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Cannabinoid Market Snapshot:
GW's Epilepsy Success Bodes Well

▶ By Emily Hayes, November 25 2016

OVER 50 CANNABINOID DRUGS ARE IN development, most commonly targeting central nervous system diseases. Analysts think the relaxation of restrictions on medical cannabis is helping with perception problems, but so far there's little evidence the market isn't just smoke and mirrors.

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The market for pharmaceutical-grade cannabinoid drugs is looking brighter following the success of GW Pharmaceuticals PLC in a third pivotal trial in hard-to-treat forms of epilepsy.

UK-based GW Pharmaceuticals recently announced that its cannabinoid *Epidiolex* – which includes cannabidiol (CBD) but not the psychoactive tetrahydrocannabinol (THC) – hit efficacy endpoints with strong statistical significance in a study of Lennox-Gastaut syndrome, a rare and severe kind of child-onset epilepsy. (*Also see "Dravet Syndrome Indication Will Set GW Pharma Apart On US Epilepsy Market" - Scrip, 27 Sep, 2016.*)

Cannabinoids may be derived from cannabis plants (*see box for cannabinoids found in marijuana plants*) or produced synthetically to mimic nature.

This marked the third positive study for the drug, which is derived from the marijuana plant, following another positive Phase III trial in Lennox-Gastaut syndrome and a third study in Dravet syndrome. *(Also see "GW Succeeding With Cannabinoid Drug This Time Around" - Pink Sheet, 14 Mar, 2016.)* The company plans to file the drug for both epilepsy indications with FDA in a single appli-

Cannabis plants used to make Epidiolex

Some Types Of Cannabinoids

Tetrahydrocannabinol (THC): Cannabinoid responsible for psychoactive effects.

Cannabidiol (CBD): Non-psychomimetic cannabinoid.

Tetrahydrocannabivarin (THCV): Researched as treatment for metabolic disorders, including diabetes, as well as a potential appetite suppressant.

Cannabicyclol (CBL): Non-psychomimetic cannabinoid found in the Cannabis species.

Cannabinol (CBN): Mild-psychoactive cannabinoid that comes from degradation of THC

Cannabichromene (CBC): Bears structural similarity to other natural cannabinoids, including THC

Source: Cowen Research Cannabis Compendium Sept. 12 2016, from Indiegogo.com, MyDx.com

cation in the first half of 2017.

At least four pharmaceutical-grade cannabinoid drugs are approved.

- AbbVie Inc.'s synthetic THC product *Marinol* (dronabinol), first approved by FDA in 1985, is used for appetite stimulation in AIDS patients and as an anti-emetic for patients on chemotherapy.
- Mylan NV's *Cesamet* (nabilone) is a synthetic THC, also approved initially by FDA in 1985, for chemotherapy-induced nausea and vomiting.
- Insys Therapeutics Inc.'s *Syndros* (generic dronabinol) was approved by FDA in July for chemotherapy induced nausea and vomiting as well as wasting syndrome in AIDS patients.
- GW Pharma's *Sativex* (nabiximols) buccal spray, which includes CBD and THC and is derived from cannabis plants, is approved outside the US for spasticity associated with multiple sclerosis. Sativex is marketed ex-US through deals with a range of partners including Bayer AG and Novartis AG. GW also has a deal with Otsuka Pharmaceutical Co. Ltd. to develop Sativex in the US. Otsuka has been pursuing cancer pain as the lead indication for the drug. Sativex failed in three trials in this indication but the company said that the data showed positive outcomes for US patients and therefore that there was still potential. (*Also see "Cannabis Derivative Sativex 'Shows Promise In US Patients' Despite Further Phase III Failure" - Scrip, 29 Oct, 2015.*)

Moving On From The Past

Cannabinoids have a rocky history, but in a field that has been considered, rightly or wrongly, to be more of a lifestyle issue than serious disease – obesity. Sanofi withdrew an NDA for *Zimulti* (rimonabant) in 2007 after an FDA panel unanimously voted against approval in 2007 (*Also see "Sanofi Withdraws Zimulti NDA For Weight Loss" - Pink Sheet, 29 Jun, 2007.*) The drug was withdrawn from the European market within a few years in light of psychiatric side effects, which had a damaging effect on other drugs in the same class being tested for weight loss. (*Also see "Death knell sounds for CB1 antagonists" - Scrip, 6 Nov, 2008.*)

The focus of development in more recent years has been on conditions deemed to be more serious than weight loss.

