MAY 16 2018

The Honorable Robert W. Patterson
Acting Administrator
Drug Enforcement Administration
U.S. Department of Justice
8701 Morrissette Drive
Springfield, VA 22152

Dear Mr. Patterson:

Pursuant to the Controlled Substances Act (CSA), U.S.C. §811 (b), (c), and (f), the Department of Health and Human Services (HHS) is recommending that the substance cannabidiol (CBD) and its salts be controlled in Schedule V of the CSA. CBD is a cannabinoid with no significant affinity for cannabinoid receptors (CB_1 or CB_2). It also does not have significant affinity for other sites in the brain, including opioid, GABA, dopamine, norepinephrine, serotonin, glutamate, adenosine, histamine, ion channels, or monoamine transporters.

CBD, in a rat drug discrimination study, did not generalize to delta-9-tetrahydrocannabinol (THC), suggesting it does not have cannabinoid-like effects. It also does not produce cannabinoid-like responses in the tetrad test with rats. In a separate drug discrimination study, CBD did not generalize to midazolam. CBD is not self-administered by rats, suggesting that it does not have sufficiently rewarding properties to induce reinforcement. In a human abuse potential (HAP) study with CBD, there were slight but statistically significant increases in positive subjective responses after administration of high and supratherapeutic doses of CBD. These responses were just outside the acceptable placebo range, and were much less than those produced by the two positive control drugs: THC and alprazolam. CBD also does not appear to produce physical dependence. CBD as the single active ingredient in a drug product formulation is not yet marketed or available for sale in any country.

The Food and Drug Administration (FDA) is currently reviewing a new drug application (NDA) for CBD. Upon approval of this pending NDA, CBD will be marketed as a prescription drug as an oral adjunct treatment of two epilepsy conditions in children who remain on their current antiepileptic medication: Dravet syndrome, also known as severe myoclonic epilepsy of infancy (SMEI) for ages 4-10; and Lennox-Gastaut syndrome, for ages 2-18.

FDA and the National Institute on Drug Abuse have also considered the abuse potential of CBD. After reviewing the available information, the agencies conclude that CBD and its salts should be controlled in Schedule V of the CSA. Enclosed is a document prepared by FDA's Controlled Substance Staff that is the basis for the recommendation.

Should you have any questions regarding this recommendation, please contact Corinne P. Moody, Science Policy Analyst, Controlled Substance Staff, Center for Drug Evaluation and Research, at (301) 796-3152.

Sincerely yours,

Brett P. Giroir, M.D.
ADM, USPHS
Assistant Secretary for Health

Enclosure

BASIS FOR THE RECOMMENDATION TO PLACE CANNABIDIOL IN SCHEDULE V OF THE CONTROLLED SUBSTANCES ACT

A. Background

The Food and Drug Administration (FDA) recommends that the substance cannabidiol (CBD), a new molecular entity, chemically known as 2-[1R-3-methyl-6R-(1-methylethenyl)-2-cyclohexen-1-yl]-5-pentyl-1,3-benzenediol, be placed in Schedule V of the Controlled Substances Act (CSA). CBD derived from the *Cannabis sativa* plant is currently controlled as a Schedule I substance under the CSA.[1]

CBD has not been approved as a drug product for therapeutic use in any country.[2] However, a new drug application (NDA) for CBD was submitted by GW Pharmaceuticals, Inc. ("Sponsor") on October 27, 2017. CBD is proposed as an oral adjunct treatment of two epilepsy conditions in children who remain on their current antiepileptic medication: Dravet syndrome, also known as severe myoclonic epilepsy of infancy (SMEI) for ages 4-10; and Lennox-Gastaut syndrome, for ages 2-18. The pharmacological mechanism of action of CBD is not known. Although it is a cannabinoid, it does not have significant affinity for cannabinoid receptors (CB_1 or CB_2). It also does not have significant affinity for other sites in the brain, including opioid, GABA, dopamine, norepinephrine, serotonin, glutamate, adenosine, histamine, ion channels, or monoamine transporters. The Sponsor is seeking approval to market CBD as an oral solution (100 mg/ml) with a recommended dosing up to 20 mg/kg/day.

As stated above, CBD derived from the *Cannabis sativa* plant is currently controlled as a Schedule I substance under the CSA. Drugs in Schedule I cannot be legally marketed in the United States. Thus, the Drug Enforcement Administration (DEA) must reschedule or remove CBD from CSA controls before it can be legally marketed. In a letter dated May 8, 2017, the DEA requested that the Department of Health and Human Services (HHS) conduct a medical and scientific evaluation and a scheduling recommendation for CBD. The predicate for that request was a modified petition submitted by the Sponsor to the DEA on March 9, 2017, to initiate proceedings for the issuance of a rule that would

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[1] The CSA defines "Marihuana" in [21 U.S.C 802(16)] as "(16) The term "marihuana" means all parts of the plant Cannabis sativa L., whether growing or not; the seeds thereof; the resin extracted from any part of such plant; **and every compound, manufacture, salt, derivative, mixture, or preparation of such plant**, its seeds or resin. Such term does not include the mature stalks of such plant, fiber produced from such stalks, oil or cake made from the seeds of such plant, any other compound, manufacture, salt, derivative, mixture, or preparation of such mature stalks (except the resin extracted therefrom), fiber, oil, or cake, or the sterilized seed of such plant which is incapable of germination" (emphasis added).

[2] A drug product containing a 1:1 ratio of CBD and tetrahydrocannabinol (THC) has been approved and marketed in other countries under the trade name Sativex. We have not included epidemiology or other abuse-related data related to Sativex as part of our evaluation of the abuse potential of CBD with (b) (4) % residual THC. THC, which is in Schedule I of the CSA, has a high risk of abuse. Because of the high levels of THC in Sativex, the abuse-related data regarding Sativex would likely be caused by the presence of THC.

transfer such drug product from Schedule I to Schedule IV of the CSA. This petitioner has since modified their request again, requesting that such drug product be transferred from Schedule I to Schedule V of the CSA. The NDA described above, submitted to FDA by the petitioner, is for the same drug product that is the subject of the pending petition to DEA, now referred to HHS. The medical and scientific evaluation and the scheduling recommendation that follow address both CBD and the petition that DEA has referred to HHS.

Pursuant to section 201 of the CSA (21 U.S.C. § 811), the Secretary of HHS is required to consider in a scientific and medical evaluation eight factors determinative of control under the CSA. Following consideration of the eight factors, the Secretary must make a recommendation for scheduling, rescheduling, or removing a substance from CSA control. The eight factors are:

1. Its actual or relative potential for abuse;
2. Scientific evidence of its pharmacological effect, if known;
3. The state of current scientific knowledge regarding the drug or other substance;
4. Its history and current pattern of abuse;
5. The scope, duration, and significance of abuse;
6. What, if any, risk there is to the public health;
7. Its psychic or physiological dependence liability; and
8. Whether the substance is an immediate precursor of a substance already controlled.

Administrative responsibilities for evaluating a substance for control under the CSA are performed for HHS by FDA, with the concurrence of the National Institute on Drug Abuse (NIDA) according to a Memorandum of Understanding (50 Fed. Reg. 9518; March 8, 1985).

This evaluation considers the scientific and medical information relative to each of the eight factors, and makes a recommendation regarding scheduling. In determining the abuse potential of CBD, FDA evaluated all available abuse potential data on CBD, which include *in vitro*, animal, and human data from studies conducted by the Sponsor and submitted in the NDA.

