Safety of CBD in Humans – A Literature Review
(As of December 12, 2019)

Contents

A Note Regarding this Literature Review

There are many unanswered questions about the science, safety, and quality of products containing cannabidiol (CBD). As part of Food and Drug Administration's (FDA or Agency) effort to evaluate potential regulatory pathways for FDA-regulated consumer products containing CBD, the FDA continues to stay apprised of information about the safety of CBD. This literature search is one of multiple steps FDA is taking as part of the evidence-based approach toward understanding the safety profile and use of CBD products.

For this peer review, five experts were selected by Versar, Inc., an independent contractor, to evaluate and provide written comments on the appropriateness of the procedures and criteria used in the inclusion of clinical and animal studies in the literature review, clarity of the presentation of scientific content, and consistency with the goal of presenting a compilation of data, not an analysis of findings. Because this literature review summarizes literature available as of December 12, 2019, it does not include scientific information that has been subsequently published.

This document, *Safety Risks of CBD Products to Humans – A Literature Review*, is based on a search on PubMed and ClinicalTrials.gov (as of December 12, 2019), as well as the publicly available information included in FDA's safety evaluation of the clinical trials and animal studies that supported approval of Epidiolex, which is currently the only approved drug containing CBD***. It is important to note that the literature review is a description of published scientific findings on CBD's safety profile, not an analysis or evaluation of those findings or of any specific product. This document does not represent FDA's scientific conclusions.***

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Introduction

Interest in cannabis and cannabis-derived products increased when Congress passed the Agriculture Improvement Act of 2018 (Public Law 115-334) (the 2018 Farm Bill). The Farm Bill removed hemp (defined as cannabis (Cannabis sativa L), and derivatives of cannabis, with extremely low (not more than 0.3% on a dry weight basis) concentrations of THC) from the definition of marijuana under the Controlled Substances Act (CSA). However, the Farm Bill preserved FDA's authorities, including those under the Federal Food, Drug, and Cosmetic Act (FD&C Act) and the Public Health Service Act, such that hemp products, while not controlled under the CSA, are subject to the same authorities and requirements as FDA-regulated products containing any other substance. This allows the FDA to continue enforcing the law to protect patients and the public while also providing potential regulatory pathways, to the extent permitted by law, for products containing cannabis and cannabis-derived compounds (including cannabidiol, or CBD).

The term "cannabidiol" is a single chemical compound and is often abbreviated as "CBD" by scientists. However, the broad use of the term "CBD" is not well-defined. This can lead to the inaccurate assumption that all products claiming to have "CBD" are the same and all contain the single molecule cannabidiol.

The CBD Policy Working Group was formed in April 2019 to coordinate FDA's approach to CBD policy making, including exploring the appropriateness of potential pathways for dietary supplements and/or conventional foods containing CBD to be lawfully marketed, including with respect to sections 301(ll) and 201(ff) of the FD&C Act; examine potential pathways and a regulatory framework for cosmetics and veterinary products; develop an understanding of the existing science and evidence related to CBD and identify gaps in knowledge that are key to inform regulatory policy discussions; and consider what statutory or regulatory changes might be needed.

FDA is committed to sound, science-based policy on cannabidiol (CBD). While we recognize the potential for scientific studies demonstrating the benefits of CBD, questions remain regarding its safety. Therefore, we conducted a literature review of the publicly available scientific data to identify the current state of the science as it relates to the safety of CBD in humans in order to inform our work related to CBD use and marketing.

This literature review is based on safety findings from clinical and preclinical testing of CBD identified through a search on PubMed and ClinicalTrials.gov (as of December 12, 2019), as well as the publicly available information included in FDA's safety evaluation of the clinical trials and animal studies that supported Epidiolex approval. The literature review is a description of published scientific findings on CBD's safety, not an analysis or evaluation of those findings.

The information below provides a high-level summary of the literature reviewed. A full list of the literature is referenced below in Section 4 and is organized by the category under which they were reviewed (i.e. safety related to ingestion, safety related to inhalation, etc.).

