Medical Cannabis in Europe

The GMP Standards guide

MAY 2018

PROHIBITION PARTNERS

IN ASSOCIATION WITH ORION GMP Solutions

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Background

The cannabis plant is gaining international credibility as an herbal drug substance with potential to treat multiple disease states and the side effects of disease states. Clinical evidence for medical cannabis as treatment for disease states and the side effects is summarised in the 2017 ***National Academies of Sciences*** report on the ***Health Effects of Cannabis and Cannabinoids***. This comprehensive literature review describes the different disease states hypothesised to be treated with medicinal cannabis, and weighs the credibility of each clinical study available in scientific publications. The report also describes some of the problems for medicinal cannabis finding its place in medicine, mentioning standardised pharmaceutical grade products being critical for use in rigorously designed and reviewed clinical studies to further support or disprove the hypotheses behind the medicinal potential of cannabis. As such, there is an explicit need for basic scientific and medical research within the current context of national and international regulations.

Clinical studies of specific cannabinoids have shown some evidence of effectively treating certain disease states and their side effects, including AIDS wasting, multiple sclerosis, and intractable epilepsy[1]. The international community of patients and medical practitioners stand only to benefit from continued research in clinical settings. It is our hope that this report will elucidate the tools that exist for the international community to develop robust policies and programmes that fit the needs of public health worldwide.

The importance of understanding the UN treaties cannot be understated for anyone seeking to operate in a legal medical cannabis programme, or for future nations seeking to develop programmes. The international legislative framework is clear and there are examples of nations that have successfully deployed cannabis programmes and agencies. In 1961, the United Nations treaty known as the ***Single Convention on Narcotic Drugs (SCND)*** set the international framework for the prohibition of any production and/or supply of specific drug compounds or substances, including cannabis and its derivatives. Countries wishing to establish medicinal and/or research-based cannabis programmes are required to follow the SCND and subsequent treaties. The legislative and policy requirements established by these countries vary, but they all fulfill specific treaty obligations. This report provides a review of how national cannabis programmes, with an emphasis on the European Union (EU), are being implemented and managed within the framework of the UN treaties. It is critical for parties interested in the legal production or sale of cannabis to understand how these treaties have shaped cannabis regulations. These parties include:

- EU and Foreign entities importing/exporting to/from the EU,
- Medical Professionals and Health Organisations interested in the protection of public health through ***EU Good Manufacturing Practices***,
- Regulators and legislators developing or maintaining cannabis programmes using ***EU Good Manufacturing Practices.***

United Nations Treaties and Cannabis Programmes

The United Nations ***Single Convention on Narcotic Drugs (SCND)*** of 1961 established the framework from which, 186 countries are required to follow when developing a cannabis programme. This foundational document describes cannabis, its legal status, how it can be produced, scheduled, allowed for import/export, and the ***system of controls*** for its manufacture. The SCND takes the perspective of fighting against 'illicit traffic' as it looks to champion the treatment and rehabilitation of drug addicts, create extensive 'records on international traffickers' and looks to promote the 'simplification of international control machinery'.

The SCND also outlines how countries may develop a ***national cannabis agency***, that delegates the use of cannabis for legitimate medical reasons and research purposes. These agencies act as a stakeholder in the international regulatory requirements of the Convention.

Such agencies ensure that their national medical cannabis programmes are executed without violation of treaty requirements by enforcing things such as cultivation location requirements, the licensing of manufacturers, the amount of land that may be used,

[1] *National Academies of Sciences, Health and Medicine Division, The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research.*

the chain of custody, importing, exporting, and wholesale trading guidelines.

The SCND provides guidance to cannabis agencies on various issues: the regulation of cannabis manufacturing, limitation of quantities manufactured for export based on market need, prevention of misuse and illicit trade, licensure of manufacturers and scope of control by the cannabis agency, controls for international trade and distribution, requirements for supervision and inspection of manufacture of cannabis products, as well seizure and confiscation of products.

In addition to the ***SCND***, the United Nations ***Convention against illicit traffic in narcotic drugs and psychotropic substances*** of 1988 (the Conventions[2]) further describes mechanisms for the legal and controlled international distribution of cannabis. While this treaty does not change the approach of cannabis as an illicit narcotic drug, it does provide the 'legislative and administrative measures in conformity with the fundamental provisions of their respective domestic legislative systems' which guide all respected national cannabis policies and agencies that currently allow the production, manufacture, and distribution of cannabis for medical and scientific purposes.

Cannabis Agencies and How Policies Are Developed

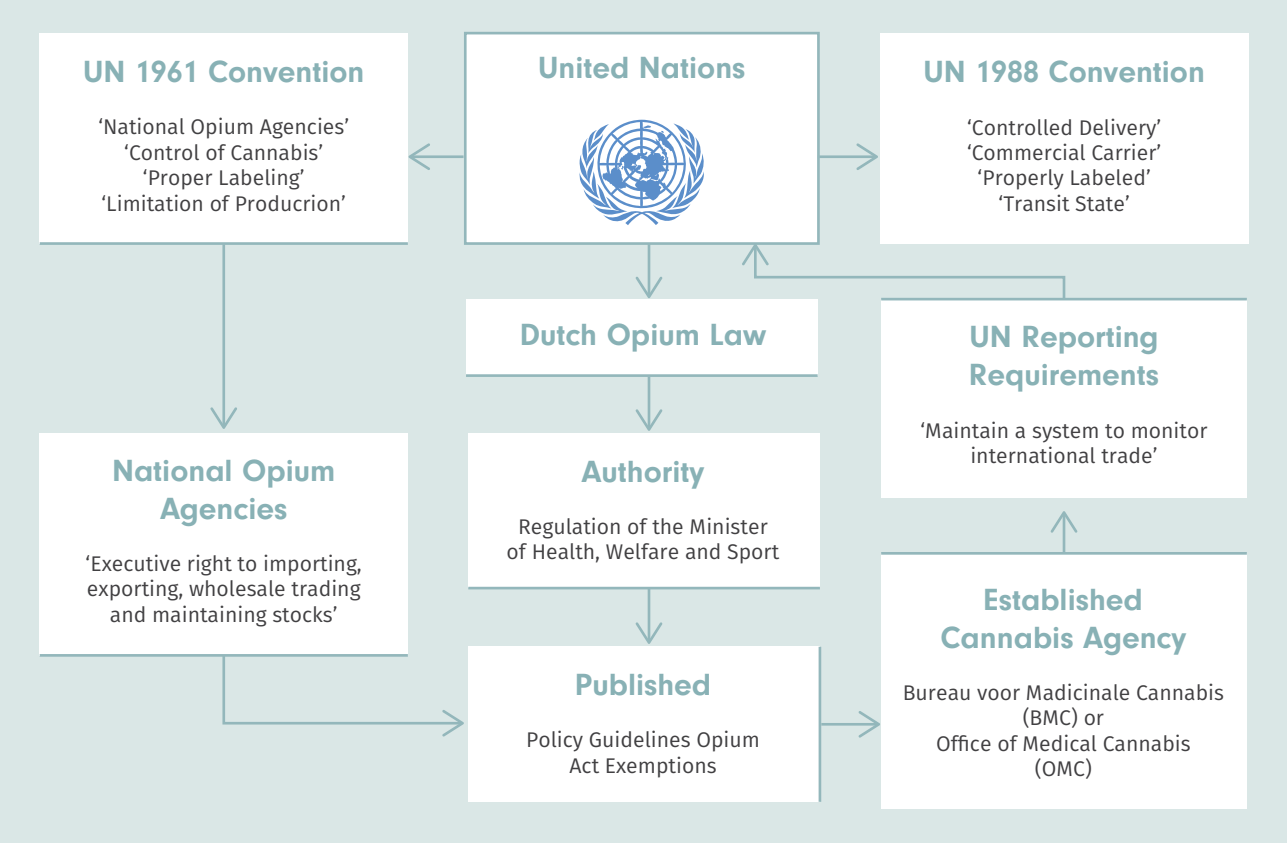
Canada, Germany, and the Netherlands have assigned responsibility of the cannabis agency duties to ***Health Canada***, the ***Federal Institute for Drugs and Medical Devices***, and the ***Office of Medical Cannabis***, respectively. These agencies act as delegates to the ***National Competent Authority*** of the respective member state while fulfilling requirements of the UN Conventions and serving the needs of medical patients. They ensure controlled systems compliant to Good Manufacturing Practices (GMP) and Good Distribution Practices (GDP) are used and enforced, resulting in herbal medicinal substances and herbal medicinal products that come from a certified source through a traceable supply chain all the way to the patient.
National cannabis agencies and national legislative bodies must rely on monographs for pharmaceutical preparations, herbal drug substances, herbal drug products, herbal drug preparations, herbal drug extracts, substances for pharmaceutical use, and dosage form, while recognising that not all of the details are clearly spelled out in the regulations. Canada, Germany, and the Netherlands have used these guidelines, and are represented in their respective cannabis programmes and policies. Such programmes and policies ultimately lead to specifications for product types and categories, and the appropriate application of GXP[3] in the medicinal cannabis supply chain.

[2] *Collectively, the Single Convention on Narcotic Drugs and Convention against illicit traffic in narcotic drugs and psychotropic substances.*

[3] *GMP, GDP, GCP, etc.*

Country Report: Netherlands

How the Netherlands regulate cannabis exports to other EU member states.



Overview

The Dutch government regulates the cannabis plant under the 1928 Opium Act, which was originally developed for the regulation of opium and other narcotic substances. The Opium Act has been amended several times, and still stands as the primary legislation that dictates manufacturing of cannabis in the Netherlands.