In this document, FDA has evaluated, pursuant to section 201(c) of the CSA, the eight factors that the Secretary must consider for a scheduling recommendation for CBD. These considerations include the evaluation of data from *in vitro*, animal, and human studies submitted in the NDA. We conclude, based on consideration of these data and with respect to the eight factors, that CBD and its salts, with a limit of (b) (4) % (w/w) residual (−)-*trans*-Δ^9-tetrahydrocannabinol (THC), do not have a significant potential for abuse and could be removed from control under the CSA.

As discussed below, however, there are treaties to which the United States is a signatory, which dictate international drug controls for substances listed among the various treaties.

In a letter dated April 6, 2018, from Robert W. Patterson, Acting Administrator of DEA, to Dr. Donald Wright, HHS's Acting Assistant Secretary for Health ("April 6, 2018, DEA Letter"), the DEA has asserted that the United States would not be able to keep its obligations under the 1961 Single Convention on Narcotic Drugs if CBD were decontrolled under the CSA.[3] If this is so, to maintain treaty obligations, and reflecting our scientific findings to the extent currently possible, we recommend CBD and its salts, with a limit of (b) (4) % (w/w) residual (−)-*trans*-Δ^9-tetrahydrocannabinol (THC), be placed in the least restrictive CSA schedule, Schedule V. If treaty obligations do not require control of CBD, or if the international controls on CBD change in the future, this recommendation will need to be promptly revisited.

In the event that FDA approves the NDA submitted by the Sponsor, our recommendation to move CBD from Schedule I to Schedule V of the CSA will, as noted by DEA in the April 6, 2018, DEA letter, "requir[e] DEA to issue an immediately effective interim final rule" in accordance with section 201(j) of the CSA. Under these provisions, DEA would be required to publish an interim final rule scheduling the drug within 90 days of the later of (1) FDA approval or (2) receipt of the scheduling recommendation from the Secretary. The interim final rule would be immediately effective, and the drug could be marketed on the date of publication in the *Federal Register*. Additionally, under section 505(x) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the date of issuance of the interim final rule controlling the drug would be the date of approval of the Sponsor's NDA. This result would be consistent with the statutory goal of expanding patient access in the interest of the public health.

Separately, and also discussed in the Recommendations section below, FDA concludes that, with this recommendation for placement of CBD in Schedule V, and in the event that FDA approves the submitted NDA for the CBD product, scheduling of CBD should proceed under the provisions of section 505(x) of the FD&C Act and section 201(j) of the CSA. These provisions express the intent of Congress that there be an expedited process in the interests of the public health for DEA to schedule or reschedule certain drugs that have been approved by FDA, so that these drug products may more rapidly be available to patients. NIDA concurs with this recommendation.

Pursuant to section 201(c) of the CSA, the eight factors pertaining to the scheduling of CBD are considered below.

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[3] In a report published following its November 2017 meeting (Report), the Expert Committee on Drug Dependence (ECDD) of the World Health Organization stated that although CBD is not listed in the schedules of the 1961, 1971, or 1988 United Nations International Drug Control Conventions (Conventions), CBD that is produced as an extract of cannabis is currently included in Schedule I of the 1961 Convention. The Report stated that CBD had not been previously reviewed, and would be the subject of an ECDD meeting in May of 2018 (since revised to June of 2018).

B. Evaluating CBD Under the Eight Factors

This section presents the current scientific and medical information about CBD under the eight factors that must be considered pursuant to section 201(c) of the CSA.

1. Its Actual or Relative Potential For Abuse

The first factor the Secretary must consider is the actual or relative potential for abuse of CBD. The term "abuse" is not defined in the CSA. Since CBD has not been approved by FDA for therapeutic use in the United States, or approved in any other country, information on actual abuse of CBD is limited. The legislative history of the CSA suggests that the following criteria are applicable when determining whether a particular drug or substance has a potential for abuse.

a) Individuals are taking the substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community;

b) There is significant diversion of the drug or substance from legitimate drug channels;

c) Individuals are taking the substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such substance; and

d) The substance is so related in its action to a substance already listed as having a potential for abuse to make it likely that it will have the same potential for abuse as such substance, thus making it reasonable to assume that there may be significant diversions from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community.[4]

CBD is a new molecular entity and thus has not been marketed in the United States or any other country. It is not currently available for medical treatment, has not been diverted from legitimate sources, and individuals have not taken the substance in amounts sufficient to create a hazard to public health and safety. Therefore, criteria (a), (b), and (c) do not apply; (d) is the only known relevant criterion that applies to CBD.

Although CBD is a cannabinoid, it does not have affinity for cannabinoid receptors (or other sites in the brain). In a rat drug discrimination study, CBD did not generalize to THC, a cannabinoid that, in its various forms or drug product formulations, is controlled

[4] Comprehensive Drug Abuse Prevention and Control Act of 1970, H.R. Rep. No. 91-1444, 91st Cong., Sess. 1 (1970), reprinted in 1970 U.S.C.C.A.N. 4566, 4603.

in Schedules I, II and III. This lack of generalization suggests CBD does not have cannabinoid-like effects. It also does not produce cannabinoid-like responses in the tetrad test with rats. In a separate drug discrimination study, CBD did not generalize to midazolam, a Schedule IV sedative. CBD is not self-administered by rats, suggesting that it does not have sufficiently rewarding properties to induce reinforcement. In a human abuse potential (HAP) study with CBD, there were slight but statistically significant increases in positive subjective responses after administration of high and supratherapeutic doses of CBD. These responses were just outside the acceptable placebo range, and were much less than those produced by the two positive control drugs: THC (Schedules I, II, and III) and alprazolam (Schedule IV). CBD also does not appear to produce physical dependence.

For these reasons, CBD does not appear to have abuse potential under the CSA.

2. SCIENTIFIC EVIDENCE OF ITS PHARMACOLOGICAL EFFECT, IF KNOWN

The second factor the Secretary must consider is the scientific evidence of the pharmacological effects of CBD.

Neurochemical Activity of CBD (*In Vitro* Studies)

Receptor Binding Studies

In receptor binding studies with CBD, there was no significant affinity of CBD for cannabinoid (CB1 or CB2) sites. There was also no significant affinity of CBD for other sites associated with abuse potential: opioids (mu, kappa, or delta), GABA/ benzodiazepine, dopamine (D1 or D2), serotonin (1A, 1B, 2A, 3, 5A, 6, or 7), NMDA/glutamate, channels (calcium, potassium, sodium, or chloride), or transporters (dopamine or norepinephrine). CBD also did not have significant affinity for sites that are not associated with abuse potential: acetylcholine (muscarinic or nicotinic), adenosine, norepinephrine (alpha or beta), histamine, and neurokinin. CBD inhibits the transient receptor potential cation channel subfamily M member 8 (TRPM8) channel and activates TRPV1, TRPV2, TRPV3, and STRPV4 and TRPA1 channels, but it is unclear how this activity might contribute to the behavioral effects of CBD. These receptors are not currently associated with abuse potential.

Central Nervous System Effects

Animal Behavioral Effects

The animal behavioral effects of CBD were determined through general behavioral studies in mice and rats, evaluating whether CBD produces CNS activity, as well as through studies to determine if CBD produces abuse-related CNS activity using the tetrad

test, drug discrimination studies, and self-administration studies in mice, rats, and monkeys.

