EDISON

Cannabis

Where are we and where are we going?

Healthcare

30 April 2019

The cannabis sector is relatively broad, spanning FDA-approved drugs to consumer products. Both markets are still at a fraction of their potential peak sizes due to laws forbidding the use of cannabis and also regulatory hesitance to approve drugs with related active ingredients. Worldwide sales for all regulator-approved cannabinoid therapeutics were only $53m in 2018 while the total legal cannabis market in the United States was only around $8bn in 2017 compared to $234bn in sales for the alcoholic beverage industry. However, things are changing, mainly due to two reasons: legalization is popular with voters and politicians recognize that the tax revenue that could be extracted through sales taxes/VAT could fill budgetary holes.

The tide has turned in North America

Despite a relatively benign safety profile even compared to alcohol, cannabis use has been broadly banned historically, even for medical use. This is all changing. Canada became the first major western country to legalize medical and recreational cannabis in 2018. In the United States, 10 states have legalized recreational cannabis and 33 states have legalized medical cannabis (though it remains illegal on a federal level). Additional states, such as New Jersey and New York, are expected to follow shortly. More importantly, several prominent Democratic presidential candidates have endorsed removing cannabis from the Schedule of Controlled Substances.

Epidiolex leading the way

Prior to 2018, the FDA had only approved three cannabinoid products (with two of them based on the same active ingredient, dronabinol) with all of them being synthetic compounds. Then in June 2018, the FDA approved Epidiolex (cannabidiol, CBD) from GW Pharma for the treatment of certain rare epilepsies. Consensus estimates expect sales of $1.7bn in 2024, which would make it the largest cannabis-related FDA approved drug in history (it is also the first plant-based cannabinoid to gain approval).

Europe moving toward liberalization, slowly

Europe has been slower than North America to reform its cannabis laws, as no European countries have fully legalized recreational cannabis. The Netherlands and Spain are the most liberal, with personal recreational use allowed in some areas (though the Netherlands has legalized medical cannabis while Spain has only legalized cannabis-derived drugs). The other large economies in Europe have been moving in that direction as well. Since 2017, medical use in seriously ill patients is legal in Germany. Medical cannabis was allowed in France in 2013 and penalties for possession were reduced to a €200 fine in 2018. In Italy, the medicinal use of cannabis was legalized in 2013, while possession of small amounts has effectively been decriminalized. The UK legalized the medical use of cannabis in November 2018, though recreational legalization efforts are stymied by the fact that the Liberal Democrats are the only major party coming out in support of it.

Companies mentioned in report

GW Pharmaceuticals (GWPH)
Insys (INSY)
Lilly (LLY)
Tilray (TLRY)
Corbus (CRBP)
Zynerba (ZYNE)
Arena (ARNA)
Therapix* (TRPX)
Intec (NTEC)
Cronos (CRON)
Amyris (AMRS)
InMed* (IN.TO, IMLFF)
Intrexon (XON)
Johnson and Johnson (JNJ)
Novartis (NVS)
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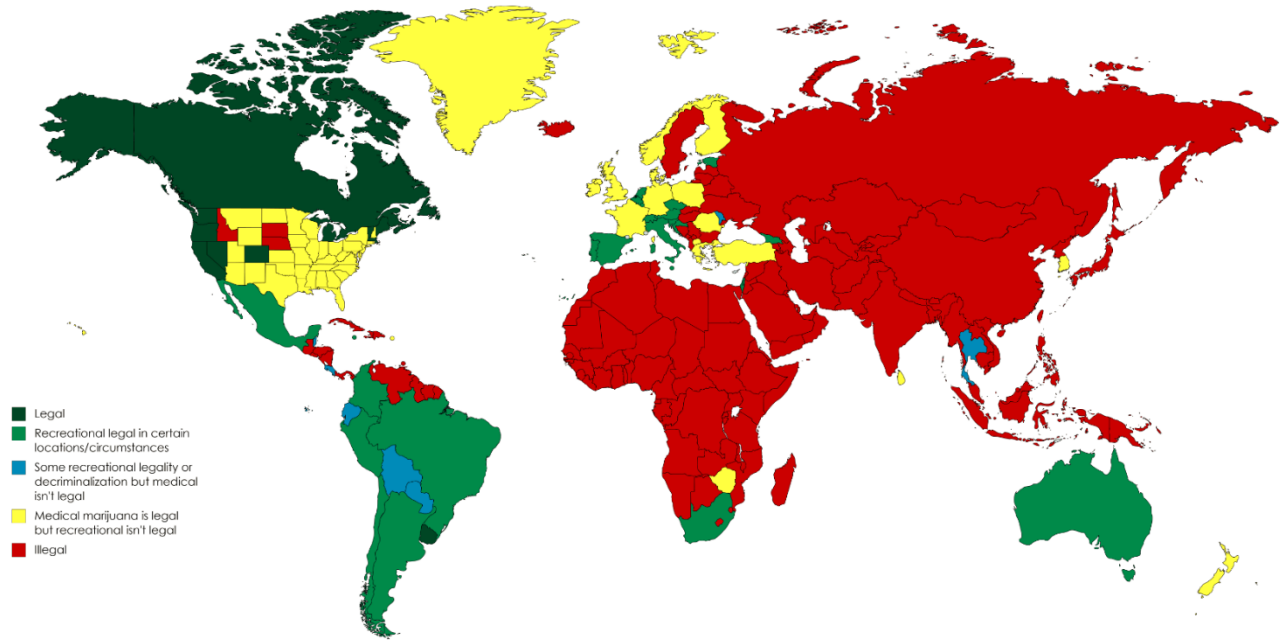
It’s not just hype, it’s real

Cannabis is thought to be one of the oldest plants cultivated by humans with multiple medicinal uses (including problems with the eyes, gynecological disorders as well as to fight inflammation) documented in Ancient Egyptian texts. In all, cannabis was used to treat a wide variety of different indications, including pain, spasticity, cancer, epilepsy, nausea, anorexia and infectious disease.[1]

In the 1800s and early 1900s, cannabis was included in certain patent medicines and elixirs for a variety of indications though with little evidence to back up claims. Regulation in the US started with the Pure Food and Drug Act of 1906 (which also led to the creation of the FDA) and continued with numerous state laws until the possession and transfer of cannabis, outside of medical and industrial use, was made illegal by the Marihuana Tax Act of 1937. The modern regime for the regulation of cannabis was born in 1970 with the passage of the Controlled Substances Act, which assigned cannabis a Schedule I classification and prohibited all uses, even medical ones. Regulation outside of the United States had a similar progression with generally broad illegality by the early 1970s.

Exhibit 1: Current status of cannabis laws globally



Source: European Monitoring Centre for Drugs and Addiction, National Organization for the Reform of Marijuana Laws, various. Created with mapchart.net

The Netherlands was the first major Western country to loosen the iron grip of the state on cannabis. In 1976, cannabis was made available for recreational use in licensed coffee shops and possession of up to 5g for personal use was decriminalized. Then in 2001, Portugal decriminalized possession of up 25g of cannabis plant material and 5g of hashish (purified cannabis resin). As of today, most major western jurisdictions have legalized at least the medicinal use of cannabis or cannabis derivatives, with recreational use only legal in certain jurisdictions or circumstances, though that list is growing. Political momentum does not seem to be there yet in the UK as the Liberal Democrats are the only major UK party to come out in favor of recreational legalization, while in Germany, there is support from the Free Democrats (FDP), the Left and the Greens, but neither the Christian Democrats (CDU) nor the Social Democrats (SPD) have backed it.