As one of 186 signatories to the United Nations drug conventions, the Netherlands conforms to the Conventions[4] . Together, the conventions afford provisions for the procurement and use of cannabis for specific purposes and for entities within a nation to engage in trade with other nations. With well-defined exemptions, the Dutch Opium Act provides the requirements to produce, import, or export cannabis under a debated monopolistic programme.

The Opium Act states that it is 'illegal to grow, prepare, treat, process, sell, supply, provide, transport, possess and manufacture cannabis or cannabis derived substances'. Fortunately, the Dutch Opium Act considers the 'interest of public health' as good cause for having a national cannabis programme.

[4] *Collectively, the Single Convention on Narcotic Drugs and Convention against illicit traffic in narcotic drugs and psychotropic substances.*

The Opium Act and Opium Act Exemptions

The Netherlands has been considered a utopia by cannabis consumer, where one can purchase and consume cannabis without legal repercussions. While this is fundamentally true, it should be noted that cannabis in all forms is still illegal, as formal legalisation would be in direct violation of the UN Conventions. Rather, the Netherlands takes a harm reduction approach and avoids incarceration unless personal choices of drug use affect others or are a nuisance.

Cannabis and its derivative products are defined as List I and List II substances. The Dutch Opium Act defines ***Hemp, Hashish,*** and ***Hemp Oil***, with ***Hemp*** and ***Hashish*** on List II and ***Hemp Oil*** on List I. It places cannabis in the same categories as prescription opioids and benzodiazepines such as buprenorphine (Buprenex), alprazolam (Xanax), and zolpidem (Ambien). Any of these List I & II drugs require an exemption that allows for their manufacturing. Cannabis requires the same exemptions and is treated the same as these scheduled narcotics.

When applying for a manufacturing exemption of List I and II substances, for example ***Hemp*** and ***Hemp Oil***, two separate exemption applications must be submitted. In accordance with the Act, the Bureau ***voor Medicinale Cannabis (BMC)*** or Office of Medicinal Cannabis (OMC) is the government office responsible for the control of

production and distribution of cannabis for medicinal and scientific purposes, which is a division of the Dutch Ministry of Health, Welfare and Sports. Unique to this market, the OMC acts as the distributor of all exempted products, thus creating a monopoly on the market.

At the time writing, Bedrocan is the only producer of cannabis flower to have been granted an exemption through the OMC, leaving the market open to high-quality producers wishing to capitalise on operational markets, should they be able to prove market demand to the OMC. Bedrocan currently produces six formulae that have specifications on the concentration of THC and CBD in their flower

A Unique Export Model

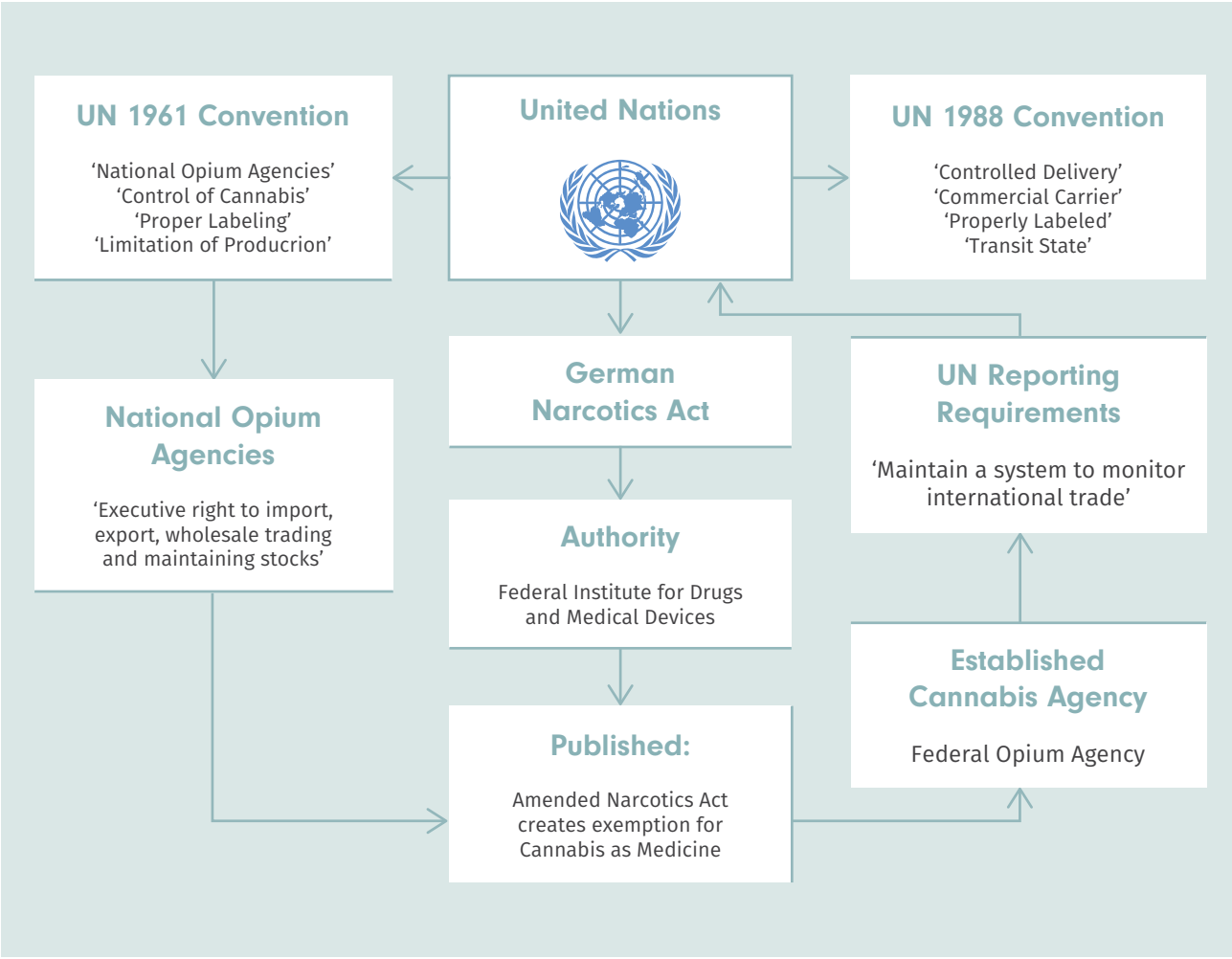
A special health inspector, appointed by the Health Care Inspectorate has the full authority of the Health Ministry and oversees the application process for exemption. These exemptions are temporary, lasting five years, and subject to revocation at any time if they are found to be non-compliant.

Entities that are successful at securing an exemption status are allowed to produce the approved product within strict limits that are set in proportion to a defined need in the international community. Entities must sell exclusively to the Netherland's minister within four months of production and destroy any surplus. Sale of products directly to another international entity is strictly prohibited, and is monitored by the Public Health Inspectorate and Tax department.

Ultimately, all cannabis is delivered to the OMC, who acts as the sole distributor, releasing products either within the Netherlands or the country of import. Although the OMC controls all aspects of distribution, it leaves the licence holders accountable for the legwork required to be granted exemptions for export and coordination with the authorised exemption/licence holder of the destination country.

Country Report: Germany

How Germany legalises and controls the importation and distribution of cannabis within the EU.



Overview

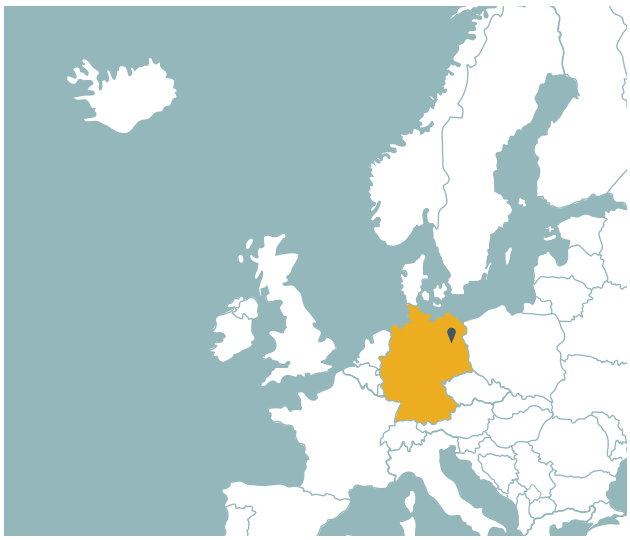
While some would arguably consider Germany one of the stricter Member States for the use of drugs and narcotics in the EU, they have a taken a progressive stance in the use of cannabis as medicine by allowing government insurance reimbursement for qualifying patients.

The German government regulates the cannabis plant under the Narcotics Act provisions concerning narcotic substances listed under Annex I-III of the Act. The Narcotics Act was recently amended in March of 2017 to include reforms for the legalisation of cannabis for medicinal use under a more moderate platform that expands previous laws. New legislation relaxes the stringency for prescribing cannabis as an alternative medicine to opium and other highly addictive narcotic drugs. Like most medical cannabis programmes, it requires specific ailments to qualify for cannabis medicines.

The Narcotic Drugs Act

The Narcotics Act requires a permit issued by the Federal Institute for Drugs and Medical Devices (BfArM) to 'grow, manufacture, trade in, import, export, sell, and otherwise market or acquire narcotics'. This legislation was developed to allow alternatives to opium-based drugs with known addiction risks. In addition to less restrictive exemptions on cannabis as a medicine, an exemption has been created for the cultivation of hemp fibre as an industrial good.

