

INNOVATION SPOTLIGHT:



Medical Cannabidiol (CBD)



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There is an expanding list of ailments that cannabis and its derivatives are being used to treat. Chronic pain leads the field and has for some time (see first table). But variants of cannabis are also being used for treatment of primary disorders such as irritable bowel disorders, glaucoma, hepatitis, HIV/AIDS and some psychiatric disorders such as PTSD. It has also shown efficacy in secondary symptoms common to several disorders, such as nausea, loss of appetite, insomnia and seizures.

Figure 24
Global Market Shares of Medical Cannabis: Pain vs. All Other Uses, 2020 (%)

Use	2020 (%)
Pain (all types)	79.8
Other	20.2
Total	100

The current state of play with all legal and still illegal cannabis is beyond the scope of this white paper. Suffice to say, there has been widespread relaxing of both legal and emotional resistance to cannabis across the U.S., as well as sharp increases in research into the substance, its many derivatives and the corresponding cannabinoid receptors in the human brain. Just in chronic pain there were 98 publications in 2012; there were 282 in 2018. All of this research, of course, is leading to an increase in clinical trials associated with cannabis-based drug candidates. To date, there is only one natural cannabis derivative, GW Pharmaceuticals’ purified form of cannabidiol (CBD) called Epidiolex, that has been approved by the FDA. It is likely the dramatic increase in research will lead to more approvals for prescribed forms of cannabis.

In the meantime, we can look at the growth of the legal medical cannabis market as a guide. Recreational cannabis sales are ignored completely in this short report, but BCC Research has multiple full-length reports covering that aspect of the industry. From a high level, ALL of legal cannabis sales—recreational, medical, industrial—globally in 2020 are estimated at \$19.7 billion with a forecast of a 22% CAGR to reach \$47.2 billion by 2025.

So just focusing on medical cannabis sales, we see a large and rapidly growing industry. Of the states where medical cannabis is legal, we see a widely uneven adoption so far (see next table). Even states with similar populations can have wild discrepancy, see Colorado (5.4 million) versus Arizona (6.8 million).

