



July 12, 2019

Amy P. Abernethy, MD, PhD
Principal Deputy Commissioner of Food and Drugs
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: FDA-2019-N-1428: Scientific Data and Information about Products Containing Cannabis or Cannabis-Derived Compounds; Public Comment

Dear Deputy Commissioner Abernethy:

The Epilepsy Foundation is pleased to submit comments on the Food and Drug Administration's (FDA) request for *Scientific Data and Information about Products Containing Cannabis or Cannabis-Derived Compounds*. We are encouraged by the FDA's public process regarding regulations on cannabis and cannabis-derived compounds, including cannabidiol (CBD), to ensure that products on the market are safe, reliable, and properly tested, but urge the agency to allow these products – particularly those with therapeutic levels of CBD – to remain available and accessible for those in the epilepsy community who rely on CBD.

The Epilepsy Foundation is the leading national voluntary health organization that speaks on behalf of the at least 3.4 million Americans living with epilepsy and seizures. We foster the wellbeing of children and adults affected by seizures through research programs, educational activities, advocacy, and direct services. Epilepsy is a medical condition characterized by seizures, which are sudden surges of electrical activity in the brain, that affects a variety of mental and physical functions. Approximately 1 in 26 Americans will develop epilepsy at some point in their lifetime.

There is no "one size fits all" treatment option for epilepsy, and about a third of people living with epilepsy – approximately 1 million – suffer from uncontrollable or intractable seizures despite available treatments, with many more living with significant side-effects from medications. Uncontrolled seizures greatly impede quality of life and can lead to disability, injury, and even early death. Each year, about 1 out of 1,000 adults and 1 out of 4,500 children with epilepsy die from Sudden Unexpected Death in Epilepsy (SUDEP). This is why people living with uncontrolled seizures and their physicians turn to medical cannabis and/or CBD when other treatment options have failed.



The Epilepsy Foundation is committed to supporting physician-directed care, and to exploring and advocating for all potential treatment options for epilepsy, including CBD and medical cannabis. Individuals with uncontrolled seizures live with the continual risk of injury and loss of life. If an individual and their health care providers feel the potential benefit of medical cannabis and/or CBD outweigh any potential risks, then families need to have that legal option as well as meaningful access to products. Nothing should stand in the way of individuals gaining access to this life-changing and potentially life-saving treatment option.

Individuals in the epilepsy community with intractable or treatment-resistant seizures, in consultation with their treating providers, have relied on CBD products as part of their daily routine for more than a decade – before an FDA-approved CBD product came to market. While the majority of available products, save products that fall under state-regulated medical programs, have largely been unregulated, the Epilepsy Foundation strongly believes that the FDA should set up regulatory requirements for CBD products, including the obligation that companies comply with the *Dietary Supplement Health and Education Act of 1994*. The Foundation would also like to see more robust labeling requirements for these products that include information such as drug to drug interactions. When labels are accurate and reflect the nature of the substance, individuals are less likely to mistake CBD for a natural substance free from side effects and recognize the nature of the substance. When individuals are provided accurate information, they are more likely to include their treating provider in the decision to incorporate CBD into their routine. For the health and safety of individuals living with epilepsy, including those who are currently stable on commercial market CBD, regulations and safety mechanisms must be set up to ensure consistency in manufacturing and labeling among products while still preserving meaningful access for consumers.

Scientific and Anecdotal Evidence Show that CBD Can be an Effective Treatment for Some Individuals Living with Intractable or Treatment-Resistant Epilepsy

The epilepsy community is in a unique position when it comes to evidence that cannabis or cannabis-derived products, including CBD, works as a safe and effective treatment option for individuals living with epilepsy when used in consultation with their treating provider. It is currently difficult and expensive to conduct research into the medical benefits of cannabis or cannabis-derived products in the United States and the Epilepsy Foundation advocates for removal of these barriers to research. Despite the challenges, there are a number of evidence-based studies and reports demonstrating the efficacy of these products as it relates to epilepsy and seizures.

