



GUIDING RESEARCH AND REGULATION
FOR THE CANNABIS INDUSTRY

A glass dropper bottle containing a golden-brown liquid, likely CBD oil, is the central focus. It is surrounded by several vibrant green cannabis leaves. The background is a soft-focus bokeh of blue and green light. The entire scene is set against a dark blue gradient background that contains the title and author information.

Mainstreaming CBD Infused Food and Beverages; An Overview of Cannabis

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Food and beverages containing cannabidiol or CBD seem to be everywhere. But is any of this legal? You would think so given the number of products in the market and the 2018 Farm Bill that legalized hemp at the federal level. However, from the perspective of the Food and Drug Administration (“FDA”) and other federal agencies the answer is no, with a few limited exceptions. The lack of clear regulations from the FDA makes it difficult for major consumer packaged goods companies to enter this market and meet the surging demand by the public for CBD infused food and beverages. This article provides an overview of cannabis (the plant from which CBD is derived), including its physical properties and purported health benefits. A follow-up article discusses the FDA and federal regulatory framework relevant to CBD infused products going mainstream.

The Cannabis Plant

There are three species of the cannabis plant: cannabis sativa, cannabis indica and cannabis ruderalis.

Cannabis Sativa

Cannabis sativa is a species of cannabis that most persons associate with this plant. Sativa was first described by Karl Linnaeus, who named it Cannabis sativa L, with the L referring to his surname. It grows naturally in tropical regions, such as Central America, Africa and Asia, and has long and thin leaves. Sativa grows the tallest among the three species, often reaching several feet in height.



Cannabis Indica



Cannabis indica leaves are shorter and bushier. Indica grows in arid, mountainous regions, such as the hilly regions of Afghanistan and India.

Cannas Ruderalis

Cannabis ruderalis leaves have elements of the other two species; it is the smallest, hardiest and rarest of the three species.



Cannabis ruderalis grows in harsh climates and environments, primarily in northern hemisphere countries such as China, Russia and Poland.

Over time these three species have been inter-bred and today it is often hard to distinguish among them.

Cannabis has been used medicinally for thousands of years in Asia. It is thought to have been introduced to the Americas, first through the slave trade into South America,

and then from indentured Indian workers that were brought to Jamaica. Through the work of an Irish physician working in India, William Brooke O’Shaughnessy, who published several treatises on the efficacy of cannabis, by the late 19th century cannabis was widely used in the British and American medical community. However, the situation changed dramatically in the 1930’s. when cannabis became effectively illegal in the United States (more on this below).

Cannabinoids and Terpenes

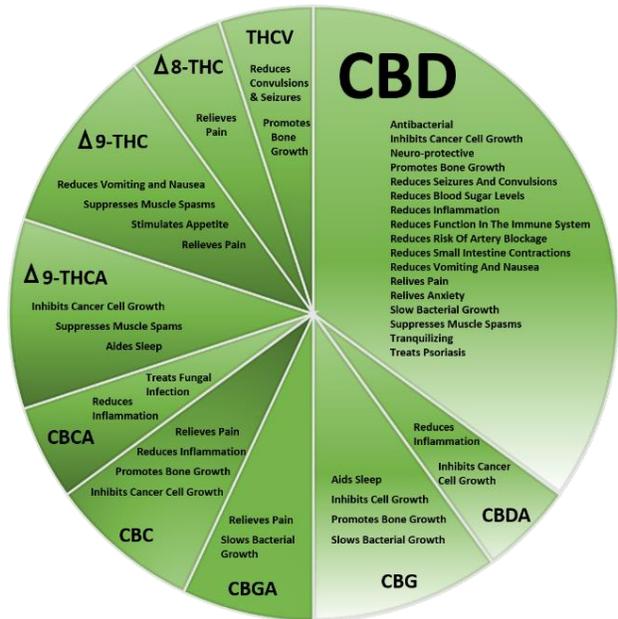
Cannabinoids

Compounds found in the cannabis plant are called “cannabinoids”, and more than 100 of them have been identified. While much has been learned in recent years about the science of cannabinoids, we are still in the early stages of understanding how cannabinoids interact with human and animal bodies.

