GW Pharmaceuticals' Submission on Scientific Data and Information about Products Containing Cannabis or Cannabis-Derived Compounds

I. Introduction

Since our founding in 1998, GW Pharmaceuticals has been singularly focused on unlocking the potential of cannabinoids as medicines to address serious medical conditions with limited treatment options. With the approval of Epidiolex in 2018, GW became the only company to have brought an FDA-approved cannabis-derived therapy to patients in need. We have accumulated the most comprehensive body of scientific research on cannabinoids, including cannabidiol (CBD). We fully support FDA's thoughtful consideration of new regulatory pathways for consumer-focused products, especially those containing CBD, and will draw on our scientific research to assist this process.

As a result of GW's long-term involvement in cannabinoid research, we have a deep understanding of the promise that patients and their families see in cannabis-based products to treat intractable illnesses. The needs of patients motivated our efforts to research and bring Epidiolex through the FDA process. Many of the nearly 4,000 comments posted thus far to the docket are moving testimonials from individuals sharing their experiences treating serious ailments with unapproved cannabis drugs. As FDA undertakes the process of evaluating consumer-market pathways for CBD, we believe that the needs of these patients should be prioritized and addressed.

In opening the door for consumer-market CBD products, FDA risks further diminishing the likelihood that more cannabis-derived product will be developed into proven medicines for these patient. The exclusionary rule embodied in the Dietary Supplement Health and Education Act (DSHEA)—which FDA would have to waive for the first time ever before authorizing CBD consumer goods—was intended by Congress to protect medical innovation. Jeopardizing innovation incentives is a serious concern in any circumstances, but it is particularly concerning for cannabis products. That is so for several reasons:

(1) The cannabis plant holds promise to treat serious and intractable conditions, but without FDA-caliber research, its potential will never be realized, nor will its limitations ever be understood.

(2) Due to a variety of factors—including competition from unapproved products—incentives to develop and drive competition among FDA-approved cannabis medicines are weakened to begin with.

(3) Millions of Americans are self-treating serious and life-threatening ailments with unproven, inadequately regulated, and unapproved cannabis and cannabis-derived products.

GW supports a comprehensive federal framework for cannabis-derived products that brings more FDA-approved treatments to patients while also ensuring the safety of consumer products. Such a regulatory framework should 1) encourage the development of additional FDA approved medical products for serious and life-threatening diseases; 2) ensure that consumer products containing cannabis derivatives, including CBD, can be safely used in a mass-market setting without healthcare professional oversight; and 3) establish clear differentiation between FDA-approved medicines and consumer-focused foods and dietary supplements.

II. A comprehensive framework for cannabinoid products should operate to capture the potential of cannabis as a medicine and bring breakthrough therapies to patients

A. Epidiolex demonstrates the pressing need for more FDA-approved cannabis therapies

In June 2018, FDA approved Epidiolex, a pharmaceutical formulation of CBD, marketed in the United States by our subsidiary, Greenwich Biosciences, Inc. Three randomized, placebo-controlled trials demonstrated Epidiolex effective in treating seizures associated with two rare, pediatric-onset epilepsies—Dravet Syndrome and Lennox-Gastaut Syndrome (LGS).

The approval of Epidiolex brought a new treatment option to two patient populations in desperate need. No drug had ever before been proven safe and effective to FDA standards for the treatment of Dravet seizures. And not since 2011 had FDA approved a treatment for LGS seizures. LGS and Dravet are both highly resistant to therapy, have extremely high seizure frequency, and have high mortality rates, ranging from 7 – 18 percent before adulthood. This mortality rate is 14 times the mortality in the general pediatric population. The majority of deaths are epilepsy related, with Sudden Unexpected Death in Epilepsy (SUDEP) and status epilepticus (seizures lasting more than 5 minutes and requiring acute treatment) being the most common causes of mortality. Epidiolex trials showed that the drug was able to reduce seizure frequency for a significant percentage of patients and, more broadly, validated the potential for cannabis-derived products to treat certain serious medical conditions.

As with any medicine, with efficacy comes side effects, and Epidiolex's approval shed light for the first time on CBD's safety profile. Heralded as having great promise in the treatment of an incredible array of diseases and conditions, little was known about CBD's potential risks before completion of the Epidiolex studies. Before GW studied CBD in controlled trials, it was not known, for example, that CBD causes damage to the liver. Our pre-clinical testing identified signals of potential fetal toxicity. And our studies in healthy volunteers suggested that side effects like diarrhea and somnolence may occur even at low doses.

FDA's approval of Epidiolex set another precedent. It showed that cannabis-derived products can be shepherded through the FDA-approval process—that they can satisfy the same rigorous standards for proving safety and efficacy applicable since 1962 to virtually all other drugs in the United States. Hurdles to research unique to Schedule I products proved surmountable and successful trials were conducted in compliance with all applicable federal requirements.

GW began researching the medicinal potential of the cannabis plant in 1998. In the 21 years since, we have conducted over 50 placebo-controlled trials, over 100 preclinical studies, and published over 200 research papers elucidating the safety and medicinal promise of cannabis-derived products. Our studies have demonstrated efficacy of specific cannabis preparations in Dravet and LGS (U.S.) and spasticity in multiple sclerosis (>25 countries, non-U.S.). We recently announced positive Phase III results for Epidiolex in treatment of seizures associated to Tuberous Sclerosis Complex (TSC) and will file a Supplemental New Drug Application with FDA for that indication. And we have Phase I, II, and III programs in other serious conditions—including Rett syndrome, autism, multiple sclerosis, schizophrenia, neuropathic pain, and neonatal hypoxic ischemic encephalopathy (NHIE).

Over the same period, cannabis and cannabis derivatives have become widely available, in a dizzying variety of forms, online and in retail establishments, without evidence of quality, safety, or efficacy for any specific products or formulations. Preclinical studies with cell cultures and animal models abound, but the applicability of these data to human patients is uncertain. A number of small "proof of concept" studies have been conducted with cannabis products by individual researchers in patients or healthy human subjects,[1] but these studies—many of which are not placebo-controlled—are not credible evidence of safety and efficacy nor are they adequate to support use of cannabis products as medicine.

Despite a dearth of reliable scientific evidence, the belief in efficacy, fueled by media reports of individual cases, has resulted in a torrent of interest in cannabis not just as a wellness product, but as a medicine for serious conditions. State "qualifying condition" laws—47 states plus the District of Columbia have legalized cannabis for medical use in some form—seem to lend credibility to the use of unapproved cannabis products to treat epilepsy, cancer, post traumatic stress disorder, MS, HIV/AIDS, hepatitis C, Lou Gehrig's disease, anorexia, glaucoma, Parkinson's disease, and Crohn's disease, among many others.