1 Russo et al., History of Cannabis and Its Preparations in Saga, Science, and Sobriquet. *Chemistry and Biodiversity* – Vol. 4 (2007) 1614-1648)

Exhibit 2: Prevalence and legal status in select countries

Country	Prevalence of use (15–64)	Estimated using population (millions)	Medical cannabis status	Recreational cannabis status
United States	17.0%	36.7	Legal in 33 states. Cannabis itself is illegal at federal level. Only FDA approvals have been for synthetics and CBD	Legal in 10 states but cannabis itself is illegal at federal level. Hemp (<0.3% THC) was de-scheduled in December 2018.
Canada	14.7%	3.5	Legal	Legal.
Germany	6.1%	3.3	Legal for seriously ill patients with no alternative	Illegal but not always prosecuted. CBD with <0.2% THC is legal.
Italy	9.2%	3.4	Legal	CBD with <0.2% THC is legal. Small amounts with higher levels are decriminalized.
France	11.1%	4.5	Cannabinoid drugs are legal with a prescription	Illegal. CBD oil with less than 0.2% THC is legal.
Spain	9.5%	2.9	Cannabinoid drugs are legal with a prescription	Somewhat legal in private areas unseen from public spaces via cannabis social clubs though sale continues to be illegal. CBD is legal.
UK	6.3%	2.7	Legal	Illegal. CBD oil without THC is allowed.
Israel	27.0%	1.4	Legal	Decriminalized.
Australia	10.4%	1.7	Legal	Decriminalized in three territories.

Source: United Nations Office on Drugs and Crime, World Bank, The European Cannabis Report, 4th Edition by Prohibition partners

US market provides enormous opportunity

The US, which will likely be the most important market for cannabis for some time, is a hybrid state. Ten states and the District of Columbia (around 25% of the US population) have legalized the recreational and medical use of cannabis. Another 23 states, representing 43% of the US population, have legalized the medical use of cannabis. In 14 states, only CBD has been legalized (either for medical-only or for any use); CBD is not psychoactive and hence deemed not abusable., Only three relatively small states continue to deem all forms of cannabis illegal.

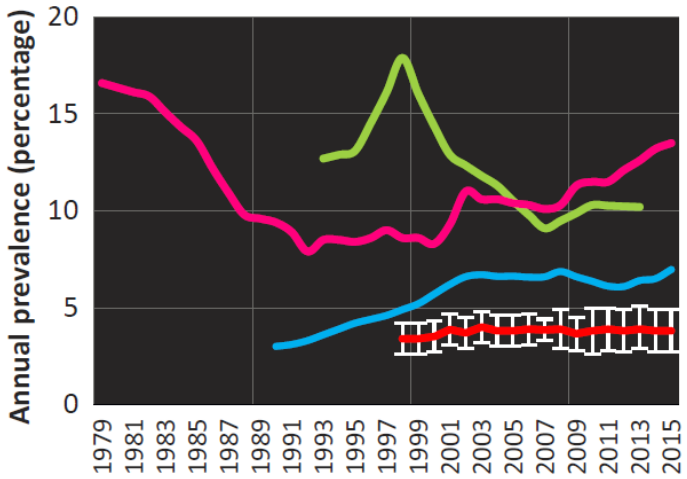
Both New Jersey and New York are targeting legalization in the very near future. One major motivator for this trend towards legalizations is the tax revenue involved as all the states that have legalized so far have effective sales taxes of between 20% and 47% on sales. Even politicians who have not had some sort of grand libertarian awakening can see the logic of this.

US federal law for cannabis is different and in many states, it contradicts state law. CBD derived from hemp (a cannabis plant with only trace levels of Δ9-tetrahydrocannabinol [THC]) is legal on the federal level (but also requires state level legalization to be sold) thanks to the 2018 Agriculture Improvement Act but cannabis itself remains illegal in all forms. The federal authorities, however, have not been enforcing federal law, instead deferring to state law. As this policy is not based on any legislation, it could change at any moment, although President Trump has indicated his support of a legislative solution to take the US cannabis industry out of regulatory limbo. However, until there is federal legislation that legalizes cannabis, the ability to import cannabis or even move it across state lines would continue to be illegal (state laws would not apply in either situation). Any manufacturer of cannabis products needs to have facilities in each state where it sells products, which does hamper the ability for a company to scale up into a multi-state business. This could all change though as Corey Booker, a Democratic senator from New Jersey and presidential candidate, has introduced the Marijuana Justice Act of 2019, which is cosponsored by several prominent senators vying for the Democratic nomination for president, namely Bernie Sanders, Elizabeth Warren, Kamala Harris and Kirsten Gillibrand. It is unclear whether such legislation will pass before the 2020 election cycle.

Even with this regulatory limbo, the US market for cannabis products is already the largest of any developed market and growing (see Exhibit 2 and 3). Colorado, for example, which has a population of 5.5 million (1.7% of the total US population and about one-seventh the size of Canada), had legal cannabis sales of $1.5bn in 2018 (recreational sales began in 2014) according to the Colorado Department of Revenue, with 79% of that being recreational. As the ability to buy

and sell cannabis for recreational use only started in California in January 2018, it is too early to tell the size of that market but it is likely to be very large. As of August 2017, there were 1.5 million medical cannabis patients in the state according to the Marijuana Policy Project with sales totaling $2.7bn in 2016, according to the Hemp Business Journal.

Exhibit 3: Annual prevalence of cannabis use across the US, EU, Australia and globally



Source: United Nations Office on Drugs and Crime, World Drug Report 2017. Note: Green = Australia prevalence aged 14 and up; pink = US prevalence 12 and older; blue = EU prevalence aged 15–64; red = global prevalence aged 15–64, 1998-2015.

The therapeutic market

Despite the fact that cannabis has been used for various medical purposes for thousands of years (and has a safety profile that is superior to alcohol in many respects),[2] there are surprisingly few therapeutics containing cannabis that have been approved by major regulatory authorities, with worldwide sales totaling only around $53m in 2018 according to Evaluate Pharma. However, Epidiolex was only launched at the end of 2018 and is expected to have $1.7bn in sales in 2024 based on consensus forecasts. Also the World Health Organization, in January of 2019, called on a rescheduling of cannabis to facilitate trade for medicinal and scientific purposes.

Exhibit 4: Cannabis therapeutics currently authorized by regulators

Brand name	Originator	Description	Indications	Form	Location of approvals
Sativex (nabiximols)	GW	Extract of cannabis: mix of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), 1:1 ratio	Multiple sclerosis-related spasticity	Sublingual spray	25 countries in Europe, Latin America, North America and Australasia. Not approved in the US
Marinol (dronabinol)	Unimed	Synthetic delta-9-THC	Loss of appetite in people with AIDS and nausea and vomiting caused by chemotherapy	Capsules	US, Canada, Germany, Australia and New Zealand
Syndros (dronabinol)	Insys	Synthetic delta-9-THC	Loss of appetite in people with AIDS and nausea and vomiting caused by chemotherapy	Liquid	US
Cesamet (nabilone)	Lilly	Synthetic cannabinoid similar to THC	Nausea and vomiting caused by chemotherapy	Capsules	US, Canada, Europe, Australia
Bedrocan (dried cannabis flower tips)	Bedrocan	Medical grade cannabis	Various	Cannabis flower tips	Certain countries within Europe where medical cannabis is legal
Epidiolex	GW	Cannabidiol (CBD)	Dravet and Lennox-Gastaut syndromes (pediatric epilepsies)	Liquid	US

Source: European Monitoring Centre for Drugs and Addiction, FDA, drug labels, company reports

2 Lachenmeier et al., Comparative risk assessment of alcohol, tobacco, cannabis and other illicit drugs using the margin of exposure approach. *Scientific Reports*. 5:8126, 1-7.

Marinol and Cesamet were both approved by the FDA in 1985 and were the first cannabinoids to gain approval though Cesamet was withdrawn in 1989 for commercial reasons (it was resuscitated by Valeant, which regained approval for the drug in 2006). There were no additional US approvals until 2016 when Syndros, a reformulation of dronabinol into a liquid, was approved and then Epidiolex (CBD) was approved for Dravet and Lennox-Gastaut (LGS) syndromes in 2018. Sativex, an extract of the cannabis plant, was first approved in the UK in 2010 but never approved in the US.

The pipeline of cannabinoids for regulatory approval is relatively sparse and generally consists of reformulations of CBD and/or THC rather than anything truly novel or innovative (see Exhibit 5), with a heavy focus on pain indications as that is one of the areas in which data on the efficacy of cannabis are the strongest.

