

Endocannabinoid Therapeutics and Pharmaceutical-Medical Cannabis

Market Overview

BACKGROUND

The investment thesis of Óskare Fund I focuses on two closely linked investment areas:

- **Therapeutics that target the Endocannabinoid System (ECS)** to treat a range of diseases ([This article](#) from Harvard Medical School outlines the significance of this system in human homeostasis), that include synthetic compounds as well as phytocannabinoids (compounds isolated from hemp and cannabis plants)
- **“Picks and shovels” investments**, that enable the building out of the value chain to help bring novel treatments to market (especially phytocannabinoids) and facilitate patient access to treatments

This document will outline the current and projected market for **therapeutics that target the ECS**. Many of the known active compounds that target this system are called cannabinoids¹, defined as: *chemical substances, regardless of structure or origin, that bind to cannabinoid receptors of the body and brain, producing similar effects to those elicited by the Cannabis Sativa plant.*

Research has found that the cannabis plant produces between 80 and 100 cannabinoids and about 300 non-cannabinoid chemicals. The two most extensively studied cannabinoids are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD).

Pharmaceutical cannabinoids are synthetic or naturally occurring compounds that directly interact with the cannabinoid receptors in the body. These include drugs such as dronabinol and nabilone, which are used to treat conditions such as nausea in chemotherapy patients, as well as chronic pain and spasticity in multiple sclerosis. On the other hand, non-cannabinoid medicines can act upon the ECS by modulating the activity of the body's own ECS messengers, endocannabinoids. These include drugs such as Metformin, which is a drug commonly used to treat type 2 diabetes.

Metformin acts upon the ECS by downregulating the abundance of some endocannabinoids, which can lead to improved insulin sensitivity and glucose metabolism. Olanzapine, another non-cannabinoid ECS drug, is used to treat schizophrenia and bipolar disorder. Other ECS targeting therapies include certain antidepressants, antipsychotics, neurodegenerative treatments and painkillers.²

¹<https://adf.org.au/drug-facts/cannabinoids/>

² <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6423672/>

From a trade sale/exit potential, therapeutics that target the ECS is a segment of the life sciences market that are gaining steam³. Several high profile, multi-billion dollar exits have occurred in 2021-2022:

- 1) **Phytocannabinoids: GW Pharma** (Epidiolex, a drug that targets rare forms of pediatric epilepsy and its drug pipeline using proprietary cannabinoid formulations) **acquired by Jazz Pharma for 7.2 B\$** in 2021, the press release can be [viewed here](#).
- 2) **Synthetic compounds that target ECS: Arena Pharmaceuticals** was acquired by **Pfizer in 2022 for 6.7 B\$**. Arena has several drugs in the pipeline including a Phase II treatment for irritable bowel syndrome that targets the ECS to reduce inflammation, the press release can be [viewed here](#).

Several pharma companies are looking at the sector for new molecules as drug candidates as IP on blockbuster drugs are soon going to lose their exclusivity in areas such as oncology, ophthalmology, pain and central nervous system (CNS) disorders. Hence, they need to renew their pipelines. Óskare Capital has mapped out (available on request) current “big pharma activity” in the sector.

Óskare Fund 1 is well positioned to capture some of the opportunities in the sector; a detailed review of our life science pipeline is available upon request.

The Pharmacological Potential of the ECS

Discovered in the 1990s, the endocannabinoid system (ECS) is found in man and all vertebrate species⁴. It is a **major homeostatic mechanism and helps humans fight infection, recovery from disease states, and adapt to environmental changes**. Modulation of this widely distributed regulatory system appears to have therapeutic (medical) value depending on the disease entity and severity.

Endocannabinoid receptors:

- **CB1 Receptors:** Located in parts of the central nervous system, particularly those concerned with cognition, movement, coordination, pain and sensory perception, emotion, memory, nervous control and endocrine function.
- **CB2 Receptors:** Found in the gastrointestinal tract; the tonsils, spleen and thymus gland (parts of the immune system); bone, muscle and blood vessels; the heart, lungs and many other tissues.

Despite the ubiquity of the ECS in the human body and the seeming involvement of the system in a plethora of human diseases and medical conditions, there are only a handful of drugs on the market whose mechanism of action has been identified specifically for its modulation effect on the ECS. This is likely due to our limited understanding of the system in different disease states as well as a history of strict legislation surrounding the research and development of cannabinoid based therapies.

