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BIOTECHNOLOGY

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INDUSTRY REPORT

Biosynthesis of Cannabinoids: Vanguard of The Bio Revolution

Biosynthesis is the production of molecules by living organisms. This happens naturally, every day, in every organism. But, engineers have learned to harness these powerful biological manufacturing systems to produce specific materials for humanity's benefit. Things we *want*, like vanilla or fragrances or detergent or medicines. **By engineering the instructions for these materials' production into the genetic code of simple organisms**—e.g. bacteria, algae, yeast and other fungi—**they can acquire the novel ability to produce molecules they usually wouldn't.** A cornerstone technology of the bio revolution.

Biofuels: Yesterday's Vanguard of the Bio Revolution

First came biofuels in the early 2010s: visions of massive tanks and ponds of engineered microbes like algae, yeast, bacteria, all designed with the singular purpose of becoming **factories that promised to manufacture large-scale fuel replacements more reliably, more sustainably, and, importantly, less expensively,** offsetting the world's dependence on fossil fuels. But then came the end-game: the oil price crash of 2014/15. While very few companies survived, those that emerged from the ashes did so as bearers of **broad institutional knowledge, deeply experienced teams, and powerful intellectual property.**

Cannabinoids: Today's Vanguard of the Bio Revolution

The production of **cannabinoids**—in our view—**represents a flagship application for bio-driven processes**: highly valued, low (but growing) volume molecules that are difficult to access in nature, but demanded by large global markets for a massive diversity of end-uses. And, **we stand at the perfect moment in history: a beautiful era of computational, mechanical, and biological technology convergence.** We believe bio's success in providing access to pure, consistent, stable, and scalable sources of cannabinoids to large CPG and Pharma companies—beyond the "cottage industry" that is cannabis today—could bring about **a renewed wave of innovation and investment into bio-based technologies, not seen since biofuels**. A bio revolution accelerant.

How Big is the Cannabinoid Biosynthesis Market?

We have undertaken a probability-adjusted scenario analysis of the potential penetration of cannabinoid biosynthesis technology into the CPG and Pharma markets and, from this, we estimate the **global market for products derived by cannabinoid biosynthesis growing from $10 bln in 2025 to $115 bln by 2040.** Capturing even a small slice of 2040's $115 bln cannabinoid biosynthesis product market makes for a compelling investment case.

The Players

Based on our years-long excavation of the space, and leaning on our relationships in the broader synthetic biology community**, we have spoken with all key players that populate today's landscape of beyond-the-plant cannabinoid manufacturers.** The collection of companies described (and ranked) herein is about as exhaustive as it gets, comprising **the most important companies developing cannabinoid biosynthesis technology the world over**.

Table of Contents

THE CONVERGENCE OF BIOLOGY AND ENGINEERING

"Simply scaling up our current tools and technology will not solve the daunting challenges that face us globally," Prof. Susan Hockfield[1] writes in her 2019 book *The Age of Living Machines.* Her reflection informed by humanity's means of escaping the horrors of Malthusian catastrophe predicted to unfold during the 19th century: by way of significant, previously unimagined technological advances[2]. Today, we face similarly daunting global challenges. She—and we—believe these challenges may be met, again, by revolutionary advances in even today's robust suite of technologies: "**Biology and engineering are converging in previously unimaginable ways, and this convergence could soon offer us solutions to some of our most significant and seemingly most intractable problems.**"

The Bio Revolution is Upon Us

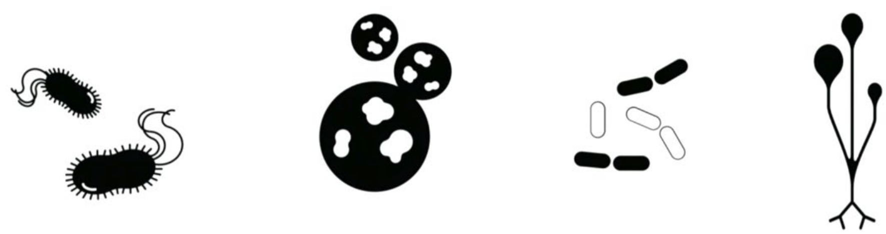
How humanity has solved problems using biology, over centuries, has come in increments—some truly fantastic (e.g. penicillin, insulin, vaccines)—**but today, we have reason to believe that bio-driven insights, innovations, and solutions will soon come in torrents, changing the equation forever**. *(And, if you won't take our word for it, take McKinsey's, or BCG's, or The Economist's.)*

What do we mean by 'bio'? All that is involved in leveraging the power and diversity and efficiency and complexity inherent in nature—in biology—to solve the world's most challenging problems. **Why now?** The bio revolution is coming to pass as a result of breakthroughs in biological science and the benefits this field enjoys from *decades* of compounding advances in physics, electronics, computing, data science, diagnostics, automation, materials science, and a multiplicity of other seemingly incongruent fields. **Today, they converge at bio**. *(See Appendix IV for more.)*

ENGINEERED BIOSYNTHESIS: RISE, FALL, RE-EMERGENCE

Broadly, biosynthesis is the production of molecules by living organisms. This happens naturally every day, in every organism. But, engineers have learned to harness these powerful biological manufacturing systems to produce specific materials for humanity's benefit. Things we *want*, like vanilla or fragrances or detergent or medicines.

Exhibit 1: Engines of the Bio Revolution



Source: Biofabricate LLC

By **engineering the instructions for these materials' production into the genetic code of simple organisms**—e.g. bacteria, algae, yeast and other fungi (Exhibit 1)—**they can acquire the novel ability to produce molecules they usually wouldn't.**

Biofuels: Yesterday's Vanguard of the Bio Revolution

First came biofuels in the early 2010s: visions of massive tanks and ponds of engineered microbes like algae, yeast, bacteria, all designed with the singular purpose of becoming fuel factories—from

[1,2] See *Postscript* for full footnote: 1) Hockfield's *Convergence 2.0*-driven Presidency at MIT, and; 2) Malthusian catastrophe.

biodiesel to ethanol to energy-rich molecules brand new to the bioenergy world—that promised to offset the world's dependence on fossil fuels (>US$100/barrel oil). Companies such as Amyris (AMRS-NASDAQ, not covered), Genencor (now DuPont [DD-NYSE, not covered]), LS9 (now REG [REGI-NYSE, not covered], KiOR (now, in part, REGI), Solazyme (now Corbion [CRBN-AMS, not covered]), Synthetic Genomics Inc. ("SGI"; now Codex; private), and Sapphire Energy (private) commanded lofty valuations—several in multi-billion dollar territory—built on the energy crisis-driven premise that they could **manufacture large-scale fuel replacements more reliably, more sustainably, and, importantly, less expensively.** But then came the end-game: the oil price crash of 2014/15. While very few companies survived, those that did (e.g. AMRS, Genomatica [biofuels-adjacent; private], Synthetic Genomics [now Codex; private]) emerged from the ashes with **broad institutional knowledge, and deeply experienced teams, harnessing powerful intellectual property.**

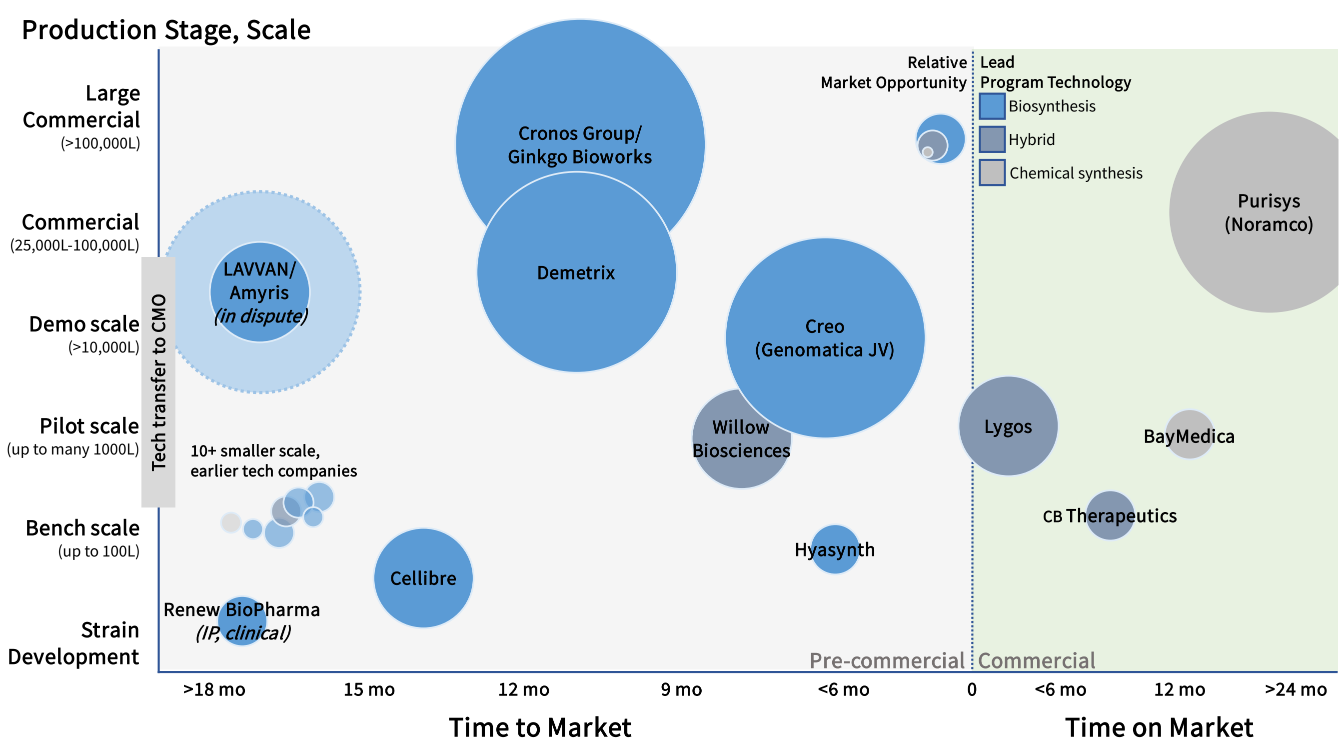
Since then, the diversity of tools developed, problems solved, and manufacturing processes empowered by bio is truly mind-boggling. And now, with a full appreciation for just how challenging it can be to break into high-volume, high-competition commodity product markets (e.g. fuels), many of the **surviving companies are pivoting their focus toward engineering the production of low(er) volume, high(er)-value molecules**. A small sample of applications in which bio-driven processes have found a home during the last decade—creating valuable products for consumers, and material value for shareholders—are in the manufacture of fine chemicals, flavours, fragrances, cosmetics, household cleaners and detergents, vitamins and nutritional supplements, small-molecule therapeutics, complex precision medicines, and animal-free meats. Yet, to date, limited value has been attributed to the bio-driven manufacturing of most of these materials, even though they enable massive markets. In our view, this is because these bio-produced molecules have been substitutes for previously commoditized materials, so their economic impact has been relatively small. But, as we see it, bio's early, low-profile successes in manufacturing lower-valued—we clarify, not lower value, but lower valued—molecules has provided a set of critical forerunner applications required to begin targeting higher valued molecules in emerging or already large markets.

Cannabinoids—a set of **highly valued molecules** in a **large, emerging market**—sit squarely within engineered biosynthesis' value and volume wheelhouse. **A perfect target.** Further, we believe a successful demonstration of bio's capacity to transform a sector like this will be **catalytic for the bio revolution at large.**

Cannabinoids: Today's Vanguard of the Bio Revolution

The production of **cannabinoids**—in our view—**represent a flagship application for bio-driven processes**: highly valued, low (but growing) volume molecules that are difficult to access in nature, but demanded by large global markets for a massive diversity of end-uses. And, **we stand at the perfect moment in history—a beautiful era of computational, mechanical, and biological technology convergence**—for these bio-production platforms to be developed using multiple powerful approaches. We believe bio's success in expanding access to cannabinoids from the "cottage industry" that is cannabis today, through to large CPG and Pharma companies—given these molecules' cultural profile and the ease with which one can explain bio's use case here (storytelling matters)—will bring about **a renewed wave of innovation and investment into bio-based technologies, not seen since biofuels**.

Exhibit 2: Competitive Landscape—Beyond-the-plant Cannabinoid Production



Note: Relative Market Opportunity is the relative scale of cannabinoid-based product markets accessible by each company given its own—plus its partner's—channels to market

Source: Raymond James Ltd.