Over the past 10 to 15 years, there has been a resurgence of interest in cannabis and/or CBD as a treatment option for intractable epilepsy, in part due to media attention as well as the expanded access to these products through state-regulated medical cannabis programs and the



growing popularity of commercially-available CBD products that have been on the market, in some cases, for almost a decade.¹ Research into the medical benefits of cannabis and/or CBD is not a new endeavor, however. While there is a long historical record of the medical benefits of cannabis dating back almost 1,800 years,² more precise evidence-based studies have been conducted in both human and animal models for the past century. During the 1970s and 1980s, a number of studies were conducted on rodent models into the efficacy of CBD as an anticonvulsant property. Many of these studies reported promising findings including reduced seizure activity in rodents.³ Additionally, over the past decade, randomized controlled in humans with treatment-resistant epilepsy with several different epilepsy syndromes (most significantly, Lennox-Gastaut syndrome and Dravet syndrome) have shown definitive proof that CBD is a safe and effective treatment for some seizures.⁴

The epilepsy community benefits from being the only complex, chronic disease with the FDA-approved CBD product Epidiolex[®], resulting in data from rigorous randomized, double-blind placebo studies proving that CBD can be a safe and effective option for some individuals living with epilepsy and seizures. For this study, patients between the ages of 2 and 18 years of age from Dravet⁵ and 2 to 55 years for Lennox-Gastaut with treatment-resistant epilepsy were recruited.⁶ Dravet syndrome is a rare genetic epileptic encephalopathy (dysfunction of the brain) that begins in the first year of life and Lennox-Gastaut syndrome is a type of epilepsy with multiple types of seizures particularly tonic (stiffening) and atonic (drop) seizures. For the studies, a 2-week titration period was followed by 12 weeks of treatment at the target dose for a total of 14 weeks. Enrolled patients maintained a stable medication regimen (median of three anti-seizure drugs). Other treatments such as the ketogenic diet and VNS (when used) were kept stable for at least 4 weeks prior to the study. In patients with Dravet syndrome, a significant decrease in the median convulsive seizure frequency was seen in patients using Epidiolex[®] when compared with placebo within the first month, and the primary outcome

¹ Ex. <https://www.charlottesweb.com/helpcenter/faqs>; <http://haleighshope.co/meet-jason/>

² <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5345167/>

³ See Izquierdo I, Orsingher OA, Berardi AC: Effect of cannabidiol and of other cannabis sativa compounds on hippocampal seizure discharges. *Psychopharmacologia*. 1973;28(1):95–102; Izquierdo I, Tannhauser M: Letter: The effect of cannabidiol on maximal electroshock seizures in rats. *J Pharm Pharmacol*. 1973;25(11):916–7; Cox B, ten Ham M, Loskota WJ, et al. : The anticonvulsant activity of cannabinoids in seizure sensitive gerbils. *Proc West Pharmacol Soc*. 1975;18:154–7; Consroe P, Benedito MA, Leite JR, et al. : Effects of cannabidiol on behavioral seizures caused by convulsant drugs or current in mice. *Eur J Pharmacol*. 1982;83(3–4):293–8.

⁴ See Devinsky O, Cross JH, Laux L, et al. : Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. *N Engl J Med*. 2017;376:2011–2020; Devinsky O, Patel AD, Cross JH, et al. : Effect of Cannabidiol on Drop Seizures in the Lennox-Gastaut Syndrome. *N Engl J Med*. 2018;378(20):1888–97.

⁵ Devinsky O, Cross JH, Laux L, et al. : Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. *N Engl J Med*. 2017;376:2011–2020.

⁶ Devinsky O, Patel AD, Cross JH, et al. : Effect of Cannabidiol on Drop Seizures in the Lennox-Gastaut Syndrome. *N Engl J Med*. 2018;378(20):1888–97.



showed a median reduction of 38.9% in seizures compared to just 13.3% for those on placebo. Similarly, for patients with Lennox-Gastaut syndrome, the primary outcomes showed a 41.9% median decrease in drop seizures for those taking 20 mg/kg per day and a 37.2% median reduction for those taking 10mg/kg per day versus 17% for the placebo group. The Epilepsy Foundation is grateful that there is one FDA-approved CBD product, but it has a narrow indication and is not widely available for use. We have not seen evidence to suggest that this product differs chemically or medically from commercial brands – only that it is a purified version.