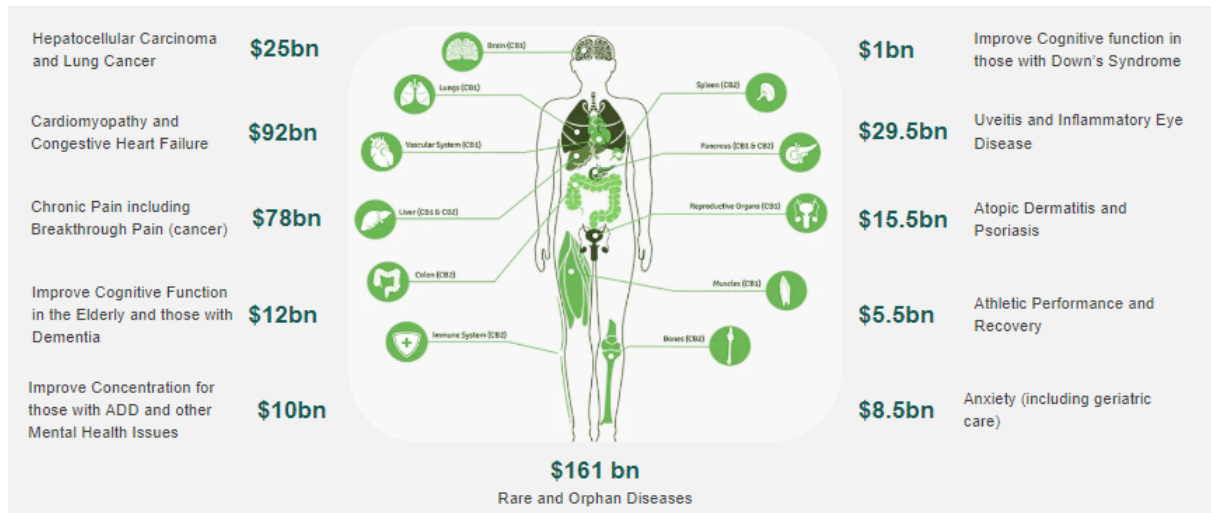
The ECS has only been recognized for approximately 30 years and much remains to be understood in terms of the form and function of it, there is a significant amount of value to capture. Government prohibition of the cannabis plant has hindered research for decades (especially in the US), and it was not until the turn of the millennium that exploration of the ECS commenced, this being due to a combination of increased interest and decreasing levels of prohibitive legislation. It is thought that around **250 clinical trials using compounds that target the ECS are carried out each year**. There is plenty of room for growth in these figures considering the central metabolic role played by the ECS.

³ <https://www.fiercepharma.com/special-report/top-15-blockbuster-patent-expirations-coming-decade>

⁴ All mammals have an ECS, there are applications in animal health as well that will not be examined in this document.

The market for pharmaceutical products which leverage the endocannabinoid system to treat illness remains largely untapped. The real opportunity is in exploiting the endocannabinoid system: targeting unmet needs, new indications, rare diseases and alternatives to current therapies in markets that exist today but are ripe for disruption.

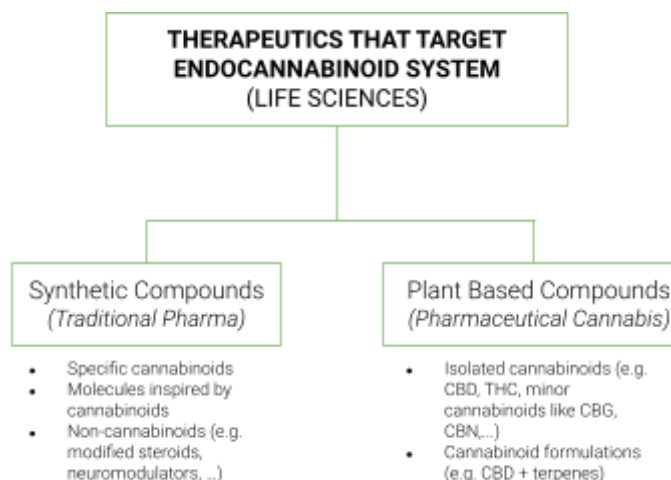
Endocannabinoid System Total Addressable Market



The market segments outlined above depict areas addressable via the Endocannabinoid System, all of which have research and products in development or already deployed. The sum of targeted outcomes gives a global market size of **\$438 billion**. If ECS targeted therapeutics (and Óskare Fund I) can capture even a fraction of this market, the opportunity is quite large.