General Behavioral Studies

In an Irwin test of general behavior in rats, acute oral doses of CBD (10, 50, and 100 mg/kg) did not produce any changes in behavior or body temperature relative to vehicle. When the test was conducted in mice, acute intravenous doses of CBD (3, 10, and 30 mg/kg) produced a slight transient alteration in gait and a decrease in pain response relative to vehicle, suggestive of a sedative effect. However, when mice were given acute intravenous dose of CBD at 120 mg/kg, there were no changes in behavioral or muscular tone relative to vehicle.

In an open-field test in mice, in which animals are allowed to transverse a cage, acute intraperitoneal CBD (30 mg/kg) did not alter behavior, but the 100 mg/kg dose reduced locomotor activity, both relative to vehicle. When the test was conducted in rats, acute intraperitoneal CBD (60 and 120 mg/kg) produced a decrease in locomotor activity relative to vehicle. These data suggest CBD produces some sedative activity at high doses.

In the rotorod test, which evaluates the muscular coordination of an animal to maintain itself on a slowly rotating rod, acute intraperitoneal CBD (200 mg/kg) produced no changes in latency to fall relative to vehicle.

These results show that CBD produces some CNS activity, as evidenced by changes in general behavioral effects, but this occurs only at doses that are equivalent to human supratherapeutic doses. These sedative-like effects were transient, however.

Cannabinoid-Specific Behavioral Test

Mice were evaluated using the Tetrad Test, a screening study that measures changes in four behaviors that are known to be altered by THC, which include locomotor activity, immobility, hypothermia, and antinociception. In this study, mice received intraperitoneal doses of CBD, THC, or vehicle prior to observation.

CBD did not alter locomotor activity, immobility, or antinociception at 1, 10, 50, or 100 mg/kg, but did produce slight hypothermia at 50 and 100 mg/kg, relative to vehicle. In contrast, THC produced a decrease in locomotion as well as hypothermia and antinociception (but no changes in immobility) at 50 and 100 mg/kg, but produced no changes in response at 1 and 10 mg/kg, relative to vehicle.

These results show that CBD only produced positive signs on one of the four tetrad test behaviors. In contrast, THC produced positive signs in three of the four tetrad behaviors. This suggests that CBD does not have THC-like effects.

Drug Discrimination Study Evaluating Similarity to Known Drugs of Abuse

Drug discrimination is an experimental method of determining whether a test drug produces physical and behavioral responses that are similar to a training drug with specific pharmacological effects. Any centrally acting drug can serve as the training drug. When the training drug is a known drug of abuse, drug discrimination in animals serves as an important method for predicting whether the effects of a new drug will similarly have abuse potential. Drugs that produce a response similar to known drugs of abuse in animals are also likely to be abused by humans.

In drug discrimination, an animal learns to press one bar when it receives the training drug and another bar when it receives a placebo. Once responding to the training drug and placebo is stable, an animal is given a challenge session with the test drug. A test drug is said to have "full generalization" to the training drug when the test drug produces bar pressing ≥75% on the bar associated with the training drug (Doat et al., 2003; Sannerud and Ator, 1995).

Three drug discrimination studies were conducted with CBD in rats that had been trained to discriminate THC from vehicle or midazolam (Schedule IV) from vehicle.

In the first two studies, rats (n = 7/study) were trained to discriminate THC (3 mg/kg, i.p., 15 minute pretreatment time) from vehicle using a fixed ratio (FR) 10 schedule of reinforcement. When rats could stably discriminate THC from vehicle, challenge sessions with CBD began. CBD was tested orally with a 2-hour pretreatment time at 20, 75, and 150 mg/kg (first study) and at 1, 3, and 10 mg/kg (second study). THC was tested as a positive control using oral administration (1, 3, and 10 mg/kg, p.o., 90 minute pretreatment time).

As expected, THC (3 and 10 mg/kg) produced full generalization (70-99%) to the THC cue. In contrast, CBD did not produce full generalization to the THC cue at any dose: 1 mg/kg (9%), 3 mg/kg (9%), 10 mg/kg, (8%), 20 mg/kg (14%), 75 mg/kg (46%), and 150 mg/kg (27%). Vehicle produced no generalization (<11%) to the THC cue (which is full generalization (>89%) to the placebo cue). Only the two highest CBD doses produced partial generalization (27-46%) to the THC cue, but each of these responses was < 50% for the THC cue. These same data can be inverted as showing that the partial generalization was >50% for the placebo cue (54% for 75 mg/kg and 73% for 150 mg/kg). These data suggest that CBD is more like placebo than THC. Thus, these data show that CBD does not produce interoceptive effects similar to those produced by THC in rats.

In the third study, rats (n = 6) were trained to discriminate midazolam (0.5 mg/kg, i.p.) from vehicle. Once responding was stable, rats were challenged with midazolam (0.50, 1.0, and 1.50 mg/kg, p.o., 30-minute pretreatment time), alprazolam (0.125, 0.25, 0.50,

and 1.0 mg/kg, p.o.), CBD (20, 75, and 150 mg/kg, p.o.), or vehicle. Full generalization to the midazolam cue was seen after administration of midazolam (1.0 and 1.5 mg/kg) and alprazolam (0.50 and 1.0 mg/kg). However, CBD produced no generalization (<11%) to the midazolam cue at any dose. These data can be inverted to show >89% generalization to placebo. These data show that CBD does not produce interoceptive effects similar to those produced by midazolam in rats.

Self-Administration Studies Evaluating Rewarding Effects

Self-administration is a method that assesses whether a drug produces rewarding effects that increase the likelihood of behavioral responses in order to obtain additional drug. Drugs that are self-administered by animals are likely to produce rewarding effects in humans, which is indicative of abuse potential. Generally, a good correlation exists between those drugs that are self-administered by animals and those that are abused by humans (Balster and Bigelow, 2003). It is notable that self-administration is a behavior that is produced by drugs that have been placed into every schedule of the CSA. Additionally, rates of self-administration for a particular drug will go up or down if the available drug dose or the work requirement, i.e., bar pressing for drug, is altered. Positive results from a self-administration test provide an abuse potential signal, suggesting that a drug has rewarding properties but does not necessarily produce more rewarding effects than another drug in humans.

Two separate self-administration studies were conducted in rats (n = 5-7/group) to evaluate whether CBD produces sufficient reward to be reinforcing. Animals were initially trained to press a lever to receive either the Schedule II stimulant, cocaine (0.32 mg/kg/infusion, i.v.), using a fixed ratio (FR) 10 final schedule of reinforcement, or to lever-press for the Schedule I opioid, heroin (0.015 mg/kg/injection, i.v.), using FR3. Once responding for cocaine or heroin was stable, animals were also allowed to lever-press for CBD (0.02, 0.1, 0.5, or 1.5 mg/kg/infusion, i.v.), amphetamine (Schedule II; 0.05 mg/kg/infusion, i.v.), midazolam (Schedule IV; 0.0003, 0.001, 0.0015, 0.003 mg/kg/injection, i.v.), diazepam (Schedule IV; 0.001, 0.003, 0.0045, 0.01 mg/kg/injection, i.v.), or vehicle (i.v.). Rats were given access to each drug treatment for 3 consecutive days.