Exhibit 5: Select clinical-stage cannabis programs

Company	Product	Generic name	Phase	Indication
Insys Therapeutics	Cannabidiol	Cannabidiol	III	Epilepsy, Prader-Willi syndrome
Tilray	Cannabidiol oil capsule	Cannabidiol;	III	Anxiety
Corbus	Lenabasum	Ajulemic acid	III	Systemic sclerosis, dermatomyositis, lupus, cystic fibrosis
Tetra Bio-Pharma	PPP005	Cannabidiol; tetrahydrocannabinol	II/III	Cancer pain
Zynerba	ZYN002	Cannabidiol	II/III	Fragile X
Arena	APD371	Olorinab	II	Gastrointestinal pain
Therapix Biosciences	THX-110	Dronabinol; palmitoylethanolamide	II	Tourette syndrome, obstructive sleep apnea and pain
CMXTwenty	CMX-020	CMX-020	II	Pain
Tilray	Cannabis (vaporized)	Cannabidiol; tetrahydrocannabinol	II	PTSD
Tilray	TN-TC19LM	Cannabidiol; tetrahydrocannabinol	II	HIV
Tetra Bio-Pharma	PPP001	Cannabidiol; tetrahydrocannabinol	II	Cancer pain
GW Pharmaceuticals	GWP42006	Cannabidivarin	II	Epilepsy, autism, Rett syndrome
GW Pharmaceuticals	GWP42002	Cannabidiol; tetrahydrocannabinol	II	Glioblastoma
GW Pharmaceuticals	GWP42003	Cannabidiol	II	schizophrenia, neonatal hypoxic-ischemic encephalopathy
Kalytera Therapeutics	CBD	Cannabidiol	II	GvHD
Botanix	BTX 1503	Cannabidiol	II	Acne
Botanix	BTX 1204	Cannabidiol	II	Atopic dermatitis
Tilray	TN-TC11G	Cannabidiol; tetrahydrocannabinol	I/II	Glioblastoma
Intec Pharma	AP-CBD	Cannabidiol	I	Pain
Intec Pharma	AP-THC	Tetrahydrocannabinol	I	Pain
Artelo Biosciences	ART27.13	ART27.13	I	Anorexia
Bird Rock Bio	Nimacimab	Nimacimab	I	NASH, diabetic kidney disease
Veritas Pharma	CTL-X	Undisclosed	I	Acute pain

Source: EvaluatePharma, company reports, clinicaltrials.gov

One big issue with developing an FDA-approved cannabinoid product is that while the clinical trial process is no shorter, the period of exclusivity is especially short if the product is simply a reformulation of THC or CBD. First, Hatch-Waxman exclusivity is only three years for a product that is not a new chemical entity. Second, any patents in this area will likely be particularly narrow due to the high level of prior art affecting patentability of THC and CBD formulations. And any granted patents will likely be challenged once the Hatch-Waxman exclusivity expires. This challenging intellectual property landscape is likely a major reason that larger biotechnology and pharmaceutical companies have not involved themselves in this space.

One strategy that could get around this intellectual property issue would be to develop one of the 100+ minor cannabinoids that exist in cannabis plants into a drug as the level of actual invention would be far higher than with THC and CBD. Besides the possibility of cleaner and broader intellectual property, these cannabinoids may also have a differentiated efficacy and toxicity profile (see Exhibit 6). Research into these minor cannabinoids is still in relatively early days due to the

expense of harvesting them, but new synthetic processes promise to make them available at a lower cost, which would encourage additional research.

Exhibit 6: Select cannabinoids and what they do

Name	Abbreviation	Comments
Tetrahydrocannabinol	THC	Most abundant cannabinoid in cannabis. Responsible for the euphoric feeling. A synthetic version is FDA approved for treating anorexia in AIDS patients and to treat nausea in cancer patients. Believed to have efficacy with regards to pain, anxiety, depression, nausea, spasms and certain cancers. CB1 agonist (central nervous system disorders).
Cannabidiol	CBD	Second most abundant cannabinoid. Not psychoactive. A natural version has been approved by the FDA for refractory epilepsy. Also thought to work against pain, anxiety, depression, nausea, insomnia, spasms, psychosis and certain cancers. Antagonist of CB1/CB2 agonists, CB2 inverse agonist (anti-inflammatory), positive allosteric modulator (pain), TRPA1 agonist (pain), TRPM8 antagonist (prostate cancer), TRPV1 agonist (psychosis, pain).
Cannabichromene	CBC	Third most abundant cannabinoid. Not psychoactive. Preliminary studies indicate a potential to treat acne, diarrhea, pain, inflammation, depression, anxiety, multiple sclerosis and increase bone growth. Anandamide reuptake inhibitor (various neurological conditions).
Cannabigerol	CBG	Cannabis plants usually contain less than 1% CBG. Not psychoactive. Potential to treat pain, bacterial and fungal infections, cancers and depression. CB1 and CB2 partial agonist (neurological conditions), anandamide reuptake inhibitor (neurological conditions), TRPA1 agonist (pain), TRPV1 agonist (pain), TRPM8 antagonist (prostate cancer).
Cannabigerolic acid	CBGA	Precursor to all other cannabinoids. Not psychoactive. May have applications in pain and inflammation.
Cannabinol	CBN	Produced through the degradation of THC and typically plants contain less than 1% CBN. Minor psychoactive effects. Potential against bacteria, epilepsy, inflammation, anorexia, cancer, insomnia, glaucoma, bone healing and pain.
Delta-9-Tetrahydrocannabinolic acid	THCA	Precursor to THC, which turns into THC when burned or vaporized. Not-psychoactive. Potential to treat inflammation, nausea, cancers and act as a neuroprotective. TRPA1 partial agonist (pain), TRPM8 antagonist (prostate cancer).
Cannabidiolic acid	CBDA	Precursor to CBD, suggested to have efficacy in cancer, pain, nausea and inflammation. TRPA1 partial agonist (pain), TRPV1 agonist (pain), TRPM8 (prostate cancer), COX-2 inhibitor (pain/inflammation).
Tetrahydrocannabivarin	THCV	Works very differently from THC. Potential to treat obesity, diabetes, anxiety, Alzheimer's disease, epilepsy and stimulate bone growth. CB1 antagonism (epilepsy).

Source: Izzo et al., Non-psychotropic plant cannabinoids, *Trends in Pharmacological Sciences*. 2009 Oct;30(10):515–27. 2018 Cannabis Investment Report by Ackrell Capital

Cannabinoids for epilepsy

Earlier last year, the most monumental approval of a cannabinoid occurred in the neurologic realm, specifically for the treatment of epilepsy. In June of 2018, the FDA approved Epidiolex for the treatment of a pair of pediatric epilepsies, namely Dravet and LGS. Epidiolex is a natural pharmaceutical-grade version of CBD and was able to demonstrate efficacy in a heavily pre-treated refractory population suffering from a debilitating disease (see Exhibit 7).

Exhibit 7: Epidiolex trial data in Dravet and LGS

Indication	Doses tested	Number of patients	Average age	Average number of AEDs currently prescribed	Number of previously tried AEDs	Median baseline seizure frequency	Epidiolex seizure reduction	Placebo seizure reduction	p value	Dropouts due to AEs
Dravet	20mg/kg	120	10	3	4	13 convulsive seizures	-39% (20mg/kg)	-13%	0.0123	13%
LGS Trial 1	20mg/kg	171	15	3	6	74 drop seizures	-44% (20mg/kg)	-22%	0.0135	14%
LGS Trial 2	20mg/kg and 10mg/kg	225	16	3	7	85 drop seizures	-42% (20mg/kg), -37% (10mg/kg)	-17%	0.0047 (20mg/kg), 0.0016 (10mg/kg)	8% (20mg/kg), 1% (10mg/kg)

Source: GW Pharmaceuticals

Dravet syndrome is an extremely malignant form of childhood epilepsy that typically presents itself within the first year of life with prolonged febrile and afebrile, generalized clonic or hemiclonic epileptic seizures in otherwise normally developing children. Around 10–14% of Dravet patients end up dying, typically around the age of six or seven.[3] Besides the risk of death, by the time the children are teenagers they exhibit either severe or profound learning disabilities. In one study of 31 typical and borderline Dravet patients (14 were typical Dravet, 17 were borderline) who were

3 Sakauchi et al. 2011 *Epilepsia*, 52(6): 1,144–1,149.

followed until adulthood, 22.6% could speak no words at all, 29% could speak several words, 29% could make primitive conversation and 16.1% could make simple conversation and read to some extent. Only one (3.2%) with borderline Dravet could lead an independent life, although he developed psychosis.[4] The incidence of Dravet ranges from 1:20,000 to 1:40,000 births, which suggests an overall disease prevalence of 5,500 patients in the US and 6,700 European patients.[5]

LGS, like Dravet, is a rare form of epilepsy, although it typically starts later in life, at between two and eight years of age vs six months for Dravet. As with Dravet, outcomes are extremely poor for these patients, with 90% becoming mentally handicapped with a progressive reduction in IQ. The mortality rate is high, although the exact percentage varies based on the study and ranges between 3% and 25%.[6] Incidence estimates for LGS vary, but it accounts for approximately 2–5% of all childhood epilepsies. This suggests 16,000 pediatric patients with LGS in the US and 24,000 in Europe with prevalence potentially doubling if including adult LGS patients according to the LGS Foundation.