It has been estimated that over 3,500,000 Americans use unapproved medical cannabis products.[2] And while for some, these products may offer symptom relief, there are risks to patients from self-directed treatment with unapproved products. A recent case study in Epilepsy and Behavior, 2018, describes deaths in two patients who had discontinued conventional therapies in

[1] See studies funded by the Center for Medicinal Cannabis Research (CMCR) at the University of California San Diego, https://www.cmcr.ucsd.edu/index.php/studies/active-studies.
[2] Pro Con, Number of Legal Medical Marijuana Patients May 17, 2018 https://medicalmarijuana.procon.org/view.resource.php?resourceID=005889

favor of self-directed care with unapproved cannabis-derived products.[3]

Quality deficiencies in unapproved cannabis products also pose safety risks for patients. Recent analyses show that unapproved CBD products frequently go to market containing either significantly higher or lower concentrations of CBD than indicated on the product label.[4] Because these manufacturers do not subject themselves to FDA oversight, there is no robust system in place to ensure product quality, identity, purity, or stability among unapproved cannabis preparations. A 2017 analysis found that after 14 days of storage, CBD content in commercial products is reduced by 15%–20% of initial concentrations, depending on method of oil preparation.[5]

Gaps in quality assurance practices for unapproved cannabis preparations allow products to reach the market that are contaminated with a variety of harmful substances, including synthetic cannabinoids, molds, and bacteria.[6] In some cases, such quality deficiencies have serious consequences for patients. A recent case report described an eight-year-old boy who was admitted to the emergency room after consuming a commercial CBD product contaminated with synthetic cannabinoids. The child experienced heightened tonic-clonic episodes, intermittent agitation, delirium, depressed mental status, tachycardia, and mydriasis.[7]

The result is a public health challenge on a nation-wide scale. Not since before 1962 has there been such widespread, uncontrolled use of non-FDA approved products in vulnerable populations and for serious medical conditions. Families and patients see hope in cannabis-based products to treat intractable illnesses, but outside of Dravet and LGS, have no choice but to resort to unapproved drugs.

B. FDA should implement new policies that encourage development of more approved cannabis-derived therapies

GW is the only company to have secured FDA approval for a cannabis-derived drug. Although we remain focused on discovering, developing, and commercializing novel botanically

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[3] Kollmyer DM, Wright KE, Warner NM, Doherty MJ, *Are there Mortality Risks for Patients with Epilepsy who use Cannabis Treatments as Monotherapy*, Epilepsy & Behav. Case Report 11(2019) 52-53.

[4] Bonn-Miller M.O., et al., Labeling Accuracy of Cannabidiol Extracts Sold Online, JAMA. 2017. Vol 318, No. 17 (finding nearly 70 percent of artisanal CBD products tested were mislabeled with respect to CBD content); FDA, Warning Letters and Test Results for Cannabidiol-Related Products, https://www.fda.gov/news-events/public-health-focus/warning-letters-and-test-results-cannabidiol-related-products

[5] Pacifici R, Marchei E, Salvator F, et al. Evaluation of cannabinoids concentration and stability in standardized preparations of cannabis tea and cannabis oil by ultra-high performance liquid chromatography tandem mass spectrometry. *Clin Chem Lab Med.*2017;55(10):1555-1563.

[6] Horth RZ, Crouch B, Horowitz BZ, et al. *Notes from the Field*: Acute Poisoning from a synthetic Cannabinoid Sold in as Cannabidiol—Utah, 2017-2018. MMWR Morb Mortal Wkly Rep 2018;67:587-588; Thompson GR, Tuscano JM, et al. *Letter to the Editor:* A microbiome assessment of medical marijuana. Clinical Microbiology and Infection 23 (2017).

[7] Tony Rianprakaisang, Roy Gerona & Robert G Hendrickson (2019): Commercial cannabidiol oil contaminated with the synthetic cannabinoid AB-FUBINACA given to a pediatric patient, Clinical Toxicology, DOI: 10.1080/15563650.2019.1619758

derived cannabis therapeutics, existing legal frameworks have been insufficient to stimulate broader investment in the FDA-approval pathway.

Accelerating more FDA-approved products to market would accomplish a number of important public health objectives:

First, it would help mitigate the ongoing public health threat from self-directed use of unapproved cannabis drugs. Development incentives might be the only viable approach to doing so—FDA lacks the resources to fully tame the flow of products bearing illegal medical claims or lacking adequate quality control, and market forces will continue to drive cannabis investors toward less expensive and less risky commercialization pathways. A framework that encourages development of more FDA-approved therapies will, over time, afford more patients the choice of approved medications with tested and proven product profiles, over unapproved products. Taking a risk-based approach, FDA should encourage development programs targeted toward serious conditions and vulnerable populations, those arguably most at risk from harm from unregulated products.

Second, a framework that encourages development of more FDA approved medicines will help society realize cannabis' potential as a source for therapeutic breakthroughs. More than one hundred cannabinoids have been found in the plant, as well as hundreds of other plant components with potential differentiated activity. Each cannabinoid has its own pharmacology and therefore its own potential therapeutic action. Combination products and therapies offer additional therapeutic possibilities.

For all other molecules, the FDA approval process is the only path to answering important questions about each unique molecule, about the disease it seeks to treat, and about the safety considerations unique to the patients who will take the drug. Molecules from the cannabis plant should be treated no differently. Without extensive FDA-caliber studies, we will continue to have only incomplete science and mere anecdotal evidence of the cannabis plant's therapeutic value, and we will never realize the plant's full potential.

The urgency to boost development incentives for FDA-approved cannabis drugs is even more pronounced in the context of the current debate over authorizing CBD in mass-market consumer products. When Congress created a regulatory framework for dietary supplements in DSHEA, it also included the IND/NDA exclusionary rule, which prohibits marketing prescription drug ingredients in dietary supplements. In doing so, Congress recognized two now-settled principles that, since passage of DSHEA, have yet to be disrupted. First, prescription drug ingredients are not suitable for mass-market use without physician oversight. Second, permitting an FDA-approved pharmaceutical ingredient (e.g., CBD) in dietary supplements will serve as a disincentive to the substantial investment required to gain FDA approval as a new drug. FDA-approved prescription drugs should not be left to compete with dietary supplements that are not subject to the same development burdens and requirements.

FDA has never waived the IND/NDA exclusionary rule. Epidiolex and, if eventually approved in the United States, Sativex, would be the first prescription drugs since enactment of DSHEA to be marketed in parallel with previously barred dietary ingredients. Principal arguments proffered for FDA making this exception are economic and pragmatic: economic in the sense that strong consumer demand for CBD products is expected to support new business and agricultural opportunities; pragmatic in the sense that CBD products have proliferated already, and consumers would be better off with a market regulated by FDA and served by law-abiding companies.

GW appreciates these dynamics and agrees that consumers should have access to quality products in regulated markets. We also support the creation of new agricultural and business opportunities. But stakeholders should also recognize that authorization of CBD in consumer-focused products further diminishes incentives to continue research and development of new medicines—incentives that are already challenged in the cannabis-derived product space by a number of factors, including the proliferation of unapproved products. GW's support of FDA's process does not change the fact that other innovators will take notice of FDA's action here, as will the investors who help fund important medical research.

A framework that waives the IND/NDA exclusionary rule should rebalance incentives and include new policies to ensure medical research of cannabis and its derivative products continues and expands. FDA should focus efforts on drug development programs that target serious conditions and populations with unmet medical needs, utilizing an "all hands on deck approach" and exercising regulatory flexibility wherever possible and appropriate.

