

The biggest challenges and opportunities of the medical cannabis value chain

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The purpose of this paper is to provide a better understanding of the cannabis industry for medical use, its challenges and opportunities. Many studies have indicated therapeutic benefits of a cannabis treatment for a variety of indications. Some of the cannabis-based products are currently on the market in specific countries. Based on the value chain of activities developed by Porter, the value chain of the cannabis industry has been divided into 3 main market actors for the purpose of classifying associated challenges and opportunities in the cannabis industry:

- *Cultivators*
- *Manufacturers*
- *Distributors*

As a result of interviews given and research findings, the principal challenges for the actors are:

- *Uncertain demand (incomplete planning, difficulty in evaluating pricing risks)*
- *Complexity of laws and regulations*
- *Intellectual property protection*

Significant opportunities are:

- *High potential for developing new technologies specific to this market*
- *Building a community of cannabis experts throughout the value chain*
- *Possibility of achieving a zero carbon footprint throughout the cannabis value chain*
- *High potential margin for all the market actors due to the development of the cannabis industry*

In the light of these observations, it will be necessary to consider challenges for market actors in order to build a robust risk management framework, eventually reducing them. An exploration of opportunities in an immature market based medical cannabis industry will need to be undertaken.

Introduction

After years of disinterest, recent decades have witnessed a concern for the therapeutic potential of cannabis. Countries like Canada, Netherlands, Israel, and certain states in the United States of America have developed programs to allow access to cannabis for therapeutic purposes.

In the context of development of the cannabis industry for medical use, this paper presents the most prominent components of the cannabis plant with their proved therapeutic benefits and a list of the cannabis-based medical products that are currently in the market.

According to the research and interviews with cultivators, manufacturers and distributors, the main challenges and opportunities will be defined through the Porter's value chain with the potential margin, so as to create value into the marketplace for cannabis-based medicinal products.

Clinical indications

There are more than 500 constituents, including hydrocarbons, nitrogenous compounds, flavonoids, fatty acids, non-cannabinoid phenols, phytosterols, vitamin K, carotene and xanthophylls as pigments, various simple alcohols, aldehydes, ketones, carboxylic acids, esters and lactones. Cannabis compounds of great interest are the cannabinoids¹, organic compounds that become biochemically active after inhalation, digestion or absorption through the skin. The most frequently studied components in cannabis plant are shown in Figure 1.



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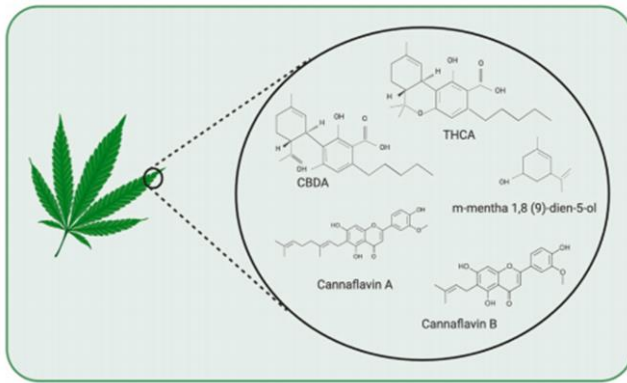


Figure 1: Key components of the cannabis plant

Cannabinoids, terpenoids and flavonoids comprise the most interesting classes of biologically active compounds found in cannabis plant, due to their health potential.

The CBDA, the cannabidiolic acid and the THCA, the tetrahydrocannabinolic acid are the most important molecules identified in cannabis¹.

The neutral forms of THC (delta-9-Tetrahydrocannabinol) and CBD (cannabidiol), that are pharmacologically active, are not produced by the metabolism of cannabis but formed during thermal decarboxylation^{2, 3}.

THC is the major psychotropic cannabinoid found in cannabis. It is a pharmacologically and toxicologically a relevant constituent, with several biological effects. CBD is the major non psychotropic cannabinoid found in cannabis. It is more abundantly found in hemp - a fibrous-variety of *C. Sativa* - in its acid form. It has a variety of biological effects, such as antioxidant and anti-inflammatory properties and immunomodulatory effects². Twenty-three flavonoids have been reported in cannabis and they have potential antioxidative, anti-inflammatory, antimutagenic, and anticarcinogenic compounds. Among them, two are unique in the cannabis plant: cannafavin A and cannafavin B^{2, 3}.

An overview of the current evidence for the medical use of cannabis, with its limitations is shown in Table 1.