With regards to the total pediatric epilepsy market, it is estimated that 20–30%[7] of those treated for epilepsy are considered to be uncontrolled, with seizure free rates plummeting dramatically after failing the first drug. As the US pediatric epilepsy population alone is over 466,000 patients,[8] the uncontrolled pediatric population is between 93,000 to 140,000 in total. With an average annual price for Epidiolex at $32,500, this suggests a $3bn to $4.5bn addressable market in the US alone (note that in Europe the submission is under review with approval for Epidiolex expected around the middle of 2019).

As caregivers discuss the possibility of substituting cheaper, non-standardized grade CBD products for Epidiolex, it is important to remember the fate of ZYN002, a synthetic transdermal cannabidiol that was being developed for adult epilepsy patients with focal seizures by Zynerba. In its Phase II trial, the drug failed to show significance in any of the primary or secondary endpoints. While Epidiolex was able to show a ~40% reduction in seizure frequency in its three Phase III trials (in pediatric population), ZYN002 was only able to show an 18.4% reduction in the low dose and a 14.0% reduction in the high dose (both in adults). Simply put, not all CBD products are the same and with such high-quality data from GW, it has set a very high bar.

Cannabinoids in other approved indications

Marinol and Cesamet have been approved for chemotherapy-related nausea and a review of data from 23 trials indicates that cannabinoids are superior to placebo and approximately in line with other anti-emetic therapies, though the cannabinoids were associated with dizziness, dysphoria, euphoria and sedation.[9]

Both Marinol and Cesamet have also been approved to improve the appetite of those with HIV, which makes sense as smoking cannabis has been associated with 40% greater caloric intake.[10] In a review of four studies with 255 participants, one review concluded that “there was some evidence that dronabinol is associated with an increase in weight when compared to placebo. More limited

4 Akiyama M et al. 2010, *Epilepsia*, 51(6): 1043–1052.

5 Brunklaus A et al. *Brain* 2012: 135; 2329–2336.

6 Rijckevorsel, K. *Neuropsychiatric Disease and Treatment* 2008:4(6) 1001–1019.

7 French J et al., *Neurology* 2004;62;1261–1273.

8 Russ et al., *Pediatrics* 129, 2, February 2012.

9 Smith et al., Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy (Review). *Cochrane Database of Systematic Reviews* 2015, 11

10 Foltin et al., Effects of smoked marijuana on food intake and body weight of humans living in a residential laboratory. *Appetite* 11(1):1–14

evidence suggested that it may also be associated with increased appetite, greater percentage of body fat, reduced nausea and improved functional status."[11]

Sativex is also approved in 25 countries (though not the US) for spasticity due to multiple sclerosis (MS), a condition that affects approximately 60% of MS patients (there are an estimated 900,000 MS sufferers in the US according to the National Multiple Sclerosis Society and 400,000 in the EU according to European Union estimates). Data are mixed. In a large 337-patient trial sponsored by GW Pharma, on an intent to treat basis, Sativex improved the spasticity numeric rating scale score by 1.05 points, compared to 0.82 points for placebo (p=0.219), a not statistically significant result. However, in a per-protocol analysis, which excluded 21% of patients who had protocol violations, Sativex improved spasticity scores by 1.3 points compared to 0.84 points for placebo (p=0.035), a statistically significant result. None of the 15 other secondary endpoints were positive on an intent to treat basis but three were positive on a per protocol basis. Needless to say, Sativex's market adoption has been limited with only $30m in worldwide sales in 2018.

Cannabinoids for pain

After epilepsy, pain is probably the area with the highest quantity of evidence associated with the efficacy of cannabinoids and is simply an enormous market. According to the Centers for Disease Control, 20.4% of adults in the US (around 50 million people) have chronic pain, with around 40% of those (around 19.6 million people) experiencing high-impact chronic pain. In Europe, the prevalence of moderate to severe pain in the adult population is estimated to be similarly high at 19%[12] (around 80 million people). However, while pain is a very promising and large market for cannabinoids, the clinical data have been a little inconsistent. In a review of 28 studies covering 2,454 patients, the authors concluded "studies generally suggested improvements in pain measured associated with cannabinoids but these did not reach statistical significant in most individual studies".[13] In one of the few high-grade clinical trials in the space, which was sponsored by GW Pharmaceuticals, Sativex was tested versus placebo in 298 patients with pain due to diabetic neuropathy, but only showed a minor benefit that did not reach significance with a p value of 0.63. However, usage data from states that have legalized medical cannabis indicates that patients are using it for pain and this has led to less opioid use. In one survey of 244 medical cannabis patients in Michigan, cannabis use was associated with a 64% decline in opioid use,[14] a tremendous decrease that would speak to at least some efficacy for the drug. Also, in an analysis of Medicare Part D data, medical cannabis legalization was associated with a statistically significant 11.4% reduction in the use of prescription pain medication statewide.[15]

One of the most advanced programs belongs to Arena Pharmaceuticals, which is developing a full CB2 agonist for the treatment of pain associated with irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD), two highly prevalent indications. According to the International Foundation for Gastrointestinal Disorders, between 25 and 45 million people in the US suffer from IBS, while the Centers for Disease Control estimates that 1–1.3 million Americans have IBD.

11 Whiting et al., Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 313(24):2456-2473

12 Breivik et al., Survey of chronic pain in Europe: Prevalence, impact on daily life and treatment. *European Journal of Pain 10* (2006) 287-333

13 Whiting et al., Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 313(24):2456-2473

14 Boehnke et al., Medical cannabis use is associated with decreased opiate medication use in a retrospective cross-sectional survey of patients with chronic pain. *Journal of Pain* 17(6):739-744

15 Bradford et al., Medical Marijuana Laws Reduce Prescription Medication Use in Medicare Part D. *Health Affairs* 35, no. 7 (2016):1230-1236.

Around 30% of IBD patients[16] and 35% of IBS patients[17] receive opiates for their pain. The company conducted a 14-patient Phase IIa trial in adults with Crohn's disease where patients received either 25mg or 100mg three times daily. At peak effect, 85% of those with evaluable data at week four (13 of the 14 patients) and 100% of those with evaluable data at week eight demonstrated a greater than 30% change from baseline in their average abdominal pain scores (AAPS) with the data being consistent at both doses. Importantly, there were no psychotropic effects and no discontinuations due to adverse events.

Exhibit 8: Cannabinoid pipeline in pain

Company	Product	Generic name	Phase	Comments
Tetra Bio-Pharma	PPP001	Cannabidiol; tetrahydrocannabinol	II/III	Smokable cannabis pellets for cancer pain. Only data so far have been Phase I study in healthy volunteers. Phase III program ongoing.
Arena	APD371	Olorinab	II	CB2 agonist for the treatment of GI-based visceral pain. In a Phase IIa in 14 patients, 79% had clinically relevant reductions in pain at weeks four and eight. Preparing for Phase IIb.
Therapix Biosciences	THX-110	Dronabinol; palmitoylethanolamide	II	Dronabinol and PEA for chronic low back pain. No data yet. Phase IIa ongoing.
CMXTwenty	CMX-020	CMX-020	II	Oral and intravenous cannabinoid. Current status uncertain.
Tetra Bio-Pharma	PPP005	Cannabidiol; tetrahydrocannabinol	II	Cannabis oil for cancer pain. No data so far.
Intec Pharma	AP-CBD	Cannabidiol	I	Sustained release CBD for low back pain, neuropathic pain and fibromyalgia. In Phase I.
Intec Pharma	AP-THC	Tetrahydrocannabinol	I	Sustained release THC for low back pain, neuropathic pain and fibromyalgia. In Phase I.
Veritas Pharma	CTL-X	Undisclosed	I	Undisclosed cannabinoid product for acute pain.