III. A comprehensive framework should ensure that consumer products containing cannabis derivatives, including CBD, can be used safely in a mass-market setting without healthcare professional oversight

An equally critical element of a comprehensive framework for cannabis-derived products is ensuring that consumer-focused products are safe. CBD is not a benign substance— it can present real safety risks if not used under the supervision and monitoring of a healthcare professional. The Epidiolex development program indicates that:

- Side effects of CBD emerge at all doses studied in clinical trials in humans.
- Liver toxicity manifests at the lowest dose for which it has been systematically monitored and may occur at lower doses.
- Drug-drug interactions appear at low doses.
- Miscellaneous variables can impact the body's exposure to CBD's risks, like whether CBD is taken with food, and the composition of such food. When taken with a high

fat meal, for instance, the body is exposed to up to 500% more CBD than if taken while fasting.

In a prescription drug, these risks can be managed primarily through physician oversight guided by labeling and recommended physician monitoring processes. To protect consumers from ingesting unsafe amounts in a setting without physician supervision, non-pharmaceutical CBD products should be subject to:

(1) Total daily serving limits,

(2) Concentration and total package limits,

(3) Enhanced quality requirements, including finished-product testing for harmful contaminants,

(4) Appropriate labeling statements, including warnings,

(5) Robust adverse event reporting, including a specific portal through which consumers, health care providers, and others may report adverse events from consumer products and improper marketing practices, similar to the FDA Adverse Event Reporting System (FAERs) database and the "Bad Ad" programs implemented to protect consumers from potential harms of pharmaceutical products or misleading claims by companies,

(6) Limitations designed specifically to protect vulnerable populations (e.g., elderly), and

(7) All other existing requirements and limitations applied to dietary supplements and food additives.

A. The parameters for consumer-market products should be grounded in sound scientific data

GW's research and development program for Epidiolex and other cannabinoids provides the most comprehensive source of safety data for evaluating appropriate parameters for consumer products. But important limitations apply even to our data:

First, GW's data evaluates CBD and other cannabinoids as prescription medications, not as consumer products for mass-market distribution without physician supervision. This is important because physician supervision mitigates risk. In its approval of Epidiolex, for example, the FDA relied on the likely involvement of specialist physicians as a factor in approving the drug:

> This combination of a pharmacoresistant epilepsy and the need for adjunctive treatment should result in most of these patients being diagnosed, receiving care, and being

prescribed cannabidiol in comprehensive epilepsy centers. These centers with neurologists, pediatric neurologists and epileptologists should have the experience with anticonvulsants and the risks associated with them both generally and specifically for cannabidiol and the adjunctive therapies that are required when using cannabidiol. The risk of liver toxicity associated with cannabidiol is also a risk associated with other anticonvulsants used for the treatment of DS and LGS, and the healthcare providers prescribing cannabidiol should be familiar with appropriate laboratory monitoring.[8]

Second, our Phase II and III clinical data evaluated specific formulations of CBD and other cannabinoids in specific populations with specific conditions. This data cannot be freely extrapolated to support safety in a mass-market setting with the level of certainty that FDA would typically require. GW cannot provide data to FDA, for example, about whether Epidiolex or any other CBD formulation is safe for use in various vulnerable populations, such as pregnant women and patients over 55. Our clinical trials have not focused on these groups.

These limitations apply not only to our data, but also to data in the public domain about CBD, including, as described later in this comment, the WHO study. **The available data cannot provide complete assurance of safety in the environment of explosive demand for CBD-based consumer products.** As a result, and because consumer-market products have not established therapeutic benefit against which to balance safety risks, FDA should take a cautious approach in setting parameters.

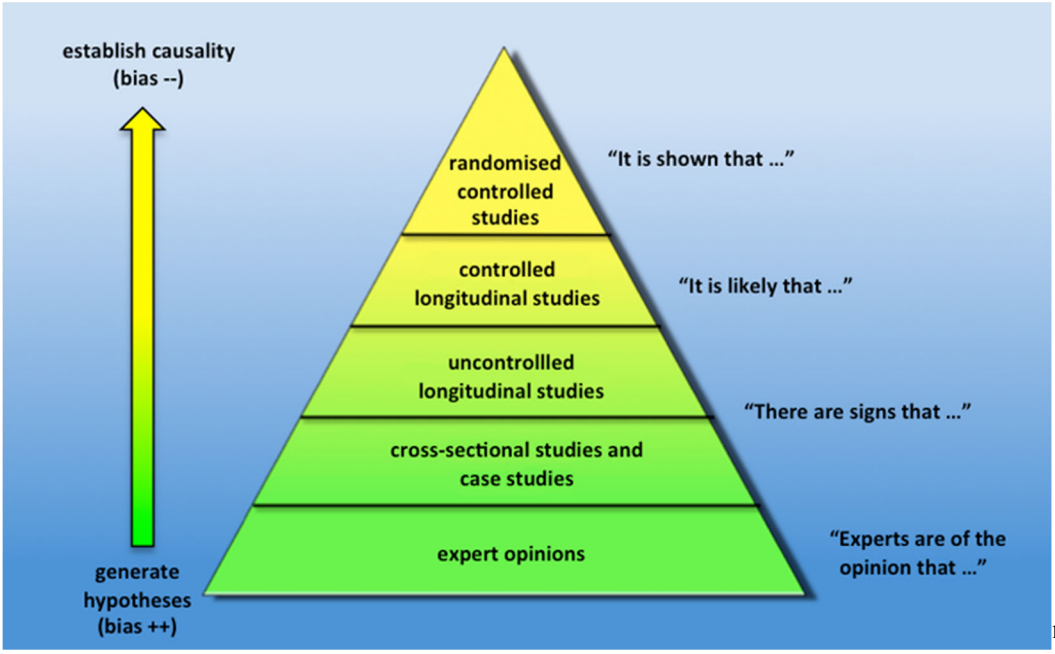
Many of the studies cited for the proposition that CBD is safe lack scientific rigor and do not provide a sound basis for regulatory decision-making. The levels of evidence are well-known in the scientific and medical community.[9] The highest levels of evidence are systematic reviews or meta-analyses of randomized, placebo-controlled, double-blind clinical trials (RCTs), followed by evidence from well-designed RCTs. While descriptions of the "levels of evidence" can vary in small ways, in general, the levels are as follows:

[8] FDA Drug Approval Package: Epidiolex
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210365Orig1s000RiskR.pdf

[9] See, e.g., Burns, P.B., Rohrich, R.J., and Chung, K.C., The Levels of Evidence and their role in Evidence-Based Medicine, Plast Reconstr Surg. 2011 July ; 128(1): 305–310. doi:10.1097/PRS.0b013e318219c171.

Level of Evidence		
Level	**Evidence Type**	**Evidence Strength**
Level 1	Systematic review & meta-analysis of randomized controlled trials; clinical guidelines based on systematic reviews or meta-analyses	Very strong
Level 2	One or more randomized controlled trials	Strong
Level 3	Controlled trial (no randomization)	Moderate
Level 4	Case-control or cohort study	Limited
Level 5	Systematic review of descriptive & qualitative studies	Insufficient
Level 6	Single descriptive or qualitative study	Weak
Level 7	Expert opinion	Very weak
Level 8	No evidence (Individual public reports)	Ignore

[10]



[11]

Lower levels of evidence can be useful for hypothesis generation, but are insufficient to demonstrate safety and efficacy, especially for a mass market that includes supplements, foods, cosmetics, and drugs. Only RCTs can adequately account for the risks of bias and of confounding factors.