Table 1: Summary of the evidence for the medical use of cannabis and cannabinoids⁴

Disease/symptoms	Products tested	Strength of evidence	Limitations
Nausea and vomiting associated with cancer chemotherapy	Cannabinoids	Weak	Few studies testing against newer, more effective anti-emetics. Newer chemotherapy regimens produce less nausea. Little evidence available about use in other types of nausea.
Appetite stimulant in patients with AIDS-related wasting	Dronabinol/THC	Weak	Fewer AIDS-related cases available to treat now. Little evidence available about use to stimulate appetite in people with other conditions.
Muscle spasm in patients with multiple sclerosis	Nabiximols	Moderate	Patients report reductions, but more limited impact on clinician ratings.
CNCP, including neuropathic pain	Cannabis and cannabinoids	Moderate	Small (but statistically significant) effect compared with placebo.
Palliative care for cancer	Cannabinoids	Insufficient	Larger, better-designed trials are needed.
Intractable childhood epilepsy	CBD	Moderate	Evidence for use in adjunctive therapy in people with Dravet or Lennox-Gastaut syndrome. More studies are needed to look at dosage, interactions and use in people with other forms of epilepsy.
Other medical uses, such as sleep disorders, anxiety disorders, depression, degenerative neurological disorders, and inflammatory bowel disease	Cannabis or cannabinoids	Insufficient	Some evidence for short-term effects in some conditions (e.g. sleep disorders) but larger, better-designed trials are needed, with longer follow-up.

CNCP: For chronic non-cancer pain (NASEM, 2017). This includes neuropathic pain, arthritis, back pain, neck and shoulder pain, and headaches.



Pharmaceutical Cannabinoid products

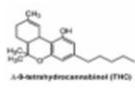
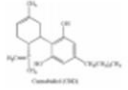
Cannabis-based medical products can vary from purified single compounds (often THC or CBD), to complex mixtures of hundreds of molecules, in multiple formulations (oils, solutions, sublingual sprays, tablets and capsules),

with multiple delivery routes (oral, nasal, rectal, and inhalation).

Table 2 below summarizes some of the current medical cannabis products that patients use today, their typical routes of administration and their common indications⁵.

Table 2: Summary of the Cannabis based medicines

Cannabis based medicines include a wide variety of product types from single active pharmaceutical ingredient (API, e.g. THC or CBD) to complex mixtures of 100s of molecules, which are also consumed/administered through a variety of routes.

	THC products	Purified CBD	CBD:THC ratios	Whole flower products	Enriched products
Active pharmaceutical ingredients	 <chem>CC1=C(C(=C(C=C1)OC(=O)C)C)C</chem> Δ-9-tetrahydrocannabinol (THC)	 <chem>CC1=C(C(=C(C=C1)OC(=O)C)C)C</chem> Cannabidiol (CBD)	Often 1:1 but 20:1 and 50:1 products becoming popular in neurological conditions	100s molecules; phytocannabinoids, flavonoids, terpenes. Modern medicinal products have specified THC:CBD ratios.	THC or CBD dominant products with a % (variable) of other phytochemicals
Typical examples	Nabilone (THC analogue) and Dronabinol (synthetic THC-Senzer; Candex)	Epidiolex; Zygel; ClaraCeed	Sativex (1:1); Cellen Satoline- various ratios; Lyphe Group Noidecs- various ratios	Khiron flower, Lyphe Noidecs flower, Cellen Satoline flower; Bedrocan various flowers	Lyphe Noidecs, Bod Aus Medicabalis
Typical routes of administration	Oral (tablets, capsules, solution), inhaled	Oral solution, tablets, capsules, gels	Sublingual spray, oils	Smoked, vaporised, inhaled, edibles, oils	
Typical indications	CINV, appetite stimulation, pain	Intractable epilepsy, Fragile X syndrome	Multiple sclerosis, pain, intractable epilepsy	Pain, anxiety, sleep, intractable epilepsy	

CINV: Chemotherapy Induced Nausea and Vomiting

Value chain of cannabis-based medical products

Cannabis-based medical value chain is part of a larger value system in the industry that includes the cultivator, the raw material carrier, the manufacturer, the finished product distributor and the retailer (see in the Figure 2).

The cultivator is the grower of the plant, providing the herbal starting raw material as a flower or a trim. The phases of cultivation include the selection of the seed, the sprouting of the seedling, the growth, the maturation, the harvesting and the curing of the cannabis plant.

There is another form of cultivation that does not require seeding. Essentially, the cultivator clones the female plant to obtain a guaranteed female plant. This method eliminates the process of having to identify the gender and to separate males from females but stands at the detriment of a loss of strength of the plant and a higher probability of disease occurring.

The raw materials, primarily flowers or trim- others parts of the plant, are tested to ensure plant quality, safety, and composition in cannabinoids, mainly THC and CBD.