Annex I of the Narcotics Drugs Act is research reserved for non-negotiable narcotics such as heroin and MDMA includes all parts of the cannabis plant and cannabis resin. Annex II drug substances include purified forms of delta-9-tetrahydracannaibinol. Annex III is for marketable prescription drugs and contains cannabis and cannabis derivatives, listing synthetic cannabis substitutes such as nabilone or dronabinol. In spite of being labeled as a non-negotiable narcotic §3 (2) creates



an exception in which BfArM can issue a permit for an Annex I drug for 'scientific interest or other purposes of public interest'.

Limited Supply of Medical Cannabis

The Federal Opium Agency is currently accepting applications for cultivation and manufacturing of cannabis. However, only cultivation of hemp strains with less than 0.2% THC is allowed. Cultivation is expected to begin within the country around 2019 after additional legislation is implemented. Cannabis will be grown exclusively for medicinal purposes, thus only those cannabis plants cultivated in accordance with Good Agricultural and Collection Practice (GACP) and Good Manufacturing Practice Guideline (EU GMP Parts I & II) would qualify for the programme and subsequent distribution. GACP and EU GMP also contain references to relevant annex guidelines as well as monographs for representative testing criteria.

The policies are currently creating a strict supply of medical[5] or pharmaceutical[6] grade cannabis that may be imported into the country, as the infrastructure is not yet in place. Importation is currently the only means of supply as all products must meet GMP and GACP certifications through an accredited body within the EU.

At the time of writing of this report, companies from the Netherlands and Canada have met the regulatory requirements and received the appropriate export/import licences. Imports are subject to the monographs of 'cannabis flos (C-052), adjusted, refined cannabis oil resin (C-054), and cannabidiol (C-053)' listed in the German Drug Codex (DAC).

Bedrocan BV represents the only licenced Dutch importer of cannabis flower, while two Canadian companies, MedCann GmbH and Peace Naturals, have been licenced to import medical grade cannabis and cannabis extracts to Germany. Bedrocan BV currently produces five formulae that have specifications on the concentration of THC and CBD in their flower. MedCann GmbH and Peace Naturals intend to produce and import four and six formulae, respectively. The products can be obtained from the German companies of Fagron GmbH and Pedanios GmbH that act as the licenced importer into the country.

[5] *Medical Grade has potential to go through clinical trials, for example, product development phase*

[6] *Pharmaceutical Grade has gone through clinical trials, for example, Sativex*

German Government Controlled Cannabis Cultivation

The BfArM will not directly conduct any activities of cultivation, transportation, or distribution of cannabis. These steps will be supplied by the respective growers or other contracted companies. The cannabis agency has to buy cannabis according to the requirements of the unit convention. The cannabis agency will then set a manufacturer's bid price and sell the cannabis to manufacturers of cannabis medicines, wholesalers or pharmacies.

In doing so, the BfArM will not achieve any profits or surpluses from the activities of regulating sales price. When calculating the price, however, the personnel and material costs incurred by the BfArM are taken into account. Crucially, the BfArM has no influence on the actual selling price in the pharmacy. The distribution channels of manufacturers and distributors will comply with the legal regulations and are therefore identical to the regulations for the distribution of other narcotic drugs.

Prescribing Cannabis as Medicine

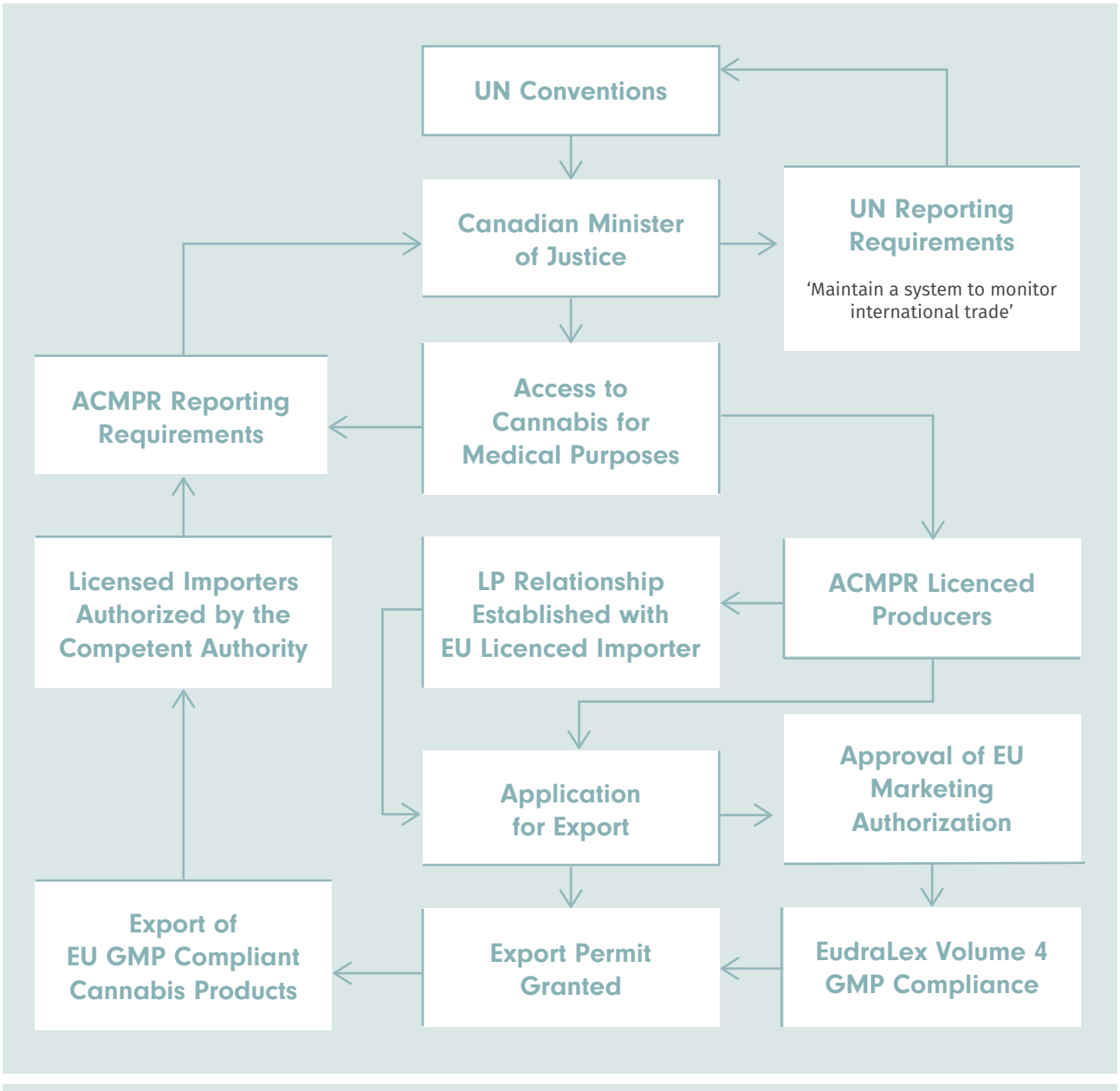
The Federal Opium Agency is expected to maintain a stable supply of cannabis to keep up with demand to ensure a consistent source of medicine to patients. However, the exact future volume requirement can only be estimated at the moment. As of Q1 2018, about 10,000 patients have procured an exemption to purchase cannabis for medical purposes. With an average daily requirement of one gram per person, 3,650 kilograms per year would be needed to continuously provide these patients with cannabis alone. In the future, it will be possible to record how the prescriptions develop and to what extent cannabis represents an adequate form of treatment for patients.

Doctors will be able to prescribe medicinal cannabis flower or pharmaceutical-grade cannabis extract on a narcotic prescription. In doing so, they must comply with the requirements of medical and narcotic law. In addition to the new regulations, previous treatments and prescription options for the finished medicinal products such as Sativex® and Canemes® and the prescription drug dronabinol will remain.

As with other medical treatments, the BfArM will not advise on the therapy itself or on the fields of application of cannabis as medicines.

Country Report: Canada

How Canada is structured for export of cannabis to the EU.

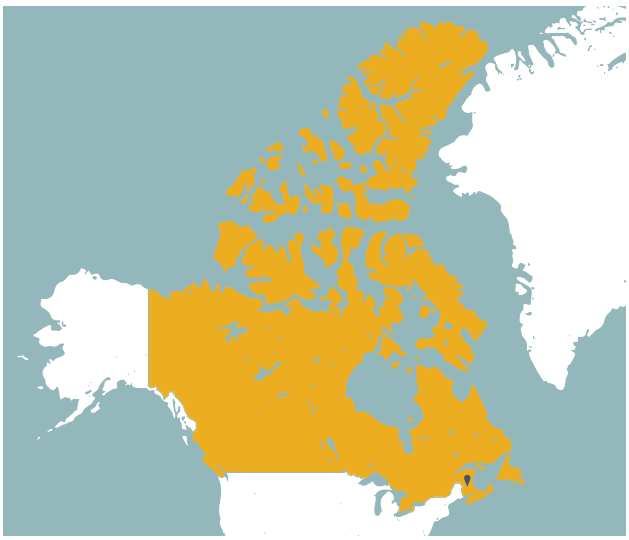


Overview

Canada is the first G20 nation to establish the precedent of successfully exporting whole cannabis plant products to other nations. As of Q1 2018, several Canadian Licenced Producers (LPs) have successfully exported cannabis to nations including Australia, Germany, and Chile. The mechanisms built into Canada's cannabis policy, the ***Access to Cannabis for Medical Purposes Regulation (ACMPR)*** allow Canadian LPs to manufacture, import, and export cannabis.

The ACMPR requires Canadian LPs to be vertically integrated, meaning that they are also the distributing entities within Canada in comparison to the Netherlands, where the Office of Medical Cannabis is the only authorised distributor. Canada, by contrast, has the ability to export directly to an authorised license holder in their respective country.

