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Biosynthesis

Taking the cannabinoid market to new heights

The cannabis and cannabinoid industry and markets are booming, despite the COVID-19 pandemic. Global cannabis sales reached \$21.3bn in 2020, a jump of nearly 50% compared to 2019, with a forecast of \$55.9bn in 2026 according to **BDSA**, a leading cannabis market research firm. BDSA also projects US cannabis sales to hit \$41bn in 2026. Cannabinoid-containing consumer products – such as food and drink, beauty and skin products, cleaning products and detergents – are already on local and **big-box store** shelves. The addressable market is large and growing fast, driven by increased consumer acceptance and changes in legislation. In meeting this growing demand, advances in biotechnology, specifically biosynthesis, have the potential to produce high quality, sustainable, rare cannabinoids consistently, quickly and at a lower cost than conventionally grown cannabis and hemp. The supply side changes are attracting significant investment. SynbioBeta, a synthetic biology networking organisation estimates \$8bn of investment in 2020 in synthetic biology, and after a Q121 that quadrupled the funding compared to Q120, are projecting \$36bn of investment in 2021.

A convergence of factors is driving demand growth

A timely convergence of factors is driving the growth in cannabis/cannabinoid sales. Leading the list is the increasing legalisation of cannabis and cannabinoid products across the US and around the world. Next is increased demand for consumer products containing the non-psychoactive cannabinoid extracts of the cannabis plant, touted to have health and wellness properties. Not to be underestimated is the withering of the long-held stigma associated with cannabis and cannabinoids.

Biosynthesis is changing the market landscape

Cannabinoid biosynthesis, which uses simple living organisms to produce desired compounds at scale, is at a potential tipping point. Canadian investment bank ATB Capital believes this technology will 'substantially improve the economics for the production of rare cannabinoids', which it adds 'will open the gates for pharmaceutical and consumer packaged goods (CPG) companies to use them as key inputs for products in the health, wellness, and recreational segments'. Solving the key challenge of producing high-quality product on a regular sustainable basis at scale looks to be near. Cronos, which has partnered with Ginkgo Bioworks, has successfully fermented cannabigerol (CBG) at research scale and is expected to commercialise products in September 2021.

Cannabinoid biosynthesis market: \$30bn NPV market

The global market for CPG and pharma cannabinoid biosynthesis products is predicted to reach C\$10bn in 2025 and C\$115bn by 2040 according to Raymond James. Based on these numbers Edison estimates a c \$30bn NPV for the cannabinoid biosynthesis market. The companies most likely to profit are those able to bring high-quality, high-demand cannabinoid products to market at a lower production cost. In this report we highlight Cronos Group and its partner Ginkgo Bioworks, Creo and its partner Genomatica, and Demetrix.

From the street

'We are very excited to support Octarine on its journey towards growth and scaling of its technology. Octarine is working in one of the promising areas of biotechnology, synthetic biology. The company's unique fermentation platform enables production of active compounds from plants in a very sustainable manner. This is an important aspect for Vækstfonden, as we are continuously looking for green technologies.'

Lene Gerlach, investment manager, Vækstfonden, Denmark's State Investment Fund

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Companies mentioned in this report (Edison clients in bold)

Amyrin
Baymedica
Canopy Growth Corporation
CB Therapeutics
Constellation Brands
Creo
Cronos Group
Demetrix
Evolva
Genomatica
Ginkgo Bioworks
Hyasynth Biologicals
InMed Pharmaceuticals
Jazz Pharmaceuticals
LAVVAN
Libede
Lygos
Purisys
Renew Biopharma
Willow Biosciences

Companies mentioned above do not translate into buys or sells as other themes (and valuation parameters) may conflict with this one.

Legalisation opening the door to new markets

Medical cannabis is legal in most US states (see Exhibit 1). However, this should not be confused with the very few cannabis-derived or synthetic cannabis-related FDA-approved drugs that require a prescription from a licensed healthcare provider. About 20 of these states have also legalised recreational cannabis. BDSA reported that in 2020, legal sales in the US reached \$17.5bn, a 46% increase over the prior year, noting the market remained resilient despite the pandemic.