The extraction and product manufacturing requires licenses and permits. Specific equipment is used to convert the flower/trim into extracts and the concentrate extracts into finished products such as oil, ointments, solutions, sublingual sprays, tablets or capsules.

The cannabis-based medical products are tested to ensure traceability and guarantee human safety and efficacy of the products.

The distribution of the products involves dispensaries where medical use cannabis is available for retail, physical logistic services and E-commerce applications. The distributor needs permits or licenses to be able to handle cannabis-based medical products⁶.

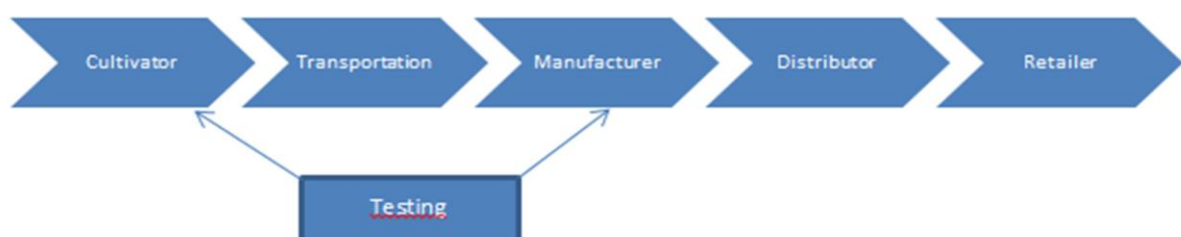


Figure 2: Cannabis-based medicinal value chain

Challenges and opportunities for the medical cannabis value chain

It is through the value chain of activities that an organization transforms raw input into valuable output, products, and/or services, for sale/delivery to its consumers. The important supply chain challenges and opportunities of the medical cannabis industry are presented according to Michael Porter's value chain for cultivators, manufacturers and distributors value chain respectively⁷ (see in the Figure 3).

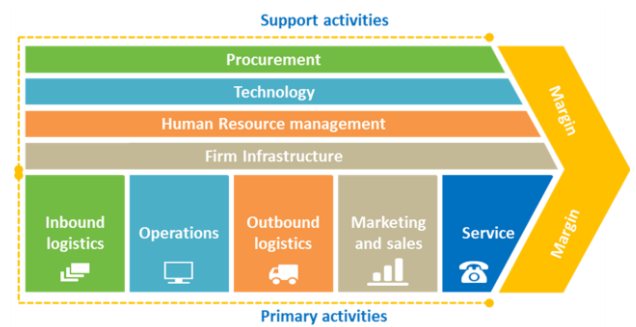


Figure 3: Michael Porter's value chain⁷

Challenges and opportunities for the cultivators

To understand the challenges and opportunities for cultivators in the cannabis value chain, the company Chanvre DC, located in Plan-Les-Ouates, Switzerland was interviewed. The biggest challenges and opportunities for cultivators are described in Table 3 below.

Table 3: Main challenges and opportunities for cultivators based on the Michael Porter's value chain

Challenges for the cultivators	Opportunities for cultivators
Firm infrastructure :	Technology :
<ul style="list-style-type: none"> ✓ Capital equipment and specific infrastructure (security and environmental conditions) needed ✓ Frequently evolving legal frameworks with license required ✓ Immature market (unskilled and limited talent pool) ✓ Fund source traceability requirements 	<ul style="list-style-type: none"> ✓ Develop automation for indoor cultivation (harvesting, drying, extraction, ...) ✓ Transformation of farming techniques and equipment for the cannabis plant ✓ Develop freeze-drying and the super critical fluid method
Technology :	Operations:
<ul style="list-style-type: none"> ✓ Non-mature farming techniques/equipment ✓ Intellectual property protection 	<ul style="list-style-type: none"> ✓ Organic farming approach to be developed with labels (because there is no organic label for an out of pot culture) ✓ Assessment of zero carbon potential in cannabis value chains
Operations :	Marketing and sales:
<ul style="list-style-type: none"> ✓ Farm security ✓ Environmental conditions to maintain (temperature, humidity and light rates) ✓ Weather and crop contamination exposure ✓ Quality control challenges (control of microtoxins, microbiological contamination, THC & CBD contents, humidity, pesticides and heavy metals) 	<ul style="list-style-type: none"> ✓ Guidance on how cannabis crops could be beneficial to natural ecosystems ✓ Possibility of using the remaining parts of the plant for other applications (eg. fertilizer, textile, sale of cuttings...) ✓ Develop cooperatives to limit costs (equipment sharing, networking, knowledge sharing for the GMP certification) ✓ Cultivator can transform part of the plant to finished products (eg. oil or balm) to sell directly to costumers
Inbound logistics:	
<ul style="list-style-type: none"> ✓ Seed procurement difficulties for the cultivators who use seeds ✓ Genetic instability of the plants for the cultivators who use cuttings 	
Procurement :	
<ul style="list-style-type: none"> ✓ Limitation of the seeds based on the European catalog which is not adapted to current quality requirements ✓ Price and availability of utilities 	
Outbound logistics :	
<ul style="list-style-type: none"> ✓ Permit regulations restricting transport ✓ Quality and traceability requirements 	