We have screened over 500+ opportunities in the sector and have identified companies in each therapeutic area mentioned above.

We break down the market in the following subsegments:



ÓSKARE CAPITAL's investment strategy includes companies that develop drugs that mimic cannabinoids and also non cannabinoid-based medicines which modulate the ECS.

As an example, the fund invested in [AELIS Pharma](#), a company which has developed CB1 Signaling Specific Inhibitors (SSi), a new pharmacological class that appears able to treat different neurological conditions. The first two proprietary molecules in their portfolio are for cannabis abuse disorder (addiction to recreational cannabis) currently in Phase II in the USA and the second, for treatment of cognitive deficits (restoring functional memory) in Phase I/II underway in France and Spain.

PHARMACEUTICAL AND MEDICAL CANNABIS MARKET AND USAGE

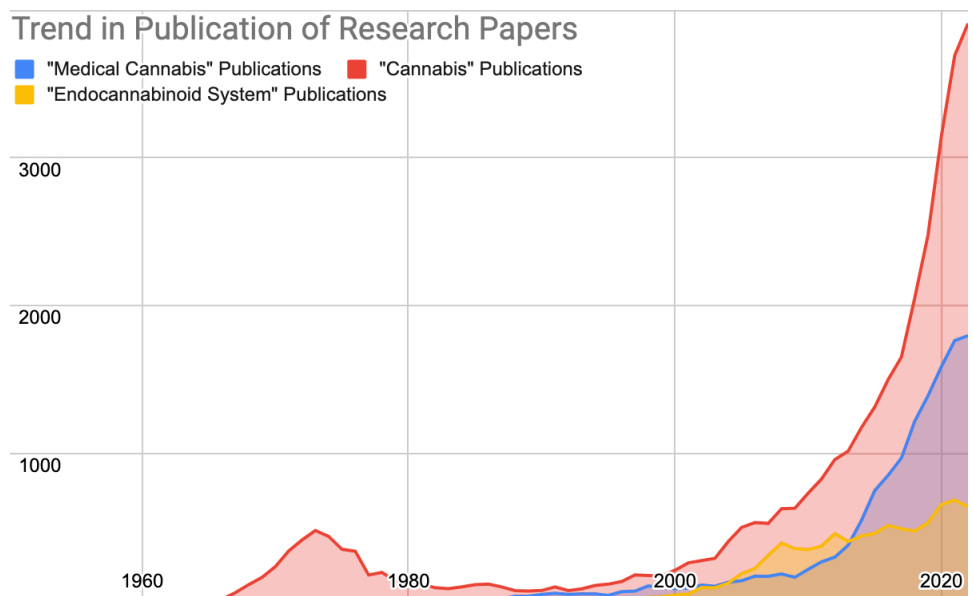
It is difficult to assess each target market size in terms of therapeutic area with regards to ECS related therapeutics (notably synthetic compounds that target the system that are not phytocannabinoids or synthetic cannabinoids). However, in this section we break down the submarket of this fast growing submarket of ECS related therapeutics.

In most European countries medical cannabis is federally legal for several years, enabling public R&D to operate legally and obtain funding and perform research. As such, there has been a surge in spin-offs and company creations since 2017.