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1. Method

Clinical data

The FDA literature review on the safety of CBD in humans was initially focused on clinical trial data only. This included:

- Publicly available information contained in the FDA clinical review of the Epidiolex New Drug Application (NDA) and Epidiolex labeling;[1]
- Published, peer-reviewed scientific literature on PubMed; and
- CBD clinical trials that were not yet published but had posted safety results on ClinicalTrials.gov (i.e., not including trials that posted only efficacy results but not safety results).

The procedures and criteria used in the identification of clinical trials from PubMed and ClinicalTrials.gov are listed below.

	PubMed	**ClinicalTrials.gov**
Step 1: Search on PubMed or ClinicalTrials.gov		
Keywords used in search	Cannabidiol, CBD, Epidiolex; filtered by "clinical trials" (as of 12/12/19)	Cannabidiol, CBD, Epidiolex; filtered by "completed" and "with results" (as of 12/12/19)
Step 2: Apply exclusion criteria		
Excluded	• Review articles[2] • Clinical trials that used cannabis, marijuana, THC,[3] or CBD-THC combination • Surveys on human use of "CBD" products	• Clinical trials that used cannabis, marijuana, THC, or CBD-THC combination • Clinical trials that have been published on PubMed

For completeness of data on human exposure to CBD in a clinical trial setting, this review includes clinical trials that presented safety data, as well as clinical trials that either: 1) were silent on safety findings; or 2) did not present safety data, but only made conclusory statements about CBD safety.

[1] See the drug approval package for Epidiolex, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210365Orig1s000TOC.cfm.
[2] In the background section, we provide high-level information on CBD's mode of action (MOA) and oral pharmacokinetic profile. To provide the background information on MOA, FDA relied on three review articles (Bergamaschi 2011, Iseger 2015, and White 2019) and a 2017 report of the National Academy of Sciences. . For the purposes of this literature review on CBD's safety risks, other literature reviews were excluded from the search criteria.
[3] THC refers to delta-9-tetrahydrocannabinol.

Animal data

We were made aware of animal studies that identified toxicity that have not been evaluated by clinical testing – i.e., male reproductive toxicity and developmental toxicity – through other publicly-available sources (e.g., review of submissions to docket number FDA-2019-N-1482, FDA nonclinical evaluation of Epidiolex). For completeness of animal studies identifying such toxicities, we conducted a search on PubMed using keywords listed below; the animal studies are included in the literature review per procedures and criteria described below.

- Step 1: Identify any potential toxicities seen in animal studies that were not evaluated by clinical testing based on various sources (e.g., docket submissions, FDA nonclinical evaluation of Epidiolex)
    - Through this process, two toxicities were identified: male reproductive toxicity and developmental toxicity
- Step 2: Search on PubMed (using keywords ["cannabidiol" or "CBD" or "Epidiolex"] and ["toxicity" or "reproductive" or "testosterone" or "developmental"])
- Step 3: Apply inclusion/exclusion criteria:

  Included: Animal studies that:

    - Reported findings on male reproductive toxicity or developmental toxicity

  Excluded:

    - Review articles[4]
    - Animal studies that used products such as cannabis, marijuana, THC, or CBD-THC combination
    - Nonclinical testing such as cell culture/in vitro studies, analytical studies, and studies that used anesthetized animals
    - Surveys on animal use of CBD products

[4] In the background section, we provide high-level information on CBD's mode of action (MOA) and oral pharmacokinetic profile. To provide the background information on MOA, FDA relied on three review articles (Bergamaschi 2011, Iseger 2015, and White 2019) and a 2017 report of the National Academy of Sciences. For the purposes of this literature review on CBD's safety risks, other literature reviews were excluded from the search criteria.