Source: EvaluatePharma, company reports, clinicaltrials.gov

Cannabinoids in other neurological disorders

Cannabinoids have been tested in a variety of problems including Tourette's, anxiety and post-traumatic stress syndrome (PTSD), though the evidence of efficacy so far is rather limited as there have been few large trials.

Two small-scale randomized, controlled clinical studies have been performed examining dronabinol for the treatment of Tourette's. In the US, the CDC estimates that 138,000 children are diagnosed with the disease,[18] while the National Institute of Neurological Disorders and Stroke estimates that there are 200,000 children and adults with Tourette's.[19] The first study was a randomized crossover trial of 12 individuals, and it showed a 22% improvement in the Yale Global Tic Severity Scale (YGTSS), although it did not reach statistical significance.[20] However, a statistical improvement was seen for complex motor tics (p=0.015) and for patient reported symptoms (p=0.015). The second study examined 24 patients in placebo and dose escalation cohorts (ranging from 2.5mg to 10mg of dronabinol per day). It reached similar results, showing improvement in symptom ratings of motor tics (p=0.04) and patient reported symptoms (p<0.05), but failed to reach statistical significance in the overall YGTSS.[21] Also, in 2018, Therapix, which is combining dronabinol with palmitoylethanolamide (PEA), saw a 21% reduction in tic severity (p=0.002) in a trial of 16 Tourette's patients.

16 Burr et al., Increasing Prescription of Opiates and Mortality in Patients with Inflammatory Bowel Diseases in England. *Clinical Gastroenterology and Hepatology* 2018;16:534-541

17 Camilleri et al., Opioids in Gastroenterology: Treating Adverse Effects and Creating Therapeutic Benefits. *Clinical Gastroenterology and Hepatology* 2017;15:1338-1349

18 Tourette Syndrome (TS), Data and Statistics. *Centers for Disease Control and Prevention.*

19 Tourette Syndrome Fact Sheet. *National Institute of Neurological Disorders*

20 Müller-Vahl KR (2002) Treatment of Tourette's Syndrome with Δ9-Tetrahydrocannabinol (THC): A Randomized Crossover Trial. *Pharmacopsychiatry* 35, 57-61.

21 Müller-Vahl KR et al. (2003) Delta 9-Tetrahydrocannabinol (THC) is Effective in the Treatment of Tics in Tourette Syndrome: a 6-Week Randomized Trial. *J. Clin. Psychiatry* 64, 459-465.

In anxiety, in a 24-patient trial in which patients either received 600mg of CBD or placebo and then had to conduct simulated public speaking, the CBD arm saw a greater improvement in anxiety compared to placebo. This data is likely the basis of a 50-patient, eight-week trial being sponsored by Tilray studying CBD oil capsules in patients with anxiety. Data is expected in Q420. As a reminder, anxiety disorders are highly prevalent, with 19.1% of adults suffering from them on an annual basis according to the National Comorbidity Survey conducted by Harvard Medical School.

With regards to PTSD, in a trial in 10 Canadian military personnel in which the participants alternated between receiving Cesamet and placebo, patients on Cesamet saw a statistically significant reduction in nightmares (p=0.03) as well as a general improvement in Clinical Global Impression of Change (p=0.05) in seven of 10 patients compared to only two of 10 on placebo.[22] While small, this is an interesting signal as military-related PTSD is notoriously difficult to treat. Only 20% of military-related PTSD patients were effectively treated in previous SSRI studies (the current standard of care).[23] And if you count both civilian and military PTSD, it is a rather large indication. Based on the results of a national comorbidity survey, 3.5% of the adult population have PTSD.[24] Tilray is conducting a 42-patient trial of vaporized dried cannabis in patients with PTSD with data expected in Q220.

There is also some data related to using cannabinoids in the treatment of recurrent glioblastoma. In a 21-patient trial in recurrent glioblastoma sponsored by GW Pharmaceuticals, patients who received a combination of CBD and THC had an 83% one-year survival rate, compared to 44% for patients on placebo (p=0.042). Median survival was also 662 days in the CBD/THC combination group compared to 369 days for patients in the control arm. According to the Central Brain Tumor Registry of the United States, glioblastoma represents 15% of all brain and central nervous system tumors, amounting to approximately 11,000 new cases per year.[25] GW is continuing the program and Tilray is involved with a 30-patient glioblastoma trial for another CBD and THC combination product, TN-TC11G, with data expected around the middle of 2020.

The retail market

The market for legal cannabis has been growing very quickly and has a meaningful size, but it is a small fraction of its full potential. In the US, the legal cannabis market is estimated to have been $8bn in 2017 (both recreational and medical) by Ackrell Capital, an investment bank focused on cannabis companies. If the level of consumption per capita becomes similar in the states that recently legalized recreational cannabis to that seen in Colorado, the market could grow to $18.8bn in just a few years, as markets mature in these states alone. If there were a full legalization in the US, at Colorado per-capita usage levels, the US could potentially be an $88bn market. As a comparison, total alcoholic beverage sales in the US were $223bn in 2016 according to the Beverage Information Group. And these sales are likely to have a major impact on other industries, including the liquor industry. In a study of purchase data between 2006 and 2015, medical cannabis legalization by itself was associated with a 15% reduction in alcohol sales.[26]

22 Jetly et al., The efficacy of nabilone, a synthetic cannabinoid, in the treatment of PTSD-associated nightmares: A preliminary randomized, double-blind, placebo-controlled cross-over design study. *Psychoneuroendocrinology* 51:585-588.

23 Walter Alexander, Pharmacotherapy for Post-traumatic Stress Disorder in Combat Veterans, *P&T*, January 2012.

24 Kessler et al, *Arch Gen Psych* 2005;62:617-627

25 Ostrom et al., CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2008-2012. *Neuro-Oncology*, 17(suppl 4), iv1-iv62.

26 Baggio et al., Helping Settle the Marijuana and Alcohol Debate: Evidence from Scanner Data. *SSRN*.

Exhibit 9: Annual legal sales of cannabis in the US by market

Market	Annual sales
Total legal cannabis market in the US (recreational and medical, 2017)	$8.0bn
Total medical cannabis market (2016)	$4.7bn
California medical cannabis market (2016)	$2.7bn
Colorado (recreational and medical, 2017)	$1.5bn
Washington (recreational and medical, 2017 annualized)	$1.4bn
Oregon (recreational and medical, 2017)	$470m
CBD oil (2017)	$358m

Source: Ackrell Capital, LLC, New Frontier Data, Colorado Department of Revenue, Washington State Liquor and Cannabis Board, Hemp Business Journal.

While the illegal market was primarily focused on the buying and selling of cannabis flower product itself, the legal market has evolved into something more complex. Approximately half of product sold is still flower, but the rest is concentrate (vape, wax and shatter), edibles and pre-rolled (see Exhibit 10).