As expected, in rats, cocaine and heroin produced a relatively high degree of self-administration (~45 and ~18 infusions/session, respectively) and vehicle produced a low degree of self-administration (<10 infusions/session). The positive control drugs produced varying degrees of self-administration: cocaine = ~25 infusions/session, midazolam and diazepam = <10 infusions/session. Each of the four doses of CBD produced self-administration that was similar to that of vehicle (<10 infusions/session). In the heroin-trained animals, the 0.1 mg/kg/infusion dose of CBD produced a response that was statistically significantly greater than vehicle ($p<0.05$), but was numerically in the range of vehicle responding (e.g., 7 infusions/session).

A self-administration study was also conducted in monkeys (n = 5) trained to self-administer midazolam (0.01 and 0.032 mg/kg/infusion, i.v.) using an FR30 schedule of reinforcement. Both doses of midazolam produced ~13 infusions/session. In comparison, vehicle produced <1 infusion/session. When CBD (0.1, 0.32, 1.0, and 3.2 mg/kg/infusion, i.v.) was substituted, it did not maintain self-administration (<1 infusion/session).

Data from all these self-administration studies suggest that CBD produced insufficiently rewarding properties to sustain reinforcement.

Human Behavioral Effects

The human behavioral effects of CBD are evidenced by a human abuse potential study and by adverse events (AEs) reported in the clinical efficacy studies conducted with CBD.

Human Abuse Potential Study (Study #GWEP1431)

A human abuse potential study was conducted to evaluate the oral abuse potential, safety, tolerability, and pharmacokinetics of CBD (750, 1500, and 4500 mg) compared to alprazolam (Schedule IV) (2 mg), dronabinol (THC in the drug product Marinol (Schedule III); 10 and 30 mg), or placebo using a randomized, double-blind, double-dummy, placebo- and active-controlled, 6-period, crossover design in healthy non-dependent recreational polydrug users (n = 40). The doses of CBD represent the two therapeutic doses (10 mg/kg and 20 mg/kg) and a supratherapeutic dose (3 to 6 times greater than the therapeutic doses), scaled for a 75 kg adult.

Subjective Responses

As shown below in Table 1, on the primary subjective measure of Drug Liking visual analog scale (VAS), the two positive control drugs alprazolam (2 mg) and dronabinol (10 and 30 mg) produced significantly higher maximum (Emax) scores compared to placebo ($P < 0.001$ to 0.0001), which validates the study.

CBD at the two highest doses (1500 and 4500 mg) produced small but statistically significantly higher Emax scores on Drug Liking compared to placebo ($P < 0.05$ for both). However, both of these responses were just outside the placebo range (40-60, with 50 being "neutral" on a bipolar scale of 0 to 100) and had large standard deviations. CBD at the lowest dose (750 mg) did not differentiate statistically from placebo on Drug Liking. Additionally, the response to any dose of CBD was statistically significantly less than that produced by the positive control drugs, dronabinol and alprazolam.

These data contrast with data from previously conducted HAP studies with Schedule V drugs such as ezogabine, pregabalin, and lacosamide, in which these drugs produced

Drug Liking that was statistically similar to, or greater than, that produced by alprazolam or diazepam.

Table 1: Effects of Oral Placebo, Alprazolam (2 mg), Dronabinol (THC, 10 and 30 mg), and CBD (750, 1500, and 4500 mg) on Subjective Measures (VAS) – Emax Scores

Measure	Placebo (n = 37)	ALZ 2 (n = 40)	THC 10 (n = 39)	THC 30 (n = 40)	CBD 750 (n = 38)	CBD 1500 (n = 39)	CBD4500 (n = 40)
Drug Liking VAS bipolar	55 ± 11	79 ± 16 ^	74 ± 19 ^	87 ± 15 ^	57 ± 14	61 ± 17 *	64 ± 17 *
Overall Drug Liking VAS bipolar	50 ± 17	87 ± 16 ^	75 ± 21 ^	87 ± 19 ^	55 ± 16	57 ± 19	60 ± 26
Take Drug Again VAS	11 ± 25	85 ± 24 ^	65 ± 39 ^	85 ± 27 ^	20 ± 31	28 ± 37 *	42 ± 42 ^
Good Drug Effects VAS	11 ± 26	77 ± 25 ^	55 ± 39 ^	83 ± 22 ^	22 ± 33	29 ± 38 *	38 ± 38 #
High VAS	9 ± 22	55 ± 38 ^	38 ± 40 ^	71 ± 35 ^	10 ± 25	20 ± 35 *	31 ± 38 #
Stoned VAS	6 ± 19	45 ± 39 ^	37 ± 38 ^	78 ± 28 ^	14 ± 27	14 ± 29	24 ± 37 ^
Bad Drug Effects VAS	9 ± 23	23 ± 33 *	16 ± 30	26 ± 35 *	9 ± 21	11 ± 20	15 ± 26
Alert/ Drowsy VAS	55 ± 12 41 ± 17	57 ± 15 10 ± 14 ^	58 ± 15 26 ± 21 ^	65 ± 17 14 ± 14 ^	55 ± 14 33 ± 18 *	54 ± 11 30 ± 20 *	54 ± 11 29 ± 19 #
Agitated/ Relaxed VAS bipolar	50 ± 11 38 ± 19	54 ± 14 9 ± 13 ^	52 ± 14 22 ± 20 ^	58 ± 16 14 ± 16 ^	52 ±12 34 ± 21	52 ± 9 32 ± 21	53 ± 10 29 ± 21 *
Any Drug Effect VAS bipolar	18 ± 31	75 ± 26 ^	55 ± 38 ^	87 ± 17 ^	23 ± 32	34 ± 36 *	46 ± 39 ^
Hallucinations VAS	1 ± 2	18 ± 29 ^	3 ± 11	15 ± 34 *	1 ± 2	1 ± 2	1 ± 3
Bowdle (Internal Perception) VAS	1 ± 0	1 ± 0 ^	1 ± 0 *	1 ± 0 ^	1 ± 0	1 ± 0	1 ± 0
Bowdle (External Perception) VAS	1 ± 0	1 ± 0 ^	1 ± 0	1 ± 1 ^	1 ± 0	1 ± 0	1 ± 0
Drug ID: Benzodiazepine	12 ± 27	88 ± 24	27 ± 39	29 ± 39	21 ± 35	23 ± 36	27 ± 36
Drug ID: THC	9 ± 24	24 ± 35	58 ± 44	91 ± 22	20 ± 33	18 ± 29	28 ±37
Drug ID: Placebo	71 ± 44	2 ± 11	27 ±42	3 ±17	54 ± 46	52 ±48	36 ±44

* $p < 0.05$; #$p < 0.001$, ^ $p < 0.0001$ compared to placebo. All scales are unipolar (0-100 with 0 as neutral) unless marked as bipolar (0-100 with 50 as neutral).

Results from the secondary subjective measures show that:

- The positive control drugs alprazolam (2 mg) and dronabinol (10 and 30 mg) produced statistically significantly increased scores compared to placebo on other positive subjective responses such as the VAS for Overall Drug Liking, Take Drug Again, Good Drug Effects, High, Stoned, and Bowdle (Internal Perception).

- CBD at the high therapeutic and supratherapeutic oral doses (1500 and 4500 mg) produced small but statistically significant increases compared to placebo in positive subjective responses such as VAS for Take Drug Again, Good Drug Effects, and High. The positive subjective responses to CBD were always statistically significantly less than those produced by either alprazolam or dronabinol. Notably, the response to CBD at any dose did not produce Overall Drug Liking that fell outside the placebo range (40-60, bipolar scale). Similarly, the response to CBD for Stoned was either within or just outside the placebo range (0-20, unipolar scale).