In a December 2015 report on the potential of medical cannabis published by Bank of America/Merrill Lynch, analysts noted that the market for these products is very small, with total estimated sales of $200m to $250m.

For the CINV and cachexia indications, cannabinoids face competition from "better drugs," and have side effects that limit use, the analysts noted.

Meanwhile, research into use of cannabinoids for spasticity has highlighted central nervous system effects (dizziness, somnolence and memory disturbance) as well as gastrointestinal events (increased appetite, nausea and vomiting).

"The risk of serious adverse psychopathologic effects was less than 1% but in our view important since THC is a known psychoactive agent," Merrill Lynch analysts noted.

"Altogether, this information in our view suggests that FDA-approvable cannabis-based products for MS spasticity in the US are buried beneath unclear data readouts, appropriately cautious regulatory speedbumps, unconfirmed mechanisms of action, and the lack of standardization protocols," the report stated.

Sativex use has been limited to use as a last measure for MS spasticity and is not recommended by the UK's National Institute for Health Care Excellence, the analysts added.

GW reported sales of $43m for the fiscal year ending Sept. 30, 2015. Still, the Merrill Lynch report notes that "although Sativex has achieved limited commercial success, it can be counted as a trailblazer among cannabis-based products approved for clinical use."

Perception Problem Up In Smoke?

The trial readouts from GW can act as a gauge for receptivity by FDA and the general public, analysts noted. GW's stock was trading at $68.46 at the start of January and much higher at $116 in the week of Nov. 21.

Association with recreationally used marijuana has been a negative for cannabinoid products, but "isolating cannabinoids from cannabis" could improve the percep-

tion, the Merrill Lynch analysts concluded.

"According to IMS, the 2014 US pharmaceutical market was over $400bn and the global market over $1tn. With a 1% market share, the cannabinoid therapeutics market would be $4bn in the US and $10bn worldwide," they said.

"Isolating cannabinoids from cannabis" could improve the products' perception, Merrill Lynch analysts say.

"We are in the infancy of what is about to happen on the pharma side of cannabinoid-based medications," said Robert Hunt, president of Teewinot Life Sciences, which has a technology platform that may be used for biosynthesis of cannabinoids to mimic nature's plants.

There are a wide array of uses and settings for these products. Cowen analysts noted in a Sept. 12 report that "the cannabis healthcare sector has expanded into several science-based business lines," including over-the-counter pain medications and sophisticated biotech treatments for a range of conditions, including epilepsy, diabetes, schizophrenia, glioblastoma, post-traumatic stress syndrome and Huntington's disease.

Development has benefited from the relaxation of restrictions on use of cannabis for medical cannabis research trials, the analysts noted.

"If this early pharmaceutical research is successful, and if OTC cannabis remedies and treatments begin gaining acceptance among consumers – one can imagine that medical cannabis will start to attract attention both from big pharmaceuticals as well as national retailers such as Costco, Target, Walmart, Walgreens and CVS," Cowen analysts concluded.

Epilepsy Opportunity

The epilepsy opportunity has captured the attention of investors and researchers.

"We think one of the most highly anticipated applications of cannabinoids in the clinic is for treatment of pediatric epilepsy," Merrill Lynch analysts noted.

In a white paper titled *Epilepsy's New Pipeline Drugs: Can They Meet The New Challenges?*, Citeline analyst Deborah Jeanfavre noted that the cannabinoid receptor is the second most popular target for drugs in development for epilepsy.