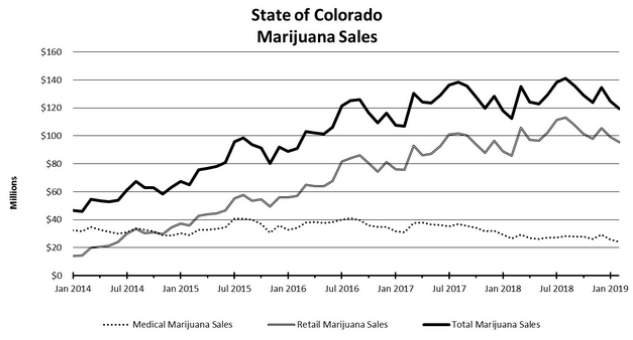
Exhibit 10: Market share of cannabis product types by state, 2017

	Flower	Concentrates	Edibles	Pre-rolled	Others
California	55	25	12	5	4
Washington	55	23	9	11	1
Oregon	51	22	14	7	6
Colorado	48	27	15	5	5

Source: Statista

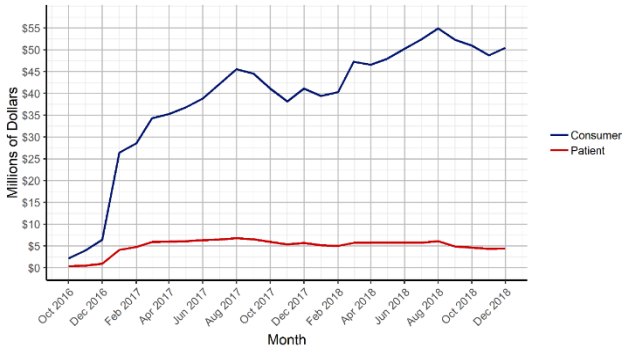
Also, the markets seem to mature quickly with the high growth phase lasting two to three years and then levelling off as outlets to purchase product have already become ubiquitous (see Exhibits 11 and 12). Another factor that might be curtailing sales growth in individual states is the feedback effect from legalization becoming more widespread in more areas of the country. Around 12% of cannabis use in Colorado is estimated to have come from tourists in 2017, with California being the largest home state for these visitors. Another important item to note is that medical cannabis sales tend to fall post-recreational legalization as medical prescriptions are no longer necessary. In Colorado, medical cannabis had represented 39% of legal sales two years after legalization but currently only accounts for around 20% of sales.

Exhibit 11: Colorado Legal Cannabis Sales (monthly)



Source: Colorado Department of Revenue

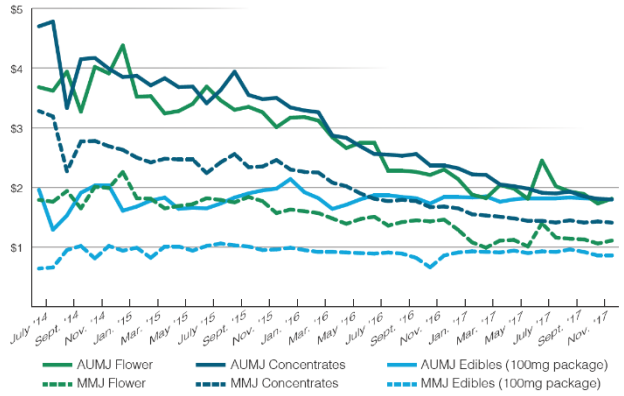
Exhibit 12: Oregon Legal Cannabis Sales (monthly)



Source: Oregon Liquor Control Commission

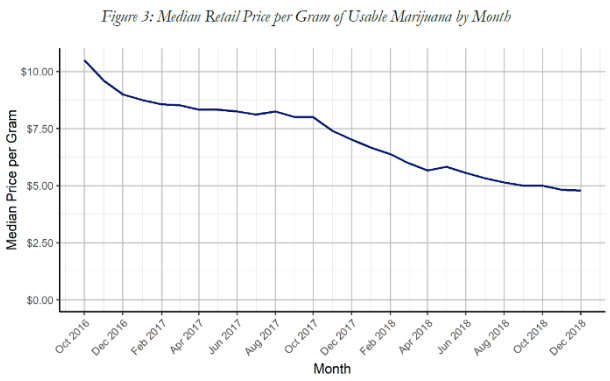
In addition, as more producers and retailers enter the growing cannabis market, prices have fallen precipitously (see Exhibits 13 and 14). In Colorado, according to the Colorado Department of Revenue, wholesale prices fell 47% from the beginning of 2017 to the beginning of 2019, while they fell by almost 40% in Oregon for indoor growers and over 50% for outdoor growers over the same period, according to the Oregon Liquor Control Commission. Oregon especially is facing a massive supply glut. Recreational producers harvested 2,000 metric tons of cannabis in 2018 with current inventory levels amounting to 6.5 years' worth of supply. The Oregon Liquor Control Commission estimates that if all pending producer applications were approved, production would nearly double, so there is probably no end in sight to the supply glut and falling prices.

Exhibit 13: Colorado Price per THC serving



Source: Colorado Department of Revenue

Exhibit 14: Oregon median retail price per gram



Source: Oregon Liquor Control Commission

This supply glut will make it more challenging for certain businesses and many will likely fail. However, just as we saw with the dot-com businesses, branding helps to separate the wheat from the chaff. The top five brands have 52% market share in California, 71% share in Colorado and 73% share in Oregon, according to BDS Analytics.

With regards to the CBD market, while historically it has been a relatively small proportion (~5%) of the overall cannabis market, it will likely get a boost by the removal of CBD derived from hemp (a cannabis plant with only trace levels of THC) from DEA scheduling thanks to the 2018 Agriculture Improvement Act, which was signed into law in December 2018. This removed federal restrictions on hemp-derived CBD but there are still state restrictions in place in certain states. There also is a move towards "CBD-infused" products though the FDA has recently reiterated that adding CBD to food and drinks is still not allowed. So while that market is growing, the industry is awaiting some regulatory guidance from the FDA, which will put it on firmer footing. A public hearing is currently scheduled for 31 May on the topic.

The size of markets outside the United States

While the US is clearly the key market for the cannabis industry due to its size and high rate of cannabis use, other markets are also quite meaningful. New Frontier Data estimates that the recreational cannabis market in Canada with reach $4.7bn by 2025. Prohibition Partners in its European Cannabis Report estimates that the recreational market size in Germany, Italy, France, Spain and the UK would total €41.3bn in 2028 if recreational cannabis were legal, and the medicinal market would be €36.5bn. However, please note that while the firm's European recreational market estimates are in the ballpark of what we would expect based on the size of their cannabis-using populations, its medicinal cannabis market assumptions are much higher than our estimates. Mature markets in the US where both recreational and medicinal cannabis are legal indicate that the recreational market would be much larger than the medicinal markets by a wide margin (in Colorado, medicinal cannabis is only 20% of the market).

Exhibit 15: Estimated size of key European cannabis markets in 2028 post-legalization

	Medicinal cannabis market value 2028 (€bn)	Recreational cannabis market value 2028 (€bn)	Total market value (€bn)
Germany	7.7	8.5	16.2
Italy	7.5	8.2	15.7
France	9.5	9.7	18.6
Spain	3	5.3	8.3
UK	8.8	9.6	18.4

Source: The European Cannabis Report, 4th Edition by Prohibition Partners

Then there is the question of whether cannabis will be legalized at all, as Europe has been behind North America in this respect. In Germany the biggest proponents are the Greens, who have 67

seats out of 709 in the Bundestag, although both the FDP (80 seats) and the Left (69 seats) have also voiced support for legalization. In July 2017, the Greens proposed the Cannabis Control Act, which would legalize recreational cannabis and create a regulated market on the supply side. With the CDU and SPD in a grand coalition, and unsupportive of legalization, reform is unlikely before a new federal election, scheduled for 2021. Currently the Greens are polling at twice their level in the last election and may become the second-largest party in Germany. If that happens, they may be able to form a government and work to legalize cannabis in the country.

For the other major countries in Europe, the chance of broad legalization is quite slim in the foreseeable future. In Italy, the Five Star Movement has called for legalization but its coalition partners are against it. Five Star has not made it much of a legislative priority, so legalization is unlikely in the near future. The next election is scheduled for 2023 but none of the other major parties or coalitions have come out for any major reform. Regulatory reform is also unlikely in France, Spain and the UK, where the Liberal Democrats are the only major party to back legalization but they have little chance of gaining power.

Taxes incentivize legalization

One major motivator for the recent legalizations has been to transform an illegal market into a legal one that could be taxed. There is significant pressure on countries to find new sources of revenue due to massive unfunded liabilities related to state employee pensions and retiree health benefits as well as servicing debts from prior budgets. They are also taking full advantage of the new legalizations as the states in the US that have legalized it so far have effective sales taxes of between 20% and 47% on sales.