- When Take Drug Again was evaluated for CBD (750-4500 mg) on an individual basis, 46-66% of subjects reported a score of 0 out of 100, indicating the subject would never be inclined to take CBD again. In contrast, the positive control drugs would be taken again by 83% of those who received 2 mg alprazolam and 60-77% of those who received 10 and 30 mg THC.

On the Drug Identification question, alprazolam (2 mg) was identified as a benzodiazepine (88 out of 100). Dronabinol (10 and 30 mg) was identified as dronabinol (58 and 91 out of 100). Placebo was identified as placebo (71 out of 100). CBD did not produce a strong signal for any substance except for placebo in response to the 750 and 1500 mg doses (54 and 52 out of 100). The 4500 mg dose of CBD was not identified as any substance (<36 out of 100 on any scale) and was notably not identified as dronabinol. This lack of identification of CBD as similar to THC by human subjects parallels the animal drug discrimination data, where animals did not indicate that CBD produced THC-like sensations.

Although these subjective data produced some statistically significant signals of abuse potential at the two higher doses of CBD (1500 and 4500 mg), these responses were either inside or just outside of the placebo range and had large standard deviations. Most importantly, any positive subjective response to CBD was always much lower than that produced by the positive control drugs, alprazolam and dronabinol. Additionally, CBD was never identified as dronabinol.

Abuse-Related AEs

CBD (750, 1500, and 4500 mg) produced reports of the AE euphoria in a few subjects (5.3% (2 of 38 subjects); 5.1% (2 of 39 subjects); and 7.5% (3 of 40 subjects),

respectively). Alprazolam (2 mg) produced a similarly low level of euphoria (7.5%, 3 of 40 subjects) while placebo produced no reports of euphoria (0%, 0 of 37 subjects). In contrast, dronabinol (10 and 30 mg) produced higher levels of euphoria (30.8% (12 of 39 subjects) and 62.5% (25 of 40 subjects)).

When an individual analysis was conducted on CBD responses, a euphoria-related response for most subjects either did not predict whether the individual reported positive responses on the subjective measures, or the positive subjective response was equivalent to that reported following placebo. Conversely, a high rating on a positive subjective response by any subject did not predict a report of a euphoria-related AE. Thus, although two of the nine subjects who reported euphoria as an AE following 4500 mg CBD also reported a high degree of positive subjective response on Drug Liking or Take Drug Again, seven of the nine subjects did not. Thus, the small degree of euphoria signals following CBD administration were not consistent with any other reports of positive subjective responses to the drug.

Residual THC Levels

The CBD product studied in all clinical investigations under the GW Pharmaceuticals NDA contained <0.15% residual THC. In the HAP study, the CBD batches used contained 0.03% and 0.06% residual THC. This means that the amount of THC present in the test doses ranged from 0.3-0.45 mg (750 mg CBD) to 0.45-0.90 mg (1500 mg CBD) to 1.35-2.70 mg (4500 mg CBD). The lowest FDA-approved dose of dronabinol in the Marinol drug product (Schedule II) is 2.5 mg. Thus, it is possible that THC may have contributed to the subjective responses following CBD administration.

However, when plasma concentrations of THC from subjects in the HAP study were evaluated following administration of CBD, they were low compared to the plasma levels produced in the same subjects following administration of the two doses of dronabinol. Following administration of CBD, the Cmax levels of residual THC were 0.30 ng/ml (750 mg CBD), 0.44 ng/ml (1500 mg CBD), and 0.48 ng/ml (4500 mg CBD), which demonstrates a nonlinear pharmacokinetics. These concentrations are much lower than the Cmax reported following administration of 10 mg dronabinol in the HAP study (Cmax = 7.90 ng/ml).

Thus, it is unlikely that THC contributed to the slight positive responses on some of the subjective measures or contributed to the euphoric AE responses reported following the higher doses of CBD.

Overall Conclusions

The 750 mg dose of CBD (the low 10 mg/kg therapeutic dose) did not produce abuse potential signals. Although the two higher doses of CBD tested in this study (1500 and 4500 mg, representing the 20 mg/kg therapeutic dose and a supratherapeutic dose)

produced some signals of abuse potential, they were small and often inside or just outside the acceptable placebo range. Additionally, these signals were always statistically significantly less than those produced by dronabinol or alprazolam. In a drug identification test, CBD at any dose was not identified as dronabinol and was most frequently identified as placebo. The low degree of the AE of euphoria produced by the higher doses of CBD did not predict reports of positive subjective responses. Thus, these data show that although CBD is a cannabinoid, it is not producing dronabinol-like responses that are indicative of abuse potential.

AEs in Clinical Studies with CBD

Phase 1 Clinical Safety Studies (Excluding HAP Study)

Abuse-related AEs were evaluated from the Phase 1 studies with CBD, which included studies investigating pharmacokinetics, hepatically-impaired patients, renally-impaired patients, impact on sleep, and physical dependence.

None of the individuals in these Phase 1 studies with CBD reported that they experienced "euphoria"-related AEs, which are the key AEs in determining whether there are abuse-related signals from clinical studies.

There was a high rate of "somnolence" in the two pharmacokinetic studies. In one study, 750 and 1500 mg CBD produced "somnolence" in 2-4 of 9 subjects (22-44%) compared to 2 of 9 subjects (33%) from placebo. In the other study, 750 and 4500 mg CBD produced "somnolence" in 5-11 of 49 subjects (10-22%) compared to 4 of 50 subjects (8%) from placebo. However, in the absence of "euphoria"-like AEs, "somnolence" is not interpreted as producing an abuse-related signal. Interestingly, no subjects in the sleep study (n = 18) reported "somnolence" in response to CBD or placebo. No other AEs that can be indicative of abuse were reported in any of these studies.

In conclusion, the AE data in Phase 1 studies conducted with CBD do not have any signals suggesting that CBD has abuse potential.

Phase 2/3 Clinical Efficacy Studies

Three Phase 2/3 clinical studies were conducted to support the efficacy and safety claim for CBD as an adjunct treatment of two epilepsy conditions in children: Dravet syndrome (also known as severe myoclonic epilepsy of infancy; for ages 4-10) and Lennox-Gastaut syndrome (for ages 2-18).

It is not possible to evaluate these Phase 2/3 studies for abuse signals related to CBD because of the underlying neurological impairment of patients and the confounding effects of other medications. Specifically, the children in the studies are too ill or too young to volunteer accurate information regarding psychiatric or neurological AEs

indicative of abuse potential. Additionally, since CBD is proposed as an adjunctive treatment, children in these studies remained on their current antiepileptic medications.

In conclusion, AE data from the Phase 2/3 clinical efficacy studies cannot be evaluated for abuse-related AEs directly related to CBD.

3. THE STATE OF CURRENT SCIENTIFIC KNOWLEDGE REGARDING THE DRUG OR OTHER SUBSTANCE

The third factor the Secretary must consider is the state of current scientific knowledge regarding CBD. This knowledge includes information on the chemistry and pharmacokinetics of CBD.

Chemistry

Cannabidiol (USAN name) is a new molecular entity identified by CAS registry number: 13956-29-1. It is chemically known as 2-[1R-3-methyl-6R-(1-methylethenyl)-2-cyclohexen-1-yl]-5-pentyl-1,3-benzenediol. It has a molecular formula of $C_{21}H_{30}O_2$ and a molecular weight of 314.5. It is a white to pale yellow crystalline solid with a melting point of 65-67 °C. It is soluble in methanol, ethanol, acetone, dichloromethane, sesame oil, and other oils, but insoluble in water.