Cultivators are required to adopt Good Agricultural and Cultivation Practices (GACP) to assure the quality and the traceability of cannabis crops by way of a documentation process monitored by internal and external auditors. This offers an opportunity to apprehend illegal harvesting and biopiracy in medicinal plant value chains⁶. The margin is high due to the possibility of developing an automation of cultures. There is also a potential of finding new genetic seeds based on our needs. Cultivators can also advocate for premium prices, improve product quality and promote environmental sustainability.

Challenges and opportunities for the manufacturers

A manufacturer, Panaxia Pharmaceutical Industry, based in Israel, was interviewed to define the biggest challenges and opportunities for the manufacturers (see Table 4). Good Manufacturing Practice (GMP) ensures that products are consistently manufactured and controlled according to quality standards appropriate for their intended use and that finished products are effective and safe for market distribution. Though GMP has served as the golden standard in these industries for years, the cannabis industry has not been fully legislated under the same procedures.

Table 4: Main challenges and opportunities for manufacturers based on the Michael Porter's value chain

Challenges for manufacturers	Opportunities for manufacturers
Firm infrastructure :	Technology :
<ul style="list-style-type: none"> ✓ Capital equipment needed and specific infrastructure (security and environmental conditions) ✓ Frequently evolving legal frameworks (licenses and permits required) and GMP certification ✓ Traceability of financing 	<ul style="list-style-type: none"> ✓ Develop new methods for manufacturing the finished products to reduce the cost of goods and to improve the automation (R&D)
Technology :	Human resources management:
<ul style="list-style-type: none"> ✓ Intellectual Property protection for specialized production equipment (Research & Development) and techniques 	<ul style="list-style-type: none"> ✓ Opportunities of staff development (high level of staff training required)
Human resources management:	Inbound logistics :
<ul style="list-style-type: none"> ✓ Difficulties in recruiting because there is no specific training for the staff 	<ul style="list-style-type: none"> ✓ Find a trusted supplier of cannabis crops
Inbound logistics :	Operations:
<ul style="list-style-type: none"> ✓ Supply and raw material procurement challenges (availability and price of the raw material and challenges to find double sourcing of critical starting raw material) ✓ High traceability requirements of raw material (from cultivators, mainly due to heterogeneity of the raw material based on the organic plant, not the same composition depending on the supplier/climatic zone ...) 	<ul style="list-style-type: none"> ✓ Develop new methods of product quality control based on PAT (Process Analytical Technology) methods to perform tests on the manufacturing lines ✓ Assessment of zero carbon footprint throughout cannabis value chains ✓ Development of protocols and standards for a sustainable production
Operations :	Marketing and sales:
<ul style="list-style-type: none"> ✓ Regulatory requirements for traceability and manufacturing of the product based on GMP guidelines. ✓ Quality and Production Management Systems in place ✓ Unpredictability of the regulatory compliance ✓ Quality control and price control challenges ✓ Operational security and storage challenges ✓ Stability studies of all commercialized finished products 	<ul style="list-style-type: none"> ✓ Develop new products (innovative dosage forms) or based on other herbal raw materials ✓ Develop the software to stay connected with patients (inform patients on posology, side effects and provide scientific support)
Outbound logistics :	
<ul style="list-style-type: none"> ✓ Challenges to identify distributors based on the security, product constraints, GDP guidelines and agreement on pricing ✓ Transportation, testing and traceability restrictions 	

Manufacturers are required to show quality, safety, traceability, certifications and reliability in the cannabis starting raw material in order to produce cannabis-based medical products. Consistency, third-party audits, away from stakeholders for critical actors, would mitigate financial and reputations risks and reduce the cost of enacting recalls.

The processes are complex, resources and time consuming to be GMP certified, a manufacturer has to align with the pharmaceutical guidelines in force and closely collaborate with local Health Authority. GMP certification ensures the traceability and guarantees human safety and efficacy of the products. The margin is high due to the potential market with a large diversity of dosage forms of cannabis-based medical products to develop despite high regulatory challenges.