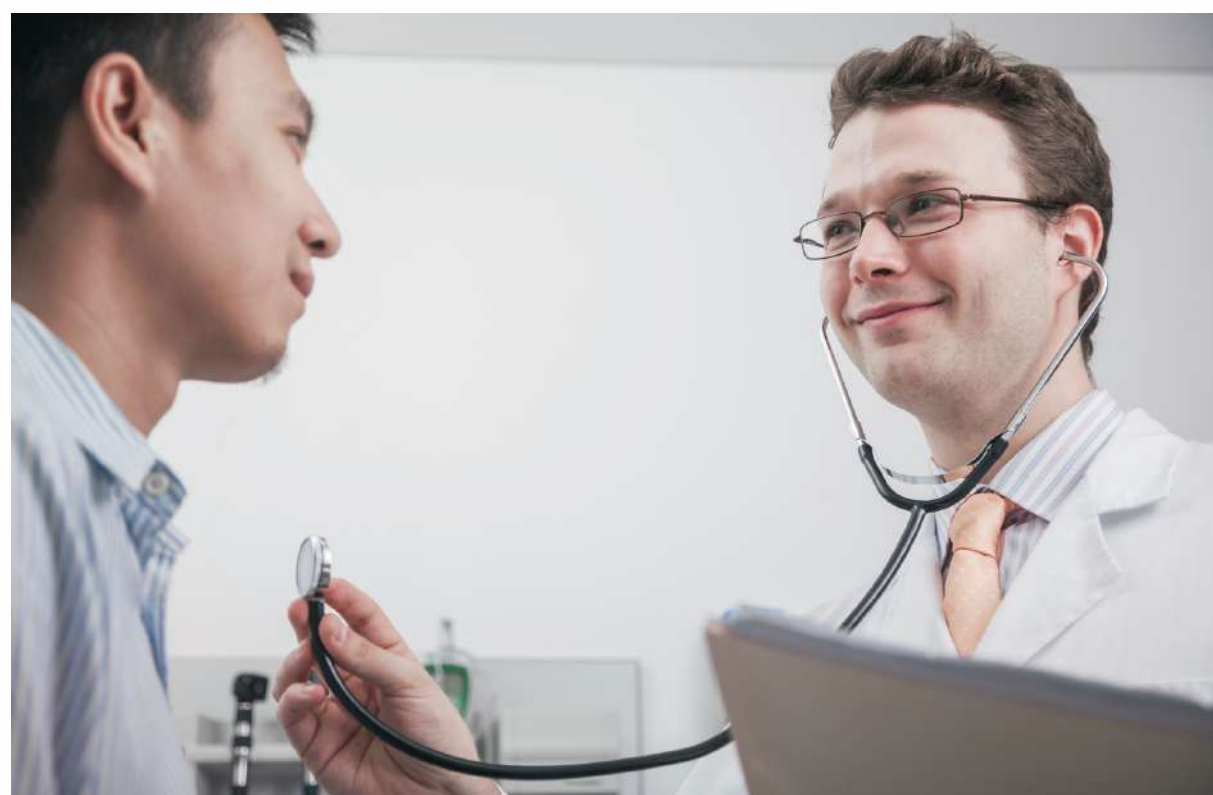


Sales of Medical Cannabis, by State, 2018
(\$ millions)

State	Sales
Washington	975
Oregon	502
California	2,756
Nevada	102
Arizona	406
Colorado	1,128
Montana	31
Minnesota	9
Michigan	633
Illinois	91
Florida	17
Massachusetts	106
District Columbia	17
New Hampshire	7
New Jersey	37
New Mexico	54
New York	40
Rhode Island	60
Connecticut	50
Delaware	7
Hawaii	17
Total	7045