The drug product is a 100 mg/ml oral solution of CBD (b) (4) sesame oil, (b) (4) (sucralose (b) (4)), and flavoring agent. It is available in (b) (4) mL amber glass bottles with child-resistant screw caps.

Manufacturing of CBD for the Drug Product

The manufacturing of CBD for the drug product is described by the Sponsor in the NDA.

(b) (4)

(b) (4)

[redacted]

Stability studies conducted by the Sponsor confirm that the drug product will remain within specification limits up to 24 months when stored at the conditions tested (25 °C/60% relative humidity, and 30°C/ 75 % relative humidity). Additionally, no evident degradation was observed during the photostability study.

Pharmacokinetics

Following a single oral dose (1500, 3000, 4500, and 6000 mg), CBD appeared rapidly in the plasma, with maximum plasma concentrations (Cmax) typically occurring within 3-5 hours post dosing and remaining detectable up to 72 hours post-dose. CBD has an elimination half-life of 30 hours.

Based on data from a human abuse potential study in which a lower-range therapeutic dose (750 mg = 10 mg/kg), higher-range therapeutic dose (1500 mg = 20 mg/kg), and a supratherapeutic dose (4500 mg = 3-6X) were tested, the pharmacokinetics of CBD (and residual dronabinol) are nonlinear (see Table 2, below).

Table 2: Cmax of CBD and Residual Dronabinol After Oral Administration of CBD in a Human Abuse Potential Study

	750 mg CBD	1500 mg CBD	4500 mg CBD
CBD levels	372 ng/ml	608 ng/ml	619 ng/ml
dronabinol levels	0.30 ng/ml	0.44 ng/ml	0.48 ng/ml

A 2-fold increase in an oral dose of CBD (from 750 mg to 1500 mg) produced a 1.5-fold increase in plasma levels of CBD (from 372 ng/ml to 608 ng/ml) and residual dronabinol (from 0.30 ng/ml to 0.44 ng/ml). Most critically, a 3-fold increase in an oral dose of CBD (from 1500 mg to 4500 mg) produced no meaningful change in plasma levels of either CBD (from 608 ng/ml to 619 ng/ml) and residual THC (from 0.44 ng/ml to 0.48 ng/ml). These data show that increasing the oral dose of CBD does not produce proportional increases in plasma concentrations of CBD and residual THC.

Medical Use in the United States

In the Sponsor's submitted NDA, CBD is proposed as an oral treatment of two epilepsy conditions in children who remain on their current antiepileptic medication: Dravet syndrome and Lennox-Gastaut syndrome. If this NDA is approved by FDA, CBD will for the first time have a currently accepted medical use in the United States.

CBD has also been available in the United States under an expanded access program (EAP) established by the Sponsor. Over (b) (4) treatment-resistant epilepsy patients have gained access to CBD through investigational new drug (IND) applications submitted to FDA by independent physician investigators, as well as by state governments to support CBD access programs in several U.S. states. An analysis of 214 of these individuals enrolled in a 1-year period during 2014-2015 was recently published (Devinsky et al., 2016). According to this evaluation, AEs were reported in 128 (79%) of the 162 patients within the safety group. AEs reported in >5% of patients were somnolence (n=41 [25%]), decreased appetite (n=31 [19%]), diarrhea (n=31 [19%]), fatigue (n=21 [13%]), and convulsion (n=18 [11%]). Notably, none of these AEs included euphoria or other abuse-related AEs.

4. ITS HISTORY AND CURRENT PATTERN OF ABUSE

The fourth factor the Secretary must consider is the history and current pattern of abuse of CBD.

CBD as a single active ingredient in a drug product formulation has not been approved for therapeutic use in any country, so such information pertaining to a well-characterized formulation of CBD as the only or predominant active ingredient is limited. However, there is widespread availability and use of CBD-containing products, which are illicit under federal law, that are marketed in various states under the laws of those states. While these products typically contain other psychoactive substances such as THC, which limits our ability to assess the effects of CBD alone, we considered any available epidemiology data stemming from use of CBD-containing products in various states. With these limitations, no signal for abuse of CBD was identified from these data.

The FDA/CDER Office of Surveillance and Epidemiology (OSE) performed a formal assessment of all AEs associated with CBD use available in the FDA Adverse Event Reporting System (FAERS) database and AEs relating to abuse potential in the medical literature. OSE also evaluated the . Their evaluation and conclusions follow below.

AE reports for CBD-containing products are entered into the FAERS database when received by FDA. Importantly, the FAERS database is designed to capture AE reports for FDA-approved products. Since CBD is not an FDA-approved product, FAERS reports may instead be received from manufacturers of approved co-suspect products, or from health professionals or consumers with unapproved CBD as the primary suspect drug. It is not known if FAERS would capture serious, rare, or new toxicity of CBD, given that it is not an FDA-approved product. Other general FAERS limitations include the lack of certainty that the reported event was caused by the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain sufficient detail to properly evaluate an event. Further, FDA does not receive reports for every AE or medication error that occurs with a product. Many factors can influence whether an event will be reported, such as the time a product has been marketed and publicity about an event.

OSE identified 83 FAERS cases in which AEs were reported with CBD as a suspect drug. Most of these cases were reported in 2017. The source of CBD was reported in 34 of the cases, where in all 34 cases CBD was provided in clinical trials, while for the remaining 49 cases the exact source could not be determined. The most frequently reported reason for use of CBD was treatment of epilepsy/seizure conditions and the most frequently reported concomitant medications were anticonvulsants, which are often recognized drugs of abuse that are controlled in Schedules II, IV, and V.

The most frequently reported AE preferred term (PT) was drug interaction. Clobazam (Schedule IV) was the most frequently reported concomitant medication used with CBD, and increased plasma levels of clobazam was the most frequently reported drug-drug interaction outcome.

OSE identified 55 cases reporting specific abuse-misuse PTs with CBD use, but none appear to provide convincing evidence of abuse potential. There were no euphoria-related terms in the review, except for one patient with pre-existing schizoaffective disorder who experienced visual hallucinations after using a product reportedly containing a mixture of CBD and dronabinol. Since dronabinol (Schedules I, II, and III) can produce hallucinations, it is not possible to attribute this event to CBD.

A search of the medical literature by OSE suggest minimal or low abuse potential with CBD.

OSE did not identify any additional cases of abuse with CBD in the AAPCC-NPDS or NEISS-CADES databases. NPDS case records are self-reported mainly from the public (68.9% from a residence vs 23.2% from a Health Care Professional). Although Poison Control Centers perform follow-up calls, they are not able to verify the accuracy of every report made to AAPCC member centers. Although OSE identified 88 cases from these databases that were documented as marijuana (dried plant)-related, it cannot be excluded

that some of these cases may represent exposure to CBD (unapproved product) due to the potential misclassification resulting from patient self-reporting.

The limitation of NEISS-CADES data available from 2004-2015 is that it does not include cases with intentional drug injuries resulting from alcohol, tobacco, and illicit substances. It is likely that the reason OSE did not capture any cases of CBD abuse during 2004-2015 is that the NEISS-CADES database only started to collect information about drug abuse in 2016. The data relating to emergency department visits from drug abuse are not yet available in NEISS-CADES.

To conclude, based on the preclinical and clinical study data (see Factor 2, above), and on available epidemiological data, there is no signal for the development of substance use disorder in individuals consuming CBD-containing products. In addition, there is no signal of abuse of CBD in the available AE reporting data and epidemiology data.