Sales in mature medical and adult-use markets continued to grow. The top four states (California, Florida, Colorado and Oklahoma) in this area each saw sales growth of over \$400m in 2020. Markets that opened in 2019 and 2020 had \$1.6bn in sales in 2020. BDSA forecasts US sales to reach \$41.3bn in 2026, a CAGR of 15%. Driving this growth is the opening of new markets for medical and adult use, with four new medical and five new adult-use markets to commence sales in 2021.

The other North American market to focus on is Canada. In October 2018, Canada legalised recreational marijuana. In 2020, legal cannabis sales totalled an estimated \$2.6bn and BDSA forecasts the market to grow to nearly \$6.4bn in 2026.

Exhibit 1: Legalisation of cannabis and cannabinoids in the United States

	As of	Places
Medical use	18 May 2021	36 states and four territories allow the medical use of cannabis products
Adult use (recreational)	22 June 2021	18 states, two territories and the District of Columbia have enacted legislation to regulate cannabis for adult use

Source: National Conference of States Legislatures, June 2021

Traditional cannabis production: Grass is not always greener

Fields and greenhouses

While the market for medical, recreational and retail cannabis and cannabinoid products is growing, growing cannabis is fraught with obstacles. Cannabis is literally and figuratively a weed, which makes all aspects of its growth and production unpredictable.

Whether in fields or greenhouses, growing cannabis and extracting cannabinoids is costly, labour intensive and has a high environmental impact.¹ Moreover, traditional farming is vulnerable to unanticipated costs, such as the vagaries of weather, pest infestations and plant-disease outbreaks. All these factors have an impact on harvest yield, quality and cost. Another big drawback is that these methods do not produce active pharmaceutical ingredient-quality cannabinoids needed to meet pharmaceutical industry standards.²

To produce a sufficient cannabinoid yield, cannabis farms must be large. GW Pharmaceuticals' Wisington facility is 45 acres, while British entrepreneur Maximillian White has announced plans for a 100-hectare facility in Portugal, which he predicts will be the largest in the world. Moreover, traditional farming methods have only a three-month growing season. Harvesting must wait until the

¹ [Vavitsas K, Costa K, Limas M, Joseph-Nelson B, and Cumbers J. Cannabinoid Fermentation: Scalability, Purity, and Sustainability for an Emerging Market. Genetic Literacy Project. June 19, 2019.](#)

² [ALTA Corp Capital. Synthetically derived cannabinoids: The next generation of cannabinoid production. February 20, 2019.](#)

plant matures and flowers (the flowers and buds contain the cannabinoids). Indoor cultivation can boost harvests to four to six times a year. But even in controlled indoor environments, cannabinoid content can vary by 300% from cycle to cycle.¹ Some growers are undertaking the difficult task of selectively breeding plants to increase the amounts of cannabinoid.³

While avoiding some of the drawbacks of field growing, greenhouse cultivation is not without challenges. Setting up an indoor growing process requires a large, initial capital investment in space and equipment. Greenhouse cultivation requires high energy use for the intense lighting, fertilisers and chemical solvents, among other environmental concerns.¹ Some greenhouses use high-pressure, heat-intense sodium lamps. To counteract heat emissions from inefficient illumination, plants might be over-watered. Installing heat, ventilation and air-conditioning systems and dehumidifiers is an expensive outlay initially and likely an unsustainable model. Some growers are turning on less-heat-emitting LED lighting. While the overall cost of these might be lower in the long run, these lights have a higher capital outlay.⁴

Currently, plant extraction is the most common cannabinoid production method.² Once harvested, the active ingredients – tetrahydrocannabinol (THC), cannabidiol (CBD) or other cannabinoids – must be isolated in a multi-step, chemical-solvent extraction method.¹ Even before attempting to extract and purify some of the rarer, newly sought-after cannabinoids, extracting and purifying THC and CBD is a complex process. Whether from fields or greenhouses, cannabis is a low-yield product with a large [carbon footprint](#). Cannabis contains 2–5% of THC and CBD and miniscule amounts (0.1%) of the rarer cannabinoids (such as cannabiol, CBG, cannabichromene and tetrahydrocannabivarin). Therefore, as much as 95% of the plant must be handled as waste.⁵

Chemical synthesis

Chemical synthesis of cannabinoids is a time-consuming laboratory process in which the desired product is built one molecule at a time through a series of chemical reactions. As in plant-based derived cannabinoids, the compound must go through a purification process to remove undesirable, potentially toxic and generally less stable, contaminants.