The two most prolific cannabinoids are delta-9 tetrahydrocannabinol (“THC”) and cannabidiol (“CBD”), which were discovered in the early 1960’s by a Bulgarian-born Israeli chemist, Raphael Mechoulam. THC contains the psychoactive compound that results in users having the sensation of being high; CBD, when ingested by itself, will not get a user high. Both THC and CBD are thought to have medicinal benefits, including in the areas of anti-anxiety, anti-bacterial, anti-cancer, anti-depressant, anti-inflammatory, anti-insomnia, anti-nausea, anti-spasm, appetite stimulation, bronchodilation, neuroprotection, bone-growth stimulation and pain relief.

Other non- psychoactive cannabinoids found in very small amounts in the cannabis plant include:

- *Cannabichromene (“CBC”)*: Believed to have medicinal benefits in the areas of anti-bacterial, anti-cancer, anti-depressant, anti-fungal, anti-inflammatory, anti-insomnia, bone growth and pain relief.
- *Cannabigerol (“CBG”)*: Believed to have medicinal benefits in the areas of anti-bacterial, anti-cancer, anti-depressant, anti-fungal, bone growth and pain relief.
- *Cannabigerolic Acid (“CBGA”)*: Believed to have medicinal benefits in the areas of anti-inflammation and pain relief.
- *Cannabinol (“CBN”)*: Believed to have medicinal benefits in the areas of anti-bacterial, anti-convulsive, anti-inflammatory, anti-insomnia and pain relief.
- *Delta-9-Tetrahydrocannabinolic Acid (“THCA”)*: Believed to have medicinal benefits in the areas of anti-cancer, anti-inflammatory and anti-spasm.
- *Cannabidiolic Acid (“CBDA”)*: Believed to have medicinal benefits in the areas of anti-cancer, anti-inflammatory and anti-nausea.



Terpenes

Cannabis also includes another group of over 100 compounds known as “terpenes,” which are responsible for the smell (such as citrus, berry, mint and pine) of each cannabis plant. Terpenes develop based on a variety of factors—the cannabis plant’s species, climate, soil type, fertilizer and the age of the plant. The most abundant terpene is myrcene, which has a musky smell. Other common terpenes are listed below.

Different terpenes are thought to have different effects, not unlike the differing effects that different cannabinoids are purported to have. It is believed that when particular cannabinoids and terpenes are consumed together, they have a greater combined and different effect than if consumed alone—what is commonly called the “entourage effect”. Additional research is ongoing to understand this effect better.

10 Common Terpenes Found in Cannabis				
Terpene	Aroma	Also Found In	Physical Effects	Medical Benefits
Linalool	Floral, Citrus, Spice	Lavenders, Citrus, Laurels, Birch	Sedating, Calming	Insomnia, Stress, Depression, Anxiety, Pain, Convulsions
Terpinolene	Pine, Floral, Herbal	Oregano, Cumin, Lilac	Sedating	Antibacterial, Anti-tumor, Antifungal, Insomnia
Phytol	Floral, Berry, Balsamic	Green Tea	None	Anti-oxidant, Anti-inflammatory
β-Myrcene	Cloves, Earthy, Herbal	Mango, Hops, Bay Leaves, Eucalyptus	Sedating, Relaxing	Anti-tumor, Anti-inflammatory, Spasms
Citronellol	Floral, Citrus, Rosy, Sweet	Geraniums, Rose, Citrus Rind	None	Antibiotic, Anti-inflammatory, Anti-tumor
Caryophyllene Oxide	Peppery, Spicy, Woody, Cloves	Black Pepper, Cloves, Rosemary	None	Anti-oxidant, Improves CB2 Receptor Uptake
α-Pinene	Sharply Sweet	Pine Needles, Orange Rind, Parsley	Memory, Alertness	Inflammation, Asthma
Limonene	Citrus, Bitter	Citrus, Juniper, Peppermint	Elevated Mood, Stress	Depression, Anxiety, Gastric Reflux, Antifungal
β-Caryophyllene	Spicy	Thai Basils, Cloves, Black Pepper	None	Antioxidant, Inflammation, Muscle Spasms, Pain, Insomnia
Humulene	Woody, Earthy	Hops, Vietnamese Coriander	Suppresses Appetite	Anti-inflammatory, Anti-Bacterial, Pain

The Human Endocannabinoid System

ECS System

The human endocannabinoid system (“ECS”) is a body-wide network that regulates chemical messaging among cells in order to ensure that bodily functions remain balanced and healthy, a process called “homeostasis”. When this balance is upset, normal bodily functions and processes are disrupted, which is thought to result in serious diseases and conditions such as arthritis, cancer, epilepsy, strokes and Alzheimer’s disease. The ECS is also an adaptogenic system, meaning that it plays a role in how our bodies respond to injuries and diseases. Many experts believe that the ECS system is involved, at least in part, in the development of most diseases because of its important role in inflammation and how it signals major systems in the body, such as the gastrointestinal tract and central nervous system, to perform.

