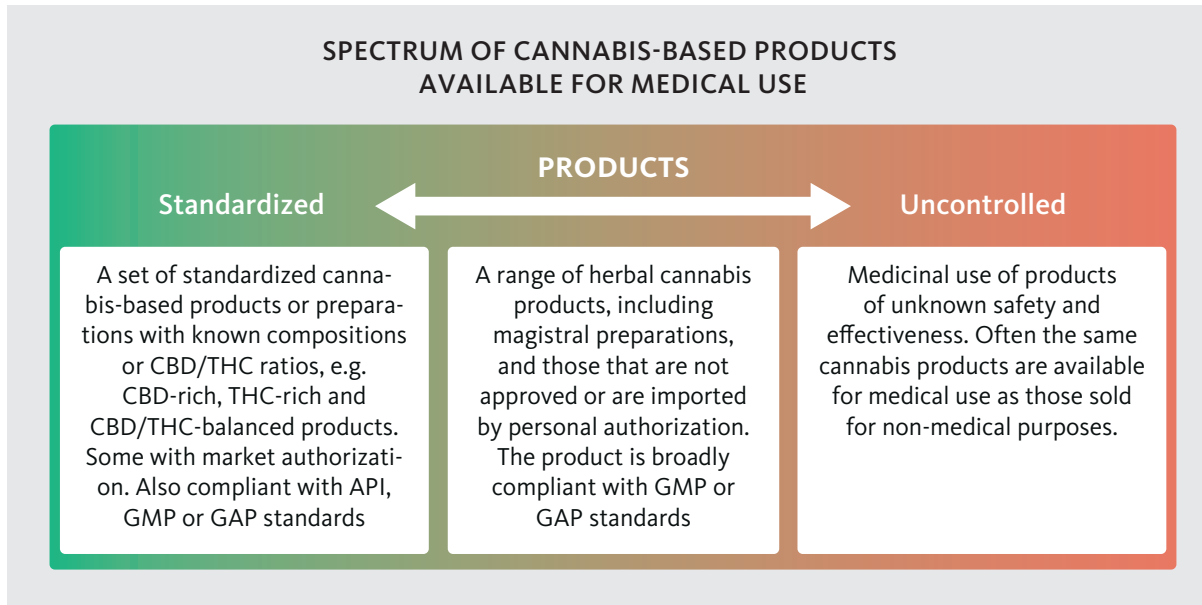
### Medical cannabis-based products on the market: from standardized products to cannabis preparations of unspecified composition

One of the challenges in regulating the medical use of cannabis-based products is defining which products to make available, whether the plant only or plant-based derivatives or extracts will be allowed, and what production processes will be permitted.

Different cannabis-based products based on cannabis flowers and cannabis extracts are marketed in some countries as herbal medicinal preparations, often without regular marketing authorizations. These range from strictly approved standardized products with known contents and concentrations to any cannabis preparation with an unspecified composition. For example, on the one hand, in many countries in the European Union, pharmacies can prepare patient-specific products (magistral preparations) based on a physician’s prescription.<sup>27, 28</sup> On the other hand, in some jurisdictions in the United States and Canada, products with high THC content, including smokable cannabis products with known carcinogens, tars and other harmful effects on health<sup>29, 30</sup> (such as respiratory illnesses),

Medical cannabis products in the Kingdom of the Netherlands			
Category	Product	THC	CBD
High THC, low CBD	Bedrocan®	≅ 22	<1
	Bedica®	≅ 14	<1
	Bedrobinol®	≅ 13.5	<1
THC and CBD balanced	Bediol®	6.3	8
Low THC, high CBD	Bedrolite®	<1	9

Source: Brunetti, Pietro, Simona Pichini, Roberta Pacifici, Francesco Paolo Busardò, and Alessandro Del Rio. “Herbal Preparations of Medical Cannabis: A Vademecum for Prescribing Doctors.” *Medicina (Kaunas, Lithuania)* 56, no. 5 (May 15, 2020): 237.



cannabis leaf, inflorescence and extracts, are available as herbal medicinal preparations.<sup>31, 32, 33</sup> 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.<sup>34</sup> 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.<sup>35</sup>