This suggests that these types of drugs potentially could be very important for the treatment of this disease and may have a large market, Datamonitor Healthcare analyst Sally Hannah said in an interview.

GW is among the companies at the forefront of development. It has a broad development program for Epidiolex, with clinical trials ongoing in Dravet syndrome, Lennox-Gastaut syndrome, tuberous sclerosis, epilepsy, ulcerative colitis, steatohepatitis and schizophrenia.

In their Cannabis Compendium, Cowen analysts observed that GW has developed one of the most sophisticated platforms in the world for producing cannabinoid-based pharmaceuticals, with a state of the art facility north of London, where it breeds special cannabis plants.

"The fact that GW's platform allows it to produce chemotypes with precise concentrations of various cannabinoids is important because most academic research has focused on THC rather than other cannabinoids and cannabinoid combination. Thus, GW is well positioned to unlock their potential," Cowen analysts said.

The company expects to provide a standardized, entirely pure formulation and no other parts of marijuana aside from CBD or impurities, CEO Justin Gover commented in an interview.

GW is setting up a commercial team under the leadership of Julian Gangolli, former president of Allergan PLC's North American pharmaceutical division. GW expects that it will need a team of 60 people in the US to reach the 4,000 to 5,000 physicians who treat epilepsy, Gover told *Scrip*.

The availability of medical marijuana has already generated huge interest in the epilepsy community, Gover said in an interview.

"What that means is that there is a high awareness level of this product already, even though it has not even been submitted to the FDA, within the epilepsy community and a lot of interest in this product from patients and their families," the exec said.

Cowen believes that Epidiolex is "perhaps the most valuable of the current cannabinoid programs" and that the drug will be approved and widely adopted in treatment refractory epilepsy. It projects sales of $250m worldwide in 2018 and $1.2bn in 2021.

Epidiolex is being targeted at orphan syndromes within epilepsy that are highly treatment-resistant, but GW and partner Otsuka are also developing a follow-on cannabidivarin (CBDV) candidate called GWP-42006 that is in Phase II for adults with partial seizures.

In addition to GW Pharma, Chandler, Ariz.-based Insys Therapeutics Inc. is developing a cannabidiol product for the orphan pediatric epilepsy indications of Dravet Syndrome and Lennox-Gastaut syndrome, but unlike GW this candidate is synthetic.

"The synthetic compound is not derived from marijuana, so it is pure CBD with no THC or other cannabinoid content. The synthetic formulation may be safer than plant-derived CBD because of its purity and ability to control pharmaceutical quality. The differences between synthetic and plant-derived cannabinoids however are not known," Merrill Lynch analysts commented in their report on medical cannabis.

Scanning The Pipeline

With so few drugs approved worldwide, there is a lot more room to develop and market cannabinoids, Datamonitor Healthcare analysts suggest.

According to the Pharmaprojects database, there are 53 drugs in development targeting cannabinoid receptors, of which 17 are in clinical development. There was a peak in development in 2008 and then the number of drugs decreased over a number of years until 2015. There was a sharp increase from 2015 to 2016, when the number of drugs increased from 23 to 53, analysts said.

Sanofi's CB1 agonist *Acomplia/Zimulti* (rimonabant) was approved as an obesity drug in the EU in 2006. The success of this drug in gaining approval probably triggered an interest in development that could explain the peak in 2008, Datamonitor's Hannah explained.

The number of cannabinoid drugs in development spiked from 23 in 2015 to 53 this year.

This could explain the sharp decrease of drugs in active development in the years following 2008, whereas the recent interest in cannabinoid drugs could be linked to its promise in the treatment of epilepsy and also an increasingly relaxed attitude towards medical marijuana, Hannah said.

Where Else Is There Potential?

Multiple sclerosis is another R&D target of interest for cannabinoid drugs.

In late September,Celgene Corp. paid $20m to exercise an option for ex-US rights to Abide Therapeutics Inc.'s first-in-class endocannabinoid system modulator, ABX-1431, for the potential treatment of neurological diseases, including multiple sclerosis.