Elements of the ECS System

Three principal components comprise the ECS, endocannabinoids, receptors and enzymes.

Endocannabinoids

Endocannabinoids are fat-rich molecules made by your body (“endo” the prefix means “inside”) and are like cannabinoids produced by plants (called “phytocannabinoids”). Two key endocannabinoids that have been identified are anandamide and 2-arachidonoylgly. The basic function of endocannabinoids is to provide what is called “retrograde signaling” to the body; meaning that, when activated, endocannabinoids signal the body not to overact to certain stimuli, which overreaction is thought to cause many diseases. Anandamide at proper levels in the human body is believed to reduce pain and

inflammation, relieve anxiety, promote nerve cell regeneration and reduce the proliferation of cancer cells. 2-arachidonoylglycerol has been associated with pain relief, suppression of vomiting, stimulation of appetite and inhibiting tumor growth.

Endocannabinoid Receptors

Endocannabinoid receptors are found throughout the body and, when body functions are off balance, endocannabinoids signal the ECS that it needs to take some action by binding to the receptors. The two main endocannabinoid receptors are CB1 receptors, which are primarily located in the brain and central nervous system, and CB2 receptors, which are primarily located in the peripheral nervous system outside of the brain, particularly immune cells. A person will have different experiences depending on which endocannabinoid and receptor bind together. For example, an endocannabinoid that binds to CB2 receptor in immune system cells might signal a body to reduce inflammation that is associated with an autoimmune disorder, while an endocannabinoid that binds to a CB1 receptor in a spinal nerve might signal the body to relieve pain.

THC acts directly on both CB1 and CB2 receptors; its activation of the CB1 receptors is what gives the sensation of intoxication and also feelings of anxiety. As discussed further below, CBD does not directly act on CB1 and CB2 receptors.

Other receptors that address specific needs of the ECS system include:

5-HT_{1A} Receptors: Located in the brain, like CB1 receptors, these receptors regulate pain, appetite, sleep and mood; together with the

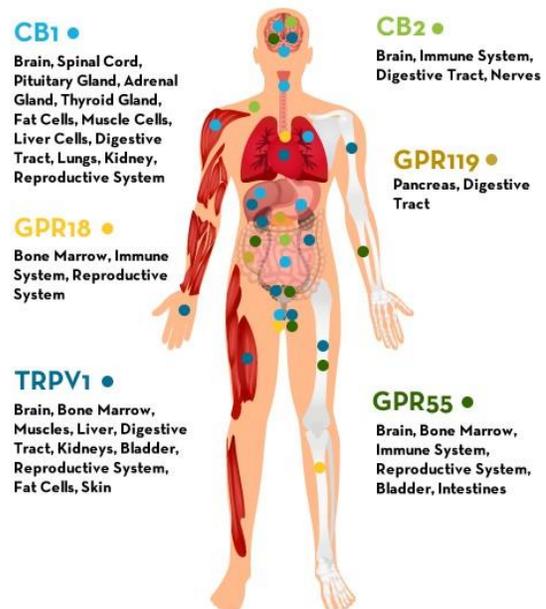
neurotransmitter serotonin, they also promote feelings of happiness.

TRPV-1 Receptors: Located outside of the central nervous system, like CB2 receptors, these receptors keep pain and inflammation in check and also monitor body temperature.

GPR55 Receptors: Located in the brain's cerebellum, these receptors regulate blood pressure, maintain bone density and guard against hypertension and osteoporosis.

GABA-A Receptors: Located in the central nervous system, these receptors regulate anxiety and are thought to protect against seizures.

ENDOCANNABINOID SYSTEM



Enzymes

Enzymes facilitate the interaction of endocannabinoids with the receptors when the ECS is off balance. When body balance is restored enzymes then break-down the endocannabinoids that were called upon to address a particular injury or disorder. The

two principal enzymes in the human body are fatty acid amide hydrolase, which breaks down the endocannabinoid anandamide, and monoacylglycerol acid lipase, which breaks down the endocannabinoid 2-arachidonoylglycerol.