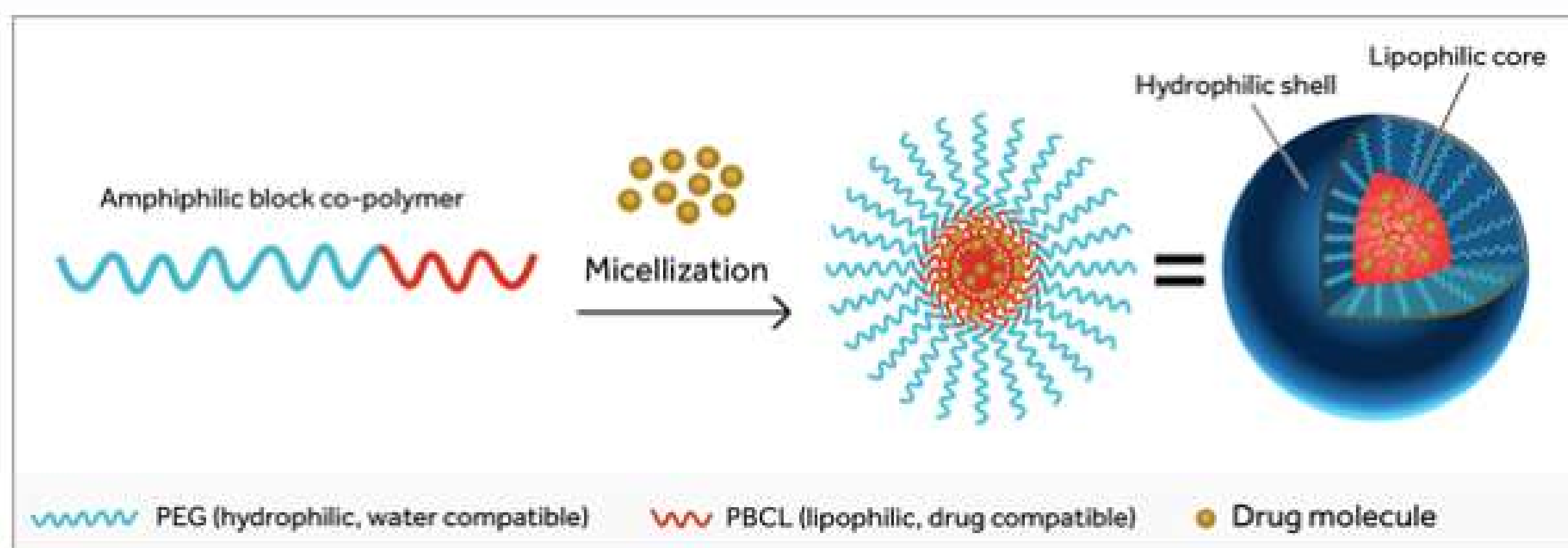


BCC's Interview With Cardiol's CEO, David Elsley



BCC likes to spotlight innovative players in the verticals we cover with our market research. Our Life Science team has been following medical cannabis for many years, and we feel our staff and our membership are well aware of the efficacy in certain medical areas, such as chronic pain. For this spotlight, we'd like to turn to cardiac disease—an area we admittedly were less aware of.

[Cardiol Therapeutics](#) is devoted to finding innovative treatments for heart injury and disease. Focused on the anti-inflammatory properties of cannabidiol, the company has developed a proprietary nanotechnology platform for the effective, targeted delivery of lipid-based APIs, like CBD, in the water-based bloodstream.



Initially focused on two conditions, heart failure and acute myocarditis, that are presently not curable and have the same standard of care over the last 20+ years, Cardiol has also filed a patent surrounding the treatment of COVID-19 patients with the aim of protecting them from heart complications commonly experienced as a result of infection. The FDA recently approved Cardiol's IND application, giving the company the green light for a combined Phase II/III trial investigating the efficacy of CBD in improving outcomes for COVID-19 patients with preexisting heart conditions and risk factors for those conditions. The company also completed a Phase I trial intended to support a separate Phase II trial of CBD as a treatment

for acute myocarditis. Acute myocarditis is a condition which may qualify for Orphan Drug Designation, and also happens to be a documented condition resulting from viral infections, including COVID-19.

Cardiol also launched its own pharmaceutical CBD product to the Canadian Medical Marijuana market. Much like aspirin and insulin are now synthesized in labs rather than derived from their natural sources, Cardiol is removing the uncertainty surrounding cannabis- and hemp-derived CBD by providing consistent, clean, THC-free CBD created in cGMP and FDA-approved labs.

BCC: Cannabidiol, or CBD, has been hailed anecdotally as a cure-all for everything ranging from sleep disorders to PTSD to chronic pain, usually without much data to back those claims. There is a growing body of research that aims to validate the therapeutic potential of CBD with real science. What have you seen to indicate CBD could be helpful in treating inflammatory cardiovascular conditions?

David E: There are many recent pre-clinical studies clearly demonstrating the anti-inflammatory properties of CBD. Here are a few links regarding the reduction of inflammation in [allergic asthma](#), [allergic contact dermatitis](#) and [diabetic cardiomyopathy](#).

In addition to CBD's anti-inflammatory properties, there is evidence that CBD is anti-ischemic, anti-arrhythmic and that it improves myocardial function in pre-clinical models of heart failure. We have also been conducting our own pre-clinical investigation in a non-ischemic model of heart failure, in which cannabidiol was shown to be cardio-protective by reducing cardiac hypertrophy, fibrosis and the production of certain re-modelling markers, such as cardiac B-type Natriuretic Peptide (BNP), which is typically elevated in patients with heart failure. These data were accepted for presentation at the American College of Cardiology's 69th Annual Scientific Session held virtually earlier this year.

BCC: Cardiol has developed its own CBD formulation, CardiolRx™, pharmaceutically produced in a Health Canada approved, FDA registered, cGMP facility in conjunction with Dalton Pharma Services. Why is a pharmaceutically produced CBD formulation so important for your research and development programs?

David E: The pharmaceutically produced CBD we use is 100% consistent and pure and is THC free. In terms of future regulatory approvals from major agencies such as the FDA, we feel our CardiolRx™ formulation and manufacturing process remove concerns regarding the stability and consistency of the medicine as we can ensure repeatable dosing, which is vitally important for patients. Our global exclusive partnership with Dalton Pharma, a world-class cGMP pharmaceutical facility, helps to ensure our ability to distribute CardiolRx™ internationally. Historically, many other organic compounds were discovered in a botanical source and then transitioned into pharmaceutical production (for example, aspirin found in willow bark) to ensure the consistency and cost effectiveness of the medicine. We have essentially done the same with CBD.