2. Background

Mechanisms of action

Before 2000, the primary research topics regarding possible therapeutic effects of CBD were related to its antiepileptic, sedative, anxiolytic, and antipsychotic activities.[5] Since then, there has been a notable increase in scientific literature on CBD, due to the identification of its potential anti-inflammatory and neuroprotective effects.[6] There is evidence that CBD could potentially be further explored for the treatment and symptom relief of various neurological disorders such as epilepsy and seizures, psychosis, anxiety, movement disorders (e.g., Huntington's disease and amyotrophic lateral sclerosis), and multiple sclerosis.[7]

This wide range of therapeutic effects can be explained by CBD's multiple mechanisms of action. The table below was replicated from a review, which describes CBD's potential receptor actions and mediated effects.[8]

Receptor	**Impact**	**Potential pharmacologic outcome**
CB1	Direct antagonism and negative allosteric modulator antagonism	Attenuation of impaired learning, memory, hypothermic, and psychosis effects induced by delta-9-THC
CB2	Antagonist + inverse agonist	Anti-inflammatory effects
GPR55	Antagonist	Anticancer effects
5HT1-alpha	Agonist	Pain relieving (allosterically regulates mu and sigma opioid receptors) and antianxiety effects
TRPV-1	Agonist	Anti-inflammatory, pain relieving, and sebum producing effects
Adenosine A2A	Enhanced adenosine concentrations	Anti-inflammatory effects

[5] Bergamaschi MM, Queiroz RH, Zuardi AW, et al. Safety and side effects of cannabidiol, a Cannabis sativa constituent. Curr Drug Saf, 2011 Sep 1;6(4):237-249 (citing Cunha JM, et al. Chronic administration of cannabidiol to healthy volunteers and epileptic patients. Pharmacology, 1980; 21: 175-185; Zuardi AW, et al. Cannabidiol, a Cannabis sativa constituent, as an antipsychotic drug. Braz J Med Biol Res, 2006; 39(4): 421-429).
[6] Bergamaschi MM, Queiroz RH, Zuardi AW, et al. Safety and side effects of cannabidiol, a Cannabis sativa constituent. Curr Drug Saf, 2011 Sep 1;6(4):237-249 (citing various publications).
[7] See The health effects of cannabis and cannabinoids, the current state of evidence and recommendations for research. A Report of the National Academy of Sciences, 2017, page 47 (citing various publications), available at https://www.nap.edu/catalog/24625/the-health-effects-of-cannabis-and-cannabinoids-the-current-state.
[8] White CM. A review of human studies assessing cannabidiol's (CBD) therapeutic actions and potential. J Clin Pharmacol, 2019 Jul;59(7):923-934.

* CB1, cannabinoid receptor 1; CB2, cannabinoid receptor 2; GPR55, G protein-coupled receptor 55; 5HT1-alpha, a subtype of serotonin 1a receptor; TRPV-1, transient receptor potential vanilloid receptor-1.

Pharmacokinetics

Below is a brief description of oral CBD's pharmacokinetics (PK), based on FDA-approved label for Epidiolex:[9]

- Cannabidiol is metabolized in the liver and the gut (primarily in the liver) by CYP2C19 and CYP3A4 enzymes, and UGT1A7, UGT1A9, and UGT2B7 isoforms.
- Cannabidiol has a time to maximum plasma concentration (T_{max}) of 2.5 to 5 hours at steady state (C_{ss}).
- The half-life of cannabidiol in plasma was 56 to 61 hours after twice-daily dosing for 7 days in healthy volunteers.
- Cannabidiol is excreted in feces, with minor renal clearance.

3. Summary of safety findings identified in the literature

The broad use of the term "CBD" in published literature, commercially available products at the state-level, e-commerce products, manufacturing websites, and elsewhere is inconsistent and not equivalent. Therefore, products claiming to contain "CBD" cannot be easily compared to one another and may result in varied safety findings depending on the product type and formulation.