Cannabis is a fledgling industry in the grand scheme, but we believe that cannabis—more precisely, its valuable constituent molecules: cannabinoids, terpenoids, flavonoids—has the genuine potential to develop multi-billion dollar markets, so long as the industry can overcome **one critical technological hurdle: the cannabis plant, itself**. Fortunately, an entire ecosystem of sophisticated companies are racing furiously toward commercial-scale, beyond-the-plant cannabinoid production (see Exhibit 2 and 5; *The Players* section; Tables 1 and 2).

The Plant is a Terrible Manufacturing System, Especially for CPG & Pharma

Cannabis agriculture is a relatively expensive, energy-intensive process where most of what is cultivated goes to waste, and where the active molecules of interest—hundreds of distinct agents—are produced as a **complex chemical mixture with wide batch-to-batch variability**. At the level of the cannabis consumer (and, importantly, the medical cannabis patient), this **variability makes for a challenging and inconsistent experience**, never knowing whether what you enjoyed today (or what provided relief from your specific ailment) will be what you find at the store, inside that same package, next week. Further, **this variability makes plant-derived cannabinoids completely unusable on the manufacturing lines of large-scale, low-tolerance global players** (i.e. CPG and Pharma).

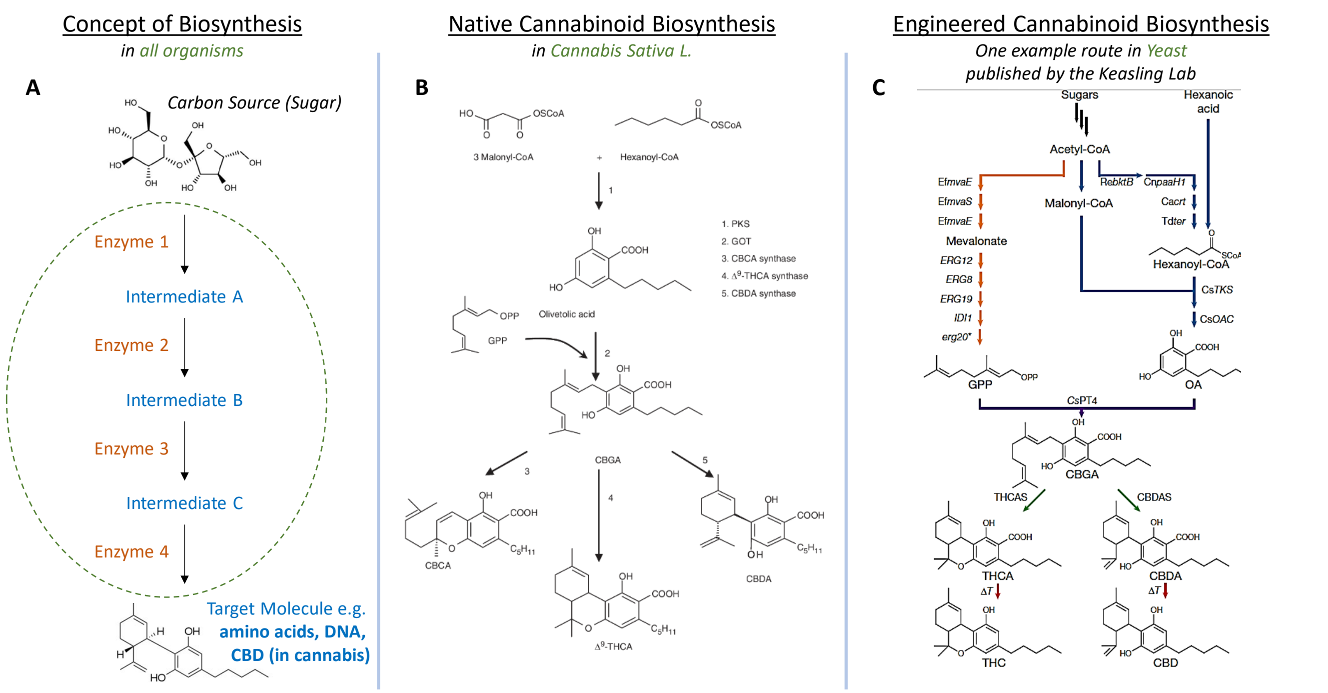
Enter Bio

We believe **the production of cannabinoids should provide a perfect beachhead application to demonstrate the powerful effect bio can have on what is now a relatively sequestered industry (but, with regulatory and legislative change proceeding in jurisdictions around the world, soon won't be).** Cannabinoids' rapidly-expanding markets, relatively high value, relative scarcity in pure, consistent, isolated form, along with the steep energy and land-use costs associated with harvesting these materials from plants, make them an ideal target for bio's disruption (and ESG initiatives, for those that are interested). **For cannabinoid biosynthesis, the techno-economic argument is right, the market demand is there, and our time in history—in relation to technological readiness—is perfect**.

THE ENGINEERED BIOSYNTHESIS OF CANNABINOIDS

This engineering technology—synthetic biology: the confluence of genetic engineering, molecular biology, systems design, and other fields—becomes particularly valuable in cases when those skilled in the art (science) can coax host microorganisms—trillions of them—into becoming tiny factories that pump out massive quantities of our favourite molecules. Importantly, since these tiny factories—and the tiny machines (enzymes) that run these factories—are designed to make exactly one product, and are not prone to mistakes, **the molecules made by biosynthesis are *exactly the same* in structure and function as those occurring in nature: *bio-identical*.**

Exhibit 3: Cannabinoid Biosynthesis, Explained



Source: Raymond James Ltd.; Flores-Sanchez, Verpoorte, *Plant Cell Physiol.* (2008) 49:1767; Luo, Keasling, et al., *Nature* (2019) 567:123

In this process, the microorganism's operating instructions—its genetic code—is engineered such that the microorganism can now make, install, and run, a variety of machines—enzymes—that, in-turn, drive the conversion of fuel—a carbon source, like sugar—into a desired end-product, typically through a series of intermediate products (molecules).

We outline this concept in Exhibit 3-A, illustrating the conversion of sugar to CBD through intermediate compounds A, B, and C, via enzymes 1, 2, 3, 4.

This sequence is carried out naturally in the cannabis plant, generally, through the conversion of 3-malonyl-CoA and hexanoyl-CoA into olivetolic acid, which is then combined with GPP by a 'prenyltransferase' enzyme to form CBGA: the precursor cannabinoid from which most other cannabinoids are converted. To produce other cannabinoids—such as THCA, CBDA, and CBCA—CBGA is converted by 'synthase' enzymes specific to the task (Exhibit 3-B). To arrive at the biologically active cannabinoid molecule, such as THC, the acid "A" group must be removed from the cannabinoid (e.g. THCA) via a decarboxylation reaction, which typically occurs through exposure to heat, but can proceed by chemical or biological transformation as well.

A challenge one might have with this **cannabis plant-driven manufacturing process is that all of these enzymes are active at once, producing a complex, highly variable soup of active molecules**[2]. **If one only wants to collect CBD and only CBD, one must weed through cannabis' 100s of other molecules to get at it: a challenging, expensive separation and isolation process.** Large-scale global enterprises tend to require highly controlled inputs to their production process. Noisy inputs make for noisy outputs: an extremely expensive problem in the context of a millions of unit per day manufacturing operation.

And so we arrive at engineered cannabinoid biosynthesis. Recapitulating the cannabis plant's natural process in a microorganism is not as simple as copying the plant's native pathway. First, cells from very different evolutionary families often don't make great hosts to each other's DNA and enzymes. Also, the conditions under which microorganisms metabolize most efficiently (e.g. temperature, pH, oxygen levels) are quite different from those of the cannabis plant. As such, genetic and metabolic engineers (such as those biofuels-oriented pioneers of the early bio revolution, and their younger, more computing-oriented compatriots), that are highly experienced in engineering their specific chassis (e.g. yeast, bacteria, algae) and have a trove of institutional knowledge and IP to draw from, have designed routes to convert carbon sources into cannabinoids using different sets of enzymes and culture conditions (Exhibit 3-C).

[2] Also, some of these natural enzymes don't carry out a dedicated conversation from, conceptually, 'A' to 'B'. Instead, the enzyme might take the 'A' input and produce 'B' 70% of the time and produce 'C' 30% of the time. This non-absolute enzyme fidelity is a reason why a truly THC-free cannabis plant is so difficult to naturally cultivate.

HOW BIG IS THE CANNABINOID BIOSYNTHESIS MARKET?

We have developed (and published Jun-23-20) a novel top-down valuation methodology specific to cannabinoid biosynthesis. We undertook a probability-adjusted scenario analysis of the potential penetration of cannabinoid biosynthesis technology into the CPG and Pharma markets (see Appendix II for details), and, from this, we estimated the **global market for products derived by cannabinoid biosynthesis growing from $10 bln in 2025 to $115 bln by 2040** (Exhibit 4).

Using a discounted cash flow analysis (10% discount, 2% terminal rates) of the estimated EBITDA yielded from these revenues—$1.3 bln in 2025, growing to $15.2 bln in 2040—we calculate a **present value of the global cannabinoid biosynthesis opportunity at ~$40 bln.** By 2040, this prize grows to $115 bln, according to our forecasts.

Exhibit 4: Total Market and DCF of Cannabinoid Biosynthesis Opportunity

Market Size: Cannabinoids by Biosynthesis		2020	2025	2030	2035	2040
CPG Market		0.0	7.9	26.7	53.4	105.2
Pharma Market		0.2	2.1	4.2	6.3	9.7
Market for Cannabinoids for Fermentation		**0.2**	**10.0**	**30.9**	**59.7**	**114.9**
Discounted Cash Flow Analysis	**Figures in CAD bln**	**aining FY2**	**FY2025**	**FY2030**	**FY2035**	**FY2040**
CPG EBITDA	1	0.00	1.0	3.5	7.1	13.9
Pharma EBITDA	1	0.03	0.3	0.6	0.8	1.3
Sector EBITDA		**0.03**	**1.3**	**4.1**	**7.9**	**15.2**
Tax Rate		*20.0%*	*20.0%*	*20.0%*	*20.0%*	*20.0%*
Free Cash Flow		**0.0**	**1.1**	**3.3**	**6.3**	**12.2**
Present Value of FCF		**0.0**	**0.6**	**1.2**	**1.4**	**1.6**
Implied EV on Rolling Annual Basis		**21.6**	**26.8**	**20.9**	**12.4**	**2.2**

FCFF Terminal Growth Rate	2.0%
Discount Rate	10.0%
Terminal Value @ FY2040	155.3
Terminal Year EBITDA @ FY2040	15.2
Implied Terminal Multiple	**10.2x**
	Present Value
Sum of Present Value of Projected FCFF	21.6
Present Value of Terminal Value	21.0
Implied Value (CAD bln)	**42.6**

Source: Raymond James Ltd.

We believe this global pie for cannabinoid biosynthesis-derived products will be divided, in part, between companies that bring cannabinoids to market at sufficiently large scale, at attractive economics, at reliable and high quality, and in varieties their customers desire (including novel cannabinoid analogues for Pharma). Capturing even a small slice of 2040's $115 bln cannabinoid biosynthesis product market, in our view, makes for an extremely compelling investment case. **We believe that most of the beneficiaries of this large and *rapidly* growing prize are included in *The Players* section below**.

For investors keen on understanding the technologies that will drive the future of cannabis—and the multiplicity of global markets cannabinoids will soon suffuse—**we suggest they direct their attention toward cannabinoid biosynthesis**.

For investors keen on understanding the technologies that will drive the future, generally—manufacturing, medicine, data storage, energy production, agriculture—**we suggest they direct their attention toward bio**.

For SPAC investors, specifically, we refer you to our section below: *The SPAC Axis*.

How We See It, What We've Found: Cannabinoid Biosynthesis

We believe the availability of multiple alternate modalities for manufacturing cannabinoids—chemical synthesis, biosynthesis, biocatalysis, plant cell culture, or some combination of these—**will change the equation for the entire cannabis industry**, shifting cannabinoid ingredient manufacture from its current plant-based "cottage industry" status to being a force capable of supplying numerous mass-market verticals—food and beverage, broader CPG, beauty, wellness, veterinary, pharmaceutical (novel molecule-focused)—with reliable, economically viable bioactive molecules.