Functioning of the ECS System

How efficiently a person's ECS system works (called the "endocannabinoid tone") depends on several factors: general health, genetics, diet, age and environmental stressors. Generally, a person with a healthy lifestyle has a more productive ECS system and is likely to have a high endocannabinoid tone. On the other hand, a person that is genetically disposed to a particular medical condition or has a poor lifestyle (smoking, overweight, etc.) is likely to have low endocannabinoid tone. A low endocannabinoid tone generally means that a person is deficient in endocannabinoids, which deficiency has been linked to a variety of medical disorders. For this reason, researchers have looked to boost endocannabinoid production (and consequently the functioning of the ECS system) by supplementing it with phytocannabinoids -- the plant produced cannabinoids such as THC and CBD--in order to boost receptor activity and restore the smooth messaging among cells. Researchers are also investigating how phytocannabinoid supplements, if used by healthy people, can keep in check inflammation, which can cause the development of autoimmune and degenerative diseases (discussed more below).

How THC and CBD Interact with the ECS

As discussed above, THC is among the two principal cannabinoids found in cannabis and is the compound that gets users high. Once ingested THC has powerful and varied effects on people because it binds to both the CB1 and CB2 receptors. For example, while ingested THC may benefit patients by reducing pain and stimulating appetite, it may also, for some patients, have the negative effect of increasing paranoia or anxiety. The other major cannabinoid, CBD, does not make users high and in moderate doses is thought to have no apparent short-term negative effects. While experts are still researching how CBD interacts with the ECS they do know that it does not bind to the CB1 and CB2 receptors directly in the same way that THC does. Rather, CBD is thought to interact with the body more generally and, through that interaction, indirectly activate the CB1 and CB2 receptors. Some experts think that CBD prevents or slows the breakdown of endocannabinoids, thus helping bodily functions to run more optimally. Other experts believe that CBD might be binding to receptors that have not yet been identified. In any event, CBD is believed to promote homeostasis, reduce pain sensation and decreases inflammation.

CBD the Medical Miracle?

CBD products seem to be everywhere. There is a dizzying array of CBD infused products; lotions to rub sore joints, oils to swallow, gummies, cookies and chocolates to eat, a variety of beverages to drink and soft gels and tablets. Many of these products are vague about what CBD can do but there are legions of articles, blogs, celebrity testimonials and news reports suggesting that CBD is a miracle drug that can cure countless conditions - epilepsy, arthritis, anxiety, sleeplessness, various types of pain, etc. Is it possible that one compound, comprised of a handful of molecules, is a miracle drug capable of treating a wide variety of seemingly unrelated maladies? Detractors would say no, pointing to the very limited number of scientific studies and the supposed far-flung benefits. Proponents, on the other hand, would say that many seemingly unrelated maladies are in fact connected by similar bodily dysfunctions and, by improving ECS tone through ingesting supplemental phytocannabinoids, body homeostasis can be improved, and diseases diminished.

What we know about the effects of THC, CBD and other cannabinoids comes from a number of sources: animal studies, an imperfect source of information since animals often react to chemicals different than humans; review papers, which analyze related studies to see if there is a consensus conclusion; observational studies, where scientists observe the health and behavior of groups of people; anecdotal evidence, which is based on the stories and experiences of individuals; and clinical trials, which evaluate under carefully controlled conditions the effectiveness of particular treatments. The most rigorous type of clinical trials is the double-blind placebo-



randomized controlled trial, meaning among a random group of people some will receive the treatment and others will not, but neither the scientists nor members of the test group actually know who has received the treatment. Based on the above some of the potential benefits of CBD and other cannabinoids are described below.

Inflammation and Autoimmunity

Inflammation is a healthy bodily response to an injury; for example, in response to a bruise a body will send special cells to protect the injured area. However, the existence of chronic inflammation has been associated with multiple diseases—cancer, dementia, heart attacks, depression and type-2 diabetes. Persisting too long, chronic inflammation could also lead to the development of an autoimmune disease; meaning that the body's immune system incorrectly sees its normal tissue as a threat and begins to attack it. Examples of these types of diseases include rheumatoid arthritis, multiple sclerosis, ulcerative colitis, thyroid conditions like Hashimoto's disease and skin conditions like eczema. CBD and other cannabinoids are thought to reduce inflammation by inhibiting cell proliferation and certain chemicals that cause inflammation, and also assist T cells, whose job is help the immune system distinguish between the body's own tissue and foreign elements.