The safety considerations found in GW's data derive from randomized, double-blind, placebo-controlled clinical trials, augmented by robust preclinical toxicology, Phase I, Phase II, long-term safety extension studies, and prospective expanded access programs conducted under protocols reviewed by FDA. Many studies cited to support CBD's safety, by contrast, are

[10] Drawn from Google image search. Source available upon request.
[11] Drawn from Google image search. Source available upon request.

retrospective in nature, based on chart reviews or surveys.[12] These sources of evidence are not sufficient to ameliorate the credible safety concerns and risk factors identified in the Epidiolex RCTs.

The non-GW studies evaluating CBD in a more controlled manner show a safety profile similar to—or potentially more sever—than that of Epidiolex. For example, in a small open label study of children with Dravet syndrome conducted with a CBD preparation containing a 50:1 CBD to THC ratio, 11 out of 19 (58%) patients were unable to reach the target dosage of 16mg/kg/day due to excessive somnolence, anorexia, diarrhea, and weight loss. Laboratory abnormalities were seen in 42% of patients.[13]

Below we describe specific safety issues identified during the Epidiolex development program. Our 21-year R&D program has generated additional data. While GW has already made numerous submissions to FDA as part of the IND and NDA for Epidiolex, and FDA disclosed some of this information as part of the Epidiolex approval package, the company is willing to make additional confidential commercial and trade secret information available to FDA where such information would help the agency ensure consumer safety.

B. Data from Epidiolex trials demonstrate risks of CBD

The full Epidiolex clinical development program now includes five completed, randomized, double blind, placebo-controlled Phase III trials and one ongoing long-term open label extension (OLE) trial in children and adults with LGS, Dravet, and TSC. The treatment duration of the four LGS and Dravet trials was 14 weeks, and all were designed to evaluate 20 mg/kg/day Epidiolex versus placebo. Two of the trials also included a lower dose of 10 mg/kg/day to assess whether there may be a minimally effective dose. The TSC trial studied doses of 25mg/kg/day and 50mg/kg/day for 16 weeks. Patients could receive up to 50 mg/kg/day in the OLE.

Based on individual clinical response and tolerability in the RCTs, the approved labeling provides that the target dose of Epidiolex is 10mg/kg/day, but it can be dosed up to a maximum recommended maintenance dosage of 20 mg/kg/day. Side effect data were collected as patients titrated up to the target dose, starting with 5mg/kg/day.

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[12] See, e.g., Pamplona, F. A., Rolim da Silva, L., and Coan, A.C., Potential Clinical Benefits of CBD Rich Cannabis Extracts Over Purified CBD in Treatment Resistant Epilepsy: Observational Data Meta Analysis, vol 9, Art. 759 (Sept. 12 2018) doi: 10.3389/fneur.2018.00759; Hausman-Kedem, M., and Kramer, U., Efficacy of Medical Cannabis for Treating Refractory Epilepsy in Children and Adolescents, with Emphasis on the Israel Experience, IMAJ, vol. 19, February 2017; Aran, A., Cassuto, H., and Lobotzky A., Cannabidiol Based Medical Cannabis in Children with Autism- a Retrospective Feasibility Study (P3.318) Neurology Apr 2018, 90 (15 Supplement) P3.318.

[13] See, e.g., McCoy, B., A prospective open-label trial of a CBD/THC cannabis oil in dravet syndrome, Annals of Clinical and Translational Neurology 2018; 5(9): 1077–1088 doi: 10.1002/acn3.621

The clinical development program for Epidiolex also includes supportive safety data from a comprehensive preclinical toxicology program, a clinical pharmacology program in healthy subjects and patients with epilepsy, and a physician initiated expanded access program (EAP) for patients with drug resistant epilepsy.

A total of 1,808 participants were exposed to Epidiolex during the development program for its approved indications (Dravet and LGS). The size of the safety database allows for a reasonable characterization of the safety profile of Epidiolex.

1. CBD induces liver injury

Epidiolex is associated with dose-related increases in liver enzymes (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)) including elevations above 5 times the upper limit of normal (ULN), which defines drug induced liver injury (DILI), and therefore causes liver injury. These elevations appear to be due to a direct hepatocellular effect of CBD Oral Solution (CBD-OS) or its metabolites. Although the mechanism is not fully understood, pathway-based investigations of the mechanism(s) responsible for this effect, including those involving mitochondrial function, are under way. Liver safety findings in humans are consistent with non-clinical toxicological data obtained during early Epidiolex development,[14] where the liver was the primary organ that was affected in two species. Findings in two species included hepatocellular hypertrophy accompanied by increases in ALT and ALP levels.[15]

FDA's approved label for Epidiolex recommends that physicians monitor patient liver function with blood tests.[16] This recommendation arises from the Epidiolex clinical trials, where liver enzyme elevations were observed at a sub-therapeutic dose of 5mg/kg/day. Of the 10 patients with Dravet syndrome who received CBD, 5mg/kg/day for three weeks, one patient developed ALT >5X ULN, which meets DILI criteria. In a separate healthy volunteer Phase I study, 5 out of 12 healthy subjects developed ALT elevations above the normal range at 5 mg/kg/day during the three-week treatment period. In the same Phase I study, no liver transaminase elevations were observed at the lowest dosage of 1mg/kg/day. Despite a limited number of subjects and the short treatment duration, there is a clear signal for hepatotoxicity, including DILI, at a dosage of 5mg/kg/day. However, below this dosage, systematic collection of data is lacking and the risk of hepatotoxicity unknown.

In controlled clinical trials, increasing exposure to CBD was closely correlated with an increased frequency of treatment emergent (TE) ALT elevations and DILI. The risk factors for

[14] These findings are confirmed by other nonclinical studies. See, Ewing L.E. et al. "Paradoxical Patterns of Sinusoidal Obstruction Syndrome-Like Liver Injury in Aged Female CD-1 Mice Triggered by Cannabidiol-Rich Cannabis Extract and Acetaminophen Co-Administration,"' Molecules 2019, 24, 2256; doi:10.3390/molecules24122256; Ewing L.E. et al. "Hepatotoxicity of a Cannabidiol-Rich Cannabis Extract in the Mouse Model." Molecules 2019, 24, 1694; doi:10.3390/molecules24091694.

[15] 26- and 39-week studies in two species

[16] See Epidiolex Prescribing Information, Section 5.1.

ALT elevations include concomitant valproate (VPA) use, ALT elevation at baseline, and CBD-OS dosage of 20 mg/kg/day or higher. The onset of ALT elevations occurred within the first 30 days of continuous treatment with CBD-OS but can appear later on, especially in patients taking concomitant VPA. Transaminase elevations resolved with discontinuation of, or reduction of CBD-OS or concomitant VPA in about two-thirds of the cases. In about one-third of the cases, transaminase elevations resolved during continued treatment with CBD-OS, without dose reduction.

2. Drug-drug interactions occur with CBD

CBD drug-drug interactions (DDIs) may pose serious safety risks, depending on the underlying concurrent medication or substance. Multiple scientific studies have demonstrated that CBD causes significant DDIs with other medications.[17] The prescribing information for Epidiolex describes and cautions on the known DDI with VPA and states that additional potential DDIs could result based on modulation of drug metabolizing enzymes by either CBD or other substrates.