- This means more sources of **pure, scaled, consistent cannabinoid varieties** available to global CPG players (many of which, we understand, have had product lines ready and waiting for this supply chain redundancy condition to be satisfied before considering their launch).
- This means increasingly **economic sources of common and rare cannabinoids** as these bio-driven processes mature and optimize (challenging incumbent chemical synthesis operators).
- This means **reduced reliance on energy-intensive agricultural processes** or solvent-intensive botanical extraction and chemical synthesis processes.
- This means **one less hurdle for large enterprises such as CPG and Pharma** to clear before incorporating cannabinoids into their product lines.

By providing supply chain stability and reliable product quality (and thus, trust) at unprecedentedly large scale and low cost (especially among "rare" cannabinoids), we predict that these **alternative modalities for cannabinoid production will be massively catalytic for the cannabis industry at large, representing one of the first multi-billion dollar sectors to be properly unleashed by bio-manufacturing.** As such, we have conducted interviews with more than 20 companies pursuing the alternative manufacturing of cannabinoids (see *The Players'* section), and our findings lead us to predict that **within the next 12 months we will see an unprecedented influx of pure cannabinoids enter global markets at commercial-scale, all produced using bio-based technologies.**

Case Study: Hemp-derived CBD and Rarer Cannabinoids

The price of hemp-derived CBD isolate is dropping rapidly—we've heard about rates lower than US$1,000/kg in the U.S.[3], albeit for ~80% pure CBD isolate—while the price of less abundant cannabinoids remains extremely high (US$15,000-50,000/kg), given how wasteful and technologically challenging it is to extract and isolate these from the plant, or to breed toward their overexpression. This problem fits exactly the "*valuable natural product that is difficult and expensive to harvest and purify*" paradigm that bio-based manufacturing—and chemical synthesis, *see note below*—solves so well: designing alternative systems to produce specific materials more efficiently than nature.

A Note on Chemical Synthesis: Today's Top Alternative Modality for Manufacturing Cannabinoids

In this report, we focus on bio-based processes for the production of cannabinoids, as we see biology representing the future of manufacturing, generally (see Appendix IV). This being true, we recognize that, today, the only truly commercial alternative modality for large-scale production of pure cannabinoids is chemical synthesis, with incumbents like Purisys (wholly-owned subsidiary of Noramco [private]) producing metric-tonnes of pure CBD.

[3] CBD Isolate: CA$10,000/kg in Canada this year, down from ~CA$50,000/kg last year.

THE PLAYERS

Based on our years-long excavation of the space, and leaning on our relationships in the broader synthetic biology community**, we have spoken with all the key players that populate today's landscape of cannabinoid manufacturers** to understand their respective approaches, stages of technological advancement, and target markets[4]. This collection of companies is about as exhaustive as it gets—*recognizing that there are, indeed, a number of 'stealth' operations that maintain their activities outside of public view*—but, we believe **this list comprises the most important companies developing cannabinoid biosynthesis technology the world over**.

We've produced an objective ranking of these companies, using the composite of two metrics:

1. Each company's current stage of process development and time to market; and
2. Each company's relative access to the total cannabinoid-based product market[5].

Exhibit 5: The Players: Ranked by Current Stage of Development, Relative Access to the Market

First Fully Commercial Player*

**Chemical synthesis only*

Purisys (private): **Noramco's** (private) cannabinoid-focused subsidiary

Top 10

Rank	Player	Partner
1	**Cronos Group** (CRON-Nasdaq, OP2)	Powered by **Ginkgo Bioworks** (private)
2-Tie	**Creo** (private, *exiting stealth mode*)	Powered by **Genomatica** (private)
2-Tie	**Demetrix** (private)	None
4	**Lygos** (private)	Powered by **Librede** technology (freshly acquired)
5	**Willow Biosciences** (WLLW-TSX, not covered)	Joint development agreement with **Purisys**
6	**LAVVAN** (private; in dispute with partner)	Powered by **Amyris** (AMRS-Nasdaq, not covered)
7	**BayMedica** (private)	None
8	**Cellibre** (private)	None
9	**Renew Biopharma** (private)	None
10-Tie	**Hyasynth Biologicals** (private)	Investment from **Organigram Holdings** (OGI-Nasdaq, MP3)
10-Tie	**CB Therapeutics** (private)	None

Other Players by Category

Active- Algae
- **Algae-C** (private)
- **Purissima** (private)
- **Solarvest Bioenergy** (SVS-CSE, not covered)

Active - Biocatalysis
- **Trait Bio** (private)

Active - Clinical
- **Emerald Biosciences** (EMBI-OTCQB, not covered)
- **InMed Pharmaceuticals** (IN-TSX, not covered)
- **Octarine Bio IVS** (private)

Active - Plant Cells
- **BioHarvest** (BHSC-CSE, not covered)

Active - Yeast
- **BioMediCan** (private)
- **Levadura** (private)

Uncertain Status
- **Biotii** (private)
- **Farmako GmbH** (owned by AgraFlora [AGRA-CSE, not covered])
- **Parallel** (private; f.k.a. Surterra): Powered by **Precigen** (PGEN-Nasdaq, not covered; f.k.a. Intrexon)

Chapter 11
- **Teewinot Life Sciences** (private)

Source: Raymond James Ltd.

[4] The company details included in this report are a compilation of information available in the public domain and information provided by each company in response to a proprietary survey issued by this Raymond James equity research team. We believe the information contained in this report is accurate, but we acknowledge that many of the commercial timelines, process development statuses, and technical capabilities indicated here were provided directly by company representatives, are future-looking, and may not reflect reality with high fidelity. More company data caveats described in Appendix III.

[5] Each company is able to access a relatively different scale of the total cannabinoid-based product market. For example, Willow does not develop or market its own products, so plans to be an ingredient supplier to other companies that in turn will formulate and market end products. Contrast this with Cronos, which is vertically integrated: manufacturing cannabinoids, formulating them into end products, and marketing said end products through its own, plus its partner Altria's massive distribution network.

Table 1: Top 10 - The Cannabinoid Manufacturing Competitive Landscape

Rank	Company (HQ)	Production Technology	Team Background	Lead Programs	Lead Host Organism	Stage and Scale of Production	Time to Market	Other Programs	Distinguishing Features, Recent Developments
First Fully Commercial Player* *Chemical synthesis only*	***Purisys*** *(Athens, GA)*	Chemical synthesis	Fine chemicals, API, ingredients manufacturing	CBD	N/A	Metric tonne (CBD); >100 kg annually (~40 other cannabinoids)	On market	**Purisys**: cannabinoids **Noramco** (parent co.): numerous controlled substances programs (e.g. opiates, amphetamines)	• Supplier to 90% of the world's active cannabinoid-investigating clinical trials (e.g. exclusive supplier to Cardiol Therapeutics [CRDL-TSX] and Botanix Pharmaceuticals [BOT-ASX, not covered]). • Jun. 2019: Noramco formed cannabinoid biosynthesis joint development agreement with Willow Biosciences (see #5 below; no tech transfer declared yet). • Sep. 2019: Purisys was spun out of Noramco (private) as a company dedicated to the supply of pharmaceutical-quality cannabinoids. • Produces cannabinoids by proprietary chemical synthesis processes at 100kg (~40 species) and tonne-scale (CBD). Purisys' lists 91 separate cannabinoid, terpenoid, and flavonoid products available as reference standards. • Secured a letter of determination from the U.S. DEA indicating that Purisys' CBD and ~30 more of its pharmaceutically produced cannabinoids will no longer be included on list of controlled substances. Purisys is the only company we are aware of to have been awarded such a determination.
1	**Cronos Group + Ginkgo Bioworks** (Toronto, ON + Boston, MA)	Biosynthesis	MIT-founded, talent from entire spectrum of top-tier industrial biotechnology companies	CBG	Yeast	Technology-transfer/scale-up: Unknown scale, but its wholly-owned Cronos Fermentation facility has 102,000L capacity	Commercial scale: September 2021 (est.)	**Cronos**: THC, CBD, CBC, THCV; CBGV, CBDV, CBCV, and all acid forms. **Ginkgo Bioworks**: myriad public and private programs (e.g. sustainable food, 'living medicine', vaccine development, agriculture, flavours and fragrance)	• Sep. 2018: First public deal in cannabinoid biosynthesis space: US$100 mln equity agreement for Ginkgo Bioworks to develop engineered organisms that can produce eight target cannabinoids at a cost less than US$1,000/kg. • Jul. 2019: Cronos acquired its own large-scale industrial fermentation and manufacturing facility in Winnipeg ("Cronos Fermentation"): combined 102,000L fermentation capacity, downstream processing capabilities, analytical laboratories, 84,000 square-feet of GMP space (a former Apotex facility). • May 2020: Ginkgo successfully completed technology transfer of cannabinoid-producing yeast strains to Cronos Fermentation (relevance). • Cronos is fully-integrated, from fermentation to product development to commercial sales in a highly-regulated space. And, when the time is right, CRON has big brother Altria, with its international distribution channels, intellectual property and regulatory expertise to lean on.
2-Tie	**Creo + Genomatica** (San Diego, CA)	Biosynthesis	Velocys, Solazyme, Tate and Lyle, Amyris, Eastman Kodak, Allylix, Evolva, Dyadic, Citibank, Hewlett Packard	CBG	Bacteria (*E. coli*)	Technology transfer: >10,000L during 4Q20 with CMO; access to >100,000L of installed capacity for future runs	Samples: September 2020 Commercial launch: 2020YE	**Creo**: CBGV, CBN, THCV, CBD, CBDV, CBC, CBCV, all acid forms, novel cannabinoids **Genomatica**: bio-butanediol ("bio-BDO"), bio-butylene glycol ("Brontide"), bio-nylon, among other programs	• Creo is a cannabinoid-focused joint venture formed between area specialists and Genomatica: a legacy industrial biotechnology company with a 20-year track record of scaling and commercializing *E. coli*-based processes that empower the very large-scale manufacture of products including bio-based plastics, cosmetics, textiles, electronics, cleaners, flavours and fragrances, and automotive materials. • Creo has been operating in stealth mode since 2016—among the earliest cannabinoid biosynthesis companies; de-stealthing now—quietly troubleshooting the microbial production of cannabinoids and accumulating a wide intellectual property moat, especially when combined with Genomatica's large patent library. • Creo is a nimble, pure-play cannabinoid biosynthesis company, but leverages big-biotech resources through its access to Genomatica's full biotechnology suite, institutional experience, relationships with global manufacturers, and >100 R&D personnel (mainly PhDs).

Rank	Company (HQ)	Production Technology	Team Background	Lead Programs	Lead Host Organism	Stage and Scale of Production	Time to Market	Other Programs	Distinguishing Features, Recent Developments
2-Tie	**Demetrix** (Berkeley, CA)	Biosynthesis	Amyris 23&Me, Novozymes, Joint BioEnergy Institute (JBEI)	CBG	Yeast	>15,000L fermentation volumes as demo for contract manufacturers	Samples: before 2020YE	Undeclared	• Founded in 2015 by two heavyweights in the world of bio: Jay Keasling and William Haseltine. Keasling, a professor at UC Berkeley, is one of the foremost authorities in synthetic biology and metabolic engineering. Demetrix's team finds its roots in developing bio-driven technologies with some of the synthetic biology world's originals: chiefly, AMRS. • Feb. 2019: Announced an exclusive license of *Nature*-published technology from Keasling's laboratory, which was the first end-to-end biosynthesis of cannabinoids using yeast published in the academic literature. • Aug. 2020: After successful runs at pilot-scale, Demetrix announced that it had progressed to demonstration scale (15,000L fermentation volumes; our note) and aims to begin providing potential partners product samples during 2020. • In parallel, Demetrix is undertaking the foundational investigation of cannabinoids' bioactivity and human outcomes, seeking to understand deeply all the molecules it will provide access to via yeast-driven biosynthesis: data that will advantage the company during forthcoming regulatory work.
4	**Lygos + Librede** (Berkeley, CA + San Diego, CA)	Biosynthesis + Chemical synthesis	JBEI, Amyris, Evolva, Solazyme	CBG, CBC, CBN, CBD	Yeast	~1kg quantities in-house today; >100kg quantities with CMO by 2020YE	On market: kg quantities available today	Rare and common cannabinoids; organic acids (e.g. malonic acid, glycolic acid, lactic acid)	• Lygos finds its roots in the U.S. Department of Energy-funded Joint BioEnergy Institute where its scientific founders[6] led efforts to engineer yeast for the conversion of sugars into fuels. Lygos has developed a proprietary acid-tolerant yeast platform to produce specialty organic acids at large scale (e.g. malonic acid, a key ingredient in flavours, fragrances, and pharmaceuticals). • Jan. 2020: Lygos acquired Librede, which had developed one of the world's first yeast-based cannabinoid production platforms, beginning work in 2014. • Lygos' in-place technology for the production of numerous organic acids in yeast provided an advantaged, industrially-proven host organism to support Librede's cannabinoid biosynthesis technology, leading to accelerated strain development and process engineering timelines. • Aug. 2020: Lygos announced that it had developed a commercially viable, sustainable manufacturing of cannabinoids via a novel pathway that enables the production of "any cannabinoid" at industrial scale, which Lygos defines as >100kg quantities.
5	**Willow Biosciences** (Burnaby, BC + Mountainview, CA)	Biosynthesis + Biocatalysis	Amyris, Antheia, Codexis, Intrexon, Zymergen	CBG	Yeast	500L fermentation volumes, targeting 1,000-10,000L fermentation runs in 4Q20	Samples: 3Q20; Commercial: 1H21	CBD, CBGV, CBDV, THCV, CBC, CBN, and other natural and novel cannabinoids	• Willow focuses on the metabolic engineering of baker's yeast for the production of cannabinoids, leveraging its differentiated research on the cannabis plant[7], from which the company has generated proprietary, high-resolution genomic databases that it actively exploits to advance its yeast biosynthetic platform. • The company has established a cannabinoid biosynthesis joint development agreement with Noramco (now Purisys; see *Today's Dominant Player* above) and, more recently, a development partnership with Albany Molecular Research Inc ("AMRI"; a premier CDMO for biomanufacturing) to optimize and scale its cannabinoid production processes (modality-agnostic: biosynthesis, biocatalysis, and chemical synthesis). AMRI has in-house expertise for the chemical conversion of Willow's first product, CBGA, into CBDA, THCA, CBCA, and CBNA. • July 2020: Announced that it had commenced its first pilot-scale (500L) production runs for CBGA with AMRI.