Safety related to route of administration

Safety related to ingestion

We reviewed four primary clinical trials that supported Epidiolex approval. In addition, a total of 94 trials (as of December 12, 2019) were identified through PubMed and ClinicalTrials.gov search that used single (34 trials) or repeated doses of oral CBD (60 trials); 30 of them were in patients with epilepsy or other seizure disorders. Twenty-four were silent on safety findings, while 21 trials included a conclusive statement (e.g., "CBD is well tolerated" from the author's perspective) without providing detailed safety results. Below is a high-level summary of the notable safety findings in the repeated dose trials.

- Repeated doses in healthy volunteers (n=24): One placebo-controlled trial assessed CBD's effect at 750 and 1500 mg for 6 days. The reported percentage of patients with adverse events (AEs) combined CBD groups vs. placebo, where CBD group exceeded

[9] Epidiolex (cannabidiol) is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in patients 2 years of age and older. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210365Orig1s000MedR.pdf.

placebo: headache (44 vs. 0%), dizziness (17 vs. 0%), presynope (17 vs. 0%), diarrhea (67 vs. 0%), and nausea (44 vs. 17%).

- Repeated doses in patients with epilepsy (in 1 randomized, placebo-controlled trial): In this trial in 198 patients with Dravet syndrome, AEs reported in more than 10% of patients treated with 20 mg/kg/day CBD included (%, CBD vs. placebo): diarrhea (26.1 vs. 12.3%), vomiting (15.9 vs. 6.2%), pyrexia (20.3 vs. 16.9%), fatigue (20.3 vs. 10.8%), nasopharyngitis (11.6 vs. 7.7%), ALT and AST elevations (both 11.6 vs. 0%), decreased appetite (27.5 vs. 16.9%), and somnolence (23.2 vs. 13.9%).

- Repeated doses in patients with epilepsy and other seizures (in 11 open-label trials): Serious AEs reported in ≥ 2 trials: status epilepticus (5.6-11.5% of patients), convulsion (4.9-14%), pneumonia (2.5-5%), liver AST/ALT elevations (1.6-5.6%), seizure (5.6-19%), and pyrexia (3.8-4%). AEs reported in ≥ 6 trials (in descending order of # of trials in which the AEs were reported): diarrhea (13-44%), somnolence (8-39%), decreased appetite (6-38%), vomiting (6-18%), upper respiratory tract infection (11-20%), convulsion (11-24%), and fatigue (10-22%).

- Repeated doses in patients with other diseases (e.g., schizophrenia and Parkinson's disease): Of the 5 placebo-controlled trials that reported safety findings, the AEs reported were similar in both CBD and placebo groups (or placebo exceeded CBD group) for two trials. In two schizophrenia trials the AEs that were higher in CBD vs. placebo group were: (1) 600 mg/day for 6 weeks (n=18 for CBD, n=19 for placebo): sedation (22.2 vs. 5.6%); and (2) 1000 mg/day for 6 weeks (n=43 for CBD, n=45 for placebo): diarrhea (9.3 vs 4.4%), nausea (7 vs 0%), and headache (4.7 vs 4.4%). In a trial in patients with fatty liver disease using 200, 400, or 800 mg/day CBD for 8 weeks, AEs with a higher incidence in the CBD group (combined CBD n=20 vs. placebo n=5) were: diarrhea (60 vs. 0%) and headache (15 vs. 0%).

FDA's review of the four randomized placebo-controlled trials describes Epidiolex's attributable risks: somnolence (18%; 3% is severe), CNS adverse reactions such as agitation and sedation (1-4%), decreased appetite (16%), diarrhea (9%), and decreased weight (3%). Based on the information in these trials, the estimated risk of severe liver injury, irreversible liver failure that is fatal or requires liver transplantation, is 0.3 to 0.4%, although no cases of severe liver injury were reported. It also notes that it is clear that many patients will develop cannabidiol-induced adverse reactions; however, those observed in the development program would be expected to be detectable by patients and/or caregivers, self-limited, and reversible. All literature references for this category are provided below in the corresponding reference section.