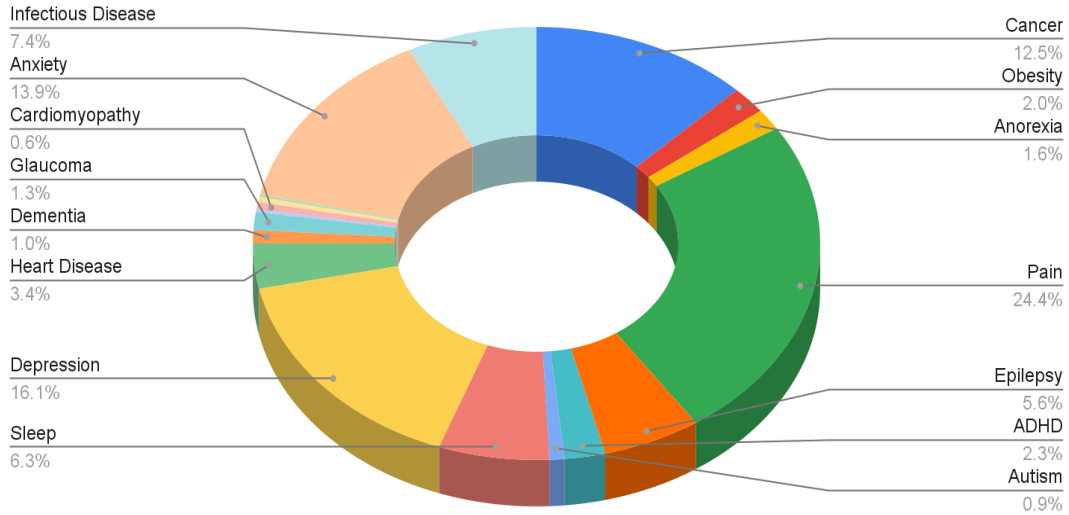
With medical cannabis in the US being federally illegal, R&D has been hindered in the USA but is starting to catch up now that President Biden signed the Medical

Marijuana Research bill last December. Thus the most promising current research is led by EU based teams who are creating the IP and data to produce the global therapeutic champions of today and tomorrow.

Looking at where the research interest and focus has been - it's pain, muscle spasticity, epilepsy, sleep disorders, appetite and weight loss associated with cancer, as well as depression and anxiety. What has emerged in the last decade has been research involving the role of the ECS in inflammation and cancer itself. As big pharma has understood the continuing need for new treatments in oncology as well as for the treatment of pain and chronic inflammation we have seen an ever increasing number of patents being filed related to treatments based on the ECS.

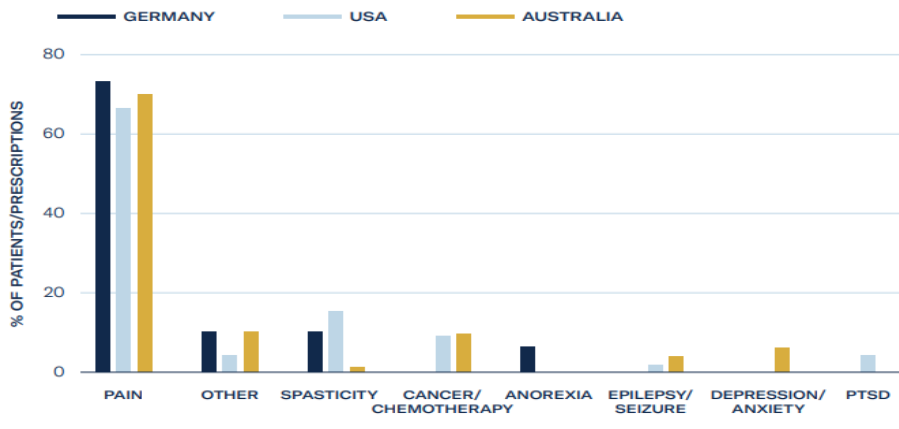


Total Proportion of Medical Cannabis Publications by Target



Pain is by far the most common condition for which cannabinoid based treatments are used. The current global spend on pain medications world-wide is estimated at US\$63-85 billion each year. CBD formulations as well as flower and plant extracts are the majority share of what is used today. Until now, no new endocannabinoid modulator drug has been approved and marketed on a worldwide basis. Prohibition Partners predict that when this occurs, it will have a profound impact on the global market for pain medications.