[6] Synthetic biology legend Jay Keasling is another key founder of Lygos. See Amyris and Demetrix for more companies Prof. Keasling has had a hand in jump-starting.
[7] Willow's plant scientists have worked with cannabis experts like Lacey Samuels and Jonathan Page from the University of British Columbia Botany Department. Prof. Jonathan Page is inventor on a suite of foundational intellectual property in cannabinoid biosynthesis, yielded from his laboratory's world-first sequencing of the cannabis genome and transcriptome. Page currently serves as Aurora Cannabis' (ACB-NASDAQ, not covered) Chief Scientific Officer. As far as we understand, ACB has no active projects focused on developing heterologous cannabinoid biosynthesis technologies.

Rank	Company (HQ)	Production Technology	Team Background	Lead Programs	Lead Host Organism	Stage and Scale of Production	Time to Market	Other Programs	Distinguishing Features, Recent Developments
6	**LAVVAN + Amyris** (New York, NY + Emeryville, CA)	Biosynthesis	LAVVAN: Former MedReleaf executive team, large-scale animal nutrition manufacturing; Amyris: top-tier industrial biotechnology talent	CBG	Yeast	Tonne-scale (>10,000L, minimum); aiming for >100,000L fermentation volumes with contract manufacturer during next 6 months	With LAVVAN's recent lawsuit vs. Amyris, unclear commercial timelines; LAVVAN previously targeted commercial production and scale during 1H21; Amyris expected first revenues before 2020YE	CBD, THC (programs in all market-demanded cannabinoids); Amyris has developed and scaled numerous commercial biosynthesis products (e.g. food, fragrances, nutraceuticals, cosmetics, therapeutics).	• Mar. 2019: LAVVAN formed a US$300mln cannabinoid biosynthesis technology partnership with Amyris—a legacy industrial biotechnology company with a large, cannabinoid-relevant IP-library—which is the largest agreement of its kind at the time of writing. • LAVVAN's CEO, Neil Closner, was the co-founder and CEO of MedReleaf, which was acquired by Aurora Cannabis (ACB-TSX, not covered) in 2018 for CAD$3.2 bln. • LAVVAN indicated that it was on pace to commercialize CBG and CBD at minimum fermentation volumes of 100,000L within the next few quarters; data supported by Amyris' Sep. 1, 2020 announcement that it had achieved tonne-scale fermentation volumes for CBG • Sep. 10, 2020: LAVVAN filed a lawsuit against Amyris, claiming patent infringement and trade secret misappropriation relating to cannabinoid biosynthesis programs. Amyris later claimed no wrong-doing. Given this legal dispute, the commercial timeline for both of these companies remain unclear.
7	**BayMedica** (San Francisco, CA)	Chemical synthesis + Biocatalysis + Biosynthesis	Novartis, Takeda, Dow Chemical, Kosan Biosciences, Amyris, Intrexon, Nestle-Purina	CBC	Yeast	Chemical synthesis: 50kg commercial lots of CBC; Biosynthesis: 2-5L bench-top reactors for CBGA,CBGVA, and THCVA	Chemical synthesis: Marketing now (CBC launched 2019); aiming for CBN launch during 2020	Novel cannabinoids for pharmaceutical and veterinary markets on horizon	• The core BayMedica team has a long history in the development of both yeast-derived proteins/enzymes and specialty chemicals, and chemically-derived small molecule therapeutics, which it has leveraged rapidly engineer biosynthetic, chemical synthetic, and hybrid production processes for a wide variety of cannabinoids. • Late 2019: BayMedica scaled the manufacturing of CBC by chemical synthesis to >50 kg lot sizes, with initial sales occurring shortly thereafter. • To date, BayMedica has produced over 20 unique cannabinoids by biosynthesis at bench scale, including CBD, CBDV, CBC, CBDV, CBG, CBGV, TCHV, CBN, CBL, CBT, all acid forms, and a number of novel cannabinoids. • BayMedica's chemical synthesis program is focused on the production of CBC (marketed now) and CBN (scaling up).
8	**Cellibre** (San Diego, CA)	Biosynthesis	Synthetic Genomics Inc. (now Codex), JP Morgan	CBG	Non-traditional	<10L fermentation scale	Late 2021/early 2022	CBD, CBGV, novel cannabinoids	• Cellibre's executive team worked together in senior roles at Synthetic Genomics Inc. ("SGI"): a leader in the genomics revolution founded in 2005 by genomics pioneers Craig Venter, Ph.D., and Nobel Laureate Hamilton Smith, M.D., after the completion of the Human Genome Project. • Cellibre takes an organism-agnostic approach to biomanufacturing. The company's team have built their careers discovering, exploring, developing tools for, and building manufacturing processes around non-traditional microbes that are naturally suited to producing particular molecules. During the technical team's respective tenures, it leveraged this body of knowledge to carry out projects for BP, Roche, Exxon, Mascoma, Archer-Daniels-Midland (ADM), Gevo, and Verdezyne. • Cellibre is currently developing processes to produce CBG, CBD, CBGV, and all acid forms. All of Cellibre's cannabinoid programs are presently in the strain development phase, and its CBG production is in proof-of-concept stage, aiming for commercialization during late 2021 or early 2022 in three verticals: regulated human therapeutics, animal health, and CPG.

Rank	Company (HQ)	Production Technology	Team Background	Lead Programs	Lead Host Organism	Stage and Scale of Production	Time to Market	Other Programs	Distinguishing Features, Recent Developments
9	**Renew Biopharma** (San Diego, CA)	Biosynthesis	Sapphire Energy, Merck, academia	Novel PPARγ-targeting cannabinoid (RBI 201012)	Yeast, Micro-algae	~1L fermentation scale	Preclinical and clinical development timelines	Expanding library of novel cannabinoid-backbone molecules to ~400 species; advancing cell-based screening and mouse models for top candidate molecules.	• Renew CEO and co-founder, Michael Mendez, is a recognized innovator and operator in the biotechnology arena, with key roles in developing revolutionary new drug discovery platforms including Xenomouse with Abgenix, Inc. (acquired by Amgen) and, more recently, creating a novel synthetic biology toolbox in microalgae with Sapphire Energy. • In contrast to other biosynthesis companies that have focused early efforts on large-scale production of a small assortment of natural cannabinoids, Renew is IP and therapeutics-focused, creating an enzymatic platform (presently yeast-hosted) that allows its team to produce 100s of novel cannabinoid derivative molecules for high-throughput drug discovery screening. • Renew recently received a Notice of Allowance from the US PTO for its patent covering derivatives of the ORF2 enzyme, a critical catalyst for the production of CBG-A. • While Renew's work is focused on creating novel molecules, its improved enzymes can also be used to increase the production of natural cannabinoids in any microbial biosynthesis chassis. • Renew's platform has been demonstrated at ~1L scale: sufficient for pharmaceutical high-throughput screening applications.
10 - Tie	**Hyasynth Biologicals** (Montreal, QC)	Biosynthesis	Academia, Amyris, Intrexon, LS9, Perfect Day Foods	THC, CBD, CBG	Yeast	>10L in-house; pilot scale with CMOs within 6 months; commercial scale before 2021YE	First commercial sale before 2020YE; leveraging OGI as part of go-to-market strategy	CBGV, THCV, CBDV, CBGO, THCO, CBDO, and others, including cannabinoid derivatives	• One of the original companies that had publicly announced work in cannabinoid biosynthesis arena (Librede [now Lygos, *#4 above*] is another). • Several of Hyasynth's founders were researchers in the laboratory of Vincent Martin, a founder of legacy biotech company Amyris and an advisor to Hyasynth. • One of a small sub-set of cannabinoid biosynthesis companies to have secured investment from a large Canadian licensed producer (LP) of cannabis, with a $10 mln investment from Organigram Holdings (OGI-Nasdaq) in 2018. • Have developed an efficient, novel biosynthesis pathway (3 steps vs. 11 steps in the plant) and have filed patents on a library of novel non-plant enzymes.
10-Tie	**CB Therapeutics** (Carlsbad, CA)	Biosynthesis + Biocatalysis	Academia (Y-Combinator incubated)	CBG, CBC, CBT	Yeast	~400L fermentation volumes	Marketing CBG, CBC, CBT now; CBD, THCV, CBDV, CBCV (and acid forms) by 2020YE	Psychedelics[8]: psilocybin, psilocin, DMT, MDMA, and related molecules	• Late 2019: Announced biosynthesis of psilocybin, psilocin, and related tryptamines. • April 2020: Signed MOU with Cleveland Clinic to produce multiple tryptamine and phenethylamine molecules for use in clinical trials, including psilocybin, DMT, and MDMA analogues. • June 2020: Announced successful biosynthesis of DMT and related tryptamines. • June 2020: Announced the execution of its first shipment of "rare cannabinoids" to a client in Colorado, for trial formulations of edible products.

Other Players by Category	Company (HQ)	Production Technology	Team Background	Lead Programs	Lead Host Organism	Stage and Scale of Production	Time to Market	Other Programs	Distinguishing Features, Recent Developments
Active - Algae	**Algae-C** (Charlottetown, PE)	Cell culture / Biosynthesis	Academia, NRC, Ocean Nutrition (now Royal DSM)	"Full spectrum"	Micro-algae	"Scale-up"	Anticipated commercial production by 4Q20/1Q21	Novel cannabinoid derivatives	• Leveraging micro-algae chassis to produce—in a single fermentation—a variety of cannabinoid molecules, in contrast to concurrent efforts across the cannabinoid biosynthesis landscape (apart from BioHarvest), which tend to focus on engineering bacteria or yeast to produce one cannabinoid molecule per fermentation. • Focused on engineering the augmented production of THC(A), CBD(A), CBG(A), CBN, and others during the course of its full-spectrum fermentations.

8 We've begun to see other companies in the cannabinoid biosynthesis realm spearhead efforts to develop fermentation-based routes to various psychedelic compounds and, importantly, to develop libraries of novel, proprietary analogues of these to explore to superior activity to their native cousins. Companies we've observed in this realm include MagicMed Industries (launched by founders of WLLW, described here) and Octarine Bio (described here). In the wake of accelerating clinical and regulatory advancements in the psychedelic medicine arena, we anticipate that these molecules could be important in forming the basis of a new treatment paradigm for psychiatric disorders such as depression and addition. Efficient, reliable, scalable, low-cost production mechanisms will be important in supporting that landscape, which an emerging group of biological and chemical synthesis companies intends to provide.