The reviewed clinical trials have the following limitations when relied upon to inform the safety about oral CBD in humans when used in non-drug settings:

- Adverse effects of repeated doses in healthy volunteers and at-risk populations may not reflect safety related to chronic exposure to CBD because the maximum length of CBD

administration in these trials was 10 weeks (tested in 20 frequent cannabis users). Thus, data on long-term exposure to oral CBD in healthy and at-risk populations are lacking.

- Clinical trials of repeated doses in patients have provided, compared to other settings, the most comprehensive safety data on repeated oral CBD use. But these trials are predominantly in pediatric patients who suffer from epilepsy and other seizure-related conditions. Therefore, it is not clear whether these safety findings would be generalizable to other populations, which may include both healthy adults and children, as well as adults and children with comorbidities other than epilepsy.

Safety related to topical use

Five trials that reported safety findings were identified: AEs in one placebo-controlled trial (250 or 500 mg/day for 12 weeks; n=321) that were >3% and exceeded placebo were (CBD vs. placebo) application site dryness (3.8 vs. 0.9%) and headache (3.3 vs. 1.9%). In an open-label trial (250 mg/day for 1 year; n=20), the most common AEs were gastroenteritis (14%) and upper respiratory tract infection (12%). Topical use of CBD was reported to be "well tolerated" in a completed phase 1 trial of healthy volunteers (n=20) and in an ongoing trial of 23 patients with acne, although no dose level or actual safety findings were reported. One placebo-controlled trial investigated the effect of topical CBD oil (250 mg for 4 weeks; n=29) in patients with symptomatic peripheral neuropathy; the authors noted that no adverse events were reported in this trial without providing further details. All literature references for this category are provided below in the corresponding reference section.

Safety related to inhalation

In general, CBD products for inhalation come in various forms (e.g., dried flowers, extracts, oil) that often utilize vaporization (i.e., flowing heated air) or combustion (i.e., open flame) as methods for delivery. The CBD content reported for these products is the amount of CBD quantitated prior to vaporization or combustion of the products. The CBD content reported in the products is different than the CBD content inhaled by participants from the delivery method (i.e., vaporization or combustion). Literature does not report quantitated values of CBD in the inhaled vapor or smoke, which likely differs from the CBD content in the pre-vaporized or pre-combustion products.

Studies report the CBD content of these products in different units (e.g., mg, mg/g, %, mcg/kg) and the product compositions also vary greatly (not always reported in literature), making comparisons challenging from one inhalation product to the next. All literature references for this category are provided below in the corresponding reference section.

Two clinical trials reported safety findings:

- CBD cigarette at 150 mcg/kg (about 10.5 mg for 70 kg; n=15) had "no effect" compared to placebo on heart rate, ability to track, and stability of stance

- Vaporized CBD at 400 mg (n=36) produced "acute intoxication effects" (distinct feelings of depersonalization and derealization).

Two clinical trials were silent on safety findings:

- CBD via inhaler, 0.4 mg/press, unclear how much CBD was used per day, for 7 days, in 12 smokers
- CBD via vaporizer, single dose, 32 mg, in 32 healthy volunteers

Other routes of administration

Limited literature reported the use of other CBD routes of administration (e.g., sublingual drops and intravenous injection):

- Crossover study (n = 6) given 20 mg CBD (maximum dose) sublingual drops; they also received in separate occasions CBD:THC sublingual drops, THC sublingual drops, placebo sublingual drops, CBD:THC aerosol, and CBD:THC nebulizer. One severe AE (i.e., conjunctival hyperaemia) occurred in the CBD sublingual drops group.
- Randomized, double-blind trial (n=33; 6 for CBD, 6 for cannabinol, and 21 for THC) in 1970s studied pharmacological activity of one-time intravenous injection of CBD, cannabinol, and THC, all at 10 mg. The trial was silent on safety findings, except for noting that CBD I.V. injection did not produce any psychological or physiological effects (through subjective evaluation of drug effects – i.e., "high", as well as monitoring of vital signs).

