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Narrative Review

# Medical use of cannabis and cannabinoids containing products – Regulations in Europe and North America

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ABSTRACT

In 1937, the United States of America criminalized the use of cannabis and as a result its use decreased rapidly. In recent decades, there is a growing interest in the wide range of medical uses of cannabis and its constituents; however, the laws and regulations are substantially different between countries. Laws differentiate between raw herbal cannabis, cannabis extracts, and cannabinoid-based medicines. Both the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) do not approve the use of herbal cannabis or its extracts. The FDA approved several cannabinoid-based medicines, so did 23 European countries and Canada. However, only four of the reviewed countries have fully authorized the medical use of herbal cannabis – Canada, Germany, Israel and the Netherlands, together with more than 50% of the states in the United States. Most of the regulators allow the physicians to decide what specific indications they will prescribe cannabis for, but some regulators dictate only specific indications. The aim of this article is to review the current (as of November 2017) regulations of medical cannabis use in Europe and North America.

## 1. Introduction

Evidence of cannabis use for medical purposes can be dated back to 2737 BCE in ancient China [1]. Since then there have been wide variations in the use and acceptance of cannabis as a drug therapy in Western medicine. In 1937, the United States of America criminalized the use of cannabis and as a result its use decreased rapidly [2]. In recent decades, there is a growing interest in the wide range of pharmacological and medical uses of cannabis and its constituents; however, the laws and regulations are substantially different between countries.

Following the Single Convention of the United Nations in 1961 (as amended by 1972), cannabis, cannabis resins and extracts were listed as Schedule I and Schedule IV. Schedule I — those substances which are, inter alia, having, or convertible into substances having a liability to abuse comparable to that of cannabis, cannabis resin or cocaine. Schedule IV - substances that are particularly liable to abuse and to produce ill effects, and such liability is not offset by substantial therapeutic advantages not possessed by substances other than drugs in Schedule IV [3,4]. The 1971 Convention of psychotropic substances listed $\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC), the psychoactive substance in cannabis, in Schedule II [5]. Schedule II — having addiction-producing or addiction-sustaining properties not greater than those of codeine but at least as great as those of dextropropoxyphene [4]. For schedule I substances, the treaties prohibited all use except for scientific and very limited medical purposes by duly authorized persons, in medical or scientific establishments which are directly under the control of their Governments or specifically approved by them [5].

The aim of this article is to review the current regulations of medical cannabis use in Europe and North America. This article will not discuss the recreational use of cannabis nor the evidence for the medical uses of cannabis. The review is based on information gathered from officials in the relevant regulatory agencies, previous reports and governmental websites.

## 2. Terminology and products

The term "medical cannabis" might refer to different substances and the distinction has both legal and medical implications [6,7]. These include:

1. **Raw herbal (botanical) cannabis** – any part of any plant of the genus Cannabis.
   The genus Cannabis belongs to the Cannabaceae family. Some people espouse cannabis as a single species with *C. indica*, *C. sativa* and *C. ruderalis* as three different subspecies and some espouse them as three different species of cannabis [8,9]. The difference between

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these species will not be elaborated here. The term 'herbal cannabis' may refer to anyone of these species.

2. **Cannabis extract** – any extract, usually by organic solvents to produce oil, which is extracted from the plant, and any preparation consisting mainly of it. **Magistral preparation** – any medicinal product prepared in a pharmacy in accordance with a specified medical prescription for an individual patient.
3. **Cannabinoids** – a class of chemical compounds that have the typical cannabinoid skeleton in common and affect the cannabinoid receptors. The cannabis plant is known to contain over 100 different cannabinoids (Phyto-cannabinoids) [10], with cannabidiol (CBD) and $\Delta^9$-THC being the most studied so far. A few synthetic cannabinoids are manufactured today as approved drugs – cannabinoid-based medicines.

In recent years, there has been a substantial change in policies and more countries are allowing the use of cannabis as a medicine. Nonetheless, the lack evidence for cannabis efficacy and safety as well as the concerns regarding addiction and other adverse events, cause many countries to be cautious before changing cannabis regulations. Most countries in Europe forbid the use of herbal cannabis, while cannabinoid-based medicines are legal in many of them. Currently, there are only three cannabinoid-based medicines available for marketing in different countries [11]:

1. **Nabiximols (Sativex®)** – oromucosal spray formulated from extracts of the *C. sativa* plant that contains the cannabinoids THC and CBD. Manufactured by GW Pharmaceuticals Plc. The most common indication for its use is multiple sclerosis associated spasticity, mostly after the failure of previous treatments. A number of countries also authorized its use for multiple sclerosis associated neuropathic pain.
2. **Nabilone (Cesamet® or Canemes®)** – oral capsules containing a synthetic cannabinoid similar to THC. Cesamet is manufactured by Meda Pharmaceuticals Inc. and Canemes is manufactured by AOP Orphan Pharmaceuticals AG. The main indication for their use is nausea and vomiting due to chemotherapy treatments, mostly after the failure of previous treatments.
3. **Dronabinol (Marinol® or Syndros®)** – oral capsules or an oral solution containing synthetic $\Delta^9$-THC. Marinol is manufactured by AbbVie Inc. Syndros is manufactured by Insys Therapeutics Inc. The main indications for their use are 1) anorexia associated with weight loss in patients with AIDS (Acquired Immunodeficiency Syndrome); and 2) nausea and vomiting associated with cancer chemotherapy, mostly after the failure of previous treatments.

Additional cannabinoid-based medicines are in different stages of development, but have not been authorized for marketing yet [11].

## 3. Regulatory authorities

The main agencies responsible for evaluating and approving drugs are the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA).

### 3.1. EMA

There are two ways of obtaining a marketing authorization for a medicine in the European Union (EU): the centralized procedure, via the EMA, which results in a single marketing authorization valid throughout the EU, and the non-centralized route where medicines may be authorized in individual EU countries through the national competent authorities [12]. To date, no marketing authorization has been granted for medicines derived from cannabis following evaluation by EMA, nor did the EMA authorized cannabinoid-based medicines. The only decisions the EMA authorized regarding cannabis and its products include rare diseases (orphan) designations and pediatric investigation plans. Rare disease designation allows pharmaceutical companies to benefit from incentives from the EU to develop a medicine for a rare disease. These include reduced fees and protection from competition once the medicine is placed on the market. An orphan designation does not allow the medicine to be marketed. A pediatric investigation plan is a development plan aimed at ensuring that the necessary data are obtained through studies in children, to support the authorization of a medicine for children [13]. Nevertheless, many European countries authorized the use of some cannabinoid-based medicines, by the non-centralized route, as will be elaborated further on.

### 3.2. FDA

Similar to the EMA, to date, the FDA has not approved a marketing application for a drug product containing or derived directly from herbal cannabis. In contrast to the FDA's position, a number of states have already approved the use of medical cannabis, as will be elaborated further on [14,15]. The FDA did approve Cesamet® [16], Marinol® [17] and Syndros® [18] for therapeutic uses in the United States.

While the main agencies defer to accept herbal cannabis or its extracts as approved drugs, an increasing number of countries and states are changing their regulation, allowing patients access to these substances.

### 3.3. Europe

Table 1 and Fig. 1 show that cannabinoid-based medicines, and especially Nabiximols, have gained wide acceptance and are authorized for use in most European Union countries. However, it should be noted that Nabiximols is still indicated only for a small number of indications and in practice it might be difficult to acquire even in authorized countries. Furthermore, authorization of a new drug by a specific European country requires the pharmaceutical company to send a specific request to the country's regulatory agency. Thus, several of the countries that do not authorize part of the cannabinoid-based medicines state that they would agree to authorize the drugs upon receiving a request from the manufacturers.

## 4. United States of America

At the federal level, by the way of the Comprehensive Drug Abuse Prevention and Control Act of 1970, a United States federal law lists cannabis as a schedule I drug and its use is prohibited for any purpose [19]. Nevertheless, different states have issued laws of their own, and most states currently enable the use of medical cannabis to some extent. California was the first state to pass a law that permits the use of medical cannabis in 1996. At the time of manuscript preparation, 29 states and the District of Columbia have authorized the use of medical cannabis, with wide variations between them [20,21].

A current list of states that have broadly authorized medical cannabis use in some form includes Alaska, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, Florida, Hawaii, Illinois, Maine, Maryland, Massachusetts, Michigan, Minnesota, Montana, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Dakota, Ohio, Oregon, Pennsylvania, Rhode Island, Vermont, Washington, West Virginia and the District of Columbia [21].

All states, except for the District of Columbia, limit the conditions for which cannabis can be prescribed [20], but some of them (e.g. Florida), also allow a broader use for "other debilitating medical conditions of the same kind or class as or comparable to those enumerated, and for which a physician believes that the medical use of marijuana would likely outweigh the potential health risks for a patient" [22].

Physicians do not need to have a specific specialty to prescribe cannabis, but most states require the physicians to obtain a state registration prior to prescribing cannabis to patients. Physicians must also

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