5. THE SCOPE, DURATION, AND SIGNIFICANCE OF ABUSE

The fifth factor the Secretary must consider is the scope, duration, and significance of abuse of CBD.

As described in Factor 4, CBD as a single entity has not been approved for therapeutic use in any country. Based on the preclinical and clinical study data (see Factor 2, above), and on available epidemiological data, the scope, duration and significance of CBD abuse is too low to quantify.

6. WHAT, IF ANY, RISK THERE IS TO THE PUBLIC HEALTH

The sixth factor the Secretary must consider is what, if any, risk there is to the public health.

The extent to which a drug has abuse potential is considered an indication of its public health risk. However, based on the preclinical and clinical study data (see Factor 2, above), and the available epidemiology data (see Factor 4, above) there is little indication that CBD has abuse potential or presents a significant risk to the public health.

7. ITS PSYCHIC OR PHYSIOLOGIC DEPENDENCE LIABILITY

The seventh factor the Secretary must consider is the psychic or physiologic dependence liability of CBD. This was addressed through a human study evaluating the ability of CBD to produce withdrawal signs after chronic administration and subsequent discontinuation.

Human Physical Dependence

An exploratory outpatient human physical dependence study was conducted to evaluate whether chronic administration of CBD produced signs or symptoms of withdrawal upon drug discontinuation. The Treatment Phase (single blind) consisted of a total of 30 adult subjects (n = 13 female) who received 1500 mg/day (750 mg *bis in die* (b.i.d.)) CBD for 28 days. In the Withdrawal Phase (double blind), subjects who completed the Treatment Phase (n = 21) were randomized to either continue receiving 1500 mg/day (750 mg b.i.d.) CBD for an additional 14 days (n = 9) or to receive placebo (n = 12). There was no positive control to validate the study procedures.

During the 6-week study period, subjects returned to the clinical research center on Days 7, 14, 21, 28, 31, 35, and 42 for evaluations. Compliance was assessed by plasma concentrations of CBD and dronabinol and their major metabolites. Although subjects were tested for drugs and alcohol on weekly visits during the initial 28 days of CBD administration, they were not tested again during the discontinuation period (Days 29-42) until Day 35 (halfway through the Withdrawal Phase).

Physical dependence was evaluated using two scales: the Cannabis Withdrawal Scale (CWS) and the Penn Physician Withdrawal Checklist (PWC-20). These two questionnaires were administered on Days 1, 21, and 28 during CBD administration, as well as Days 31, 35, and 42 after drug discontinuation (e.g., Days 3, 7, and 14 following completion of the 28 days of CBD administration). Subjects were asked to indicate the extent to which each withdrawal symptom was experienced in the last 24 hours and also to rate the negative impact on normal daily activities.

Possible CWS scores range from 0 to 190 points (0-10 points for 19 questions) based on degree of withdrawal symptoms and (separately) for impact on daily living. At the end of the Treatment Phase, the CWS score for all completers (n = 23) was 9.3 on the questionnaire and 5.8 for the daily negative impact. During the Withdrawal Phase, withdrawal scores in both groups decreased: the group that continued to receive CBD had scores on the CWS that decreased from baseline (Day 28) by up to 6 points and the placebo group had scores that decreased by up to 4 points. A similar reduction in scores was seen for the impact on daily living scores, which decreased from baseline (Day 28) for the CBD group by up to 9 points, and the placebo group, which had scores that decreased by up to 6 points.

Possible PWC-20 scores range from 0–60 points (0-3 points for 20 questions) based on degree of withdrawal symptoms. The scores for both groups were close to 0 during and immediately after 28 days of CBD administration. Similar to results on the CWS, withdrawal scores during the second phase decreased from baseline (Day 28) for the CBD group by up to 0.8 points and the placebo group had scores that decreased by up to 1.3 points.

Other Subjective Measures

There were no changes recorded during the Withdrawal Phase in the placebo group compared to CBD maintenance for evaluations on sleep disruption, Epworth Sleepiness Scale (ESS), Columbia-Suicide Severity Rating Scale (C-SSRS), or the Hamilton Depression Rating Scale (HAM-D).

Pharmacokinetics of CBD and THC

As expected, CBD levels in subjects who transitioned to placebo on Day 29 fell steadily over the discontinuation period and reached nearly pre-dose levels by Day 42. In contrast, CBD levels continued to increase for subjects who were maintained on CBD from Days 29-42. However, inter-subject variability was high, with standard deviations of the mean CBD plasma concentrations during the study ranging from 17 to 306 ng/ml. The concentration–time profiles of the major metabolites of CBD showed a similar pattern.

Dronabinol was detected in plasma at only at trace levels, with a mean plasma dronabinol concentration of 0.40 ng/ml at the end of the Withdrawal Phase in subjects who continued to receive 1500 mg CBD. This is similar to the plasma levels of dronabinol (0.44 ng/ml) produced in the human abuse potential study following acute administration of 1500 mg CBD (see Table 2, above).

Adverse Events

AEs were monitored during the Treatment Phase and the Withdrawal Phase (beginning on the third day after CBD was discontinued). As shown in Table 3 (below), few AEs were reported during the Withdrawal Phase in either the CBD or placebo group.

Table 3 All Causality TEAEs Experienced by > 1 Subject

	Treatment Phase	**Withdrawal Phase**	
	1500 mg/day CBD (750 mg b.i.d.) 28 days (n=30)	**1500 mg/day CBD (750 mg b.i.d.) 14 days (n=9)**	**Placebo b.i.d. 14 days (n=12)**
	n (%)	**n (%)**	
Gastrointestinal disorders			
Diarrhea	19 (63.3)	4 (44.4)	2 (16.7)
Abdominal pain	14 (46.7)	0 (0)	1 (8.3)
Nausea	13 (43.3)	2 (22.2)	0 (0)
Dyspepsia	4 (13.3)	0 (0)	0 (0)
Dry mouth	2 (6.7)	0 (0)	0 (0)
Nervous system disorders			

Headache	15 (50.0)	2 (22.2)	7 (58.3)
Somnolence	7 (23.3)	1 (11.1)	0 (0)
Dizziness	7 (23.3)	0 (0)	0 (0)
Disturbance in attention	2 (6.7)	0 (0)	0(0)
Dizziness postural	2 (6.7)	0 (0)	0 (0)
General disorders			
Fatigue	10 (33.3)	0 (0)	0 (0)
Influenza-like illness	2 (6.7)	0 (0)	1 (8.3)
Psychiatric disorders			
Nightmare	2 (6.7)	0 (0)	1 (8.3)
Insomnia	2 (6.7)	0 (0)	0 (0)
Mood altered	1 (3.3)	1 (11.1)	0 (0)

AEs reported during CBD administration included diarrhea (63%), abdominal pain (47%), nausea (43%), headache (50%), somnolence and fatigue (23% and 33%), dizziness (23%), and insomnia (7%). Notably for an abuse potential evaluation, there were no reported incidents of euphoria during the CBD administration phase.

During the drug discontinuation phase, influenza-like illness and nightmare were reported in only 1 of 12 subjects in the placebo group (compared to 0 of 9 subjects in the CBD group) and headache was reported by 7 of 12 subjects in the placebo group (compared to 2 of 9 subjects in the CBD group).

Conclusions

The data above, including the data collected after CBD discontinuation, provide no evidence for a classic drug withdrawal syndrome for CBD and no evidence that CBD causes physical or psychic dependence.