While GW continues to study the DDI potential of Epidiolex, case reports of DDIs continue to emerge. For instance, a case report published in 2017 observed a clinically significant interaction between Epidiolex and warfarin (7.5 mg), one of the most widely used oral anticoagulants, with a narrow therapeutic window. A patient with Marfan syndrome, mechanical mitral valve replacement, warfarin therapy, and post-stroke epilepsy was enrolled in a physician-initiated expanded access program for the compassionate use of Epidiolex. During titration of Epidiolex (starting at 5 mg/kg/day and increasing in 5 mg/kg/day increments every two weeks), an increase in international normalized ratio (INR) (blood clotting) was noted. To maintain safe levels, the patient's warfarin dose was reduced by approximately 30 percent followed by an INR decrease to pre-Epidiolex levels.[18] It is critically important that patients using warfarin remain within a certain INR range. An increase in INR increases a patient's risk of bleeding, including intracranial hemorrhage, which can be serious or fatal.[19]

The above case study showing a significant DDI with warfarin (a CYP2C19 substrate), coupled with the observation from GW Phase I DDI studies that CBD in healthy volunteers can cause potentially clinically significant CYP2C19 inhibition at doses as low as 1 mg/kg/day, strongly suggests that there is significant risk associated with co-administration of CBD at doses of 1mg/kg (or lower to account for heterogenous population uncertainty factors) with narrow

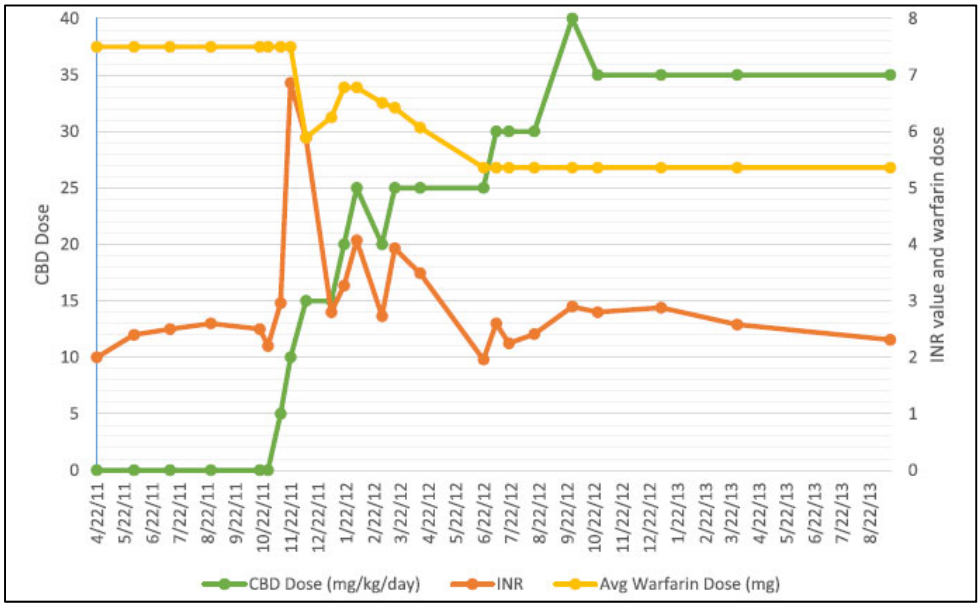
[17] Bornheim LM, Everhart, ET, Li J, and Correia MA. Characterization of cannabidiol-medicated cytochrome p450 inactivation. Biochem Pharm, vol. 45, No. 6, pp. 1323-1331 (1993)

[18] Grayson L, Vines B, Nichol K, and Szaflarski JJP. An interaction between warfarin and cannabidiol, a case report. Epilepsy & Behavior Case Reports (2017) doi:10.1016/j.ebcr.2017.10.001

[19] American Heart Association. A Patient's Guide to Taking Warfarin, https://www.heart.org/en/health-topics/arrhythmia/prevention--treatment-of-arrhythmia/a-patients-guide-to-taking-warfarin

therapeutic margin drugs metabolised by CYP2C19 (e.g., warfarin, clopidogrel, phenobarbital, tricyclic antidepressants).

INR Levels Following the Addition of Epidiolex to Regimen Including Warfarin



In another recent case study, an interaction between CBD and tacrolimus, a calcineurin inhibitor (CNI), was reported. Tacrolimus is a drug commonly used to prevent transplant organ rejection. According to the authors, "the CNIs, particularly tacrolimus, are the backbone of most immunosuppressive regimens." A participant in a CBD clinical trial for epilepsy, who was also receiving tacrolimus for interstitial nephritis, showed an approximately three-fold increase in dose normalized tacrolimus concentrations while receiving 2000 - 2900 mg/day of CBD. The authors concluded:

> Concern for an interaction with the pharmaceutical grade product should generate additional alarm for the variability that may result from less regulated artisanal products. More than 60% of *cannabis dispensary* products have been shown to be mislabeled[20] with respect to actual CBD content. Inconsistencies in product makeup and changes in route of administration may result in variable exposure to the potentially interacting substances and in turn may increase the variability of CNI exposure. In solid organ transplant recipients, variability in CNI drug levels has been shown to negatively affect long-term outcomes.[21]

[20] Bonn-Miller M.O., et al., Labeling Accuracy of Cannabidiol Extracts Sold Online, JAMA. 2017. Vol 318, No. 17 (finding nearly 70 percent of artisanal CBD products tested were mislabeled with respect to CBD content); FDA, Warning Letters and Test Results for Cannabidiol-Related Products, https://www.fda.gov/news-events/public-health-focus/warning-letters-and-test-results-cannabidiol-related-products

[21] Leino AD et al., Evidence of a clinically significant drug-drug interaction between cannabidiol and tacrolimus: a case report Am J Transplant. 2017;17 (suppl 3) (emphasis in original).

The identification of DDIs between Epidiolex and VPA, tacrolimus, and warfarin emphasizes the importance of physician oversight and the need for clinical laboratory monitoring in patients receiving cannabidiol products concomitantly with other pharmaceuticals.

3. CBD causes other side-effects

CBD causes other common side effects that can pose safety risks. In patients with Dravet or LGS receiving ≥ 5 mg/kg/day up to 20 mg/kg/day Epidiolex, the overall incidence of all-causality adverse events (AEs) increased as the dose increased and exceeded placebo. The same dose-related incidence of all-causality AEs was seen in healthy subjects receiving either a single dose of Epidiolex or multiple doses of Epidiolex. The most common adverse reactions that occurred in Epidiolex-treated patients (incidence at least 10% and greater than placebo) were:

> somnolence; decreased appetite; diarrhea; transaminase elevations; fatigue, malaise, and asthenia; rash; insomnia, sleep disorder, and poor-quality sleep; and infections. The most common adverse reactions in Epidiolex-treated patients (incidence at least 10% and greater than placebo) were somnolence; decreased appetite; diarrhea; transaminase elevations; fatigue, malaise, and asthenia; rash; insomnia, sleep disorder, and poor-quality sleep; and infections.

For most of these adverse events, the incidence typically increased with increasing Epidiolex dose. The incidence was similar in both Epidiolex dose groups for the adverse events of somnolence (most commonly reported) and pyrexia. Thus, even exposure at the lowest dose of Epidiolex studied in Dravet patients resulted in adverse events that were also commonly observed with the higher doses.