Other Players by Category	Company (HQ)	Production Technology	Team Background	Lead Programs	Lead Host Organism	Stage and Scale of Production	Time to Market	Other Programs	Distinguishing Features, Recent Developments
Active - Algae	**Purissima** (South San Francisco, CA)	Biosynthesis	Solazyme, Royal DSM, Genentech, LS9, Kosan Biosciences (JLABS-incubated)	Undisclosed	Micro-algae	Undisclosed (capability to achieve very large scale given expertise honed in algae-driven biofuel production)	Undisclosed	Bio-based ingredients for the global health, wellness, and nutrition space.	• Demonstrated production of multiple major and minor cannabinoids from its micro-algae platform as early as 2Q18, which helped the company secure a large public company in the wellness space as a lead investor and strategic partner (name undisclosed). • Discovered that its micro-algae platform—which, due to bio's early wave of innovation in biofuels, has been demonstrated at very large scale—is amenable to the production of several novel molecules with high potential value in the pharmaceutical and natural health: cannabinoids and beyond • Resident company of Johnson & Johnson's prestigious JLABS SSF incubator.
Active - Algae	**Solarvest Bioenergy** (Vancouver, BC; Summerville, PE)	Biosynthesis	Cobequid Life Sciences, Aqua Health, AquaBounty, Novartis, Phyterra, Academia	CBG, CBD, THC	Micro-algae	Initial strain development	OTC products expected available late 2021 (regulatory-permitting); pharma API products 2H22	Omega-3 oil (DHA and EPA), therapeutic proteins, bio-hydrogen, BMP, viral antigens	• Solarvest is an algal technology company with a 14-year track record in the research and development of natural and genetically modified microalgae strains for high value markets, including sustainable animal and human health-products, nutraceuticals, and veterinary biologics. • May 2019: Solarvest made an agreement with cannabis company FSD Pharma to develop an algae-based cannabinoid production system, which grants FSD Pharma an exclusive, worldwide license over any use of Solarvest-produced cannabinoid APIs that can treat diseases affecting the central nervous system. Solarvest retains rights to all other human cannabinoid pharmaceutical applications, intending to partner and license out specific therapeutic areas.
Active – Biocatalysis	**Trait Bio** (Los Alamos, NM)	Biocatalysis	Sapphire Energy, Syngenta, Bayer, Diageo, P&G, Gillette	Water-soluble CBD	Yeast (for cannabinoid glycosylation reaction)	Pilot scale with water-soluble CBD process today; commercial process will comprise multiple 2000L fermentation systems with CMO	First commercial sales of water-soluble CBD anticipated in 1Q21 (~16-20kg/mo product per 2000L system); THC and CBC sales anticipated 3Q-4Q21	Several plant genetics programs focused on amplifying overall cannabinoid production and on boosting minor cannabinoid production.	• Trait is developing a suite of cannabis and hemp oriented technologies, targeting three areas: (i) production of water-soluble cannabinoids for use in cannabinoid-infused consumer products; (ii) scaling the production of minor cannabinoids to be used in health and pharmaceutical products; (iii) plant transformation and crop protection technology. • Trait's lead program focuses on the biotransformation of plant-derived CBD (here, an input to the process) into a water-soluble format to be used in cannabinoid-infused products. The company uses engineered yeast strains to driven the fermentative glycosylation of CBD, rendering it water-soluble in the absence of additional excipients used in emulsion technologies. • With Peter McDonough—former President of Diageo—at the helm, Trait's first logical commercial target is the cannabinoid-infused beverage and derivative product market.
Active – Clinical	**Emerald Biosciences** (San Diego, CA)	Biocatalysis	OncoSec Pharma, Inovio Pharma, Zafgen, Orexigen Therapeutics, EnteroMedics, Amylin Pharma	THCVHS (NB1111)	Uncertain	Uncertain: agreement with Purisys to optimize synthesis methods and scale up manufacture	Clinical development timelines: THCVHS in preclinical testing for glaucoma	CBDVHS (NB2222) for treatment of ocular, hepatic, and analgesic clinical indications	• Emerald Bioscience is developing bioengineered cannabinoid prodrugs and analogs designed for multiple routes of clinical administration. • For its lead clinical program, Emerald has re-engineered the THC molecule through the addition of amino acids—valine and hemisuccinate—via an amide-ester bond, creating a proprietary prodrug of THC (THCVHS) with enhanced water solubility and optimized electrical charge, allowing it to better access to multiple compartments of the eye, including that which houses the optic nerve. • Preclinical studies of THCVHS (NB1111) have demonstrated its potential to reduce intraocular pressure and the reduction of biomarkers associated with inflammatory and fibrotic reactions to injury.

Other Players by Category	Company (HQ)	Production Technology	Team Background	Lead Programs	Lead Host Organism	Stage and Scale of Production	Time to Market	Other Programs	Distinguishing Features, Recent Developments
Active - Clinical	**InMed Pharmaceuticals** (Vancouver, BC)	Biosynthesis + Biocatalysis + Chemical Synthesis ("IntegraSyn")	EnGene, STEMCELL, Amgen, Phyton, 3M, Tekmira, Arbutus, Cardiome	IntegraSyn: undisclosed Clinical Programs: CBN (INM-755)	Bacteria (*E. coli*, for biocatalysis enzyme generation)	Process development with CDMO (Almac Group)	IntegraSyn: undisclosed Clinical Development: Phase 1 trial data in EB anticipated during 2H20	CBN (INM-088) clinical program for treatment of glaucoma.	• Clinical-stage pharmaceutical company developing formulations of CBN for the treatment of epidermolysis bullosa (EB; Phase I) and glaucoma (preclinical). • Also focused on developing an *E. coli*-based manufacturing system—the company calls it IntegraSyn—designed to enable the manufacture of numerous naturally-occurring cannabinoids to be used as InMed's clinical API, for R&D, or for direct commercialization. • The process integrates biosynthesis with other traditional drug manufacturing methods—biocatalysis and chemical synthesis—to enable InMed to flexibly shift from the production of one cannabinoid to another. • June 2020: Announced IntegraSyn was being optimized in collaboration with the Almac Group: a CDMO with 5,600 personnel across 18 facilities.
Active - Clinical	**Octarine Bio IVS** (Copenhagen, DK)	Biocatalysis, Biosynthesis	Evolva, Riverstone Biotech, Novozymes, Novo Nordisk	Cannabinoid glycosides (improved PK, drug candidates)	Yeast	0.5-1L process volumes (grams; sufficient scale to provide material for preclinical testing)	Preclinical testing of cannabinoid glycosides today; if pursued commercial non-clinical program, ~2 years to launch	Native cannabinoids, several families of native psychedelic tryptamines—e.g. psilocybin, DMT, 5-MeO-DMT—and novel derivatives (all proof of concept or early scale-up)	• Octarine leverages engineered yeast and custom enzymatic processes to produce rare and functionally superior cannabinoids and psilocybin derivatives for eventual applications in the pharmaceutical industry. • The company has developed proprietary technologies driving the *de novo* biosynthesis of active molecules in yeast, enzymatic transformations (biocatalysis), and tailored drug development. • January 2020: Octarine attracted seed funding from Bruce Linton—Canopy Growth founder—to advance its platforms. Further funding in March 2020. • July 2020: Published an academic paper reporting the relatively low-cost heterologous, yeast-hosted biosynthesis of psilocybin and psilocin from glucose. (Immediately higher titres than its cannabinoid program.) Also, the paper demonstrated the production of novel 4-hydroxytryptamine derivatives via versatile enzymatic transformations, demonstrating yeast's capacity as a high-precision drug development tool.
Active – Plant Cells	**BioHarvest** (Rehovot, Israel; Vancouver, BC)	Suspension culture and cultivation ("Biofarming")	Coca Cola, BTG Corp, Ferring Pharma, HealOr, Colbar LifeScience (now JNJ), MedReleaf	"Full spectrum"	Non-engineered plant cells	Small scale (yielding grams); scaling to 'medium and large' bioreactors during 2H20	2H21 for 2 tonne/year production in Israel; 2H22 for 20 tonne/year production in North America	Resveratrol ("VINIA") product on market, also produced by "Biofarming" method; plant cell profiles from pomegranate, olive and blueberries	• BioHarvest's "Biofarming" technology enables the propagation and growth of plant cells—such as those from trichomes of the cannabis plant—in bioreactors, at large scale, under controlled conditions. • The company dries its harvested cannabis plant cells following their growth in bioreactors, aiming to yield a consistent "full spectrum" chemical profile identical to those found in certain plant cultivars, free of pesticides, metals, and plant disease. Target cells are stored in a cell bank, and subsequently used for future production batches. • BioHarvest has so far achieved the production of six cannabinoids by this method: THCA, THC, CBDA, CBD, CBN, and CBC. • BioHarvest aims to market either the dried cannabis cell biomass or the purified cannabinoid products into the cannabis (extraction and derivative product players) and pharmaceutical/CPG industries, respectively.
Active - Yeast	**BioMediCan** (Fremont, CA)	Biosynthesis	BioDatomics, partnerships in academia	CBG, THCV	Yeast (*Yarrowia lipolytica*)	250mL fermentation volume tests complete; aiming for 300L pilot scale 4Q20/1Q21	Aiming for large-scale production and sales ~2H21	THCV, CBN, THCA, astaxanthin, ferruginol, sesqui-CBGA, sesqui-THCA, sesqui-CBDA	• BioMedican leverages the yeast strain *Yarrowia lipolytica* (YL)—known for its naturally high fat composition and its utility in the production of specialty lipids—as a chassis for cannabinoid biosynthesis, making its selection on the grounds that this high oil composition would protect the organism from cannabinoids' inherent anti-fungal properties and that several precursor compounds are shared between the biosynthesis processes for oils and for cannabinoids, giving rise to YL's potential natural advantage here. • BioMediCan believes it has an IP advantage by engineering its cannabinoid biosynthesis process in YL, given, first, that very few other companies use this chassis, and, second, that its process—according to the company—effectively avoids existing IP in the space, from precursor production through to CBG synthesis and end-cannabinoid production.

Other Players by Category	Company (HQ)	Production Technology	Team Background	Lead Programs	Lead Host Organism	Stage and Scale of Production	Time to Market	Other Programs	Distinguishing Features, Recent Developments
Active - Yeast	**Levadura** (San Diego, CA)	Biosynthesis	Verdezyne, Cargill, USDA	CBG, THC	Yeast (non-traditional)	Proof-of-concept	First commercial sale of CBG expected 3Q21; CBD and THC expected late 2022	CBD, CBDV, THCV, THCP	• Levadura leverages proprietary, non-traditional strains of yeast that use vegetable oil as a fuel source and, the company claims, are naturally advantaged in the production of cannabinoids. • Levadura also indicates that its strains also have the favourable characteristic of secreting the cannabinoids produced, simplifying downstream processing and potentially enabling the development of a continuous process. • Core technical team from Verdezyne, a recently liquidated company founded during the early bio-based production movement, which used yeast to develop sustainable plastic products (raising >$200 mln during its time).
Uncertain Status	**Biotii** (Boston, MA)	Biosynthesis, Biocatalysis, Chemical Synthesis	Academia	Uncertain	Uncertain	Uncertain program status	Uncertain program status	Uncertain	• Biotii describes itself as a biotechnology company pursuing genetically engineered microorganisms that express cannabinoid profiles identical to those found in nature. • September 2019: Biotii announced a CA$1.2 mln investment from ICC International Cannabis to advance technologies for producing cannabinoid profiles at a fraction of the cost of current cannabis production methods and with more consistent production quality, aiming to launch into large-scale production with a wide portfolio of (prospective) intellectual property, including: "synthetic cannabinoids; designer enzymes; proprietary enzyme pathways, and; GMO microorganisms." • The company's most recent press release was made almost one year ago.
Uncertain Status	**Farmako GmbH** (Frankfurt, DE)	Biosynthesis	Uncertain	Uncertain	*Zymomonas mobilis*	Uncertain program status	Uncertain program status	Uncertain	• February 2019: Farmako announced its patent application for an engineered *Zymomonas mobilis* bacteria—used in tequila-making—capable of producing cannabinoids from sugar by biosynthesis at extremely high rates (4.5 kg of THC produced per gram of bacterial mass during a 900hr production run, the company claimed). • Apart from a two-way supply agreement signed with Canadian cannabis producer Zenabis in April 2019, there have been no additional developments announced relating to Farmako's cannabinoid biosynthesis technology.
Uncertain Status	**Parallel** (formerly Surterra Wellness) + **Precigen** (formerly Intrexon)	Biosynthesis	Legacy bioengineering talent at Intrexon	Uncertain	Yeast	Uncertain program status	Uncertain program status	Plant propagation technology ("Botticelli", by Intrexon, for Surterra); Precigen focused on numerous clinical cell and gene therapies	• Intrexon was one of the originals in bioengineering that had spent two decades building technologies with applications in healthcare, food, energy, and the environment. The company has since undergone significant restructuring, including a name-change to 'Precigen', the CEO role transitioning from long-time leader and benefactor R.J. Kirk, and the company now focusing exclusively on the advancement of clinical assets. • June 2019: Intrexon and Surterra Wellness (now 'Parallel')—a cannabis company with US and international operations—announced a US$100mln deal to pursue commercial scale cannabinoid production using Intrexon's proprietary yeast chassis, targeting a cost of goods <US$1000/kg. • As part of Intrexon's transition, the company sold several of its "smaller non-healthcare businesses" for ~US$65. The status of Surterra's legacy cannabinoid biosynthesis deal with Intrexon is uncertain at this time. (Though, in Surterra's October 2019 name-change press release, we do see the company describing an R&D facility in Budapest as an asset; Intrexon's cannabinoid biosynthesis development centre was in Budapest.)
Ch. 11	**Teewinot Life Sciences** (Tampa, FL)	Biocatalysis	Contract research organization R&D lead, IP development	CBN	Yeast (for biocatalysis enzyme [*THCAS, CBDAS*] generation)	Pilot scale (undefined; optimizing for commercial biocatalysis)	Filed Chapter 11: timelines halted; previously anticipated commercialization of CBN, CBG, CBGV in 2021	20 cannabinoids produced by this biocatalysis process; novel cannabinoid prodrugs and analogs	• Oct. 2019: Announced CBN commercial manufacture by chemical synthesis. • Teewinot Life Sciences' (TLS) biocatalytic process has two parts: (i) yeast-based fermentation of cannabinoid synthase enzymes THCAS and CBDAS; and (ii) biocatalysis, wherein the synthase enzymes catalyze the conversion of either CBGA or CBGVA substrates into the destination cannabinoid/varin. • TLS has over 20 issued patents covering this process, novel molecules and their uses, as well as cannabinoid formulations. • Aug. 2020: TLS filed Chapter 11 in the State of Florida.