Chemically synthetic approaches to produce cannabinoids may also not prove sustainable, economical or environmentally friendly, just as with the natural alternatives.⁶ While chemical synthesis does not leave behind tonnes of plant wastes, laboratories must dispose of chemical reagents.⁷

This contributes to the overall costs of production. Purisys, a chemical synthesis producer, is reportedly selling CBD at \$20,000 per kilo.

Currently, the FDA has approved for prescription only the synthetic forms of THC, dronabinol and nabilone, for the treatment of nausea and vomiting in patients undergoing cancer treatment, and as an appetite stimulant for patients with AIDS respectively.⁸

³ Dolgin. *Nature*. PS7

⁴ [Madhusoodanab J. A greener grass. *Nature*. 28 August 2019.](#)

⁵ [Raymond James Ltd. *Biosynthesis of cannabinoids: vanguard of the bio revolution*. 2 October 2020.](#)

⁶ Iqbal S. Biosynthesis of cannabinoids vs. chemical synthesis. Biomedican.

⁷ [Chen J. *Game of cannabinoids: who will we the production war*. UCLA Cannabis Research Institute, August 2019.](#)

⁸ Marinol®. Full Prescribing Information; Sydros Full Prescribing Information; Cesamet® Full Prescribing Information.

Biosynthesis: An established production process for pharmaceuticals, vitamins, flavours and fragrances

Biosynthesis uses simple living organisms, usually bacteria or fungi, to produce desired compounds in large quantities. The process involves inserting an enzyme (or enzymes) into the chosen organism and potentially a simple carbon source such as sugar. This sets off a desired reaction. Here, the required output is an abundant amount of complex cannabinoid molecules.⁹ The fermentation process, a form of biosynthesis, has existed for millennia. It has been used to produce everything from cheese to scented detergents.

In 1982, the FDA approved the first biosynthetic prescription medication: human identical insulin to treat diabetes. In early 2019, researchers at the University of California, Berkeley, reported successfully producing the cannabinoid CBD using brewer's yeast, a single-cell organism that is used to make beer, among other products.¹⁰

Amyris (NASDAQ: AMRS, market cap \$4.25bn) has been using biofermentation since 2003. Zymergen (NASDAQ: ZN, market cap \$3.9bn) which develops genetically engineered microbes for industrial fermentation was founded in 2013 and completed a successful IPO in April 2021. ([Evolva](#) (SX: EVE, market cap CHF169m) has been using biofermentation using yeast as a vector to manufacture a number of products such as vanillin, stevia (a sweetener), valencene (a fragrance ingredient) and nootkatone (used in pest control).

Now pharma and CPG companies are turning to biosynthesis to produce molecules that are very resource intensive to manufacture or extract from the cannabis plant. These bio-factories produce bio-identical compounds to what the plant produces but in vast amounts in a fermenter.⁵

In a biosynthesis facility, which has a year-long growing 'season', the result is from about 24 'harvests' up to 100 'harvests' a year, depending on whether yeast or bacteria is used. A one-million square foot greenhouse can yield about 16 metric tonnes of cannabinoids, compared to 1,000 metric tonnes from a similarly sized bioreactor facility.¹¹ Because the quality of the output does not vary, the purification process becomes easier, and it is free of pesticides, waxes, heavy metals and other elements that can contaminate traditional field- or greenhouse-grown products.