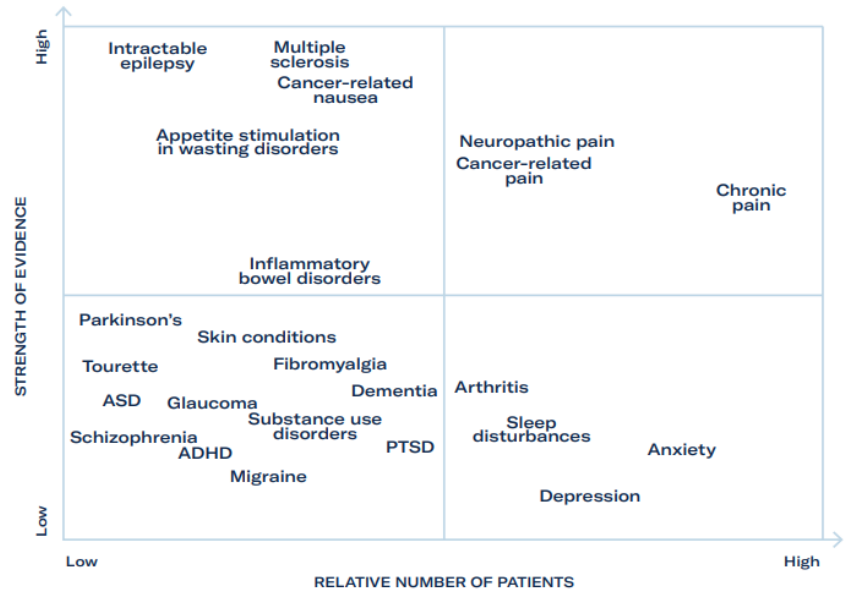
Conditions for medical cannabis usage globally



Source: Prohibition Partners, Boehnke et al 2019⁴, Bfarn⁵, Therapeutic Goods Administration Freedom of Information (TGA FOI).

While the market for pain alleviation is quite large, there are other opportunities and, in fact, regulatory and financial incentives for developing medications for rarer conditions. They are supported by national and international drug development protocols such as the granting of orphan drug status which grants certain tax breaks and extended exclusivity. For rare medical conditions smaller, less expensive trials are often sufficient to prove the efficacy of drugs. Once developed, medicines being used for rare conditions must often be charged,, e.g. Epidiolex® at >\$30,000/annum.

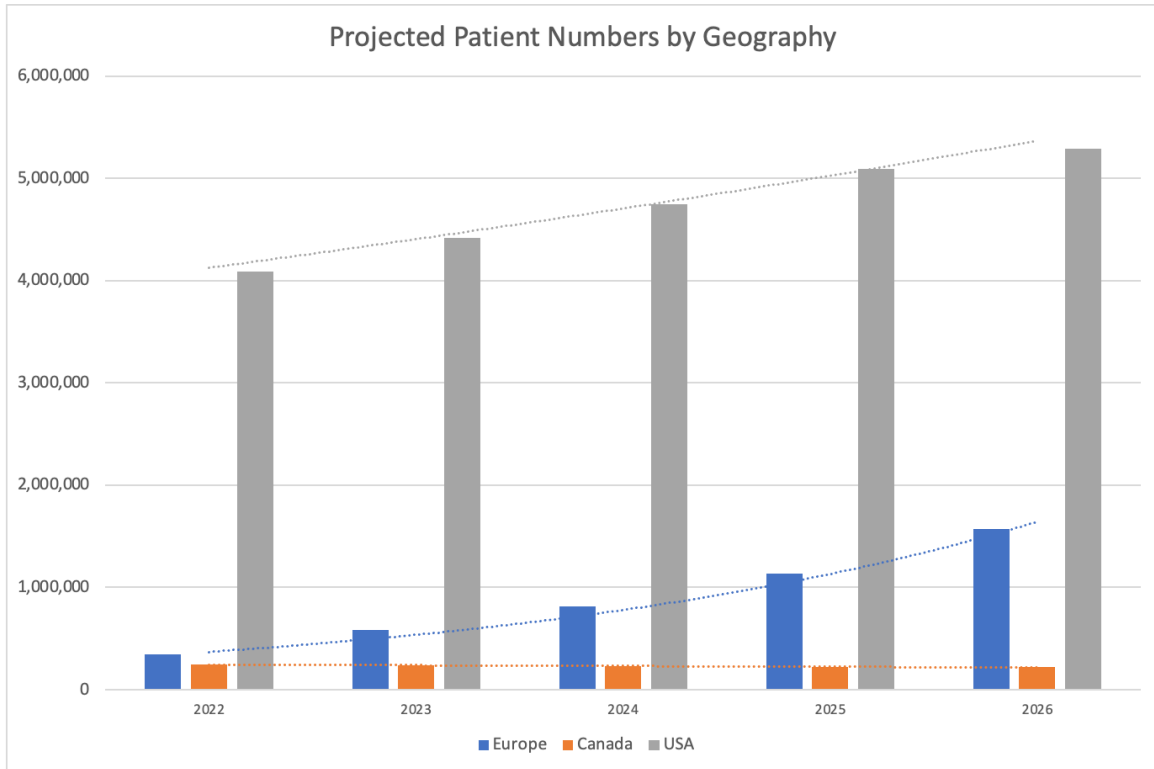
Recognising the significant size of the chronic pain market, ÓSKARE CAPITAL invested in Cellen Health, a UK digital chronic pain clinic able to prescribe medical cannabinoids and replace opioids with cannabinoids as a safe and effective treatment. Opioids today contribute to significant addiction issues and their abuse is responsible for over 98,000 deaths in the US in 2021⁵. Cellen's patient numbers are increasing significantly, which is a sign on the ground that this market is growing as quickly as predicted.