In Germany, several hundred pharmaceutical-grade cannabis herbal products, which are imported from

more than a dozen different countries, are available on the market.<sup>36</sup> 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.<sup>37</sup> 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® contains 25 per cent THC and less than 1 per cent CBD), THC and CBD balanced (e.g. Tilray THC 10® contains 10 per cent of both THC and CBD), and high CBD and low THC (e.g. Bedrolite®, contains less than 1 per cent THC and 8.1 per cent CBD).<sup>38</sup>

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).<sup>39</sup> 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”.<sup>40</sup> 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.<sup>41</sup> 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.<sup>42</sup>

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.<sup>43</sup> 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.<sup>44</sup> 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.<sup>45</sup>

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.<sup>46</sup> 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.<sup>47, 48, 49</sup> 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.<sup>50</sup> 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.<sup>51</sup> The level of THC and CBD and their ratio are important factors in the therapeutic 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.<sup>52</sup> 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.<sup>53</sup>

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

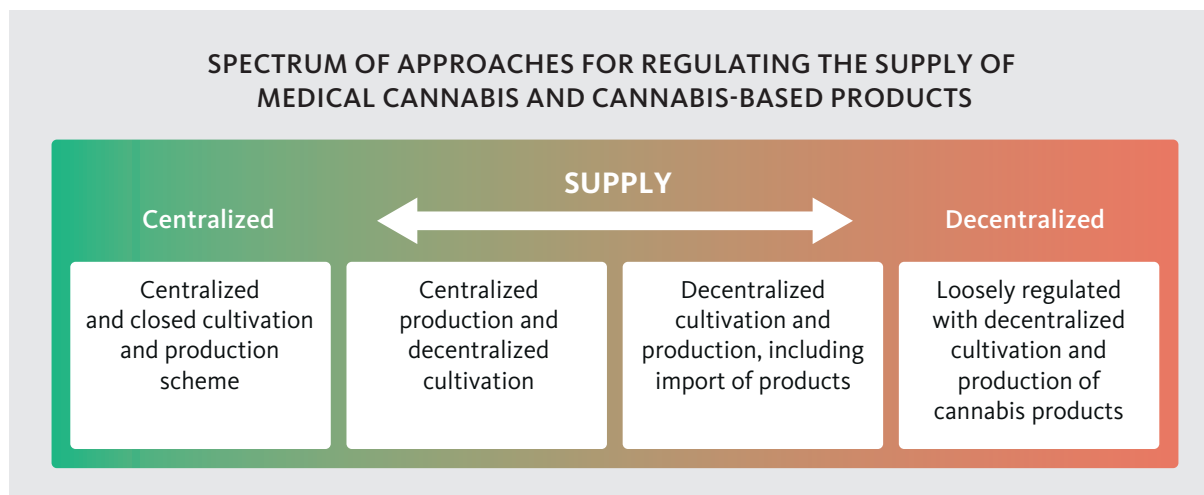
Regulatory control of the supply of medical cannabis may vary, with limits placed on the number of producers, distributors and retailers supplying medical cannabis products and limits on the actual products allowed. Regulations may also relate to the practice of cultivation and production of cannabis-based

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.<sup>54</sup> 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.<sup>55</sup> 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.<sup>56, 57</sup> 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.<sup>58</sup>

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.<sup>59</sup> 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.<sup>60</sup> 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.<sup>61</sup>



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.<sup>62, 63</sup>

### 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.<sup>64</sup> These are issues that have emerged and also may have an influence on the regulation of traditional herbal medicine.<sup>65</sup>

### 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.<sup>66</sup>

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.<sup>67</sup> 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,<sup>68, 69</sup> there is also growing evidence documenting adverse events associated with high-CBD products,<sup>70</sup> high-THC products and drug interactions with other drugs that may be used in the treatment of a condition.<sup>71, 72, 73, 74</sup>

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<sup>75, 76, 77</sup> and to an increase in the non-medical use of cannabis by adults,<sup>78, 79</sup> as well as an increase in emergency room visits and hospitalizations related to adverse effects, such as cannabis hyperemesis syndrome, after cannabis consumption.<sup>80, 81</sup>

### 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.<sup>82, 83</sup> 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.<sup>84, 85, 86</sup>

### Conclusions: what approaches can provide safe access to medical cannabis while limiting unsafe use?

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.<sup>87</sup>



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