Somnolence (sleepiness) was the most common AE across all groups in the RCTs and was consistently more frequent in patients treated with Epidiolex compared with placebo. Somnolence was the third most common treatment-emergent AE leading to discontinuation of Epidiolex. The Epidiolex label advises prescribers to monitor patients for somnolence and sedation and to advise patients not to drive or operate machinery until they have gained sufficient experience on Epidiolex. Somnolence can be a serious issue if a consumer, who is unaware of this effect, ingests a CBD consumer product and then operates a vehicle or engages in other safety-related activities. Other CNS depressants, including alcohol, could magnify the somnolence and sedation effect of CBD.

Additionally, gastrointestinal (GI) disorder-related AEs were frequently reported. The most common AEs within the GI disorders were diarrhea, vomiting, nausea and constipation.

C. In light of known risks and significant uncertainties around safety, FDA should rely on substantial safety margins when setting concentration and daily serving levels

National regulatory agencies are commonly called upon to determine whether a chemical or other substance can be safely ingested by humans and, if so, at what levels, in the daily diet. This is calculated as a margin of safety and is derived from information extrapolated from animal studies or clinical trials based on the highest doses at which no toxic effects were identified and the lowest doses at which toxic or adverse effects were observed. The terms used to describe these outcomes are:

- NOAEL — Highest dose at which there was not an observed toxic or adverse effect.
- LOAEL — Lowest dose at which there was an observed toxic or adverse effect.

In the case of CBD, 5mg/kg/day is not a safe dosage and causes an unacceptable safety signal outside of a clinical setting where there is a benefit risk consideration. This clear safety signal cannot be offset by historical use patterns in the general population because there is no historical use of CBD or hemp extract as a food. Therefore, substantial safety factors need to be applied to this LOAEL and may include: a chronicity factor of 10-fold, inter-subject variability of 10-fold, and a LOAEL to NOAEL factor of three- to 10-fold.

D. The widely-cited World Health Organization (WHO) study does not support safe use of CBD in a mass-market setting; it further supports a cautious approach

In June of 2018, the Expert Committee on Drug Dependence (ECDD) of the WHO) published a Critical Review of cannabidiol,[22] as part of its assessment of the appropriate scheduling status of cannabis and cannabis derivatives under the international drug control treaties. In the FDA's May 31 Public Meeting and in widespread media coverage, many cited the WHO report as evidence that CBD is safe, lacks toxicity, and has no abuse potential. This is not an accurate portrayal of the report. Rather, the WHO report on CBD actually supports a deliberative scientific process and a cautious approach by the FDA.

The WHO Report on CBD does note in its top-level summary that CBD is "generally well tolerated with a good safety profile." It then goes on in the next sentence to note the adverse events associated with CBD. As those in the medical profession know, "generally well tolerated" does not mean "free of adverse effects." The FDA ICH Guidance for Industry: E9 Statistical Principles for Clinical Trials (Sept. 1998) states that a drug that is "generally well-tolerated" is not free of adverse events, and is clear that tolerability is not a measure of safety.[23] On page 43, the ICH Guidance states: **"**[t]he safety of a medical product concerns the medical risk to the subject… The tolerability of the medical product represents the degree to which overt adverse effects can be tolerated by the subject." Tolerability presupposes that the patient is experiencing adverse events and is an assessment of the degree to which the patient can tolerate the adverse effects in order to

[22] Expert Committee on Drug Dependence, World Health Organization, Critical Review of Cannabidiol, https://www.who.int/medicines/access/controlled-substances/CannabidiolCriticalReview.pdf
[23] https://www.fda.gov/media/71336/download.

stay in the clinical trial or otherwise remain on therapy.[24] The fact that deaths or Serious Adverse Events (SAEs) (i.e., side effects requiring hospitalization) may not occur in a clinical trial does not mean that a product does not have risks or side effects, especially if it consumed daily from multiple sources outside of physician supervisions.

In evaluating toxicology and adverse effects in humans, WHO effectively relied only on three review articles.[25] In the Bergamaschi review, the authors noted that they did not review studies on cannabis extracts or CBD-rich extracts, since other compounds could have multiple interactions with CBD. Therefore, they examined only studies using pure or purified CBD. They cautioned that, although some of the effects of CBD are of potential benefit in some conditions, they may worsen disease progression, HIV infection, tumor genesis and metastases, and exacerbate allergic inflammation in the lung. They concluded that the data "highlights the need for careful monitoring of CBD use in humans, especially when CBD is used in clinical practice, such as in the treatment of psychiatric disorders or an option for drug abuse treatment."

The Iffland paper examined studies published after the Bergamaschi review. Those authors concluded that:

> First, more studies researching CBD side effects after real chronic administration need to be conducted. Many so-called chronic administration studies cited here were only a couple of weeks long. Second, many trials were conducted with a small number of individuals only. To perform a thorough general safety evaluation, more individuals have to be recruited into future clinical trials. Third, several aspects of a toxicological evaluation of a compound such as genotoxicity studies and research evaluating CBD effect on hormones are still scarce. Especially, chronic studies on CBD effect on, for example, genotoxicity and the immune system are still missing. Last, studies that evaluate whether CBD-drug interactions occur in clinical trials have to be performed.

The Fasinu article was merely a general overview of the history, pharmacology, and potential therapeutic applications of CBD. The authors concluded that:

> A long history of use, a good deal of experimental evidence, and a number of anecdotal and a few descriptive clinical studies point to the potential clinical utility of CBD in the management of seizures associated with epileptic syndromes.

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[24] Critical Path Institute, https://c-path.org/wp-content/uploads/2017/05/2017_coa_session1consolidatedfinal-.pdf

[25] Bergamaschi M.M., et al, Safety and side effects of cannabidiol: a Cannabis sativa constituent. Current drug safety, 2011. 6(4): p. 237-249; Iffland, K., and Grotenhermen, F. An Update on safety and side effects of cannabidiol: a review of clinical data and relevant animal studies. Cannabis and Cannabinoid Research, 2017. 2(1): p. 139-154; Fasinu, P.S., et al, . Current Status and Prospects for Cannabidiol Preparations as New Therapeutic Agents. Pharmacotherapy, 2016. 36(7): p. 781-96.

These review articles do not support the conclusion that CBD or hemp extract products are safe to consume in a mass market context that lacks physician supervision.

WHO specifically notes the risk of drug-drug interactions because CBD is metabolized by the liver and inhibits certain cytochrome P450 (CYP) enzymes.[26] Specifically, WHO cites uncertainty about the concentrations that might cause CYP inhibition and thus interactions with other medications.

With regard to fetal harm, WHO acknowledges there is *limited research* on effects of CBD on embryonic development. The evidence cited by WHO that there may be no harm is based on a single *in vitro* animal study from 1995.[27] A single *in vitro* study is not enough to support use in pregnant humans. Indeed, the Epidiolex FDA approval package contained animal data from several species suggesting fetal toxicity was present in several animal models given CBD at clinically relevant doses.[28] Because no human data exists, FDA has advised caution and monitoring for pregnant women using Epidiolex.

The WHO critical review supports the conclusion that FDA should exercise caution when considering parameters for CBD to be sold as mass-market consumer goods.

E. FDA must ensure that intoxicating or otherwise unsafe amounts of THC are not contained in CBD mass market consumer products

FDA must ensure that any authorization of CBD-containing consumer products specifically controls for THC levels—the intoxicating substance in the cannabis plant. CBD is widely marketed as safe, not intoxicating, and not habit-forming because there is no THC. It is a myth that consumer-market CBD products are non-intoxicating. CBD products on the market today can and do have significant amounts of THC even when in purported compliance with the 2018 Farm Bill.