According to Pharmaprojects, of the 17 cannabinoid drugs being studied in Phase I to III clinical trials, two are in Phase III.

These drugs are in development for a total of 40 indications, including epilepsy, multiple sclerosis disorders, pain and schizophrenia.

Out of 111 potential cannabinoids, drug development has mainly focused on only two – THC and CBD; THC for anti-nausea and appetite stimulation and CBD for anti-spasticity and epilepsy. One challenge with plant extraction has been getting cannabinoids in large enough quantities. But lesser known cannabinoids have great potential and their structure may be recreated through a biosynthetic process, Teewinot Life Science's Hunt said.

"There is still a tremendous amount of work to be done," Hunt said.

Cannabinoid Drugs In Development

Sponsor/Therapy	Description	Indications
GW Pharma's Epidiolex	21-carbon terpenophenolic compound found in cannabis sativa L. plant	**Phase III:** Dravet syndrome, Lennox-Gastaut syndrome, tuberous sclerosis, epilepsy **Phase II:** Ulcerative colitis, steatohepatitis, schizophrenia **Preclinical:** neonatal brain injury, infantile spasm
Insys' cannabidiol	Synthetic CBD	**Phase III:** Dravet syndrome, Lennox-Gastaut syndrome **Phase II:** Infantile spasm, cocaine addiction **Preclinical:** narcotic opiate addiction, cancer, neuropathy, schizophrenia, Prader Willi Syndrome
Zynerba Pharmaceuticals' ZYN-002	CBD delivered 1-2 times/day through the skin into the bloodstream via a clear, odorless gel	**Phase II:** Epilepsy, osteoarthritis **Preclinical:** Sex-chromosome abnormality/fragile X syndrome
Orphan Pharmaceuticals' nabilone	Fast-disintegrating tablet formulation of nabilone	**Phase II:** Neuropathic pain
GW/Otsuka's GWP-42002 and GWP-42003	Combo of THC and CBD	**Phase II:** Glioblastoma
Pier Pharmaceuticals' dronabinol	Low-dose proprietary formulation of dronabinol, synthetic derivative of naturally occurring substance in cannabis plant, delta-9-tetrahyrocannabinol or delta-9 THC	**Phase II:** Apnea, sleep disorder
GW's GWP 42004	Oral THC	**Phase II:** Antidiabetic
GW/Otsuka's GWP-42006	Cannabinoid extract featuring cannabidivarin (CBDV) as the primary cannabinoid under development	**Phase II:** Epilepsy (partial) Preclinical: Autism
Corbus' ajulemic acid	Orally bioavailable synthetic endocannabinoid mimetic drug, stimulating CB2 receptor	**Phase II:** Dermatological, cystic fibrosis, immunosuppressant
Axim Biotechnologies' MedChew RX	Chewing gum formulation of CBD (5 mg) and THC (5 mg)	**Phase I:** Multiple sclerosis, spasticity
Cmxtwenty's CMX-020	Analog of arachidonic acid targets CB1, CB2 and TRVP1 receptors	**Phase I:** Pain Preclinical: Arthritis, diabetes, musculoskeletal
Yissum with Hasidit ISA scientific and Kennedy Trust for Rheumatology Research	CBD	**Phase I:** Diabetes, arthritis, atherosclerosis, ulcerative colitis, cardiovascular, pain
Echo Pharmaceuticals' ECP0122A	New dosage form of CBD	**Phase I:** Schizophrenia
Abide Therapeutics'/ Celgene's 15 ABX-1431	First-in-class selective inhibitor of monoacylglycerol lipase (MGLL) which catalyzes the breakdown of the endogenous cannabinoid, 2-arachidonoylglycerol (2-AG), an endogenous ligand of the cannabinoid receptors CB1 and CB2, which are the molecular targets of THC	**Phase I:** First-in-human dosing study completed. Development under way for neurological diseases.
Arena's APD-371	Oral CB2 agonist	**Phase I:** Analgesic, musculoskeletal.

Source: TrialTrove