As with any nation that is a signatory to the UN Conventions, the destination nation must have a



cannabis agency. In Canada, the Minister of Justice is the ultimate authority and author of the ACMPR. Health Canada is the regulatory body that acts as the cannabis agency issuing licences for cannabis manufacturing.

The ACMPR and Provisions for Export

The ACMPR allows for the export of cannabis to destination countries with the appropriate cannabis agency that grants import licences. The process of applying for export requires that the organisation is licenced by Health Canada to manufacture cannabis. After obtaining the necessary licences, the next step is to apply for the export permit.

Applications for export have several requirements.

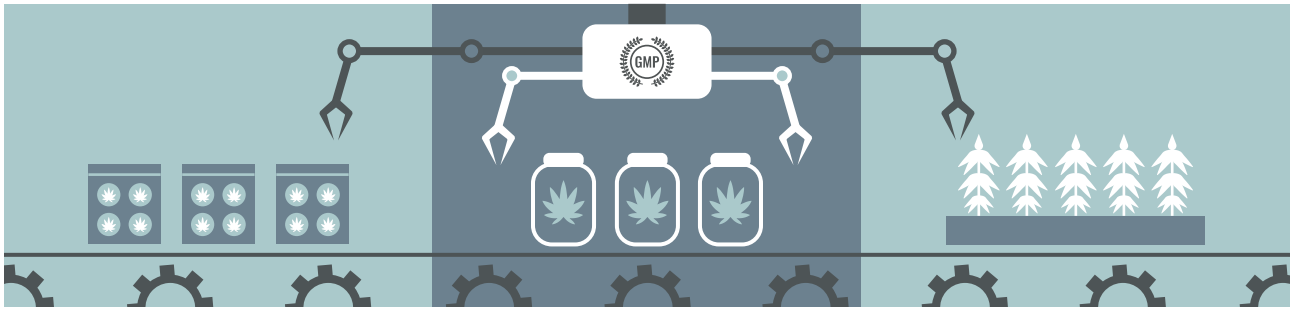
- The LP is fully operational, they must have a business relationship established with a third-party licence holder in the country of import. Without these external relationships arranged, LPs are not able to utilise their export permit.
- The LP and the third-party licence holder must be abide by all laws in their respective countries, and to the requirements of the UN Conventions.

Tying It Together

The ACMPR allows LPs to participate in the international medicinal cannabis economy as exporters. The list of LPs already includes nearly 100 LPs, with hundreds of outstanding applications pending. However, being compliant with the ACMPR alone is not sufficient for export to European nations, as their requirements are more stringent.

The EU requires the application of the EudraLex Volume 4 Good Manufacturing Practices Guidelines, hereafter referred to as ***EU GMPs***. The details of EU GMPs as they apply to cannabis is detailed later in this report, under 'The Missing Link'. Understanding the way in which requirements of ACMPR differ from the EU GMPs is essential for looking to enter an EU market.

Good Manufacturing Practices for Cannabis in the EU



History of Good Manufacturing Practices

Good Manufacturing Practices have evolved as a result of a century's worth of work by multiple countries. In the early 20th century, pharmaceutical products were manufactured mostly by independent manufacturers and pharmacies. Generalised product specifications based on available pharmacopoeia guidelines were used to establish standardisation of products, there is no regulatory oversight to ensure that the products were manufactured to ensure safety of the patient.

Early 20th century manufacturers and pharmacies had no impetus to implement 'best practices.' Even without oversight, coordinated standardisation of pharmaceutical manufacturing had not taken place by industry. Prior to manufacturing standardisation through GMP, there was no forum for subject matter experts to collectively agree on what was safe, or not safe practice for manufacturing products intended for human consumption. At the time, there was a gap in knowledge on the part of manufacturers. The knowledge gap corresponded with unidentified risks for manufacturing products intended for human consumption.

When one reads current pharmaceutical regulatory guidelines, they will be exposed to the 'Risk Based Approach.' No such approaches existed during the early 20th century. As a result, considerable risks were not identified. A handful of manufacturers worked without defined product specifications, to include microbial load and impurities. This resulted in adulterated products being brought to market that led to the death of scores of children, already compromised by illness.

Because of the early 20th century deaths of children using so-called pharmaceutical products manufactured in loosely controlled environments with little to no regulatory oversight, public concern drove legislators in the United States to develop the Pure Food and Drug Act of 1906. This legislation started an international conversation around pharmaceutical regulations that is still evolving in modern times.

Moving into the 21st century, Good Manufacturing Practices have evolved through harmonisation efforts, so that countries may abide by similar guidelines that are adopted as legislation in individual countries or a collective of cooperating countries such as the EU. The best examples are the World Health Organisation and International Conference on Harmonisation. Both organisations have taken a global view and worked to create guidelines that ensure pharmaceutical product safety regardless of the country of manufacture.

Comparing cannabis manufacturing and the potential downstream products, the same 20th century problem that faced the pharmaceutical industry is relevant to the newly sanctioned status of cannabis as a medicinal product. Despite ancient evidence of the first interaction between humans and the genus cannabis, cannabis has not yet found the same status as a safe active pharmaceutical ingredient; it is far more of a complex 'compound drug.' There is evidence for the medicinal potential of cannabis, but there are no universally accepted standards for cannabis manufacturing other than the application of current Good Manufacturing Practices and herbal drug substance and herbal drug product monographs.

At present, there is a lack of understanding of how these pharmaceutical regulations, that is, Good Manufacturing Practices, apply to the manufacture of cannabis. This report should inform the reader, whether they be regulators, manufacturers, consumers, or lobbyists, on how the EudraLex GMP guidelines apply to the cannabis industry.

EU Regulatory Compliance Bodies

There are several regulatory bodies that have scope over manufacturing pharmaceutical products. The European Medicines Agency works to 'enable timely patient access to new medicines' and 'scientific guidelines on requirements for the quality, safety, and efficacy of testing medicines'. EudraLex is the body that publishes the 'rules governing medicinal products in the European Union'. It publishes the Guidelines for Good Manufacturing Practices for medicinal products of human and veterinary use. It also publishes guidelines on Pharmacovigilance, which collects, detects, assess, monitors and prevents adverse events of pharmaceutical products.

While there is not a centralised process for cannabis marketing authorisations in the EU, these bodies still provide the pharmaceutical regulatory guidelines that must be followed. Member state national competent authorities ultimately defer to and get guidance from these EU regulatory bodies. Parties interested in the manufacture, distribution, medical use, and safety of cannabis products must similarly follow suit.

Different Levels of Compliance

The level of implementation required for any given party in the EU medicinal cannabis supply chain requires careful consideration. Good Manufacturing Practices apply to different parts of the pharmaceutical supply chain, and some requirements may not apply because of a supply chain participant taking a 'Risk Based Approach.' Ultimately, the appropriate level of compliance must be approved by the National Competent Authority and the delegated Cannabis Agency of the individual member state. Some member states may have stricter requirements for adhering to the guidelines.

Applying Good Manufacturing Practices to different parts of the medical cannabis supply chain in the EU requires thorough understanding of both cannabis manufacturing and pharmaceutical good manufacturing practices. Regardless of the step in the supply chain, the purpose of applying good manufacturing practices is to ensure there is no adulteration of the product. This means that any party involved in the supply chain must comply with the regulations that appropriately apply to their activities.

There are major steps in the medicinal cannabis 'product lifecycle.' Cultivation, harvesting, post-harvest processing (to include drying and curing), downstream product processing, packaging and labeling, and distribution. Depending on the step in the product lifecycle and supply chain, different elements are applied to the process. For example, during cultivation, Good Agricultural and Collection Practices apply, whereas during distribution, Good Distribution Practices apply. The application of Good Manufacturing Practices must be decided upon by the manufacturer and the other participants in the supply chain to ensure appropriate levels of compliance are met.

Problems Faced by Cannabis Manufacturers

The typical problems encountered by manufacturers considering going GMP, is that there are no guidelines that succinctly describe how cannabis fits into the GMP paradigm. The different steps in the pharmaceutical supply chain have been worked out by Canadian LPs for export, but the requirements for EU cannabis manufacturers have been a major barrier to entry, where only Bedrocan Netherlands holds the opportunity to distribute.

The answer to this problem requires research on how GMP applies to cannabis manufacturing, either by hiring the internal talent, or by hiring experienced consulting firms that have successfully led Canadian manufacturers into compliance with EU GMPs. The major challenge facing tender applicants in Germany, for example, is that they must develop intricate theoretical plans for how their facilities must be built out without prior knowledge of how a cannabis manufacturing facility operates, what problems cannabis manufacturers face, and how to integrate it all into a GMP environment.

Compliance and Consumer Products

Everyday manufacturing operations must adhere to a level of compliance that ensures human health and safety, and cannabis is of no exception. Regulations rooted in current day GMPs are based on cases associated with pharmaceutical products that were adulterated, resulting in early 20th century fatalities.

Our global food supply chain provides an example of Good Manufacturing Practices through Food Safety Quality Management Systems such as ***ISO 22000*** and the US Food and Drug Administration's ***Food Safety Modernisation Act (FSMA)***. These systems ensure there is supply chain integrity, where products are handled and manufactured in ways that protect the integrity of the product. Similar to pharmaceutical GMP systems, the food GMP systems are an example of how consumer products are treated where there is significant risk to consumer health by the various forms of contamination and adulteration, both intentional and accidental.

Adulteration of consumable products should be the primary public health concern. By definition, products that are not in compliance with GMPs are considered ***ineligible*** for distribution in the pharmaceutical supply chain. This is a conservative regulatory approach, but it stands to show that without such guidelines, a business entity will not be authorised to manufacture any type of consumer product. Aside from the regulatory requirement, manufacturers can realise significant benefits in applying GMPs.