This is because the Farm Bill is interpreted to allow finished products with as much as 0.3% THC, measured as a percentage of the weight of the final product. A 30 mL bottle of CBD oil (a common retail product), for example, could contain 82 mg of THC. A single 4g CBD gummy (sold at retail in 30-count jars) could contain 12 mg of THC, and still fall below 0.3% THC by dry weight. As a point of reference, smoking a full cannabis cigarette delivers only about 17mg of THC.

[26] Cytochrome P450 enzymes are responsible for metabolizing most of the medications that humans take.
[27] Paria, BC, Das SK, Dey SK. The preimplantation mouse embryo is a target for cannabinoid ligand-receptor signaling. PNAS. 1995;92: 9460–9464,cited in Bergamaschi, 2011 and again in Iffland, 2017
[28]Epidiolex, Summary Review, at 10,
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210365Orig1s000TOC.cfm

THC content is particularly concerning because many hemp extract CBD products on the market as dietary supplements do not disclose on the label that the products contain THC.[29] Intoxication can occur at as low as 5-10 mg of THC, particularly in a cannabis-inexperienced individual.[30] Individuals may unwittingly consume intoxicating and unsafe amounts of THC, raising public safety concerns. High THC content in consumer CBD products also presents potential for abuse given the wide availability of these products in locations such as grocery stores, convenience stores, general merchandisers and pharmacies, vitamin/supplement stores, pet shops, and online sales.

IV. A comprehensive framework should, finally, invoke FDA's broad authorities to ensure that consumer-market products are not just safe, but also clearly differentiated from approved prescription medications

Finally, any action FDA takes to authorize the use of CBD in dietary supplements and conventional foods must utilize the FDA's broad statutory authorities to ensure not just safe use of CBD products, but also clear differentiation from approved prescription drugs. FDA has significant authority under the Food, Drug & Cosmetic Act (FDCA) to ensure the safety of consumer products and retain, to the greatest extent possible, the DSHEA principle that prescription drug ingredients are not suitable for consumer-focused products.[31] FDA should utilize its broad authority to establish parameters for safe consumer use of cannabis-derived products (including CBD), exercise ongoing oversight of these products, and close loopholes in the FDCA that could allow for the marketing of prescription-drug-like cannabis-derived products.

A. FDA has authority to issue a broad rule that covers all CBD-containing products and forecloses potential loopholes

FDA has pointed to sections 301(ll) and 201(ff)(3)(B)(ii) of the FDCA as the primary basis for the agency's conclusion that CBD cannot lawfully be used in food or dietary supplements absent FDA action authorizing such use.[32] Sections 201(ff) and 301(ll) of the FDCA give FDA what appears to be wide discretionary authority when, through rulemaking, "approv[ing] the use" of CBD in food or "find[ing] that [CBD] would be lawful" under the FDCA.

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[29] Schonhofen, P.,et al., Cannabinoid-Based Therapies and Brain Development: Potential Harmful Effect of Early Modulation of the Endocannabinoid System, 32 CNS Drugs 697 (Aug. 2018).

[30] See Marinol Prescribing Information; Vandrey R et al., Pharmacokinetic Profile of Oral Cannabis in Humans: Blood and Oral Fluid Disposition and Relation to Pharmacodynamic Outcomes, *J. Analytical Tox*, 2017: 1-17.

[31] This intent is also expressed in section 701(a) of the FDCA, under which FDCA may issue regulations for the efficient enforcement of the FDCA to "effectuate a congressional objective expressed elsewhere in the Act." *Association of American Physicians and Surgeons, Inc.* v. *FDA,* 226 F. Supp. 2d 204 (D.D.C. 2002) (citing *Pharm. Mfrs. Ass'n* v. *FDA,* 484 F. Supp. 1179, 1183 (D. Del. 1980)).

[32] Of note, these statutory provisions also restrict the use of *approved* drugs and biologics in food and dietary supplements, though in practice, the development of any new drug or biological product will almost always trigger the IND-based restriction first.

In making that determination for CBD products, FDA should use this authority to reaffirm within any regulation or other administrative action the broad applicability of the IND/NDA exclusionary rule not just to CBD, but also to all CBD-containing substances (e.g., hemp extract). This will help prevent attempted circumvention of FDA's rulemaking and the potential marketing of prescription-drug like products in a direct-to-consumer setting. An exception to the IND/NDA exclusionary rule should, in other words, establish the ground rules for any consumer foods or dietary supplements containing CBD.

FDA should also use its broad authority to ensure that consumer products are clearly differentiated from prescription medications in CBD concentration, total package limits, and other parameters. This will result in safer consumer products and a rule that aligns more closely with the policy goals Congress sought to achieve in enacting the exclusionary rule.

B. Any use of CBD in conventional food should be reviewed under FDA's food additive authorities

If FDA authorizes the use of CBD in a food under the agency's authority in section 301(ll), FDA must as a threshold matter consider whether sufficient information exists to conclude that *any use* of CBD is Generally Recognized as Safe (GRAS). We do not believe that existing data supports a GRAS conclusion. If CBD is not GRAS for any or all intended uses, then it must be approved by FDA as a food additive before it can be used in food independent of any action FDA takes under section 301(ll). We think food additive review is the most appropriate action under the FDCA given the absence of widespread consumption data and the known risks associated with CBD consumption.

Under section 409 of the FDCA, any food is adulterated if it is or if it bears or contains any food additive that is unsafe (i.e., not authorized by regulation). A substance is not a food additive if such substance is generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures to be safe under the conditions of its intended use.[33] General recognition of safety may be based only on the views of experts qualified by scientific training and experience to evaluate the safety of a food substance, and "requires *common knowledge throughout the scientific community* knowledgeable about the safety of substances directly or indirectly added to food that there is reasonable certainty that the substance is not harmful under the conditions of its intended use."[34]

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[33] FDA, by regulation, has defined "safe" or "safety" to mean that "there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the conditions of its intended use. It is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of the use of any substance. Safety may be determined by scientific procedures or by general recognition of safety. In determining safety, the following factors shall be considered: (1) The probable consumption of the substance and of any substance formed in or on food because of its use. (2) The cumulative effect of the substance in the diet, taking into account any chemically or pharmacologically related substance or substances in such diet. (3) Safety factors which, in the opinion of experts qualified by scientific training and experience to evaluate the safety of food and food ingredients, are generally recognized as appropriate." 21 C.F.R. 170.3(i).

[34] 21 C.F.R. 170.30(a).

We think that even analyzing whether CBD is GRAS for a given use, let alone reaching a GRAS conclusion, would pose meaningful challenges given the lack of data that currently exists about CBD consumption and safety and the product-to-product variability in the marketplace (particularly as it relates to THC content). Importantly, any conclusion that a substance is GRAS for its intended use must be reached with consideration given to all publicly available safety data *and* exposure data. FDA has explained that exposure data should include information about the amount of the relevant substance that consumers are likely to eat or drink as part of a total diet (i.e., from all sources in the diet), regardless of whether the conclusion of GRAS status is through scientific procedures or through experience based on common use in food.[35] Given that CBD has not, in recent decades, been able to be lawfully marketed in food or dietary supplements, exposure data that would reflect anticipated consumption following a change in the legal status of CBD as a food ingredient or as a dietary ingredient simply does not exist. The same holds true for any other novel ingredient derived from the cannabis plant, including THC or other cannabinoids. Because overall dietary exposure is a critical factor in evaluating the safety of a food ingredient, we have significant concerns about FDA's ability *or* industry's ability to do so across a wide range of potential uses and products. A GRAS conclusion seems particularly difficult to reach given the side effects presented at low dosing levels during Epidiolex trials, as set forth above.