Mental Health

Cells in the brain, called neurons, communicate with each other by releasing chemical messengers called neurotransmitters. The neurotransmitters then interact with various receptors in the brain, which shapes our emotions and moods. CBD has the ability to bind to the serotonin receptor in a way that can improve appetite, sleep, mood and pain perception. CBD has also been shown to slow cell activity in the brain, thus reducing anxiety.

Brain Health

CBD and other cannabinoids are believed to protect brain cells by reducing inflammation and free radical damage. Parkinson's disease, which is caused by low dopamine levels, may be helped by CBD, which might increase those levels. CBD may help prevent the formation of plaque that is thought to cause Alzheimer's disease.

Gut Health

When the walls of the small intestine become damaged due to poor diet, medications or stress, particles leak to the body and cause inflammation and other adverse conditions. CBD is believed to help repair this damage, increasing absorption of nutrients and stopping the leakage of particles outside of the small intestine.

Pain

The drug Sativex (with a 1:1 CBD to THC ratio) has been approved in Canada and Europe to treat certain types of pain that are

unresponsive to opioids. CBD has been shown to activate the TRPV receptor, which plays a role in inflammatory pain. Research shows that opioids and cannabinoids work very differently on the body and the use of them in combination shows promise.

Insomnia

While CBD is promoted as a treatment for insomnia, the evidence is somewhat unclear since CBD also has an energizing effect. It may be that CBD helps with insomnia caused by anxiety, since it has a calming effect on the mind.

Seizures

As discussed below, GW Pharmaceuticals has an FDA approved drug, Epidiolex, for the treatment of seizures associated with two rare forms of epilepsy, Lennox-Gastaut syndrome and Dravet syndrome. Epidiolex is an oil-based extract from the cannabis plant that is purified to be 99% CBD. Other pharmaceutical companies are developing synthetic CBD to treat epilepsy.

Cancer

Studies are being conducted that appear to show that CBD both slows the growth of cancer cells and increase their rate of death. How this happens is still being studied but is believed to be related to the overall anti-inflammatory nature of CBD. The use of cannabis in alleviating the side-effects of cancer treatments has also been popular.



Hemp and Marijuana

While the terms hemp, marijuana and cannabis are often used interchangeably, each term has a different meaning. As discussed above, cannabis is the term that describes all three species of the cannabis plant, namely cannabis sativa, cannabis indica and cannabis ruderalis.

What is Hemp?

Hemp is a form of the cannabis sativa species that does not give users a ‘high’ sensation. This is because this species of cannabis sativa contains high levels of CBD and low levels of the intoxicating compound THC. Federal law currently defines hemp as cannabis plants containing less than 0.3% THC by dry weight. This quantity is nowhere near enough to get a user high.

Industrial Hemp

There are two types of hemp. One type, industrial hemp (which has long stalks and grows tall), has been used for over 10,000 years for a variety of industrial purposes: the cellulose rich fibers of the plant stems have been used to make a variety of items such as paper, clothing, fabric, textiles, rope, bedding, absorbents, particle board, ceiling panels, compost and other building materials; hemp seeds, which are rich in

protein, dietary fiber, vitamins and mineral and are a valuable source of food; and hemp leaves and flowers have been used to make oil. More recently, products using hemp derived CBD have been used for a variety of medicinal purposes.

Industrial hemp is a simple crop to grow in the wild since it is a hardy plant and does not require much care. Plants are grown close together, which forces them to grow straight up towards the sky and increases yield. Industrial hemp, which has both low CBD and THC content, is considered a poor source for producing cannabinoids since a lot of plant material is needed to produce a small amount of the end product. Also, hemp is a type of plant that absorbs lots of chemicals and heavy metals from the soil (called a “bioaccumulator”), and by using more plant to produce cannabinoids there is the risk of getting higher concentrations of contaminants in the end product.

Therapeutic Hemp

Sitting between industrial hemp and marijuana described below is therapeutic hemp or hemp flower. These plants look similar to industrial hemp but have a flower at the top (like marijuana), where the CBD resides in higher concentrations than the

stalk and is easier to extract in large quantities. Hemp flower can be thought of as marijuana with the THC being bred out of it so less than 0.3% THC by dry weight remains.