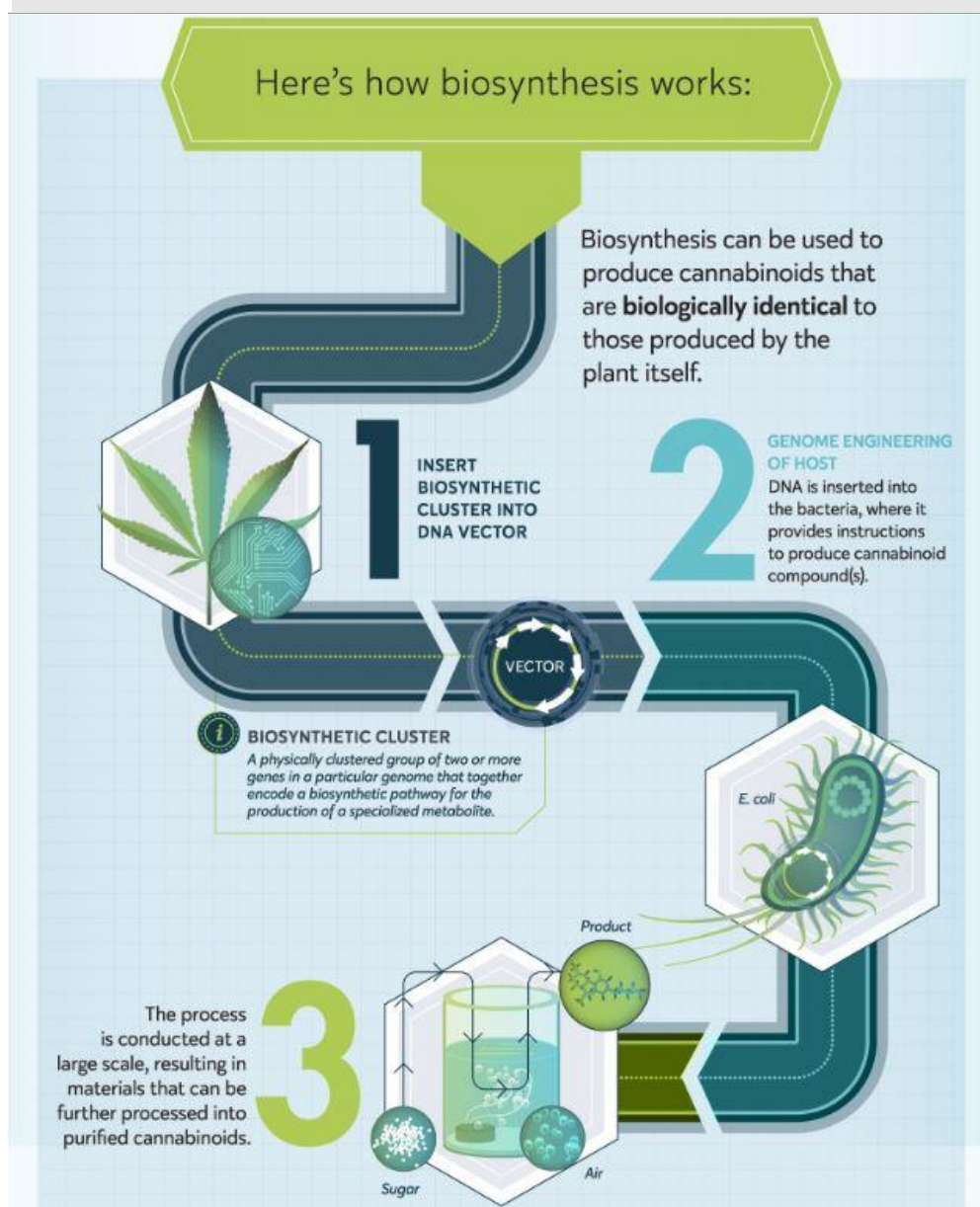
Another key advantage of cannabinoid biosynthesis is that it avoids use of the cannabis plant and can ensure there is no THC (unlike the plant). This has the key advantage of the product not falling under narcotics regulations. Although there is some progress as a consequence of the 2018 Farm Bill in the US, where cannabis derivatives with extremely low amounts of THC (less than 0.3%) are not considered controlled substances, the presence of THC still raises issues both in the US and globally. For example, California requires a proposition 65 health warning label even if THC is present below the 0.3% level, whereas countries such as France require that unlicensed products contain no THC.