In 2017, the World Health Organization (WHO) Expert Committee on Drug Dependence released a review report on CBD.⁷ In the report, WHO states that it found no adverse health outcomes, and several medical applications for CBD, including “as an effective treatment for epilepsy.” According to the report, naturally occurring CBD is safe and well tolerated in humans and animals alike and is not associated with any negative public health effects. WHO experts further stated that CBD does not induce physical dependence and is “not associated with abuse potential.” In January 2019, the WHO Committee on Drug Dependence recommended that cannabis and cannabis resin be removed from the most restrictive drug schedule (IV), and that it was appropriate in light of evidence to completely remove “preparations containing predominantly cannabidiol and not more than 0.2 percent of delta-9-tetrahydrocannabinol” from the international drug schedule.⁸

As we await further research, trials and approvals, while products that are currently available on the commercial market have not individually undergone the same FDA drug approval process, we nevertheless have anecdotal evidence that these products work for some individuals living with intractable epilepsy,⁹ including for Laine and Lily¹⁰:

Lily is a 13-year-old Texan living with intractable epilepsy. Seven years ago, her development was on par with her peers, but that changed when Lily started having focal seizures up to 20 times a day. Lily’s seizures were very painful; she maintained consciousness and could feel every shock of pain during every seizure. Lily was initially able to gain seizure control with high doses of powerful medication. However, her seizure control came at the price of her once vivacious personality, leaving Lily lethargic and depressed. She lost all interest in

⁷ https://www.who.int/medicines/access/controlled-substances/5.2_CBD.pdf

⁸ https://www.who.int/medicines/access/controlled-substances/UNSG_letter_ECDD41_recommendations_cannabis_24Jan19.pdf?ua=1

⁹ Porter BE, Jacobson C. Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. *Epilepsy Behav.* 2013;29(3):574–577. doi:10.1016/j.yebeh.2013.08.037; see also <https://static1.squarespace.com/static/59aac7b5cd39c3b55f8a2b4a/t/5a8c5a7d24a6947bb6399f0f/1519147646491/AntiepilepticTreatment.pdf>

¹⁰ *Stories used with permission*



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the things she once loved and began to regress academically. This medication only worked for a short time before Lily started experiencing breakthrough seizures. Over the next five years, Lily, her family and her physicians experimented with heavier doses and new medications, but nothing seemed to work. Each breakthrough seizure was worse than the last and eventually evolved into focal seizures with impaired awareness. By the time Lily had her first brain surgery, she was having up to 50 seizures a day. Between 2011 and 2016, Lily tried every recommended therapy including 10 medications, 9 brain surgeries, vitamin therapies and a Vagus Nerve Stimulator (VNS), but nothing provided reasonable relief. By 2016 they were out of hope, out of medications to try, and out of options – until Texas passed a medical cannabis law for individuals living with intractable epilepsy. Under the supervision of their physician, Lily and her family tried CBD as a treatment option. While it took them around 9 months to find a dose that worked for her, it only took two weeks to notice that she was becoming more clear-headed and alert, but more importantly, that she was having fewer seizures. With the help of CBD, Lily now has less than 30 seizures a month, down from her most difficult period of over 1,000 seizures a month, and she is now able to attend school regularly.

Laine is a 17-year-old high school junior from Michigan living with drug-resistant Juvenile Myoclonic Epilepsy (JME) with three seizure types – generalized tonic clonic/grand mal, absence, and myoclonic. Laine was 13 years old when she was diagnosed in 2013, which began a multi-year search for a medication that would control her seizures. In 2015, Laine had her first grand mal seizure. Her family received concerning information from their physician: just one grand mal seizure could be fatal. From her diagnosis until 2017, Laine tried, and failed, on eight different pharmaceutical medications. Even worse, the medications that did not control her seizures also came with debilitating side effects including mania, chronic and debilitating stomach pain, skin lesions, loss of balance, confusion, and in some cases, an increase in absence seizure activity. In 2017, facing the reality of Laine’s drug-resistant epilepsy, her physician agreed for her to try CBD oil. On September 20, 2017, Laine began using CBD oil; three days later, Laine had her last grand mal seizure and has not had one since – a feat she was unable to achieve on existing FDA-approved treatment options.