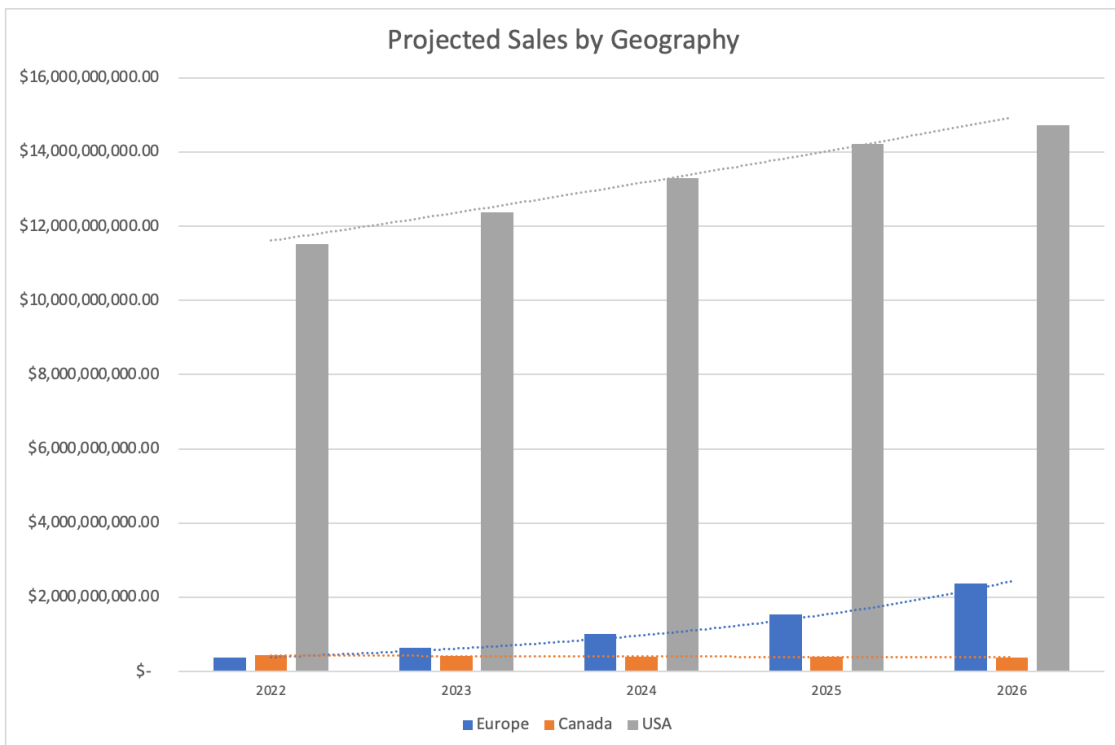
Source: Schlag et. al 2021

Although the market remains in its infancy, key target market 10 year **CAGRs range from 40% - 80%** and **can be seen as subsectors of the ECS market.**

⁵<https://injuryfacts.nsc.org/home-and-community/safety-topics/drugoverdoses/>



Source: Prohibition Partners Global Market Report 2022



Source: Prohibition Partners Global Market Report 2022

PHYTOCANNABINOIDS VS SYNTHETIC CANNABINOIDS

In our market breakdown, we split the market in two specific areas: Plant-based compounds and Synthetic compounds. In this section, we break down the difference between the plant and synthetic based cannabinoids that are, with non-cannabinoid synthetic compounds, important to the development of the industry.