⁹ [Biology Online. Definitions. Biosynthesis, updated 3 March 2021](#)

¹⁰ [Luo X, Reiter MA, d'Espaux L, et al. Complete biosynthesis of cannabinoids and their unnatural analogues in yeast. *Nature*. 2019.](#)

¹¹ [Deloitte. Cannabis biosynthesis: a promising new opportunity for life sciences companies](#)

Exhibit 2: Biosynthesis process, an example from InMed Pharmaceuticals



Source: [InMed Pharmaceuticals](#). Note: InMed Pharmaceuticals is a leading manufacturer of rare cannabinoids using multiple types of manufacturing including biosynthesis.

Biomanufacturing: The economic appeal

Biosynthesis can yield big savings for the cannabinoid industry. In 2018, the wholesale price of high-quality CBD extracted from plants was more than \$5,000 per kilogram. This has since come down towards \$4,000 in 2020. In a collaboration between Ginkgo Bioworks, a synthetic-biology company in Boston, and Cronos Group, a Toronto-based cannabis producer, the estimated cost to biomanufacture pure CBD and other cannabinoids in yeast would be less than \$1,000 per kg.

GMO or no?

There are companies trying to modify chemical synthesis in the cannabis plant itself by genetically altering its cells to produce more of the desired molecules and within the whole plant, thereby boosting yield. Other companies are also looking into manipulating the cannabis genome using CRISPR-Cas9 technology.¹² This is a controversial area. Some regulatory agencies around the world take the position that using CRISPR-Cas9 to gene-edit crops should fall under the same tight regulations as conventional GMO products. Others argue that CRISPR-Cas9 does not introduce DNA from a different organism but merely removes 'weak' bits of DNA.¹³

Biosynthesis companies point out that, unlike genetically engineered cannabis plants that contain actual genetic material, their products are chemicals, and, therefore, non-GMO and considered natural – two highly favourable characteristics.

Cannabinoid biosynthesis: Attracting capital and attention

Investment is growing

Pharmaceutical, recreational and CPG industries are increasing their investments and accelerating their research into the biosynthesis of cannabinoids. SynBioBeta's 2019 report on cannabinoid fermentation¹ shows more than 15 companies made multimillion-dollar investments in cannabinoid biosynthesis companies. The overall investments in this report include sizes of deal if products are successful and future milestones and royalties are paid. The general trend is that investment in increasing and notable deals we would highlight would include:

- Demetrix completing a \$50m series A, led by Tuatara Capital and a follow on from Horizon Ventures, Li Ka-shings investment vehicle.
- Creo, which has raised over \$40m in equity from private and institutional investors.

IP and patents

Protecting valuable IP rights in the cannabis industry is both essential for success and challenging given variations in state and federal laws. Companies are increasingly competing for patents because biosynthesis provides flexibility to design new patentable molecules.⁶ Between 2010 and 2019, the US Patent and Trademark Office issued hundreds of cannabis-related patents. Most cover cultivation, processing and extraction methods, cannabis-derived products, devices and pharmaceuticals. Applications have even been made for 'new' cannabis plants.⁵ Most recently, Creo, a leader in the cannabinoid biosynthesis sector, was issued its latest patent on 30 June 2021. It covers a new approach of producing geranyl pyrophosphate, an essential precursor for making all cannabinoids. Creo claims exclusive right to 15 fermentation-based cannabinoid patent families, plus exclusive access to more than 1,800 partner patents/applications.¹⁴ Its partnership with Genomatica broadens its IP.⁵

¹² Dolgin. *Nature*. 2019. PS7.

¹³ *National Geographic*, Genetically modified organisms. 2021.

¹⁴ Intrado, press release. 30 June 2021

Biosynthesis companies: Scaling up production and commercialisation

Cannabinoid biosynthesis is entering the critical but difficult phase of scale up in biomanufacturing. What was produced in small fermentation bioreactors might not work in larger ones. Even slight temperature changes may alter the expression of different compounds.¹¹ Only a few biosynthesis companies have the skills, resources and capabilities for large-scale production and commercialisation.¹⁵ Although timelines for these important steps are not always made public, particularly for privately held companies, market analysts have some predictions and several companies have reported results.¹⁵

Front runners in the large-scale production and commercialisation of rare cannabinoids are Amyris, Creo (and partner Genomatica) and Demetrix. In March 2021, Amyris announced it had completed a production run of CBG using 225,000 litre fermenters at the facility of its Spain-based manufacturing partner.