Manufacturers are liable for the products they manufacture. When products are mishandled in the possession of the manufacturer or elsewhere in the supply chain, the liability is on the part of the supply chain upon which the root cause can be assigned. One needs to only look at the Deepwater Horizon Oil Spill in the Gulf of Mexico or the faulty Takata Airbags that lead to the recall of millions of automobiles.

In the case of the pharmaceutical industry, ***failed specifications*** were there number one reason for Q2 recalls in 2016[7] . While it is impossible to provide absolute certainty that products will be manufactured flawlessly, adherence to Good Manufacturing Practices affords significant risk mitigation against recall events.

Benefits of GMP

Benefits exist in enhanced traceability throughout the entire product lifecycle, from product development, to technology transfer and active manufacturing. Product liability ties back into the traceability of the products, the root cause of adulteration cases, and the ability to directly remove defective products from the market. It is only through the proper use of batch records[8] that one can employ root cause analyses, a core component of GMPs, to identify where adulteration likely occurred within the product lifecycle.

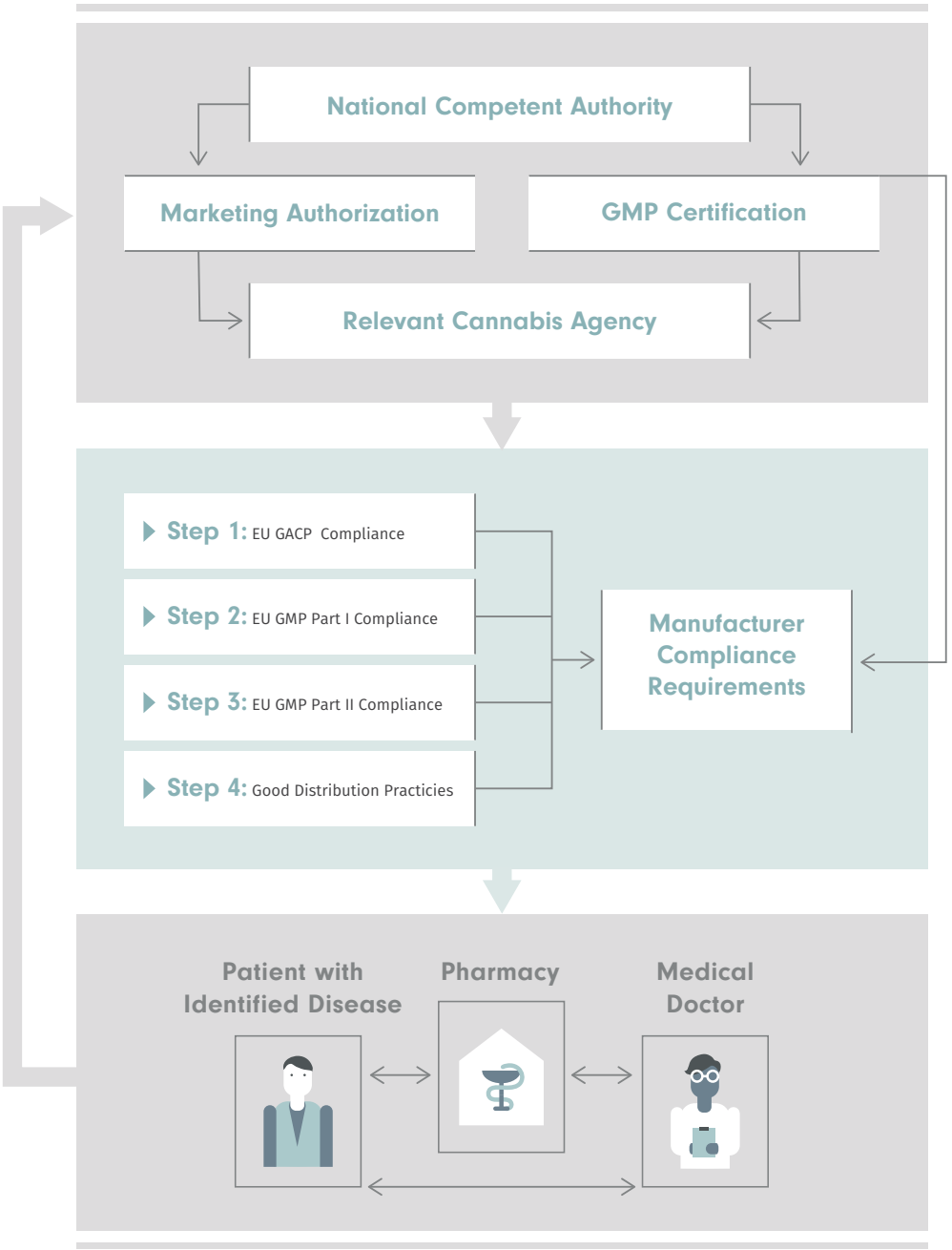
Beyond traceability, there is significant benefit in understanding variation in manufacturing of products. By clearly understanding the concept of and identifying critical quality attributes (CQAs) of the process, only then can one, whether it be a cultivator, manufacturer, or otherwise, begin to understand how process variation affects the final product and its relationship to treating disease states and disease state side effects. If the products have batch-to-batch variation the patient may find variable or no therapeutic benefit.

[7] *Stericycle Expert Solutions Recall Index, Q4 2017*

[8] *Batch records are the traceable document showing all process inputs, outputs, yields, etc. Refer to to the EU GMP guidelines for more information on generating batch records.*

EU GMP Compliant Manufacturing

There are several authorities involved in the process of allowing a manufacturer to legally produce herbal drug substances and herbal drug products. EU Member States have their own respective ***National Competent Authority***, with cannabis programmes including an additional line of oversight through a respective national cannabis agency, as described earlier within the report. These two authorities work to meet the requirements of the UN Conventions, and ensure that public health is protected. It is important for the manufacturer to fully understand the processes and procedures of these agencies in order to successfully operate. Without full GMP compliance to the specifications of these important stakeholders, a manufacturer will not be able to distribute products within their member state, or to export to other member states, posing a significant risk to stakeholders of companies seeking to utilise this model.



National Process for Compliance

Health Canada

Bundesinstitut für Arzneimittel und Medizinprodukte

Inspectie voor de Gezondheidszorg
Ministerie van Volksgezondheid, Welzijn en Sport

In the Netherlands, for example, the Healthcare Inspectorate is the authority for ensuring GMP compliance, and the ***Office of Medical Cannabis*** serves as the national cannabis agency ensuring compliance to all cannabis manufacturing requirements. Coordination between these stakeholders, including the manufacturer or distributor, is necessary to successfully achieve the level of compliance required to distribute cannabis based herbal drug substances and products within the member state.

When a manufacture is applying for licensure, regulatory inspections are handled through the national competent authority. Preparation for a successful inspection to legally distribute pharmaceutical products takes significant effort, and third-party pre-assessments with outside consulting expertise is prudent. Entities that do not build in these additional resources have a significantly higher probability of failing their first inspection, which often leads to higher level of scrutiny during follow up inspections. Additionally, the national competent authority performs risk-based inspections for all elements that may be compromised in the manufacturing supply chain.

During an inspection, an entity can expect that all of their quality related documentation (i.e. all documented aspects of the operation in question) will be fully audited. The inspector(s) will also perform a site tour, personnel interviews, review the site master file relative to the actual operations, and review batch records in order to determine conformance to the applicable regulation. Deficiencies relative to the regulations are generally flagged as ***critical, major, minor*** or as recommendations. The severity of the deficiencies will determine how any risk mitigation or corrective action must be performed and if the deficiencies warrant a failed inspection.

National Cannabis Agencies

National cannabis agencies, as described earlier in the report, fulfill the requirements of the UN Conventions. These requirements include all transactions related to cannabis, the expected needs for cannabis internal to and outside of Member States and exercising power as the ultimate regulatory authority. They may also designate manufacturing locations, issue licensing, control custody and monitoring of the supply chain, and general control of import and export activities.

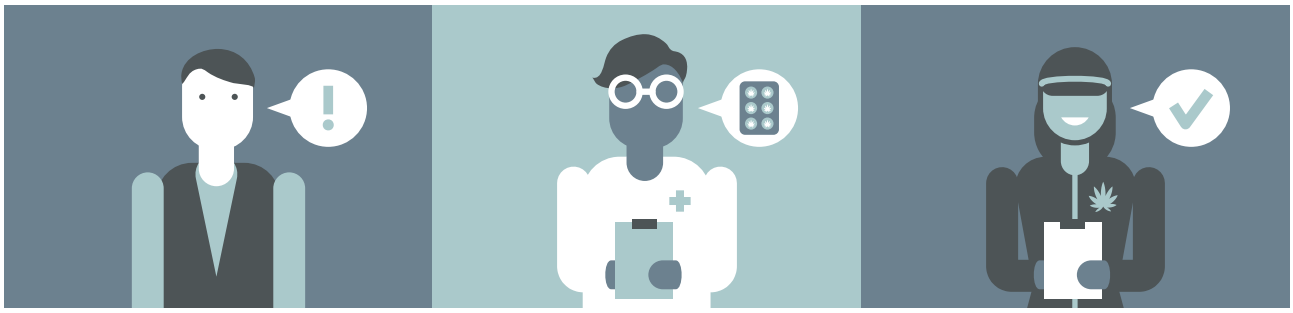
Marketing Authorisations of Medical Cannabis

Marketing authorisations are the gateway for introducing pharmaceutical products to the market, but this is not necessarily the case for all cannabis-based products, although medical cannabis could be considered an active pharmaceutical ingredient (API) or pharmaceutical product.