BCC: FDA recently approved your company's Investigational New Drug (IND) application to

commence a Phase II/III, double-blind, placebo-controlled clinical trial investigating the efficacy and safety of CardiolRx™ in 422 hospitalized COVID-19 patients with a prior history of, or risk factors for, cardiovascular disease (CVD). There is a growing amount of evidence that COVID-19 patients with cardiovascular issues often suffer worse outcomes than those without. What can you tell us about this trial and the doctors involved?

David E: As the pandemic progresses, we now see that somewhere between 30-40% of deaths from COVID-19 are attributed to cardiovascular complications. Of course, COVID-19 patients with prior history of, or risk factors for cardiovascular disease are much more likely to suffer from cardiovascular complications. We believe our extra-strength CBD formulation has the potential to provide a cardioprotective benefit in these high-risk patients.

We have assembled an independent Steering Committee of international thought leaders in inflammatory heart disease which has designed and will oversee the trial. It's an impressive group: Dr. Dennis McNamara (Chair), Professor of Medicine and Director of the Center for Heart Failure Research, University of Pittsburgh; Dr. Leslie Cooper (Co-Chair), Chair of the Mayo Clinic Enterprise Department of Cardiovascular Medicine and Chair of the Department of Cardiovascular Medicine, Mayo Clinic; Dr. Arvind Bhimaraj, Medical Director, Advanced Heart Failure, Mechanical Circulatory Support and Heart Transplant Programs, Houston Methodist Hospital; Dr. Barry Trachtenberg, Director, Cardio-Oncology and Cardiac Amyloid Programs, Associate Director, Mechanical Circulatory Support Program, Houston Methodist Hospital; Dr. Wilson Tang, Director of the Center for Clinical Genomics, Research Director and staff cardiologist in the Section of Heart Failure and Cardiac Transplantation Medicine, Cleveland Clinic; Dr. Peter Liu, Chief Scientific Officer and Vice President of Research, University of Ottawa Heart Institute; Dr. Carsten Tschöpe, Vice Director of the Dept. of Cardiology, Charité University Medicine Berlin, Germany; and Dr. Matthias Friedrich, Professor of Medicine and Chief, Cardiovascular Imaging, McGill University Health Centre.

The trial will take place at major treatment centers across the United States. Subject to study outcomes, our discussions with the FDA indicated that the design and scope of our Phase II/III trial may be used as a registration study in support of a New Drug Application. This is certainly an exciting development for our Company, and hopefully for the thousands of high-risk patients who become infected with COVID-19.

BCC: Cardiol also has completed a Health Canada-approved Phase I clinical study to assess safety, tolerability and pharmacokinetics of single followed by multiple day ascending doses of CardiolRx™ administered orally in up to 55 healthy adult subjects, both in the fasting and fed states. Can you talk about this study and how it relates to your planned Phase II acute myocarditis trial?

David E: This study was completed in December, 2020, and is believed to represent the first Health Canada approved study of a high concentration (100 mg/mL) cannabidiol formulation that contains virtually no THC (<10 ppm). The study measured standard safety parameters and the pharmacokinetics of CardiolRx™, including the degree of drug absorption and resulting

blood levels at escalating doses, and will provide important information to optimize dosing levels for our planned Phase II international trial in acute myocarditis.

Acute myocarditis is a leading cause of sudden heart death in younger people and is thought to affect around 73,000 people in North America. These numbers are in line with the requirements for

the FDA's Orphan Drug Program, which is designed to encourage and incentivize the development of treatments for indications affecting smaller patient populations. The European Medicines Agency also has a similar orphan medicines designation. The only other CBD treatment that has been approved to date was developed by GW Pharma under the Orphan Drug designation for rare forms of childhood epilepsy, so we know following this approach can be successful.

Our pending Phase II trial study in acute myocarditis patients has been designed and will be overseen by the same independent Steering Committee that designed our study in high-risk COVID-19 patients. There is an interesting connection between the two trials, as COVID-19 patients are at increased risk for developing acute myocarditis as a result of the immune reaction to the viral infection. Acute myocarditis is an inflammation of the heart tissue most commonly caused by a viral infection such as the flu, and the adverse effects of this inflammation can linger long after other symptoms of the virus dissipate.