Source: Raymond James Ltd.

The SPAC Axis

Upon review of the cannabinoid biosynthesis competitive landscape (see *The Players* section above), the reader will quickly see that most companies developing these technologies are privately-held. And, so are most companies in the broader bioengineering and synthetic biology universe.

Another convergence: coincident with the technological exponentiality we're observing across the bio landscape is the escalating rate of special-purpose acquisition companies (SPACs) entering the public markets. We believe **synthetic biology companies—especially cannabinoid biosynthesis companies—make logical targets for SPACs seeking to take future-facing technologies public.** In fact, we've educated more than a few cannabis and non-cannabis SPAC directors on the topic of cannabinoid biosynthesis technology, its near-term effect on the cannabis landscape, and its longer-term effects on global CPG, wellness, and pharmaceutical markets. In earlier publications, we flagged that the major investor or acquirer of cannabinoid biosynthesis companies would be cannabis companies, as we saw initiated by CRON, OGI, and others. Today, cannabis companies—though weakened by 2019/20's capital drought—remain natural buyers of cannabinoid biosynthesis technology and the products thereof, but **SPACs focused on cannabis, innovative consumer products, or industrial biotechnologies are becoming the most important and best capitalized group to watch in the bio space**.

Just as the internet's architecture provided the backbone for an infinity of digital businesses we couldn't have imagined 25 years ago, so will the bio revolution provide the architecture and tools and platforms and roadmaps for enterprises, industries, technologies that we can't imagine today. We are living at the perfect time in history to watch biology and engineering converge in a way, finally, that allows for the creation of massive new markets, for the development of revolutionary approaches to old industries, and for the launch of myriad new businesses: new bio 'apps'.

Those at the helm of SPACs are on the prowl for technologies just like these. **With the three axes of biology, engineering, and SPAC activity all experiencing parabolic growth at the same moment in time, the opportunity for investors in this space is difficult to ignore**. A typical condition of the SPAC is to deploy committed capital within two to three years of original investment: the original cannabis SPACs are rapidly approaching this trigger point. We anticipate that **a succession of cannabinoid biosynthesis companies will soon become the focus of 'de-SPACing' transactions**, either alone or in combination with neatly aligned cannabis or consumer goods companies.

Appendix I: The Technology

What is Cannabinoid Biosynthesis?

Cannabinoid biosynthesis, we believe, is the most disruptive technology primed to hit the cannabis industry. Imagine the impact of a technology that obviates the need for most of the world's cannabis (plant) cultivation and provides the manufacturing-oriented catalyst required for Big CPG and Big Pharma to step into the cannabis game.

What is biosynthesis? Broadly, biosynthesis is when materials are produced by living organisms. By engineering the instructions for these materials' production into the genetic code of simple organisms—e.g., bacteria, algae, and fungi like yeast and slime mold—they can acquire the ability to produce molecules they usually wouldn't. This technology—synthetic biology: the confluence of myriad fields including genetic engineering, molecular biology, and systems engineering becomes particularly valuable in cases when those skilled in the art (science) can coax host cells into becoming factories that pump out high-value molecules that would otherwise be very difficult to manufacture or to extract from natural materials. During the last handful of years, leveraging this technology has gained traction in the cannabis space, with scientists and companies alike turning their attention toward engineering simple organisms to produce cannabinoids—some of the cannabis plant's active molecules—by biosynthesis. And, since these organisms' subcellular machines (enzymes) are designed to make exactly one product and, importantly, are not prone to mistakes, the cannabinoids made by biosynthesis would be *exactly the same* in structure and function as those occurring in the plant: *bio-identical*.

Why? The plant is a messy, inefficient bio-factory: 95% of the cannabis plant's mass—which expends energy and resources to grow—ends up as botanical waste. The plant's most abundant molecular products—the cannabinoids THC and CBD—make up just ~2–5% of the whole plant structure by mass, while the hundreds of molecular products cannabis plants also produce—minor cannabinoids, terpenes, and flavonoids, several of which have shown compelling early signals of therapeutic activity—typically comprise less than 0.1%. At present, we rely on horticulture and botanical extraction techniques to access these valuable molecules. The trouble is, products of these extractions yield complex, variable mixtures of the molecules of interest, and further separation and purification of these molecules is challenging—given their relative similarity in chemical structure—and is, importantly, expensive. So, framing the plant as a biological factory, it becomes clear that the space, time, energy, and money required to produce commercial quantities of pure active ingredients using traditional methods—growing, harvesting, drying, and extracting biomass, then separating and purifying molecules—is a terribly inefficient route.

How will cannabinoid biosynthesis work at commercial scale? Instead of growing plants in fields to source cannabinoids, the new cannabis industry will grow micro-organisms in fermentation tanks (called bioreactors), much like the industrial fermenters used in the production of alcohol. While scale-up of any physical process is non-trivial, fermentation in bioreactors is a process that lends well to massive scale and reproducibility across geographies, meaning that even cannabinoids that are very rare in nature can be produced in large quantities using micro-organisms designed specifically for that purpose.

Why go to all this trouble? Pure, consistent product. Huge scale. Miniscule cost of goods.

Biosynthesis has the potential to replace *millions* of square feet that cannabis producers presently dedicate to cultivation. Commercial-scale fermentation would use a physical footprint that is orders of magnitude smaller than that used by agricultural operations. With reductions in operating footprint comes marked reductions in capital costs and improvements in process control, potentially leading to streamlined, consistent, agile, and very low-cost production of high-value ingredients. According to estimates we've received across the biosynthesis space, producing cannabinoid by biosynthesis could yield pure, bio-identical molecules at a cost of goods between $500 and $1,500/kg ($0.50 to $1.50/g). For perspective, the companies producing cannabis by indoor or greenhouse cultivation most efficiently today produce flower—with maximum 30% THC/CBD content, in a complex mixture, within plant material requiring extraction—at ~$1.00/g. Also for perspective, our industry sources indicate that purified isolate of relatively abundant cannabinoids such as CBG are being sold for US$15,000-50,000/kg. Cannabinoid biosynthesis introduces an opportunity to reduce cannabinoid production costs by orders of magnitude (many orders in the case of minor cannabinoids).

What does it all mean? Biosynthesis opens the door, for the first time, to the consistent production of pure cannabinoids at large scale and at very low cost. Cannabinoids produced by biosynthesis would not only meet the quality standard of today's cannabis industry, they would, by design, meet the stringent manufacturing standards demanded by **Big CPG and Big Pharma: premier, technology-oriented cannabis companies' eventual buyers**. In the competition for margins, stable global supply chains, and innovative and consistent products (and, thus, strong brands), we believe **companies that invest in biosynthesis technologies will be the ultimate winners.**

The Cannabinoid Biosynthesis Pathway

Exhibit 3 provides a depiction of the cannabinoid biosynthesis pathway carried out in the cannabis plant. While this is the biochemical cascade plants use to produce cannabinoids in nature—as far as we understand it today—and much can be learned from this, **the biosynthetic routes that can be engineered into micro-organisms are not required to follow the natural sequence**. Yes, engineering of the native biosynthesis mechanism is required to allow this process to proceed in organisms beyond than the cannabis plant, but, more importantly, **much of the engineering done here is to superpower the process**, making it much faster, much more precise, and, in some cases, yielding fine-tuned molecules that are brand new to the world. Important work is being done by the companies described in this report to, as quick examples:

a) improve reaction efficiency and speed at every step in the process (enzyme engineering);
b) use alternative, advantageous feedstocks and intermediates as reaction inputs (see Keasling's group supplementing with hexanoic acid in Exhibit 3);
c) reduce unwanted intermediates (e.g. ones that are toxic to the microbe) or unneeded end products (e.g., >100 cannabinoids produced by promiscuous enzymes in the plant, vs. targeting the produce of just one pure cannabinoid in microbes); and
d) allow the microbe to allocate more of its energy to the cannabinoid biosynthesis process, optimizing carbon flux from fuel to product.

We believe there is opportunity for ingenuity and creativity at every turn here, not just one solution that every company is racing toward. And thus, there will not be just one winner in the cannabinoid biosynthesis space. There is a wide variety of intellectual property to be claimed, and there is a diverse suite of end markets in which these products will fit, and in which these companies will carve their niche.

APPENDIX II: CANNABINOID BIOSYNTHESIS VALUATION

We have developed a novel, robust, defensible, top-down valuation methodology specific to cannabinoid biosynthesis. Below, we provide our scenario analyses that estimate the opportunities available to producers of cannabinoids by bio-based methods in the global CPG and Pharma sectors.

We estimate the global market for products derived by cannabinoid biosynthesis growing from C$10 bln in 2025 to C$115 bln by 2040 (see report body). **We calculate a present value of the global cannabinoid biosynthesis opportunity at ~C$40 bln.**

Exhibit 6: Estimating Cannabinoid Biosynthesis Opportunity for the Global CPG Market

Estimated Cannabis & Cannabinoid CPG Market Size

	2020	2025	2030	2035	2040
Canada	2	6	10	15	20
US	10	60	100	150	200
Europe		30	50	75	100
Other	1	6	10	15	20
Total	**13**	**102**	**170**	**255**	**340**

Scenario Analysis: Cannabinoid Biosynthesis CPG Market

Scenario Revenue

% of Market that Includes Cannabinoid Biosynthesis	2020	2025	2030	2035	2040
0%	0.0	0.0	0.0	0.0	0.0
1%	0.1	1.0	1.7	2.6	3.4
2%	0.3	2.0	3.4	5.1	6.8
5%	0.7	5.1	8.5	12.8	17.0
10%	1.3	10.2	17.0	25.5	34.0
15%	2.0	15.3	25.5	38.3	51.0
20%	2.6	20.4	34.0	51.0	68.0
25%	3.3	25.5	42.5	63.8	85.0
30%	3.9	30.6	51.0	76.5	102.0
35%	4.6	35.7	59.5	89.3	119.0
40%	5.2	40.8	68.0	102.0	136.0
45%	5.9	45.9	76.5	114.8	153.0
50%	6.5	51.0	85.0	127.5	170.0
55%	7.2	56.1	93.5	140.3	187.0
60%	7.8	61.2	102.0	153.0	204.0
65%	8.5	66.3	110.5	165.8	221.0
70%	9.1	71.4	119.0	178.5	238.0
75%	9.8	76.5	127.5	191.3	255.0
80%	10.4	81.6	136.0	204.0	272.0
85%	11.1	86.7	144.5	216.8	289.0
90%	11.7	91.8	153.0	229.5	306.0
95%	12.4	96.9	161.5	242.3	323.0