The pathway towards a centralised marketing authorisation represents a major challenge, but the introduction to the market through the national competent authorities and national cannabis agencies offers manufacturers the opportunity to 'circumvent' the authorisation process. It also provides the option to perform the research and development to ensure their product has a long-term position on the market, because the value is in the intellectual property.

Compliance with EU GMPs for medicinal products and APIs should be considered by both the product type and the regulatory context. Countries like Germany, for example, require full application of EU GMP part I (medicinal products) and II (active pharmaceutical ingredients – APIs).

EU Directive 2001/83/EC – Medicinal Products for Human Use



EU Directive 2001/83/EC is the basis for the pharmaceutical industry in Europe and sets up the requirements for the entire pharmaceutical supply chain. Cannabis, also known as an ***herbal drug substance*** or ***herbal drug product*** depending on its form, is handled similarly.

Manufacturers working towards full compliance with EU GMPs will find the review of EU Directive 2001/83/EC essential to understanding policies governing cannabis manufacturing and distribution. The importance of reading, understanding, and incorporating these guidance documents cannot be overstated. When building a compliant manufacturing operation, one must operate under the assumption that all stakeholder requirements must be met. This means the manufacturer must consider the requirements of the cannabis agency and national competent authority, from the perspective of ***their*** requirements and missions.

EU Directive 2001/83 has a mission of ensuring that there are adequate rules for the production, distribution, and use of medicinal products that safeguard public health. It recognises that its rules should not hinder research

and development for the pharmaceutical industry, that differences in national pharmaceutical regulations have effects on the entire EU market, and that 'such hindrances must accordingly be removed.' It ensures that Member States' national competent authorities are harmonised upon a similar pharmaceutical regulatory framework. For manufacturers, the framework describes their relationship with the regulations, and how they interrelate to the competent authorities.
This safeguards public health and ensures it provides guidelines to establish pharmacovigilance systems to ensure that adverse events are appropriately handled. From the healthcare perspective, it sets forth the types of products (for cannabis, in this case) that can be prescribed: ***herbal medicinal products, herbal substances, and herbal preparations.***

EU Directive 2001/83 sets up the requirement for marketing authorisation within the member state through the competent authority. Requirements include, but are not limited to: qualitative and quantitative data, description of the manufacturing method, therapeutic indications and adverse reactions, posology, pharmaceutical form, method and route of administration, expected shelf life, and description of control methods employed by the manufacturer. This offers some indication of the sophistication required in the marketing authorisation application. Attention should be given to the ***specific provisions applicable to traditional herbal medicinal products,*** as well ***as monographs 1433 and 1434*** of the European Pharmacopoeia.

EU Directive 2001/83 describes the requirements 'to comply with the principles and guidelines of good manufacturing practice for medicinal products and to use as starting materials only for active substances, which have been manufactured in accordance to detailed guidelines on good manufacturing practice for starting materials.' The assurance of compliance is then delegated to the 'qualified person', that is responsible for critical activities such as batch release.

Putting it all together and observing the framework of the medical cannabis industry in the cases of Germany and the Netherlands, it becomes apparent that EU Directive 2001/83/EC is a foundational guideline for how pharmaceutical products are manufactured in the EU. Taking into account the major elements of the directive, it is also necessary to consider the significance of the EU GMPs and how they relate to the cannabis supply chain.

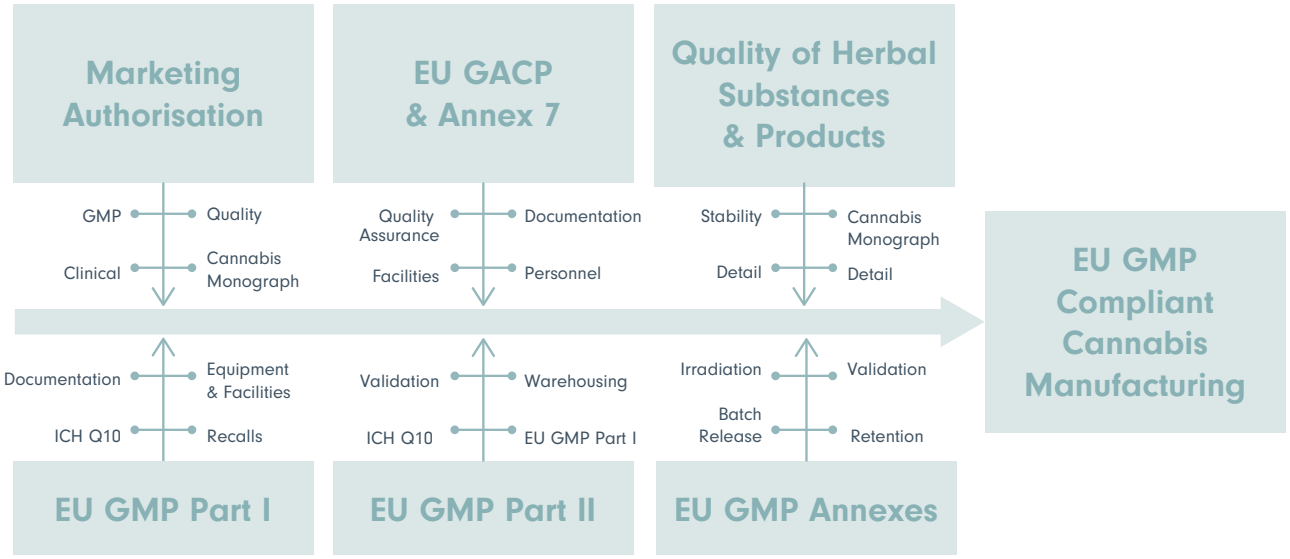
Lack of historical medicinal cannabis within the EU challenges manufacturers bringing their herbal drug substances and herbal drug products to market. Particularly where applications require historical evidence showing traditional use as a medicine. Despite the slow approval of cannabis manufacturing in the EU, several EU organisations have made partnerships with Canadian manufacturers that can import into the EU, if they are fully compliant with EU GMP guidelines.

EU GMP Guidelines

Understanding the application of GMP Guidelines at each step of the supply chain is essential for manufacturers to effectively communicate and prepare for questions by inspectors. Careful reading of the guidelines with respect to the entity's activities being performed, product types, and risks posed to patient health from the products will allow effective application of the guidelines and any associated Annexes.

Manufacturers must carefully consider their product specifications, process specifications, and how they relate to GMP regulatory compliance. This should be done with the assistance of pharmaceutical legal counsel, appropriate subject matter experts (SME), and consultants, as these critical variables influence downstream decisions.

The figure below describes the major elements for concideration in the manufacturing process, and the guidelines to be applied.



Quality of Herbal Supplements and Products

Quality underpins in multiple elements of the EU GMPs and the guidelines related to herbal drug substances and herbal drug products. Quality refers to of variation against pre-established specifications. The dialogue around quality must be clearly described based on the language provided in the various guidelines provided by the European Medicines Agency and the European Directorate for the Quality of Medicines and Healthcare. It is important to document the specifications related to Good Manufacturing Practices. Herbal Drug Substances and Herbal Drug Products require manufacturing operation specifications, intermediate product specifications, and final batch release specifications. All of these specifications are documented within batch records, which form one of the most important elements of the Pharmaceutical Quality Management System.

Batch Records

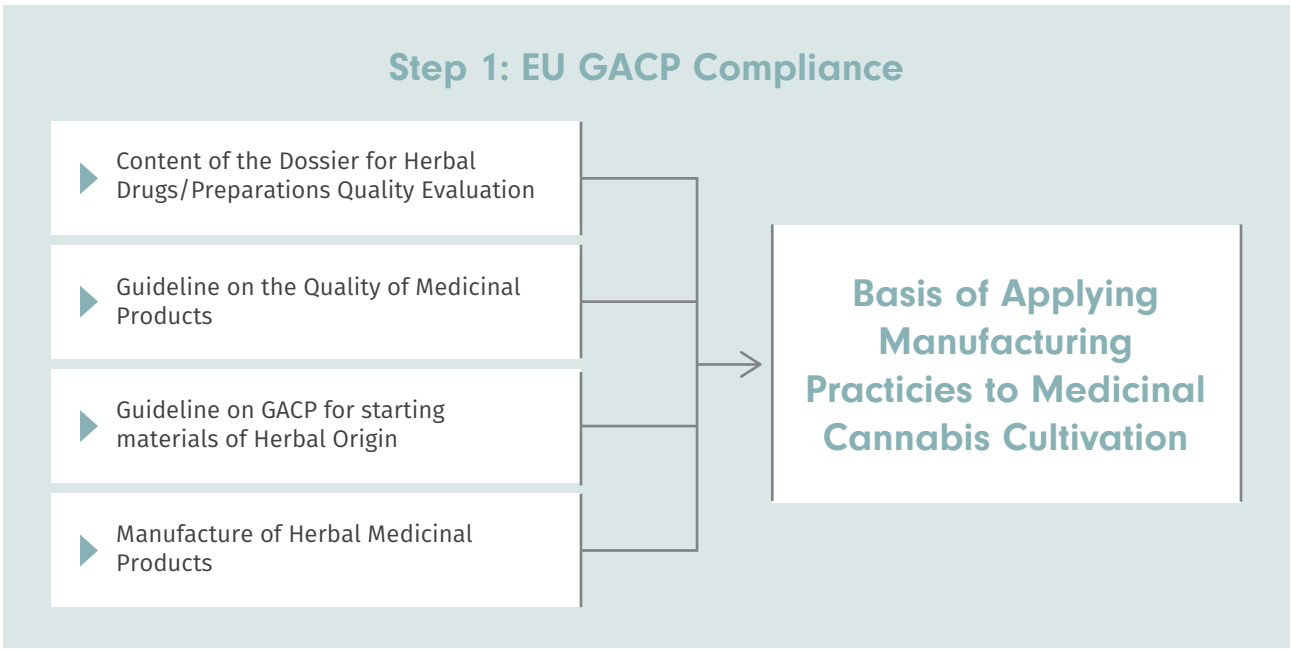
Batch record requirements become much more specific requiring information such as, but not limited to: dates and times, equipment used, weights, measures, batch numbers of raw materials, intermediate materials, critical test parameters, sampling, signatures of technicians and supervisors, in-process test results, and, most importantly, any deviations that occur during the manufacturing process. These batch records are reviewed, and final release made by the ***Responsible/ Qualified Person.***

Regardless of the stage of manufacturing or distribution, batch records must meet predefined specifications for product quality as a described previously. The Responsible/Qualified Person[9] is responsible for final batch release and ensuring all release criteria has been met.