Based on the large body of experimental evidence of the anti-inflammatory and cardioprotective properties of cannabidiol in models of cardiovascular disease, we believe there is an opportunity to develop a potential breakthrough therapy for acute myocarditis that would be eligible for designation as an orphan drug. There is currently no accepted standard of care for acute myocarditis.

BCC: In Canada, the medical cannabis community is very well established, and the country is seen as a regulatory role model for other nations interested in allowing cannabis for medical uses. Cardiol has found a unique niche for your own pure CBD product, Cortalex™. You recently introduced Cortalex™ across Canada through a partnership with Shoppers Drug Mart, the largest pharmacy chain in Canada, with over 1300 stores. How is Cortalex™ different from all the other oral CBD formulations? What benefits does it offer over other oral CBD formulations? How will the success of Cortalex™ be impacted by your research programs?

David E: Yes, this is a very exciting commercial opportunity for Cardiol that has been enabled by our dedication to developing what we believe to be the purest, most consistent cannabidiol formulation available today.

There is a growing demand from pediatricians and family physicians for a CBD formulation that does not contain THC, the psychoactive ingredient in cannabis. However, most CBD formulations currently available in Canada contain potentially psychoactive levels of THC and are therefore not appropriate for certain patient populations. This is of particular concern in

the case of children and young adults under the age of 25 where THC has been linked to a detrimental impact on brain development. It is also a concern in older individuals, such as those who do not wish to risk intoxication because of the requirements of their occupation, or seniors who might already have chronic diseases that limit coordination or cognitive function and who also wish to avoid intoxication. People over the age of 65 now represent the fastest growing segment of the over \$600 million medicinal cannabinoid market in Canada.

Cortalex™ is pharmaceutically produced exclusively for Cardiol by our global partner Dalton Pharma to the same rigorous cGMP standards set by the pharmaceutical industry to ensure the consistency and reliability of important medicines around the world. It contains less than 10 ppm THC, removing any concerns regarding intoxication. We believe the unique features of our product provide a significant market opportunity for Cortalex™ as we introduce it into one of the largest medicinal cannabinoid markets in the world, where current annual sales exceed \$600 million.

BCC: With decades of prohibition inhibiting research into CBD and similar cannabis-derived compounds, Cardiol is now in the vanguard of a new era of scientific discovery involving cannabinoids. How do you see the industry developing over the next few years?

David E: I expect we will continue to see an expansion of research efforts around the world aimed at generating valid scientific evidence through rigorously controlled clinical studies. I believe the fact that GW pharma has now developed an international pharmaceutical company valued at several billion dollars based on a CBD formulation to treat seizures associated with rare forms of childhood epilepsy, demonstrates the opportunity for companies who pursue credible clinical research strategies to address significant unmet medical needs. We are excited to be at the forefront of this important research effort in pursuit of new and potentially life-saving cannabinoid-based medicines.



What Does BCC See Ahead?

- Overall, the medical marijuana market is showing a positive, expanding trend, especially since the opioid crisis is forcing the pharma industry to consider marijuana a very viable alternative.
- In 2017, the medical cannabis market totaled \$7.3 billion, up from \$4.8 billion in 2016. This segment will likely achieve a 22.2% CAGR to reach nearly \$19.8 billion at the producer level in 2022 and will account for more than 80% of the global market.
- In addition, marijuana is also known for its other healing properties and this can be further developed into drugs for many other diseases. Indeed, scientists are also conducting preclinical and clinical trials with cannabis and its extracts to treat symptoms of other conditions and illnesses, such as: cancer chemotherapy effect; HIV/AIDS; multiple sclerosis, which causes gradual loss of muscle control, depression; PTSD; cardiovascular disease; and more.



Related BCC Research Reports

[Cannabis Market: Products, Technologies and Applications](#)

[Opioid Drugs: Global Markets to 2023](#)

[Non-opioid Pain Treatment: Global Markets to 2022](#)

[North American E-cigarette and Legal Cannabis Markets](#)