There is No Viable CBD Alternative for Individuals Living with Epilepsy

Laine and Lily are just two anecdotal examples of how therapeutic levels of CBD can improve the lives of those living with drug-resistant or intractable epilepsy – but they are not alone. The Epilepsy Foundation frequently hears from families with similar stories, and those stories have



resonated with state lawmakers as well. To date, 34 states including the District of Columbia have comprehensive medical cannabis programs. An additional 12 states allow the medical use of low tetrahydrocannabinol (THC), high CBD cannabis products.¹¹ In many of these states, epilepsy and seizures have been at the forefront of the decision-making process, with families affected by epilepsy sharing anecdotal evidence and the benefits they have experienced in advocating for passage of these programs. Families in these states rely on the state-regulated medical cannabis programs, all of which require consultation with and supervision by the treating physician, to purchase products containing therapeutic levels of CBD. Should the FDA promulgate regulations disallowing products with therapeutic levels of CBD, many thousands of individuals will lose access to the only treatment option that works for them. As with any other medication or treatment option for epilepsy and seizures, individuals who suddenly lose access to an effective treatment will experience a significant decrease in quality of life and are at a greater risk of breakthrough seizures and related complications including accident, injury, and even untimely death.

We are extremely grateful that there is currently one FDA-approved CBD product on the market to treat seizures associated with two rare forms of epilepsy, but as mentioned above, this product has a very narrow indication and is therefore not widely accessible to the one-third of individuals living with epilepsy and seizures without seizure control. For individuals living with intractable epilepsy without a Dravet or Lennox-Gastaut diagnosis, access to Epidiolex® is virtually non-existent due to insurance and price barriers. Epidiolex® is generally not approved for insurance coverage for off-label use; if families wish to pursue this treatment option entirely out of pocket, it comes with a \$32,000 a year price tag – one that prices most families out of trying this treatment option. As such, while there is currently one FDA-approved product on the market, due to its narrow indication and price, it is not a realistic alternative for individuals to turn to should they lose access to the CBD products they are currently using.

Any Emergency or Interim Regulations Must Maintain Access for Individuals Living with Epilepsy

The Epilepsy Foundation appreciates the monumental task ahead of balancing public health needs – including for those living with epilepsy who currently rely on cannabis and/or CBD products – with evidence-based research in promulgating regulations. While we are aware that this will be a multi-year process, we urge you to carefully consider the impact on the epilepsy community should you publish interim guidance before a permanent regulatory framework can be finalized.

As with our request for permanent guidance, the Epilepsy Foundation insists that meaningful access to therapeutic levels of CBD must be preserved for those living with epilepsy and

¹¹ <http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx>



seizures and their physicians who currently rely on it. While we appreciate the FDA's role in ensuring products on the commercial market are safe and reliable for consumers, there is also a very real danger for individuals and families in removing these products from the market and turning the clock back on access. Any interim guidance that delays, removes, or impedes meaningful access to therapeutic levels of CBD is wholly unacceptable and can lead to worse health outcomes and can be fatal.

Conclusion

The Epilepsy Foundation urges the FDA to preserve meaningful access to cannabis and cannabis-derived products, including CBD tinctures with therapeutic levels of the cannabinoid, while creating a regulatory framework that ensures that there is consistency in available products, manufacturing, safety, testing, and labeling standards, and increase the availability of important information such as potential side effects and drug interactions so that consumers and practitioners may be better informed. We further urge you to carefully consider the danger individuals will face should they suddenly lose access to a treatment option that has proven effective for them when all other options have failed. Please do not hesitate to contact Abbey Roudebush, Senior Manager, Government Relations & Advocacy, at 301-918-3784 or aroudebush@efa.org with any questions or concerns.

Sincerely,

A handwritten signature in black ink, appearing to read "JF", positioned above the name and title of Jacqueline French.

Jacqueline French, MD
Chief Medical Officer
Epilepsy Foundation

A handwritten signature in black ink, appearing to read "Philip M. Gattone", positioned above the name and title of Philip M. Gattone.

Philip M. Gattone, M.Ed.
President & CEO
Epilepsy Foundation