Eu Good Agricultural and Collection Practices

Agriculture related to herbal drug substances and herbal drug products falls under the scope of both ***Good Agricultural and Collection Practices and Good Manufacturing Practices.*** This is well illustrated in several GMP guidelines, to include the ***EU GMP Annex 7***, and ***EU GMP Part II*** and the ***International Conference on Harmonisation*** Q7 ***Good Manufacturing Practice Guide for Active Pharmaceutical Substances.***

[9] As described in EU Directive 2001/83/EC



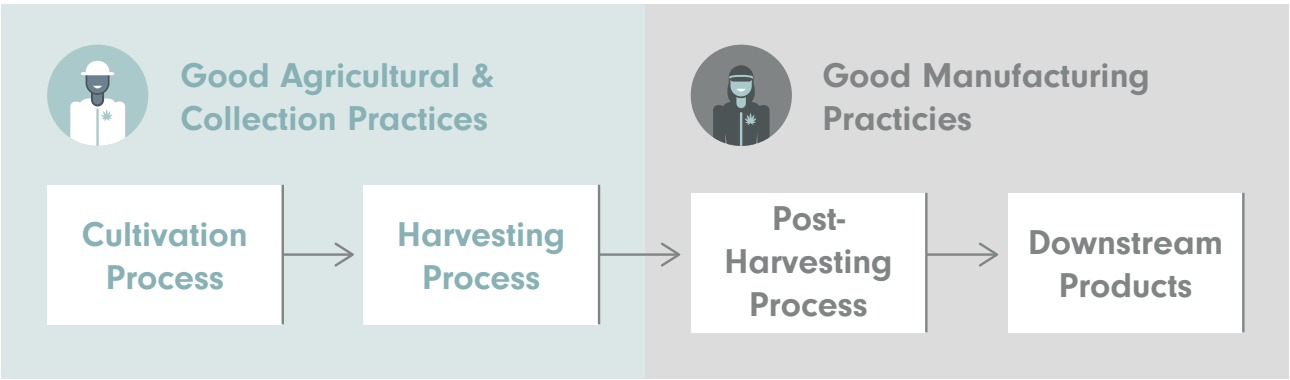
EU GMP Annex 7 – Manufacture of Herbal Medicinal Products

In addition to GACP, there are additional requirements for the manufacture of Herbal Medicinal Products, as described within the EU GMP Part II Guide. It is important to carefully consider the interrelation between the guidelines, as nuances exist for product types and the manufacturing processes required to achieve product quality specifications.

Activity	Good Agricultural and Collection Practice (GACP)	Part II of the GMP Guide	Part I of the GMP Guide
Cultivation, collection, and harvesting of plants.			
Cutting and drying of plants.			
Expression from Plants and Distillation.			
Comminution, extractions from plants, fractionation, purification, concentration or fermentation of herbal substances.			
Further processing into a dosage form including packaging as a medicinal product.			

GACP to GMP Transition

The transition from the GACP to GMP environment must be defined, depending on the product type being produced. Justifications can be made in either direction for where the GMP process starts by using a risk-based approach in addition to the guidelines.



Aside from the conservative and early application of GMP into the process, there are useful elements for collecting data that would otherwise not be tracked in a GACP compliant process. Over time, understanding data points of stability, shelf life, and contamination can be gained when more information is collected. These are just a few of the benefits of the early adoption of GMPs, in addition to GACP in the cultivation phase of manufacturing herbal drug substances and herbal drug products.

EU GMP Part I Guideline

The EU GMP Part I Guideline sets the manufacturers' requirements for managing the quality of their manufactured goods. This recommendation extends to all types of pharmaceutical and medicinal cannabis manufacturers and should be implemented to protect not only patient health, but also against product liabilities.

Step 2: EU GMP Part I Post-Harvest Processing

The Quality Management System (QMS) is the means of managing the processes of manufacturing herbal drug substances and herbal drug products. The QMS is utilised throughout the ***product lifecycle***, from product development, to tech transfer, to manufacturing, and finally to product discontinuation. EU GMP Guideline Part I, Chapter 1 is highly dependent on the well vetted ***International Conference of Harmonisation (ICH) Q10 Guideline, Pharmaceutical Quality Management System.*** This robust system was developed under the concept of harmonising a QMS for pharmaceutical manufacturing. Its utility is observed through its widespread adoption within the international pharmaceutical manufacturing industry.

Personnel are an integral component in any manufacturing setting, let along drug substances. Their training and qualifications must be well documented, tracked, and updated. The interrelation between the personnel and the Quality Management System are the means of ***managing the process***, rather than managing ***labour***.

Facilities must be designed for the intended purpose in mind and built to ***User Requirement Specifications (URS)*** that outline all activities taking place in the manufacturing environment. Facilities must deploy ***pharmaceutical containment strategies*** that ensure products are not adulterated during any processing step and be applied more rigorously further downstream towards the final product.

Equipment, similar to the facilities, must also be procured according to URS that meet the needs of the product specifications, process throughput, and ability to be appropriately sanitised. Equipment operational specifications must be developed for the specific processes in mind, and the equipment must be qualified for use. Not only must the equipment be qualified, its qualification must be traceable to specific maintenance and use events.

Documentation is the arch stone of Good Manufacturing Practices and Quality Management Systems. Documentation includes critical quality documentation such as, but not limited to: Standard Operating Procedures, Batch Records, Change Management, Corrective Action and Preventative Action, Deviations, Non-Conformances, Out of Specification events, Certificates of Analysis, and many more. Collectively, the Quality Manual and Site Master File describe the overall operations and provide a big picture perspective that will be reviewed during any GMP Inspection. The completeness and organisation of documentation must be in order and in compliance with the GMP guidelines, at the very minimum, in order to pass the GMP Inspection.

Quality Control is the essential activity taking place during critical steps of the manufacturing process. This includes both in-process testing and ***final batch release testing***. As observed throughout the cannabis industry, 3rd party testing laboratories fulfill the needs of the manufacturers QC responsibilities. Any such outsourced activity must be approved on a basis of ***vendor audits and vendor agreements.*** QC integrates into a quality-based feedback loop, that informs the manufacturer of what needs to be changed in a manufacturing process in order to meet the defined acceptance criteria, or specifications, for the product.

Product Defects, Complaints, and Recalls are major events that must be prepared through 'Mock Events,' for example, mock product recalls. All such events are treated similarly with the utmost attention paid to even the most trivial of complaints. It is the basis for identifying problems with process that lead to defects, customer dissatisfaction, adverse events, and reduction of risk for recall.

These are the minimum elements necessary to ensure product quality and that public health is protected, regardless of the product type. Combining the EU GACP guideline and EU GMP Part I guideline are the baseline for manufacturing herbal drug products. Moving into the EU GMP Part II guideline sets the baseline for herbal drug substances.

EU GMP Part II Guideline

The EU GMP Part II guideline is the basis for manufacturing Active Pharmaceutical Ingredients. As referenced above, the ***International Conference on Harmonisation*** Q7 ***Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients*** is used by a number of countries around the world, as it is a harmonised guide for pharmaceutical active substance manufacturing. Major elements of the EU GMP Part II guideline were adopted from ICH Q7, but revisions since its original use have been superseded by Part II. The EU GMP Part II Guideline clearly describes at what point an herbal drug substance should be treated as an ***herbal drug product.***

Type of Manufacturing	Application of EU GMP Part II (Shaded in Grey)				
API Extracted from Plant Sources	Collection of Plants	Cutting and Initial Extractions	Introduction of API Starting Material into process	Isolation and Purification	Physical Processing and Packaging
Herbal Extracts used as an API	Collection of Plants	Cutting and Initial Extractions		Further Extraction	Physical Processing and Packaging
API from comminuted or Powdered Herb	Collection of Plants and/or cultivation and processing	Cutting/ Comminuting			Physical Processing and Packaging

Figure 10 Source: Eudralex Volume 4 EU GMP Part II Guide

Part II of the EU GMP Guideline should be closely read for deciding how different processes require more stringent application of the GMP guideline. Some provisions are given based on the processing step as to whether any additional application of the guideline is required, such as 'bulk packaged medicinal products.' With such cases, risk-based justifications can be made for where responsibility falls in the supply chain for different application of the EU GMP guidelines.

Step 3: EU GMP Part II Active Substance Manufacturing

GMPs are applied with increasing stringency the closer a product gets to batch release in the manufacturing process.

Materials Management is an element of the Part II Guideline that has additional requirements beyond the ***Production*** guideline of Part I. Materials management requires thorough vetting of all materials vendors to agreed upon specifications. It is essential for ensuring consistent product quality and integrity throughout the supply chain, all the way to the consumer. These procedures work not only to reduce the likelihood of product liability situations, but also protect consumer health and reduce adverse event the potential for.