Active compounds in the cannabis plant, which are called **phytocannabinoids**, have been used in treating patients with various medical conditions for centuries, without knowing that the benefits were as a result of modulating the ECS.

The majority of cannabinoid therapeutics used to date have been produced from plant material. GW Pharma developed and commercialized the world's first prescription medicine derived from phytocannabinoids, Epidyolex®, approved for the treatment of seizures associated with rare epilepsies. Launched in the U.S. in 2018, Epidyolex exceeded \$500 million in annual net sales in 2020. GW Pharma was acquired by JAZZ Pharma in May 2021 for \$7.2b.

Synthetic versions of CBD and THC are already available across the globe, including the pharmaceutical products dronabinol and nabilone, but these remain in minority use for now as there is no recognized innovation associated with these products which have been marketed for many years in many countries.

However, as the value of this class of molecules is gaining recognition, a new industry for the production of synthetic cannabinoids is growing. These synthetic cannabinoids can be used in isolation or in a formulation of several different molecules to mimic what is coming from certain plant strains. The desirable terpenes or other specific molecules can be given an over-weighted position in a formulation, for example, when a specific biological effect is needed. The chemical entities can be modified to confer specific properties such as improved bioavailability or increased half-life. This type of innovation is associated with creation of patent libraries and the needed IP to attract investment for the clinical trials and realise the full commercial opportunity.

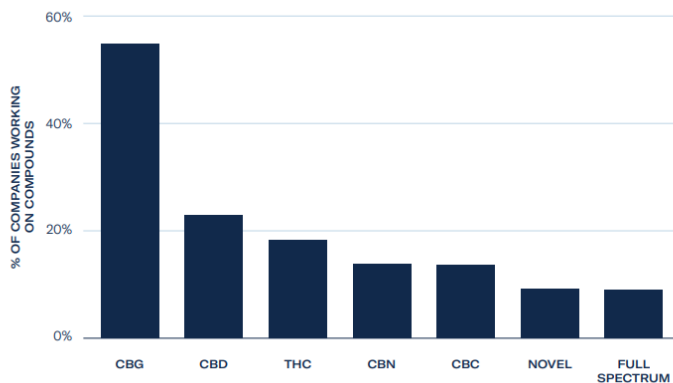
We see value in the development of plant-based products and we have identified the extraction process as a key component of the value chain. Hence the fund's invested in [Herbolea Biotech](#), a company that licenses a patent-protected solventless extraction system to transform botanicals into superior quality products at a substantially lower cost and without the use of solvents (cannot have traces of solvents in pharmaceutical formulations).

One of the most attractive aspects of the production of biosynthetic cannabinoids is the possibility that pure compounds like THC and CBD, as well as more rare cannabinoids, might be produced with predictability, purity, scalability, and significant cost savings

The biosynthesis of cannabinoids is now possible due to improvements in methods and technology and it is likely that biosynthesis of cannabinoids will enable big Pharma to find these molecules to become viable given the way these companies typically operate. There is a precedent, and biosynthesis is now common for such things as vitamins and antibiotics.

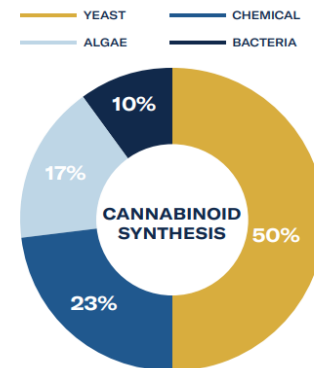
There are at least 25 companies which are currently developing processes for synthesizing cannabinoids at scale. These companies use a variety of methods including chemical synthesis as well as a range of biosynthetic methods utilizing yeast and bacteria as vectors to produce compounds (traditional routes for molecule production in pharma). An outline of the current production methods for producing isolated cannabinoids are depicted below:

Compounds being synthesised



Source: Prohibition Partners, based on previous work by Raymond James

Popular methods of cannabinoid synthesis



Source: Prohibition Partners, based on previous work by Raymond James

As an example of a synthetic cannabinoid-based drug is Arena Pharmaceuticals. The core of its cannabis operation consists of Olorinab (APD371), an investigational, oral, full agonist of the cannabinoid type 2 receptor (CB2), which aims to treat patients with diseases affecting the stomach and intestine. In December 2021, Pfizer acquired the company for a total equity value of around \$6.7 billion.