In January 2021, Creo announced a successful completion of 12,500 litre scale production of CBG and cannabigerolic acid.¹⁶ In September 2020 Demetrix began a 15,000-litre demo-scale fermentation production of CBG which was completed in November 2020.

M&A: A stepping stone to new, large markets

After several years of increasing M&A in the cannabis and cannabinoid space, transactions slumped slightly in 2019 and 2020. Activity dipped from a high of 300+ transactions, valued at more than \$7bn in 2018, to 124 valued at \$1.9bn in 2020. But things are moving again. Hailed as a big game-changer is the recent US\$7.2bn acquisition of British GW Pharmaceuticals by Ireland-based Jazz Pharmaceuticals (GW is the maker of Epidiolex, a community-based drugs initiative prescription medicine for the treatment of rare types of epilepsy). GW has a broad clinical pipeline of cannabinoid products.

Analysts see consolidations continuing with companies likely to seek to acquire businesses in new or larger markets and to find ones with capabilities to scale up. In May 2021, Ginkgo Bioworks entered into a definitive agreement to merge with Soaring Eagle Acquisition Corp. This put Ginkgo at an enterprise value of \$15bn. Ginkgo Bioworks has an agreement with Cronos to produce eight different cannabinoids.

Last year US-based Constellation Brands, one of the largest liquor companies in the world, exercised warrants originally issued in 2017 to acquire shares in Canopy Growth, a large diversified cannabis company. In 2018, Canopy Growth paid more than US\$300m in cash and shares to acquire Ebbu, a small Colorado company that had developed one of the earliest platforms for manipulating the cannabis genome using gene-editing system CRISPR–Cas9 technology.

Biosynthesis: The competitive landscape

We have reviewed the competitive landscape and have compiled a list of the principal players in cannabinoid biosynthesis (Exhibit 3).

The most comprehensive overview we have seen in the sector is the October 2020 review by Raymond James, which ranked companies based on two metrics:

- The stage of process development and time to market.
- Access to the total cannabinoid-based product market.

¹⁵ ATB Capital Markets Thematics, Biosynthetically-derived cannabinoids

¹⁶ [Creo press release, 28 January 2021](#)

Among the major biosynthesis companies, Cronos Group/Ginkgo Bioworks topped Raymond James's list. Tied for second place were Creo (Genomatica JV), one of the first companies to make cannabinoids through biosynthesis, and Demetrix.

Exhibit 3: Companies at or approaching commercial scale production in cannabinoid biosynthesis

Company	Partner	Cannabinoid	Production Method	Organism
Cronos Group (Canada)	Ginkgo Bioworks (USA)	CBG	Biosynthesis	Yeast
Creo (USA)	Genomatica (USA)	CBG	Biosynthesis	Bacteria
Demetrix (USA)		CBG	Biosynthesis	Yeast
Lygos (USA)	Librede (USA)	CBG, CBC, CBN, CDB	Hybrid	Yeast
Willow Biosciences (Canada)	Purisys (USA)	CBG	Biosynthesis + Chemical synthesis	Yeast
LAVVAN (USA)	Amyris (USA)	CBG	Biosynthesis	Yeast
InMed (Canada)*		Various	Enzymatic biotransformation, Biosynthesis	Enzymes, Bacteria
Cellibre (USA)		CBG	Biosynthesis	Non-traditional
Renew Biopharma (USA)		Novel PPARY targeting	Biosynthesis	Yeast and microalgae
Hyasynth Biologicals (Canada)	Investment from Organigram Holdings (Canada)	THC, CBD, CBG, CBDA	Biosynthesis	Yeast
CB Therapeutics (USA)		CBG, CBC, CBT	Biosynthesis + Biocatalysis	Yeast
BayMedica (USA)		CBC	Chemical synthesis + Biosynthesis	Yeast

Source: Edison Investment Research. Note: *InMed Pharmaceuticals has signed a LOI to acquire BayMedica.

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