Special attention is paid to packaging and labeling operations. As intermediate products come closer to being finished goods, the chance for adulteration increases, and the risks associated with potential adulteration must be mitigated; it is essential that labeling operations strictly adhere to the Part II guideline. The Packaging and Labeling operations in Part II are rigorously vetted through decades of continuous improvements made to GMP guidelines. If for nothing else, entities should keep in mind the risks of product liability due to contamination or recall stemming from weak or loosely detailed procedures for this critical operational step.

Good Distribution Practices

Good Distribution Practices (GDP) are the means of ensuring supply chain integrity. It ensures qualified medicinal products are delivered to patients. Many elements of GDP are similar to GMP, requiring that all transactions take place in qualified environments with full traceability. The main purpose is to ensure that 'falsified medicines do not enter the legal supply chain.'

The major elements of GDP include, but are not limited to:

- Working through qualified suppliers and customers
- Receipt and handling of materials
- Warehousing procedures
- First expiry - first out (FEFO)
- Outsourcing distribution activities
- Self-inspection
- Transporting, and wholesale activities

Collectively, these processes ensure that all products meet specifications and deliver the exact products that patients require to treat their disease state and associated side effects.

Marketing authorisation is an explicit requirement for all activities within the supply chain to comply with all aspects of GMP and GDP. This extends to wholesale distribution, where distributors are required to hold a ***Wholesale Distribution Authorisation.*** All activities within the distribution supply chain are therefore held to the regulations of EU GDP. This means that GMP manufacturers must also be compliant with EU GDP.

As required for manufacturers, distributors must maintain a quality management system. This critical system ensures that all activities are fully documented and traceable. A ***Qualified Person*** is responsible for ensuring that all quality related activities are appropriately executed according to EU GDP guideline. Systems ***premises and equipment*** must be similarly qualified and controlled throughout all distribution activities.

Documentation of distribution activities ensures traceability. All written procedures must be closely followed, and when deviations occur, the quality management system is deployed. Approval of activities through the qualified person ensures batch record final release criteria and specifications have been met, that products are not adulterated, and that they are safe for human consumption.

Qualified Suppliers must be fully vetted and audited to the GDP guideline by the manufacturer and the national competent authority. Such qualifications must be fully completed before any distribution activities take place, in addition to qualifying the customer. Customers themselves must either hold a manufacturing authorisation or be a qualified entity such as a pharmacy or pharmacist. Qualification of customers is necessary to maintain integrity of the supply chain and to monitor potential diversion.

Warehousing requirements are set according to the specifications of the product and the appropriate storage conditions to prevent spoilage of the products. ***First Expiry – First Out*** principles apply, ensuring that stock closest to expiration is distributed first. These principles require manufacturers to have established stability programmes.

Step 4: EU Good Distribution Practices

Conclusion

Nearly 60 years after the first UN convention took the stance that cannabis production must be restricted due to 'illicit traffic' and the need for treating and rehabilitating drug addicts, countries are now creating their own medicinal cannabis programmes based on the growing body of scientific evidence for the therapeutic potential of cannabis for different disease states. By following the protocols within the conventions, the countries described in this report have successfully navigated the development and regulation of compliant programmes, which will serve as a template for future development for other countries that were signatories to the UN conventions.

The adherence to well vetted pharmaceutical Good Manufacturing Practices and Good Distribution Practices sets a new precedence for the once illicit international cannabis economy. Export nations like Canada have found themselves with national cannabis regulations that, while not stringent enough for reciprocity to current export nations, provide Licenced Producers with the framework to achieve EU GMP compliance and subsequently export their products. While not required, this indicates a global shift that is changing the way medical cannabis is manufactured.

The adoption of GMP provides the assurance that medical cannabis is manufactured to predetermined acceptance criteria. If products do not meet specifications, they will not be released by the responsible person. This protects patients from adulteration and variability in the product which is necessary for the achievement of clinical safety and efficiency. It also sets the stage for clinical trials that will pave the way for scientifically documenting any therapeutic efficacy of cannabis.

It is important for manufacturers to understand the costs and benefits of choosing to become GMP compliant, regardless of their current state or country laws. While GMP standards are more costly to implement when initially starting a facility, the access to international markets will provide a significant return on investment to them and the medical community as a whole if implemented correctly.

Orion GMP Solutions, About Us

Orion GMP Solutions is a North American based cannaceutical advisory firm that focuses on implementation of international pharmaceutical Good Manufacturing Practices (GMP) and Quality Management Systems (QMS).

Orion GMP Solutions advises western hemisphere manufacturers and cultivators of herbal drug substances, products, and preparations on operational practices to comply with international markets and distributors. Full GMP compliance opens up new markets and business segments for all types of herbal based products.

Orion GMP Solutions' scopes of work include: facility and process assessments, GMP/QMS Training, Quality Management System Design, Quality Assurance Management, Project Management, Current Good Manufacturing Practices Implementation, Process Validation, Facility Buildout and Engineering, SOP and Batch Record Development, Quality Risk Management, Hazard Analysis and Critical Control Points, Scientific Technical Writing, Laboratory Method Development and Validation, 483 Warning Letter Remediation, and Lean Six Sigma.

Orion GMP Solutions is a multidisciplinary group of chemists, food scientists, and engineers with focus on Good Manufacturing Practices and Quality Management Systems, and a dedication to standards generation. Orion GMP Solutions actively participates in the ASTM International D37 Cannabis Standards Committee with multiple leadership positions in Technical Subcommittees and the Executive Committee.

About the Authors

Andrew Samann

Andrew is the founder of Orion GMP Solutions Inc. and serves as the Chief Executive Officer and Principal Consultant. As a Sergeant in the United States Marine Corps, he served two tours in Operation Iraqi Freedom leading a team of Marines responsible for quality management and documentation of over 400,000 life limited critical parts on 30+ UH-1N and AH-1W attack helicopters, with multiple deployment aircraft transfers as an advanced party auditor for documentation and records of quality maintenance management systems per the ***Naval Aviation Maintenance Program*** guidelines.

Following the Marines, Andrew earned his Bachelor of Science in Biochemistry and worked at the University of Michigan as a bio-analytical chemist, publishing several articles in peer reviewed scientific journals. Andrew's experience spans the fields of bio-analytical chemistry and purification; including pharmaceutical manufacturing and quality control of Active Pharmaceutical Ingredients under FDA and International GMP guidelines in an FDA Registered, DEA Schedule 1 Facility. Andrew formed Orion GMP Solutions in early 2015, after recognizing the need for products with low variation medical cannabis products and the lack of harmonized standards across the cannabis industry. Andrew has audited numerous GMP Pharmaceutical, Dietary, Cosmetic, and Cannabis manufacturers across North America, working for SGS, the world's leading inspection, verification, testing, and certification company.

Andrew regularly speaks on the subject of international cannabis standardisation and implementation of Pharmaceutical Good Manufacturing Practices, with recent speaking engagements such as the Emerald Science Conference (San Diego), Canna-Tech (London), and ASTM D37 meetings (New Orleans, Berlin, Toronto). Andrew actively participates in the ASTM D37 Cannabis Standards Committee as the Technical Subcommittee Chairman of Quality Management Systems and the sits on Executive Committee.

David Vaillencourt

David is the Chief Operating Officer and Managing Consultant of Orion GMP Solutions. David holds a Master of Science degree and has management of multi-million dollar federal projects as an environmental consultant. He has significant experience working in highly regulated environments including ISO 17025 environmental testing laboratories and the US Department of Defense's Chemical Weapons disarmament unit with expert knowledge in gas and liquid chromatography instrument operation.

David has managed and worked on multiple international projects at Orion, with a focus on Project Management, training, and the application of Quality Management Systems implementation. David is OSHA HAZWOPER Certified, holds a Department of Defense Security Clearance, and is the Recording Secretary and Analytical Method Validation Task Group Leader of the ASTM D37 Cannabis Standards Technical Subcommittee on Laboratory Operations. David is also an auditor for SGS, the world's leading inspection, verification, testing, and certification company.

Justin Greene

Justin is a Senior Consultant at Orion GMP Solutions. Justin holds a Master of Engineering degree and brings his process engineering background to Orion, with certification and compliance management in Automotive and Aerospace Manufacturing, as well as ISO 9001. His expertise is bolstered by his Lean Six Sigma Black Belt certification and significant experience in applied business management consulting. Justin has worked with numerous cannabis manufacturers to improve process efficiencies and identify key risks of processes related to manufacturing.

Justin has significant experience as an operational excellence management advisory in manufacturing industries. His projects typically involve larger organizations in the implementation of lean manufacturing practices, and change management to improve organisational monetary performance. Justin participates as a member of the ASTM D37 Cannabis Standards Committee. Justin is also an auditor for Orion GMP Solutions, with significant supply chain auditing experience.

Special Thanks

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Prohibition Partners, About Us

We are trusted advisors to Europe's legal cannabis industry

Europe's legal cannabis industry will gradually open up over the next three years to become the largest cannabis market in the world.

However the challenge will be combining traditional values and advocacy with the level of corporate and professional knowledge required to build robust and scalable businesses.

We work with investors, entrepreneurs and regulators to identify, qualify and maximise the many opportunities in this emerging frontier.

Our reliable and credible insight is maturing the conversation and opening up the industry. We are part of the fabric.

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Ongoing free reports and content including The European Cannabis Report™ and European Cannabis Weekly newsletter.

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Detailed research and analysis for both regulators and investors interested in the potential of the European market.

M&A Advisory

Buy side / sell side representation, joint ventures and strategic partnerships for global players entering this market.

STEPHEN MURPHY
MANAGING DIRECTOR

Contact Details

info@prohibitionpartners.com
+44 (0)7450 341252
@prohibition_p
42 Berkeley Square, Mayfair, London W1J 5AW