Challenges and opportunities for the distributors

The same manufacturer based in Israel was interviewed to define the biggest challenges and opportunities for distributors (see Table 5).

Table 5: Main challenges and opportunities for distributors based on the Michael Porter's value chain

Challenges for distributors	Opportunities for distributors
Firm infrastructure :	Technology :
<ul style="list-style-type: none"> ✓ Challenges obtaining insurance ✓ Evolving legal frameworks and security challenges (product testing, approvals, taxation...) ✓ Fund source traceability requirements 	<ul style="list-style-type: none"> ✓ Develop software for demand and product trend management ✓ Develop software to monitor the product distribution to ensure quality
Technology :	Operations:
<ul style="list-style-type: none"> ✓ Necessity to protect customer information 	<ul style="list-style-type: none"> ✓ Improvement of the Good Distribution Practices (GDP) compliance ✓ Stricter temperature and humidity conditions requirements
Inbound logistics:	Marketing and sales:
<ul style="list-style-type: none"> ✓ High traceability requirements on all products ✓ Product supply and procurement challenges due to limited number of certified manufacturers (with Quality Management System in place) 	<ul style="list-style-type: none"> ✓ Possibility of using the specific infrastructure for transportation of others products (eg. products for the opioid substitution therapy) ✓ Potential development of cannabis products home delivery ✓ Develop an expertise to become the reference for cannabis-based products distribution.
Operations :	
<ul style="list-style-type: none"> ✓ Cannabis license requirements for some countries ✓ Product quality and traceability requirement ✓ Security requirements ✓ Inventory control requirements 	
Outbound logistics :	
<ul style="list-style-type: none"> ✓ Export/import permits regulations restricting transport ✓ High quality, regulatory and traceability requirements 	

A distributor is required to continuously adapt to the laws and regulations enforced on cannabis-based medical product distribution. Many countries have different laws ruling the use and the distribution of cannabis. Nevertheless, the cannabis industry is growing rapidly even if there is a high degree of uncertainty with respects to the demand for the products. The distribution of cannabis based finished products should be extremely controlled so as not to impact the shelf-life and the oxidation of cannabis compounds. The margin is high because of a high price for the distribution of these specific products in order to guarantee a safe and a reliable supply to the customer.



Cannabis is a complex plant that has shown effectiveness in a range of various medical conditions⁸. Over 40 countries have legalized and given access to cannabis-based medicines including Denmark, Holland, France, Poland, Greece, Portugal, The Czech Republic, South Africa, Canada, Chile, Israel, Germany, U.K., Australia, and New Zealand⁸. The access mechanisms in these 40 jurisdictions vary a lot. Many clinical studies are in progress to demonstrate the efficacy of cannabis-based medical products to respond to a large number of therapeutic indications.

Cannabis value chains offers challenges and opportunities to cultivators, manufacturers, distributors and retailers. Interviews and research point out the main value chain challenges to actors who are uncertain about the demand, the complexity of laws, the regulation fluctuation and the issues of intellectual property protection. Earmarked opportunities are suggested as vectors towards the development of new technologies specific to this market, in order to build a community of cannabis experts throughout the entire value chain, while reaching a zero carbon footprint potential.

The legal status of cannabis worldwide is the biggest challenge for its future applications as a cannabis-based medical product, considering that it requires a great deal of processing and manipulation under extremely strict control. Aspects related to quality processing and maintenance, such as solubility, stability, dose, packaging, shelf-life and oxidation of cannabis compounds emerge as industrial challenges. Nevertheless, the world scientific communities, in association with cultivators and industry, have been committed to ensure that these products are widely produced and distributed, while making this portion of the market ideal for a development with a great potential. Finally, aspects related to patient safety, traceability and compliance cannot be overlooked as they are crucial to guarantee a safe and reliable supply to the population¹.

By following the guidelines (GACP, GMP, GDP, medical and pharmaceutical standards ...) and the local regulatory requirements defined by each country, different actors of the cannabis industry can be assured of adding value to the marketplace. The use of medical cannabis will grow according to the changes in the laws of many countries, along technological advances that have already brought new knowledge of its multiple pharmacological properties.

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Interviews

Throughout this paper, we incorporate academic and industrial research. We received insights and perspectives from two key market participants and industry experts, who granted us interviews:

- Sylvain Melis, Agricultural Engineer, from Chanvre DC company, cultivator of cannabis, Plan-Les-Ouates, Switzerland
- Dr. Malgorzata Meunier, Deputy General Manager Europe, VP innovation & BD from Panaxia Pharmaceutical Industry, manufacturer and distributor of cannabis-based medical product, Lod, Israel