Rather, if needed to ensure safety, FDA, on its own initiative or in response to a petition, may propose to determine that a substance is *not GRAS* and is a food additive subject to section 409 of the FDCA.[36] Any such determination that a substance is a food additive must provide for the safe use of that food additive, including adopting different approaches for different uses or levels of use of the additive (such as prohibiting certain uses).[37] If FDA decides to exercise its authority under section 301(ll) of the FDCA and take action to authorize the use of CBD in food, FDA should at this point in time regulate CBD as a food additive and evaluate a narrow and clearly defined scope of uses of CBD in food.

C. FDA must ensure that each use of CBD in a dietary supplement is safe through the New Dietary Ingredient (NDI) notification process

Similarly, because there is no history of the lawful use of CBD as an ingredient in dietary supplement products in the United States, if permitted in supplements under 201(ff), FDA should require safety review of each use before marketing. To ensure this, any action that FDA takes to allow the use of CBD in dietary supplements should close the self-affirmed GRAS loophole with respect to CBD products. This is particularly critical with regard to CBD, where inconsistencies in ingredient purity and quality and manufacturing processes have caused wide variability in the CBD and THC content of finished dietary supplements that are currently on the market unlawfully.

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[35] 21 C.F.R. 170.235.

[36] 21 C.F.R. 170.38(b)(1); *see also* "Final Determination Regarding Partially Hydrogenated Oils," 80 Fed. Reg. 34650 (June 17, 2015).

[37] 21 C.F.R. 170.38(b)(3).

Under 402(f)(1)(A) of the FDCA, any dietary supplement is unsafe if it presents, or contains a dietary ingredient that presents, a significant or unreasonable risk of illness or injury under the intended conditions of use. Under 402(f)(1)(B) of the FDCA, any dietary supplement is adulterated if it contains a new dietary ingredient for which there is *inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury*. Because CBD was neither marketed in supplements before October 1994 nor marketed for use in dietary supplements before that date, the notification requirements apply. Recommended dosage amounts and market consumption expectations will change with each use, as will the purity, quality, and strength that is achieved with different manufacturing processes[38] and sourcing practices, and, as FDA has consistently explained,[39] these factors are critical to establishing safety and providing a reasonable assurance that CBD as a dietary ingredient does not present a significant or unreasonable risk of illness or injury.

D. FDA must establish conditions of use, including thresholds and labeling statements, as needed to ensure safety

Under its food labeling authority, FDA can require labeling statements for food, including dietary supplements, to disclose facts material in the light of such representations or material with respect to consequences which may result from the use of the article to which the labeling or advertising relates under the conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary or usual.[40] This would include warning statements necessary to ensure safe use. FDA has, in the past, required warning statements for novel food ingredients to reflect material information about the consequences that may result from the consumption of a given food. One relatively recent example is olestra, where FDA required a label warning statement regarding the substance's possible gastrointestinal effects when olestra first came to market.[41]

Further, FDA can impose different limits on use for vulnerable populations and can establish maximum levels of safe use across products. FDA has taken such action in the past to

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[38] CBD products may be manufactured using a wide variety of methods, which can affect the ultimate composition and quality of the finished product. If finished products are to be manufactured from plant material, the cannabinoids must be extracted. Most commercial CBD manufacturing operations use ethanol, liquid carbon dioxide, or a hydrocarbon such as butane or hexane to extract the cannabinoids. Solvents such as hexane or butane may leave behind a solvent residue that poses safety risks. The extraction process concentrates, not only the cannabinoids, but also impurities such as pesticides. Indeed, extraction can concentrate pesticide content by a factor of 10. Cannabis Safety Institute, Pesticide Use on Cannabis, 2015, https://cannabissafetyinstitute.org/wp-content/uploads/2015/06/CSI-Pesticides-White-Paper.pdf. Chromatographic procedures may be used to remove some—or most—cannabinoids or other plant components. Distillation may be used to obtain purified cannabinoids, which may then be enriched with terpenes.

[39] *See* FDA, Revised Draft Guidance, Dietary Supplements: New Dietary Ingredient Notifications and Related Issues (Aug. 11, 2016) [hereinafter Revised NDI Draft Guidance], at page 30.

[40] FDCA § 201(n).

[41] FDA subsequently concluded in 2003 that the previously required label statement regarding the possible gastrointestinal effects of olestra was no longer necessary to prevent olestra-containing products from being misbranded because of widespread consumer awareness about possible effects and because the potential effects were relatively insignificant. 68 Fed. Reg. 46364, 46387 (Aug. 5, 2003).

ensure the safe use of approved food additives. For example, FDA's regulations authorize the use of potassium iodide in food, including dietary supplements, with varying maximum levels depending on the intended consumer population (infants, children under 4, adults and children over 4).[42] We think that thresholds on use of CBD in any food or dietary supplement are crucial given the known health risk of CBD and THC consumption described above, and the uncertainty about anticipated daily exposure and the breadth of dosage forms. FDA should also consider prohibiting altogether the use of CBD in products targeted at vulnerable populations— including children, the elderly, terminally or chronically ill patients, and pregnant women— if the agency does not receive sufficient data to establish safety specifically in those populations.

Finally, to further control risks of high levels of consumption, FDA could also prohibit bulk sales of CBD to consumers,[43] and require that CBD in foods and beverages be added only at the point of finished product manufacture and not by retail establishments, such as restaurants and cafes.

V. Conclusions and Recommendations

Patients and families living with Dravet and LGS now have the option of an FDA-approved cannabis-derived medicine. Their cannabis medicine meets the same "gold standard" applicable to every other prescription drug in the United States, such that patients and families can trust the medicine that they are taking for its:

- Proven efficacy for its specific formulation, at specific doses, tailored to LGS and Dravet seizures.

- Fully characterized safety profile specific to its formulation and recommended dose, and tailored to the unique safety considerations applicable to patients living with LGS and Dravet.

- Robust system of federal oversight to ensure the drug's strength, identity, purity, and consistency.

- Ongoing safety surveillance so that their physician always has the most up-to-date safety information about their specific CBD drug.

[42] 21 C.F.R. 172.375.
[43] FDA, Highly Concentrated Caffeine in Dietary Supplements: Guidance for Industry, https://www.fda.gov/media/112363/download

As FDA undertakes rulemaking to create pathways for consumer-market CBD products, its focus should be directed equally toward other patient populations who could benefit from safe and effective cannabis-derived treatments that have yet to be developed.

GW supports a comprehensive approach to the regulation of cannabis derived products because we believe that such an approach can create conditions that support development of new FDA-approved medicines from the cannabis plant while, in parallel, protecting consumers from unsafe products, and bringing much-needed regulation to the existing marketplace, satisfying consumer demand, and creating new economic and agricultural opportunities. We fully support FDA and stakeholders in the creation of a new regulatory framework that meets these objectives.