% of Market that Includes *Cultured* Cannabinoids

	2020	2025	2030	2035	2040
Low	0%	2%	2%	3%	4%
Low-Med	0%	5%	10%	15%	20%
Med	0%	10%	20%	30%	40%
Med-High	0%	15%	25%	35%	50%
High	0%	20%	35%	50%	65%

Cultured Cannabinoid Market Revenue

	2020	2025	2030	2035	2040
Low	0.0	2.0	3.4	5.1	6.8
Low-Med	0.0	5.1	17.0	25.5	68.0
Med	0.0	10.2	34.0	76.5	136.0
Med-High	0.0	10.2	42.5	89.3	170.0
High	0.0	20.4	59.5	127.5	221.0

Probability Weighted Market Revenue

Outcome Probability		2020	2025	2030	2035	2040
10%	Low	0.0	0.2	0.3	0.5	0.7
40%	Low-Med	0.0	2.0	6.8	10.2	27.2
30%	Med	0.0	3.1	10.2	23.0	40.8
15%	Med-High	0.0	1.5	6.4	13.4	25.5
5%	High	0.0	1.0	3.0	6.4	11.1
	Total	**0.0**	**7.9**	**26.7**	**53.4**	**105.2**

EBITDA

EBITDA %		2020	2025	2030	2035	2040
5%	Low	0.0	0.4	1.3	2.7	5.3
10%	Low-Med	0.0	0.8	2.7	5.3	10.5
15%	Med	0.0	1.2	4.0	8.0	15.8
20%	Med-High	0.0	1.6	5.3	10.7	21.0
25%	High	0.0	2.0	6.7	13.4	26.3

Probability Weighted EBITDA

Outcome Probability		2020	2025	2030	2035	2040
10%	Low	0.0	0.0	0.1	0.3	0.5
40%	Low-Med	0.0	0.3	1.1	2.1	4.2
30%	Med	0.0	0.4	1.2	2.4	4.7
15%	Med-High	0.0	0.2	0.8	1.6	3.2
5%	High	0.0	0.1	0.3	0.7	1.3
	Total	**0.0**	**1.0**	**3.5**	**7.1**	**13.9**

Source: Raymond James Ltd.

Exhibit 7: Estimating Cannabinoid Biosynthesis API Opportunity for the Global Pharma Market

Estimated Major Indications' Pharma Market Size

	2020	2025	2030	2035	2040
Inflammation	140	148	157	166	176
Cardiology	71	73	75	76	78
Oncology	140	151	162	174	188
Pain	98	102	106	110	115
Total	**449**	**474**	**500**	**527**	**556**

Scenario Analysis: Cannabinoid Biosynthesis-Derived API Pharma Market

Scenario Revenue

% of Market that Includes Cannabinoid Biosynthesis	2020	2025	2030	2035	2040
0.05%	0.22	0.24	0.25	0.26	0.28
0.1%	0.4	0.5	0.5	0.5	0.6
0.2%	0.9	0.9	1.0	1.1	1.1
0.3%	1.3	1.4	1.5	1.6	1.7
0.4%	1.8	1.9	2.0	2.1	2.2
0.5%	2.2	2.4	2.5	2.6	2.8
0.6%	2.7	2.8	3.0	3.2	3.3
0.7%	3.1	3.3	3.5	3.7	3.9
0.8%	3.6	3.8	4.0	4.2	4.5
0.9%	4.0	4.3	4.5	4.7	5.0
1.0%	4.5	4.7	5.0	5.3	5.6
1.5%	6.7	7.1	7.5	7.9	8.3
2.0%	9.0	9.5	10.0	10.5	11.1
2.5%	11.2	11.8	12.5	13.2	13.9
3.0%	13.5	14.2	15.0	15.8	16.7
3.5%	15.7	16.6	17.5	18.4	19.5
4.0%	18.0	19.0	20.0	21.1	22.3
4.5%	20.2	21.3	22.5	23.7	25.0
5.0%	22.5	23.7	25.0	26.4	27.8
5.5%	24.7	26.1	27.5	29.0	30.6
6.0%	27.0	28.4	30.0	31.6	33.4
6.5%	29.2	30.8	32.5	34.3	36.2

% of Market that Includes *Cultured* Cannabinoids

	2020	2025	2030	2035	2040
Low	0.05%	0.1%	0.2%	0.3%	0.4%
Low-Med	0.05%	0.2%	0.4%	0.6%	0.8%
Med	0.05%	0.5%	1.0%	1.5%	2.0%
Med-High	0.05%	1.0%	2.0%	3.0%	4.0%
High	0.05%	2.0%	3.5%	5.0%	6.5%

Cultured Cannabinoid Market Revenue

	2020	2025	2030	2035	2040
Low	0.2	0.5	1.0	1.6	2.2
Low-Med	0.2	0.9	2.0	3.2	4.5
Med	0.2	2.4	4.5	5.3	8.3
Med-High	0.2	4.3	7.5	13.2	22.3
High	0.2	7.1	17.5	26.4	36.2

Probability Weighted Market Revenue

Outcome Probability		2020	2025	2030	2035	2040
10%	Low	0.0	0.0	0.1	0.2	0.2
40%	Low-Med	0.1	0.4	0.8	1.3	1.8
30%	Med	0.1	0.7	1.3	1.6	2.5
15%	Med-High	0.0	0.6	1.1	2.0	3.3
5%	High	0.0	0.4	0.9	1.3	1.8
	Total	**0.2**	**2.1**	**4.2**	**6.3**	**9.7**

EBITDA

EBITDA %		2020	2025	2030	2035	2040
5%	Low	0.01	0.1	0.2	0.3	0.5
10%	Low-Med	0.02	0.2	0.4	0.6	1.0
15%	Med	0.03	0.3	0.6	0.9	1.4
20%	Med-High	0.04	0.4	0.8	1.3	1.9
25%	High	0.06	0.5	1.1	1.6	2.4

Probability Weighted EBITDA

Outcome Probability		2020	2025	2030	2035	2040
10%	Low	0.00	0.0	0.0	0.0	0.0
40%	Low-Med	0.01	0.1	0.2	0.3	0.4
30%	Med	0.01	0.1	0.2	0.3	0.4
15%	Med-High	0.01	0.1	0.1	0.2	0.3
5%	High	0.00	0.0	0.1	0.1	0.1
	Total	**0.03**	**0.3**	**0.6**	**0.8**	**1.3**

Source: Raymond James Ltd.

Appendix III: Cannabinoid Biosynthesis Company Data Caveats

1. The vast **majority of companies developing cannabinoid biosynthesis technologies are privately-held**, so most information that can be gleaned about the companies were either provided directly by the company representatives—taken at their word—or through press releases the companies choose to—i.e., were not required to—issue.

2. Given the extremely competitive nature of the cannabinoid biosynthesis space, many companies choose not to disclose fine detail relating to their highly proprietary processes. In particular, **companies are often reticent about whether their process is an end-to-end (*de novo*) biosynthesis from simple carbon inputs (e.g., sugar) to final cannabinoids, or if the process contains some workarounds**. For instance, the process may start with (or be supplemented with) more complex intermediates in the cannabinoid biosynthesis sequence. Or, the engineered organisms may produce one particular cannabinoid (often CBG), which is then transformed—by synthetic chemistry or biocatalysis—to the end cannabinoid of interest. If a company suggests that its fermentation platform can produce 'any cannabinoid', a downstream-of-fermentation transformation step is likely (instead of simple separation steps). These are certainly valid process development strategies (especially if speed to market is valued); **at the end of the day, COGS, quality, and supply stability is king.** Hence, chemical synthesis companies like Purisys describing themselves as manufacturing modality-agnostic: if a biosynthesis process—when ready for commercial production—proves superior to extant chemical synthesis or biocatalysis processes on important domains (e.g., production economies, process modularity, consumer perception driving premium pricing [fermentation product ('natural') vs. synthetic]), large manufacturers, we suspect, will quickly adopt them.

3. Some companies have disclosed in press releases details of their process development stage, but this **data is frequently provided without full context**. For instance, companies' current fermentation volumes have been provided in several recent press releases. While this provides clues about the size of the manufacturing process, one would need to understand several further parameters to provide fully-informed analysis of those operations and opportunities (e.g., fermentation titres [g/L]; time to reach those titres, or specific productivity [g/L/hr]).

4. Information relating to fermentation volumes, titres, and specific productivities are only part of the equation for answering questions that customers and investors really care about:

   a. **How much product can the company produce per day, month, year?** (Data including specific productivity, downstream processing throughput and efficiency, process downtime relating to batch change-overs [if a batch process] all required to determine.)

   b. **At what price will the company sell this product? At what purity standard? In what format?**

   c. **How much does it cost to produce 1 kg of product?** (Data including fermentation input [carbon source(s)], growth media, energy, and separation material costs, material recovery/recycle capabilities, specific productivity, overall process efficiency, and contract manufacturer tolling rates [if employed] all required to determine.) **COGS is a very, very closely held piece of information** in the cannabinoid manufacturing space.

APPENDIX IV: WHY BIO'S TIME IS NOW

Bio is going to touch every corner of our lives (and, in more than a handful of cases, it already has.)

What do we mean by 'bio'? All that is involved in leveraging the power and diversity and efficiency and complexity inherent in nature—in biology—to solve the world's most challenging problems. The single-greatest inspiration for (and source of) all medicine, all engineering, all computation and logic, all design, is nature. The way humanity has solved problems using biology over centuries has come in increments—some truly fantastic—but we have reason to believe that bio-driven solutions will soon come in torrents, changing the equation forever. And, if you won't take our word for it, take McKinsey's, or Boston Consulting Group's, or The Economist's.

The way we develop and produce high-value molecules (e.g., flavors, fine chemicals, bioactives), complex precision medicines, nutrient-rich foods, and next-generation industrial and consumer materials, to provide a short list of examples, will never be the same. Bio may serve to ween humanity from the expensive, inefficient, imprecise, energy- and carbon-intensive production processes employed today, so many of which lean heavily on the petrochemical industry.

Bio: A Story of Convergence

"Simply scaling up our current tools and technology will not solve the daunting challenges that face us globally," Prof. Susan Hockfield writes in her 2019 book *The Age of Living Machines.* She reflects on how major, unimagined technological advances proved necessary to escape the predicted horrors of Malthusian catastrophe during the 19th century, and how today, we face similarly daunting global challenges. She—and we—believe these challenges may be met, again, by revolutionary technological advances: "**Biology and engineering are converging in previously unimaginable ways, and this convergence could soon offer us solutions to some of our most significant and seemingly most intractable problems.**" Underscoring her—and our—optimism for bio's capacity to effect positive change in our world, Hockfield adds, "We are about to enter an era of unprecedented innovation and prosperity, and the prospects for a better future could not be more exciting."

Why now? This bio revolution is coming to pass as a result of breakthroughs in biological science and the benefits this field of science enjoys from *decades* of compounding advances in physics, electronics, computing, data science, diagnostics, automation, materials science, and a multiplicity of other seemingly incongruent fields. **But today, they all converge at bio**.

Through advances in molecular biology, scientists began to understand life at the level of the cell's "hardware"—the DNA, RNA, and protein building blocks of all living things—which motivated the creation of the first enterprises we consider "biotechnology" companies (e.g., Genentech, Biogen, and Amgen).

Through advances in genomics, scientists could begin study of cells' "software"—the code that provides the complete set of instructions for each living thing—in earnest. The Human Genome Project, which concluded in 2003, offered the first map of our species' instructions for life[9], but to interpret these instructions—and to even consider editing them—significant advances in computation, sequencing, and data analysis were required. Fortunately, incredible leaps in data collection, storage, interpretation, manipulation, and generating predictions therefrom were taking

[9] It took 13 years and ~US$5 bln (adjusted for inflation) to sequence that first human genome. Technologies surrounding this feat have now advanced so remarkably that whole-genome sequences have, for years, been reliably offered at ~US$1,000 by large players like Illumina (ILMN-NASDAQ, not covered) for years, and prices seem to be trending further downward.

place in neighboring high-tech spaces during the rise of Big Data. Capabilities developed to seize opportunities bound up in impossibly large volumes of complex data are now readily applied to biological data, leading us—at last—to computational technologies powerful enough to help grapple with biology's complexity: technologies to help us **read** and understand life's software, but also, importantly, technologies to help us reliably **write** new software.