Below are other examples of therapeutic companies targeting the endocannabinoid system without the use of phytocannabinoids:



- Azevan Pharmaceuticals, Inc. - Developing a drug called AZ01, which targets the fatty acid amide hydrolase (FAAH) enzyme in the endocannabinoid system to treat pain and inflammation.
- Soricimed Biopharma Inc. - Developing a drug called SOR-C13, which targets the G-protein-coupled receptor (GPCR) called OR51E2 in the endocannabinoid system to treat cancer.

*At ÓSKARE CAPITAL, we have identified **Octarine Bio** as a future leader in the Synthetic biology sector. The company has developed a platform technology with one vertical being the production of superior and novel synthetic cannabinoids that can be used in pharma. Their molecules have the highest patent protection possible, which makes them very attractive from a corporate partnership standpoint. Their glycosylation technology enhances the performance of high-value ingredients, including making CBD (and other cannabinoid) analogues that can be isolated early, produced at low cost and have much better pharmacological properties.*

Initially applied to cannabinoids which hold breakthrough potential to treat a range of human health issues and today have mainstream acceptance for use in medical and consumer applications. They have performed pre-clinical work in the colon (to reduce inflammation) and have exceptional results when compared to traditional CBD. Their cannabinoid glycosides could be used to treat Crohn's disease, Irritable Bowel Syndrome (similar to Arena Pharmaceuticals products) and other gastrointestinal diseases with total markets reaching over 15 B\$ today.⁶

⁶ <https://www.ihealthcareanalyst.com/global-crohns-disease-therapeutics-market/> and <https://www.coherentmarketinsights.com/market-insight/irritable-bowel-syndrome-treatment-market-506>

Both phytocannabinoids and synthetic cannabinoids have inherent advantages and disadvantages, they can also be blended together in specific formulations as well. An outline of the differences and pros/cons are depicted below:

Pros and Cons of synthetic cannabinoids		
	 Plant Produced	 Synthetic
Pros	<ul style="list-style-type: none"> • Easy to scale • Well established techniques and infrastructure • Product is familiar to consumers • Potential entourage effect due to presence of terpenes and other cannabinoids 	<ul style="list-style-type: none"> • Easy to obtain pure product • Easy production of rare cannabinoids • Less land and labour required • Quick turnaround between production batches • Favourable with regulators
Cons	<ul style="list-style-type: none"> • Requires large inputs of land and labour • Limited by long growing seasons • Difficult to obtain pure product • Low production of rare cannabinoids 	<ul style="list-style-type: none"> • Difficult to scale • Techniques still in development • Unfamiliar to consumers • Difficult to obtain any potential or perceived entourage effect

CONCLUSION

At ÓSKARE CAPITAL we see that the scientific community and the Pharmaceutical industry now acknowledges the importance and value of the ECS in human health and disease. Patients have by their own initiative and actions shown that treatments in this sector can be of benefit and an alternative to current treatments. The medical and pharmaceutical cannabis industry (and indirectly ECS related therapeutics) was launched in many countries thanks to patient advocacy groups, which is quite unique in the medical sector, meaning there is a high demand for these types of products. The high quality of the science and the research teams now working in the field present us with a legitimate opportunity to make targeted investments in this sector.

As outlined in this presentation, there are both plant based therapeutics as well as synthetics. We believe patients, regulators, and Pharma companies will embrace the future where there is room for products of each type to be on the market. Personal preferences, pricing, scalability of production, the medical condition being treated (the indication) will all be factors.

This research, and more like it, forms the bedrock of our rationale for investments in Octarine, Herbolea, Aelis and Cellen. Additionally, we have already identified our next set of companies for the portfolio. These are compelling investment opportunities; companies that are working on new indications, rare diseases and alternatives to current therapies in markets at favorable valuations. Please feel free to contact us with your questions, comments and the chance for further discussion.