All literature references for this category, Safety related to route of administration, are provided in the corresponding reference section.

Safety related to interactions in the body

Interactions with food

Epidiolex's label notes: (1) a high-fat/high-calorie meal increased Cmax by 5-fold and AUC by 4-fold; and (2) taking Epidiolex with CNS depressants and alcohol may increase sleepiness. One of the postmarketing requirements (PMRs) for Epidiolex is to study its effect on the pharmacokinetics of caffeine.

Interactions with THC

Many trials reported that CBD could attenuate THC's effect, including euphoria, anxiety, and motor and mental performance impairment. But in some trials lower doses or pretreatment of CBD did not counteract or even potentiate THC's effects.

Interactions with other drugs

Epidiolex's label notes: Inhibitors (moderate and strong) and inducers (strong) of CYP3A4 and CYP2C19 could affect CBD's concentration, requiring CBD dose adjustment. Dose adjustment should be considered for drugs with UGT1A9, UGT2B7, CYP1A2, CYP2B6, CYP2C8, CYP2C9 and CYP2C19 substrates. CBD can also affect other drugs, including clobazam, other sensitive CYP2C19 substrates (potentially requiring dose adjustment), and valproate (increased liver enzyme elevations potentially requiring discontinuation or dose adjustments of valproate and/or CBD). In addition, many PMRs are required to further assess potential drug-drug interactions.

All literature references for this category, Safety related to interactions in the body, are provided in the corresponding reference section.

Safety related to special populations

Pregnancy and fetal development

There are no clinical data. Epidiolex's label encourages women taking the drug during pregnancy to enroll in a registry. One of the PMRs for Epidiolex [10] is to conduct a pregnancy outcomes study. The label also notes administration of CBD to pregnant animals produced evidence of developmental toxicity. A few other studies also reported developmental risks in animals exposed to CBD.

Lactation

There are no clinical data.

Pediatric population

There is little information in this population outside the epilepsy and seizure setting.

Hepatic impairment

The Epidiolex label recommends dose adjustment in patients with moderate or severe hepatic impairment due to 2.5 to 5.2-fold higher AUC.

Renal impairment

While the Epidiolex label is silent on renal impairment, the FDA clinical pharmacology review notes that there is no effect on CBD exposure and no dose adjustments needed. There is a PMR required to assess whether the effect of Epidiolex on serum creatinine reflects an effect on glomerular filtration rate.

[10] Postmarket Requirements (PMRs) and Commitments https://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm

Male reproductive system

Animal studies have reported that CBD can cause male reproductive toxicity, with effects on the development of testes and sperm.

All literature references for this category, Safety related to special populations, are provided in the corresponding reference section.

4. References

Summary of safety findings

Safety related to ingestion

Clinical trials that supported Epidiolex approval

FDA clinical safety review of Epidiolex, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210365Orig1s000MedR.pdf.

See Epidiolex's approval letter, dated 6/25/18, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210365Orig1s000Approv.pdf.

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Limitations of oral CBD clinical trials

Safety related to topical use

2.2a Clinical data

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Interactions with food, other drugs, and THC

Interactions with food

The Epidiolex label is available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210365Orig1s000lbl.pdf; see also

See Epidiolex's approval letter, dated 6/25/18, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210365Orig1s000Approv.pdf.

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Safety related to special populations

Pregnancy and fetal development

See Epidiolex's approval letter, dated 6/25/18, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210365Orig1s000Approv.pdf.

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Pediatric population

The pediatric experience with CBD is limited to clinical trials evaluating CBD for epilepsy and seizures. Therefore, there is a large gap in our knowledge about the safety of chronic CBD exposure in the wider pediatric population, and it is not known if pediatric patients without epilepsy who take CBD would have similar safety profiles to those with epilepsy.

Hepatic impairment

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Renal impairment

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Male reproduction system

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