For the first time in history, the world has at its fingertips a full stack of computational and physical tools allowing teams to target a new bio-driven application—e.g., to engineer *E.coli* to produce nylon's building blocks (rather than sourcing these from petrochemical processes), as Genomatica (private) has done—and execute on the work of engineering a novel organism with relatively strong predictive ability with respective to cost and time. **These endeavors are no longer science projects. Today, these are businesses.**

As we observe this incredible, multidisciplinary confluence of technologies and expertise begin to allow disruptive, pie-in-the-sky ideas become plannable realities—to allow true businesses to be built upon them—**we believe the bio revolution is upon us. Bio's time is *now*.** And, it's not just us thinking this way, McKinsey analysts suggest: "As new entrants prepare to take some markets by storm [with biological capabilities] and incumbents in others invest aggressively to stay in the game and win, this is no time for inaction."

What's your bio-strategy?

POSTSCRIPT

1. Susan Hockfield, Ph.D., is a professor of neuroscience at MIT and served as that institution's president from 2004 to 2012: the first woman to do so, and the first life scientist. Inspired by the unprecedented scale of innovation brought about by the convergence of physics and engineering disciplines during and after World War II ("Convergence 1.0", which has yielded technologies such as radar, jet propulsion, digital computing, GPS, MRI, the Internet, smartphones, and basically, the entire digital economy [e.g., Amazon, Airbnb, Uber—all powered by the products of former inventions: Big Data, the Internet of Things, the Industrial Internet]), Hockfield made intense interdisciplinary collaboration a major theme of her presidency, aiming for a second major convergence between biology and engineering—"Convergence 2.0"—which, of course, leans heavily on the first. (One company that was founded and spun out of MIT during Hockfield's Convergence 2.0-themed presidency: a little company called Ginkgo Bioworks [founded 2009; private], an enterprise of particular interest given the subject of this report.) Hockfield believes Convergence 2.0 has the potential to transform the 21st century just as Convergence 1.0 transformed the 20th, all without the accelerant of war.

2. In 1798, Thomas Malthus estimated that population growth would inevitably outpace food production, which led him to predict that only widespread outbreaks of famine, war, and disease—and the corresponding deaths of many—would keep the balance. What Malthus had not anticipated: the massive expansions in food production capacity brought about by advances in agricultural technology such as crop rotation and fertilizers. We face similarly daunting challenges today, with a world population of 7.8 bln people—~9.5 bln by 2050—average temperatures and sea levels rising, and widespread drought, famine, and drugless diseases—COVID-19 is just one—affecting much of the world's population. Just scaling up today's technologies won't solve these problems; technological revolution, perhaps brought about by the convergence of biology and engineering, could soon offer us solutions for generating abundant and clean(er) energy, for producing widely available clean water, for developing more effective medicines at lower cost, and for producing more food and basic materials, all without further disruption of our world's ecological balance.

Company Citations

Company Name	Ticker	Exchange	Closing Price	RJ Rating	RJ Entity
Cronos Group Inc.	CRON	NASDAQ	$5.00	MO2	Raymond James Ltd.
OrganiGram Holdings Inc.	OGI.T	TSX	C$1.40	MP3	Raymond James Ltd.

Prices are as of the most recent close on the indicated exchange. See Disclosure section for rating definitions. Stocks that do not trade on a U.S. national exchange may not be registered for sale in all U.S. states. NC=not covered.

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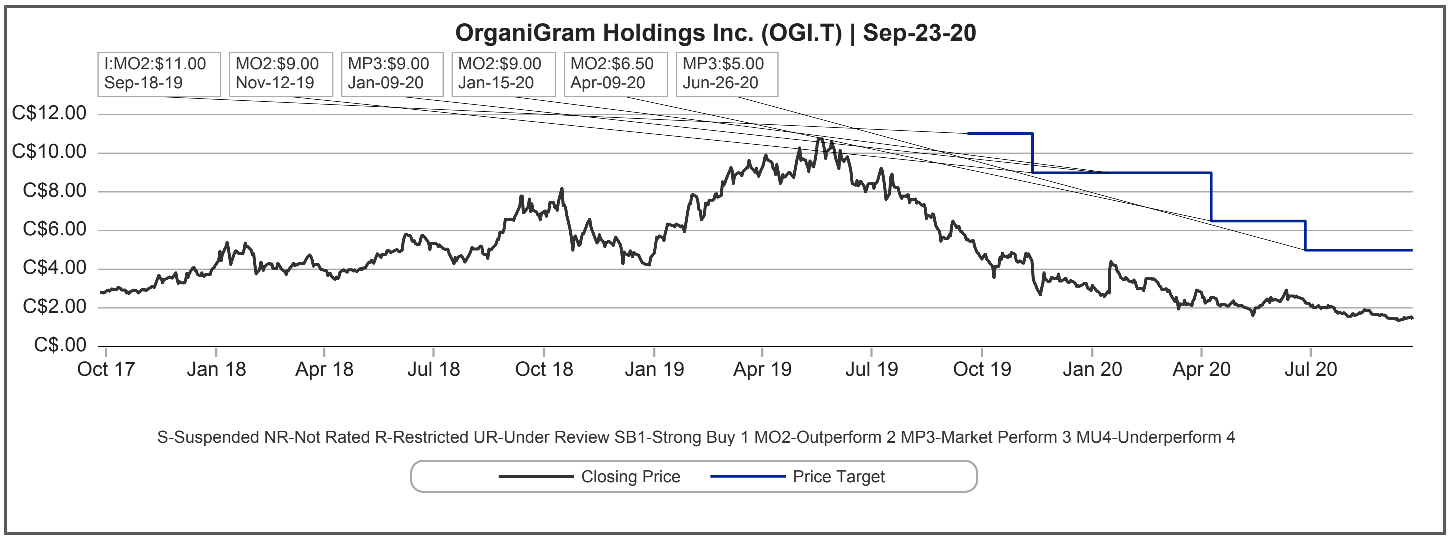

Valuation Methodology

Cronos Group Inc.
We value CRON using a sum-of-the-parts valuation methodology, including: 1) a DCF valuation (10% discount; 2% terminal rate) of the company's Canadian and U.S. revenues, 2) a comparables-driven value of its agreement with Ginkgo Bioworks, and 3) the market value of its equity stake in Cronos Australia.

OrganiGram Holdings Inc.
We have taken an intentionally conservative, fundamentals-driven approach toward: (1) valuing the Canadian market as a whole—estimating total sales over the next five years —and; (2) estimating OGI's share of that market.

General Risk Factors

Following are some general risk factors that pertain to the businesses of the subject companies and the projected target prices and recommendations included on Raymond James research: (1) Industry fundamentals with respect to customer demand or product/service pricing could change and adversely impact expected revenues and earnings; (2) issues relating to major competitors or market shares or new product expectations could change investor attitude toward the sector or this stock; (3) Unforeseen developments with respect to the management, financial condition or accounting policies or practices could alter the prospective valuation.

Company Specific Risk Factors

Cronos Group Inc.
Risks Relating to Operating in a Highly Regulated Sector in Canada:

- CRON is reliant on licenses, authorizations, approvals, and permits for its ability to grow, store, and sell cannabis and other products derived therefrom. Such licenses are subject to ongoing compliance, reporting and renewal requirements, including significant regulation under the Cannabis Act and other local legislation.
- CRON and its license holders may be constrained by law in their ability to produce and market products.
- The laws, regulations, and guidelines generally applicable to the cannabis industry are changing and may change in ways currently unforeseen by the company, including changes in the regulations governing cannabis outside of Canada, which may adversely impact CRON's business.
- There can be no assurance that the legislation governing adult-use cannabis in Canada will allow for growth.

Risks Relating to Expansion Outside of Canada:

- Investments and joint ventures outside of Canada are subject to the risks normally associated with any conduct of business in foreign countries, including varying degrees of political, legal, and economic risk.
- If CRON chooses to engage in activities outside of Canada, controlled substance and other legislation and treaties may restrict its ability to research, manufacture, and develop a commercial market for its products.
- CRON is subject to restrictions of the TSX that may constrain its ability to expand business internationally.

Risks Relating to Cannabis Operations, Markets, and Business Conduct within that Market:

- CRON's existing production facilities in Canada are integral to its operations and any adverse developments affecting these facilities may impact CRON's business, financial condition, and results of operations.
- The cannabis industry and markets are relatively new in Canada and in other jurisdictions, and this industry and market may not continue to exist or grow as anticipated. CRON must rely largely on its own market research to forecast sales and market demand, which may not materialize.
- Third parties with whom CRON does business may perceive themselves as being exposed to reputational risk as a result of their relationship with the company and may, as a result, refuse to do business with CRON.

Risks Relating to Cannabis Data, Regulation, and Intellectual Property:

- Clinical trials of cannabis-based medical products and treatments are novel terrain with very limited clinical trials history; CRON faces a significant risk that trials will not result in commercially viable products. In addition, there is limited long-term data with respect to the efficacy and side effects of cannabis products.
- Future clinical research studies on the effects of cannabis, hemp, and cannabinoids may lead to conclusions that dispute CRON's understanding of their benefits, viability, safety, efficacy, dosing, and social acceptance.
- The recent controversy surrounding vaporizers and vaporizer products may materially and adversely affect the market for hemp vaporizer products and may expose CRON to litigation and additional regulation.
- Under the 2018 Farm Bill, the FDA has retained authority over the Federal Food, Drug, and Cosmetic Act-regulated products (e.g., drugs (human and animal), food (human and animal), dietary supplements and cosmetics) containing hemp and hemp-derived ingredients, including CBD. The FDA or particular states may ultimately prohibit the sale of some or all dietary supplements or conventional foods containing hemp and hemp-derived ingredients, including CBD, which may impact CRON's business and financial condition.
- CRON is subject to risks related to the protection and enforcement of its intellectual property rights.
- CRON licenses some intellectual property rights, and the failure of the owner of such intellectual property to maintain or enforce the underlying intellectual property could have a material adverse effect on CRON.

Risks Relating to the Altria Investment:

- Altria has significant influence over CRON following the closing of the Altria Investment.
- Any common shares issued pursuant to the exercise of the Altria Warrant will dilute shareholders, and Altria's significant interest in CRON may impact the liquidity of its common shares. Also, future sales of CRON's common shares by Altria could cause the market price for its common shares to fall.
- The change of control provisions in certain of CRON's existing or future contractual arrangements may be triggered upon the exercise of the Altria Warrant in part or in full.

OrganiGram Holdings Inc.
Competition:

- There is potential that OGI will face intense competition from other companies, some of which can be expected to have longer operating histories, more financial resources, and more manufacturing and marketing experience than OGI.

- To remain competitive, OGI will require continued investment in marketing, sales, and client support. OGI may not have sufficient resources to fund such efforts on a competitive basis, which could adversely affect OGI's business, financial condition, and results of operations.

Difficulties with Forecasts:
- OGI must rely largely on its own market research to forecast sales as detailed forecasts are not generally obtainable from other sources at this early stage of the cannabis industry in Canada.
- A failure in the demand for its products to materialize as a result of competition, technological change or other factors could have a material adverse effect on OGI's business, results of operations, and financial condition.

Expansion of Operations:
- OGI's growth strategy includes expansion of its Moncton Campus and adding additional production resources thereto.
- There is a risk that these additional resources will not be achieved on time, on budget, or at all, as they can be adversely affected by a variety of factors.

Regulatory:
- OGI is subject to various laws, regulations, and guidelines by governmental authorities, particularly Health Canada, relating to the manufacture, marketing, management, transportation, storage, sale, pricing and disposal of cannabis products.
- Achieving business objectives are contingent, in part, upon compliance with regulatory requirements enacted by governmental authorities and obtaining all regulatory approvals, where necessary, for the production and sale of its products.

Reliance on License Renewal:
- OGI's ability to grow, store, and sell medical and adult-use cannabis in Canada depends on its licenses from Health Canada.
- OGI's license was renewed March 28, 2017, was migrated to a license under the Cannabis Act effective November 9, 2018, and expires March 27, 2020.
- OGI management believes it will meet the requirements of the Cannabis Act annually for extension of the license, but there can be no guarantee that Health Canada will extend or renew the license or that it will be extended or renewed on the same or similar terms.

Risks Inherent in an Agricultural Business:
- OGI's business involves the growing of cannabis (an agricultural product), which is subject to the risks inherent in the agricultural business, such as insects, plant diseases, and similar agricultural risks that may create crop failures and supply interruptions for the company's customers.

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