Exhibit 16: State tax rates for recreational cannabis

	Year of commencement of recreational sales	Effective sales tax rate (total local + state taxes and fees)	Tax revenue ($m)
Colorado	2014	~29%	263.8 (2018)
Washington	2014	~47%	319.1 (2017)
Oregon	2015	~20%	78 (2017)
California	2018	30-45%	345.2 (2018)

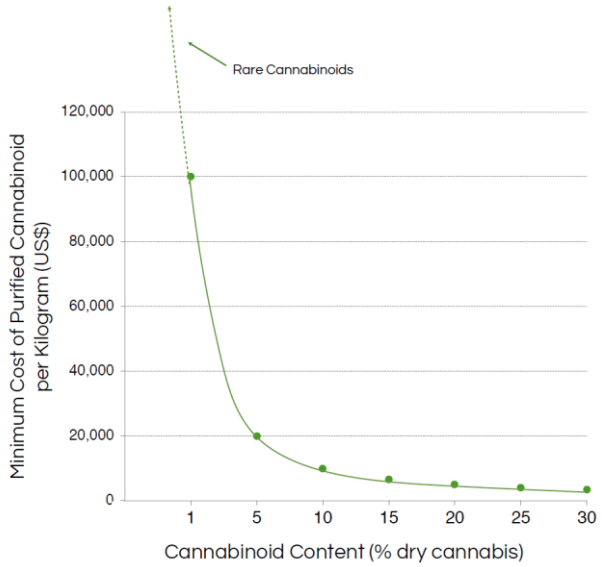
Source: Institute of Economic Affairs, Colorado Department of Revenue, California Department of Tax and Fee Administration

European countries also stand to benefit as they start with high baseline VAT rates of around 20% then could easily add a surcharge of 10–20% for cannabis sales. Germany, which could potentially have a €8.5bn recreational market, would see €3.3bn in added annual tax revenues if it adds 20% to its 19% VAT tax rate.

Is biosynthesis the future?

Current methods of extracting or manufacturing cannabinoids have some significant drawbacks. Plant-based extraction of cannabinoids is time consuming (three to 10 months just to cultivate the plant), which also requires a high degree of purification to remove unwanted pesticides, molds, fungi or bacteria, residual solvents and non-target cannabinoids. For example, it was noted during the FDA advisory committee meeting to discuss the potential approval of GW Pharmaceuticals' Epidiolex (CBD) for pediatric epilepsies that there was as much THC in its pharmaceutical-grade compound as some of the lower doses of dronabinol, an FDA-approved THC product. Also, it is not cost effective to extract the 100+ minor cannabinoids from plants, as cannabinoids that make up <1% of the plant cost over $100,000 per kilogram (see Exhibit 16) to produce.

Exhibit 17: Cost curve for extracting cannabinoids



Source: Cronos Group

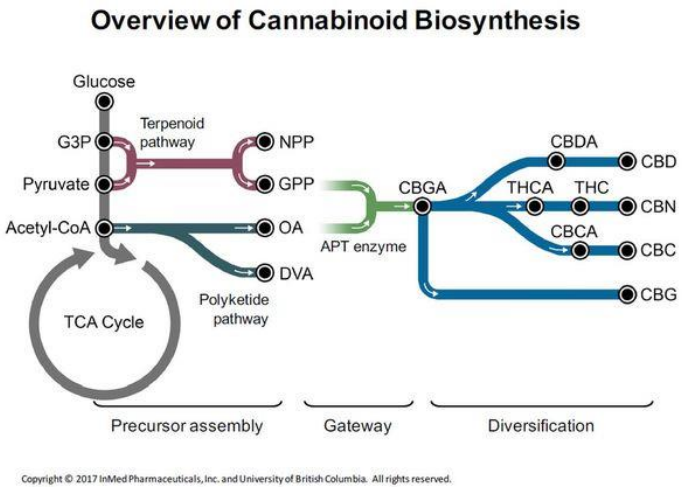
Chemical synthesis is not as time consuming as plant-based extraction but still takes weeks and has a purity problem as the process results in excessive waste and the creation of stereoisomers, which could affect the efficacy and safety of the product. Through biosynthesis, purer, more cost-efficient product may be created through cell culture bioreactions.

There are several key hurdles to reconstituting the biosynthesis of cannabinoids in a synthetic biologic system. The key enzymes for the production of cannabinoids and cannabinoid precursors must be introduced transgenically into the system. Also, although the molecular building blocks for cannabinoids are present in metabolic pathways outside of cannabis, sufficient quantities of these molecules must be generated to support cannabinoid synthesis at commercially significant levels. The key metabolic inputs for the formation of cannabinoids are geranyl pyrophosphate (GPP), a product of the terpenoid pathway common to all organisms, and olivetolic acid (OA), a polyketide product specific to cannabis. These molecules are condensed into cannabigerolic acid (CBGA), the key gateway compound for the biosynthesis of cannabinoids.

There are two main approaches to biosynthesis, one using *E. coli* and the other using yeast. Historically, CBGA biosynthesis in *E. coli* has been limited because CBGA synthase, the enzyme necessary to produce CBGA, has been difficult to express in this system and the concentration of the building blocks are low in the case of GPP and absent for OA. InMed has made several key innovations that have enabled CBGA biosynthesis in *E. coli*. The first and perhaps most significant was the development of a version of the CBGA synthase protein that expresses well in *E. coli* and is catalytically active. Additionally, the company developed a transgenic system to enhance the abundance of the GPP building block, which may increase the yield of CBGA approximately 10-fold. Finally, OA can be supplemented to the organism directly through the culture medium, abrogating the need to reconstitute its biosynthesis. By combining these elements, the company was able to achieve a yield of 14 µg of CBGA per ml of culture medium, which is likely to improve on optimization.[27] Currently, the company expects to initiate large-scale commercial batches in H220.

27 Kabiri et al., A stimulus-responsive, in situ-forming, nanoparticle-laden hydrogel for ocular drug delivery. *Drug Delivery and Translational Research* (2018) 8:484–495

Exhibit 18: Cannabinoid biosynthesis



Source: InMed

Besides InMed, there are a number of companies working on novel approaches to manufacturing cannabinoids. One is Teewinot Life Sciences, which raised a $12.3m Series B round in May 2017 and has patented a process to manufacture certain cannabinoids in yeast or *E. coli* (patent number 9,359,625), although data supporting its claims on *E. coli* are very limited. Teewinot uses two key enzymes (THCA synthase and CBDA synthase), made in a microorganism then extracted and used outside the cell in a bioreactor. This uses CBGA as a starting point. The system produces biologically active THCA, CBDA and CBCA. The CBGA input used for the process can be supplied using synthetic biology or chemical synthesis.

Another competitor is Librede, which holds a patent to manufacture cannabinoids in yeast (patent number 9,822,384). This is a full biosynthetic process possible because yeast is able to make higher-order enzymes and has the metabolic capability to feed enough starting materials to the cannabinoid biosynthetic pathway. However, this company has not yet scaled the process; although in 2018 it obtained a $1.4m US government grant to scale up the production of pharmaceutical-grade cannabidiol.

Other players in this space have made big announcements related to their entry but it is unclear at what stage they are at in developing a fermentation process. In September 2018, Ginkgo Bioworks announced a deal with Cronos Group in which Cronos will pay Ginkgo up to $122m to develop a biosynthesis process for eight target cannabinoids. Of this $22m will be to fund R&D and foundry expenses with the rest of the potential payout related to hitting milestones, namely achieving a production cost of less than $1,000 per kilogram at a scale of greater than 200 liters. It is unclear whether this is achievable due to the large amount of expensive inputs and recent data from InMed, which indicated that the yield from yeast[28] was a fraction of the yield from *E. coli*. In March 2019, Amyris announced a $300m agreement to produce cannabinoids in yeast with LAVVAN, a cannabis-focused company formed in February 2019 with undisclosed backing or capitalization. Intrexon, a well-funded company with a broad pipeline, announced in September that it has engineered a yeast strain to produce cannabinoids and has scaled the process "approaching commercially relevant targets" though no precise details are available.