What is Marijuana?

Marijuana, unlike hemp, is a variety of cannabis that contains low levels of CBD (often less than 1%) and high levels of THC, on average 5%-20% and sometimes up to 30%, which makes it a very potent way of giving users an intoxicating high. Marijuana can be a cross-bred mixture of all three cannabis species while hemp is always part of the cannabis sativa species.

Marijuana, unlike hemp, is not useable for industrial purposes; it can be smoked recreationally, to get high, or be used (as with the case of CBD) medicinally for therapeutic benefits. Since hemp is essentially all CBD and marijuana contains a mixture of THC and CBD, some believe that marijuana has more varied and impactful medicinal uses than hemp because it combines the chemicals and terpenes of multiple compounds (the “entourage effect” discussed earlier). What is important to note, though, is that regardless of how CBD is produced (hemp v. marijuana) it has the same effects, although the legal treatment as discussed below is very different.

Buying Marijuana and Hemp is Confusing

While hemp and marijuana have a clear botanical and, as discussed below, legal difference, buying them in a store can be confusing. For example, most marijuana that is bought in a dispensary will claim to have the therapeutic properties of CBD but will likely also contain enough THC to cause



intoxication. Dispensaries also use “sativa” and “indica” to describe the effects of the THC compound; a relaxing nighttime product may be labeled “indica” and an energizing daytime product may be labeled “sativa”. On the other hand, hemp-CBD products are often not labeled as such but only state that they are rich in CBD and have 0.3 percent or less of THC. Studies have shown that the amount of THC and CBD in products varies greatly from the amounts that they are purported to contain.

Consuming CBD

There are several ways to consume CBD.

Vaporizers and Smoking

Vaping and smoking are the most efficient ways for ingesting cannabis. A vaporizer heats the CBD oil in a fine mist that is inhaled. Many people think vaping is safer than smoking since there is no combustion and related release of toxins, as is the case when plant material is burned. The overall safety of vaping has been the subject of much recent discussion. The effects of vaping or smoking is detectable in the bloodstream within a few seconds, reaching peak concentrations in the bloodstream in six to seven minutes.

Sublingual Oils and Sprays

Tincture bottles (like the one on the cover of this article) typically contain CBD that is diluted with a healthy oil, such as olive oil, which helps with the absorption into the body. The correct dose is dropped under the tongue (where the dose is absorbed through mucous membranes) and after waiting about 60 second swallowed. The effects are typically felt between 5 and 20 minutes after ingestion. Spray products can also be used to spray CBD under the tongue. Peak blood concentrations are reached generally within 4-5 hours after ingestion.

Edibles

CBD oils, again mixed with a healthy oil, is added to a food or drink. The effects here are the slowest, since the CBD must be broken down by the digestive system, but those effects generally last the longest. Maximum levels of CBD in the blood are often reached in two hours, but some studies indicate that it can take up to 7 hours to reach those levels. Most people will not notice any profound effect of ingesting CBD by this method because of the slow rate of absorption and long-lasting effects.

Topicals

Topicals in the form of creams and various ointments are the least efficient way to absorb CBD. Indeed, there are questions as to the extent, if any, that topicals are absorbed in the body. Topicals are typically used to treat skin conditions such as psoriasis and inflammatory ailments like osteoarthritis.

Capsules

Capsules, like edibles, are absorbed more slowly.

There are still many questions as to the purported health benefits and safety of consuming food and beverages containing CBD. There is also a significant lack of consumer knowledge about CBD notwithstanding the countless anecdotal stories about its effects. Having said all this, there is a huge demand for these products that is not being met because of the lack of regulatory guidance from the FDA and other federal agencies. This situation needs to change. This article provides the background and basis for informed discussions, among relevant private industry and regulatory stakeholders, to agree on a framework for CBD to be included in food and beverages.

This article was prepared by Jeffrey L. Dunetz and Sheri L. Orlowitz, co-founders of the Council for Federal Cannabis Regulation (“CFCR”). The CFR, an Internal Revenue Code 501(c)(3) and 501(c)(4), serves as a forum in which stakeholders -- both from the federal government and industry -- can analyze and support the creation of informed federal regulations to govern the cannabis industry. CFR is currently focused on working with the FDA to mainstream the use of CBD and other hemp constituents.