8. WHETHER THE SUBSTANCE IS AN IMMEDIATE PRECURSOR OF A SUBSTANCE ALREADY CONTROLLED

The eighth factor the Secretary must consider is whether CBD is an immediate precursor of a substance that is already controlled under the CSA.

CBD can be converted to both Δ^9-tetrahydrocannabinol (Δ^9-THC) and to Δ^8-tetrahydrocannabinol (Δ^8-THC) through cyclization of CBD under acidic conditions (Adams et al. 1941, Gaoni and Mechoulam 1966, Gaoni and Mechoulam 1971). Although there are no reports that this synthesis takes place in clandestine laboratories, the Sponsor conducted studies to understand the feasibility of converting CBD to Δ^9-THC. Based on Internet drug forum discussions, such as Bluelight.com, the Sponsor attempted the conversion using commercially available acids at various concentrations and volumes, and studied the effects of temperature, agitation, and reaction time. Under the best conditions of reaction identified by the Sponsor, the maximum amount of CBD that could be converted to Δ^9-THC was approximately 40%.

It is important to point out that the conversion appeared to peak at a certain reaction time, after which Δ^9-THC may start to degrade. Isolation of Δ^9-THC from the reaction mixture did not prove difficult when using nonpolar organic solvents. However, the Δ^9-THC formed could not be separated from other cannabinoids (including unchanged CBD) and other components (i.e., sesame oil present in the formulation).

Even though the possibility of converting the CBD present in the product to Δ^9-THC or Δ^8-THC exists, there may be practical reasons, such as knowledge of the best reaction conditions to avoid degradation of the THC product, limited reaction yields, and purity of the THC product upon isolation, among other possible reasons, to deter initiation of this laborious route to obtain the drug.

Conclusions

Given the available data, it is unlikely that CBD would act as an immediate precursor to THC for abuse purposes.

C. Recommendation

Cannabidiol (CBD) is proposed as an oral adjunct treatment of two epilepsy conditions in children who remain on their current antiepileptic medication: Dravet syndrome and Lennox-Gastaut syndrome. Upon consideration of the eight factors determinative of control of a substance under section 201(c) of the CSA, FDA concludes that CBD and its salts, with a limit of (b) (4) % (w/w) residual (−)-trans-Δ^9-tetrahydrocannabinol, could be removed from control under the CSA [21 U.S.C. § 812 (b)(4)].

We reach this conclusion because we find that CBD does not meet the criteria for placement in any of Schedules II, III, IV, or V under the CSA. Specifically, we find that, upon consideration of the eight factors determinative of control of a substance in relation to Schedule V:

1) CBD has negligible potential for abuse relative to the drugs or other substances in Schedule V.

CBD does not bind to cannabinoid receptors or any other receptor associated with abuse potential. It does not produce overt behaviors in rodents that are suggestive of abuse potential. It also does not produce a cannabinoid response in the rodent tetrad test. CBD does not generalize to THC in a rodent drug discrimination study, showing it does not produce cannabinoid effects. It does not produce self-administration in rodents, suggesting it does not have rewarding properties. In a human abuse potential study with CBD, there were slight abuse-related signals, but these were close to the acceptable

placebo range. There were no AEs from clinical studies conducted with CBD in a non-patient population indicative of abuse potential.

Based on the totality of the available scientific data, CBD does not have meaningful abuse potential. In support of this finding, the evidence for any abuse potential is also substantially less than that of all substances currently in Schedule V.

2) CBD has a currently accepted medical use in treatment in the United States.

Upon approval of an NDA by the FDA, CBD will have a currently accepted medical use in treatment in the United States.

3) Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in schedule V.

CBD does not produce withdrawal signs or symptoms in a human study 3 days after drug discontinuation. This suggests that CBD does not produce physical dependence. Additionally, there is little evidence that CBD produces rewarding responses in animals or humans, which suggests that the drug does not produce meaningful psychological dependence.

Notwithstanding these three findings, there are international scheduling considerations that also impact our final recommendation. Although CBD is not listed in the schedules of the 1961, 1971, or 1988 United Nations International Drug Control Conventions (Conventions), Schedule I of the 1961 Convention does include "extracts" of cannabis. In a report published following its November 2017 meeting (Report), the Expert Committee on Drug Dependence of the World Health Organization (ECDD) stated that CBD that is produced as an extract of cannabis is currently included in Schedule I of the 1961 Convention.[5] Subsequently, in the April 6, 2018, DEA Letter, DEA asserted that given the controls mandated by the 1961 Convention, the United States would not be able to keep its obligations under the treaty if CBD were decontrolled under the CSA.

The CSA contemplates that scheduling decisions will be made in accordance with treaty obligations. For example, under section 201(d)(1) of the CSA, if control of a substance is required under an international treaty or convention in effect on October 27, 1970, the Attorney General is required to impose controls on such substance by placing it under the schedule he deems most appropriate to carry out such obligations.

[5] The Report went on to say that CBD had not been previously reviewed for international scheduling, and would be the subject of review and discussion at the ECDD meeting in May 2018 (a meeting later moved to June 2018).

Here, DEA has requested that HHS conduct a medical and scientific evaluation and provide a scheduling recommendation for CBD. In responding to this request, FDA will not recommend that DEA take action that will cause the United States to be unable to keep its treaty obligations. Thus, if control of CBD is required under the treaty obligations of the United States, then to continue maintaining such obligations, and reflecting our scientific findings to the extent currently possible, we recommend CBD and its salts, with a limit of (b) (4) % (w/w) residual (−)-*trans*-Δ^9-tetrahydrocannabinol (THC), be placed in the least restrictive CSA schedule, Schedule V.

If treaty obligations do not require control of CBD, or the international controls on CBD under the 1961 Convention are removed at some future time, the above recommendation for Schedule V under the CSA would need be revisited promptly to address the change in a key predicate underlying such recommendation.

As noted in the April 6, 2018, DEA Letter, in the event that FDA approves the NDA submitted by the Sponsor, our recommendation to move CBD from Schedule I to Schedule V of the CSA will "requir[e] DEA to issue an immediately effective interim final rule" in accordance with section 201(j) of the CSA. Specifically, under 201(j), DEA would be required publish an interim final rule scheduling the drug within 90 days of the later of (1) FDA approval or (2) receipt of the scheduling recommendation from the Secretary. The interim final rule would be immediately effective, and the drug could be marketed on the date of publication in the *Federal Register*. Additionally, under section 505(x) of the FD&C Act, the date of issuance of the interim final rule controlling the drug would be the date of approval of the Sponsor's NDA.[6]

In establishing the interim process under section 201(j) of the CSA, Congress ensured that access to drugs approved by FDA, but subject to a scheduling or rescheduling process, would be available more rapidly to patients. The expedited timeframe for this interim process is particularly important here. As noted in the April 6, 2018, DEA Letter, "[g]iven that the CBD drug in question here is intended for a particularly vulnerable pediatric population, any delay in marketing of the drug following FDA approval would seem contrary to the public health and safety." Accordingly, DEA's use of the section 201(j) interim process is consistent with the statutory goal of expanding patient access in the interest of the public health.

[6] This is in contrast to the statutory process by which a drug listed in Schedule I may be decontrolled entirely. Under that process, set forth in section 201(a) of the CSA, a scheduling change would not become effective until after publication of a final rule following notice and comment under the Administrative Procedure Act.

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