28 Luo et al., Complete biosynthesis of cannabinoids and their unnatural analogues in yeast, *Nature* Volume 567, pages123–126 (2019)

The promise of other forbidden fruits in psychiatry

Cannabis joining the medical, scientific and regulatory mainstream has helped open the door for other drugs with a history of recreational use, specifically within mental health (although unlike cannabis, these drugs will need to be approved by the FDA through the standard process to be adopted). Ketamine has shown remarkably rapid efficacy in treatment-resistant major depression. Major depressive disorder is highly prevalent, with 6.6% of adults (around 13.1–14.2 million in the US) suffering from it every year.[29] Of those, 35% (around five million people in the US) have failed two courses of treatment and are considered treatment resistant. Historically there have been few approvals for treatment-resistant depression, with the only medical therapy being Symbyax (a combination of the antipsychotic olanzapine and fluoxetine) developed by Eli Lilly and approved in 2003. Otherwise, the only other approved treatments are electroconvulsive therapy and vagus nerve stimulation.

First synthesized by Parke Davis Laboratories (now part of Pfizer) in 1962, ketamine was approved by the FDA as an anesthetic in 1970 and also used in animal health. Its dissociative properties, which were of fast onset (~10 minutes) and short duration (one to two hours), caused it to gain popularity as a club drug. It works through N-Methyl-D-aspartate receptor antagonism. Interest in ketamine as a treatment for depression intensified after remarkable data from an 18-person trial using intravenous ketamine was published. It normally takes weeks for antidepressants to be able to show efficacy in patients, but ketamine was able to show statistically significant improvement over placebo just 110 minutes post-injection, with the responses remaining significant for a week. What made these data especially powerful is that these patients were very treatment resistant. The mean length of illness was 23.7 years, with the mean duration for the current depressive episode at 33.6 months and the mean number of lifetime antidepressants at 5.7.[30]

As ketamine itself is relatively old and available generically, it has not been viewed as an attractive development candidate by large pharmaceutical companies. This is why Johnson and Johnson instead developed the S-isomer of ketamine, esketamine, for treatment-resistant depression, this time as an intranasal formulation. It is unclear what the differences between esketamine and ketamine are in terms of efficacy, but it is thought to have milder dissociative effects, although administration is still needed in a clinical setting. It was approved by the FDA under the brand name Spravato in September 2018 and is expected to have $1.5bn in annual sales in 2024 according to Evaluate Pharma.

Another drug with historical recreational use that has potential in treatment resistant depression is psilocybin, the active ingredient in magic mushrooms. Psilocybin has been used for healing and divination in indigenous cultures of Central and South America for years but was only discovered by westerners in the 1950s.[31] It is thought to have efficacy in depression through 5-HT_{2A} receptor (part of the serotonin receptor family) agonism. In one trial in 12 treatment-resistant depression patients who had a mean duration of illness of 17.8 years, psilocybin exhibited a response rate of 67% one week after treatment and 58% of patients in the trial maintained their response for three months, with a three-month remission rate of 42%. In another trial of 75 healthy volunteers, patients receiving the higher dose saw significant improvement in their ratings of gratitude, life meaning and

29 Kessler et al., The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA*. 2003 Jun 18;289(23):3095–105

30 Zarate et al., A Randomized Trial of an N-methyl-D-aspartate Antagonist in Treatment-Resistant Major Depression. *Archive of General Psychiatry.* 2006;63:856–864.

31 Mithoefer et al., Novel psychopharmacological therapies for psychiatric disorders: psilocybin and MDMA. *Lancet Psychiatry*. Volume 3, Issue 5, P481-488, May 1, 2016

purpose and interpersonal closeness four months after their second and final dose.[32] Compass Pathways, a UK-based start-up backed by Peter Thiel (co-founder of PayPal and the first outside investor in Facebook) is enrolling a 216-patient Phase II trial in treatment-resistant depression patients with results expected in H120. Importantly, the FDA granted the program breakthrough therapy designation, meaning it will be providing "intense guidance" on the design of the clinical trial program. Note that if approved, psilocybin would need to be rescheduled from DEA Schedule I in order to be made available to patients and a case can be made for a downgrade all the way to Schedule IV[33].

Psilocybin has also had positive data in some small open-label trials in the treatment of addiction. In one study of 15 participants looking to quit smoking, 67% were confirmed as smoking abstinent, approximately double the rate of other smoking cessation studies.[34] Interestingly, 68.7% of participants rated their psilocybin experiences among the five most personally meaningful and significant experiences of their lives. In a 10-person trial in alcoholics, psilocybin treatment was followed by significant decreases in drinking days and heavy drinking days.[35] While some might question the wisdom of using one drug to ween off people off another, it is important to remember psilocybin is considered to have less abuse potential compared to other illicit substances as the reinforcing effects are marginal (with no withdrawal symptoms) and it is associated with a benign long-term safety profile.

Lysergic acid diethylamide (LSD), which is similar to psilocybin, has also showed promise. It was first synthesized in 1938 and its psychoactive effects were discovered in 1943 by Sandoz (now part of Novartis). LSD was part of psychotherapy in the 1950s, and became more common until LSD became illegal in 1966. Working through the 5-HT_{2A}, 5-HT_{2C} and $5HT_{1A}$ pathways it is thought to reduce anxiety and depression. In a study in 12 patients with anxiety associated with life-threatening diseases (mainly cancer), there was a statistically significant reduction in anxiety with results sustained for 12 months.[36]

The party drug 3,4-methylenedioxymethamphetamine (MDMA), also known as ecstasy, is under development for the treatment of post-traumatic stress disorder (PTSD) by the Multidisciplinary Association for Psychedelic Studies (MAPS), a non-profit research and educational organization. There have been several studies in PTSD that have shown MDMA can be helpful as it is thought to increase the emotional engagement necessary to process traumatic events. In one trial in 26 service personnel suffering from the notoriously difficult to treat military-related PTSD, 86% of the participants at the moderate dose (75mg) group and 58% in the high dose (125mg) group no longer met PTSD diagnostic criteria one month after therapy. Additionally, 100% of those in the moderate dose group and 67% in the high-dose group had over 30% decreases in the Clinician Administered PTSD Scale (CAPS-IV) total score after two active doses of MDMA.[37] In November 2018, MAPS started enrolling a 100–150 patient Phase III trial in people with severe PTSD across 14 sites, with a second Phase III trial of a similar size to be initiated after an interim analysis of the first trial. As

32 Griffiths et al., Psilocybin-occasioned mystical-type experience in combination with meditation and other spiritual practices produces enduring positive changes in psychological functioning and in trait measures of prosocial attitudes and behaviors. *Journal of Psychopharmacology* Volume 32 issue: 1, page(s): 49-69.

33 Johnson et al., The abuse potential of medical psilocybin according to the 8 factors of the Controlled Substances Act. *Neuropharmacology* 2018 142, 1-24

34 Johnson et al., Long-term follow-up of psilocybin-facilitated smoking cessation. *The American Journal of Drug and Alcohol Abuse*. Volume 43, Issue 1, pages 55-60

35 Bogenschutz et al., Psilocybin-assisted treatment for alcohol dependence: A proof-of-concept study. *Journal of Psychopharmacology* Volume 29 issue:3, pages 289-299.

36 Gasser et al., Safety and Efficacy of Lysergic Acid Diethylamide-Assisted Psychotherapy for Anxiety Associated With Life-threatening Diseases. *The Journal of Nervous and Mental Disease* 202(7): 513-520.

37 (Mithoefer et al., 3,4-methylenedioxymethamphetamine (MDMA)-Assisted Psychotherapy for Post-Traumatic Stress Disorder in Military Veterans, Firefighters, and Police Officers: A Randomised, Double-Blind, Dose-Response, Phase 2 Clinical Trial. *The Lancet Psychiatry*.

with psilocybin and treatment-resistant depression, the FDA has granted MDMA breakthrough therapy designation. As a reminder, based on the results of a national comorbidity survey, 3.5% of the adult population have PTSD.[38]

38 Kessler et al, *Arch Gen Psych* 2005;62:617-627

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