FDA's Response to External Peer Review of Safety of CBD in Humans – A Literature Review (As of December 12, 2019), June 9, 2020

I. Introduction

There are many unanswered questions about the science, safety, and quality of products containing cannabidiol (CBD). As part of the Food and Drug Administration's (FDA or Agency) effort to evaluate FDA-regulated consumer products containing CBD, FDA continues to stay apprised of available scientific information about the safety of CBD. This effort has resulted in the development of a document, Safety Risks of CBD Products to Humans – A Literature Review. 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 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.

Versar, Inc., an independent contractor, coordinated an external letter peer review for FDA of this literature review. For this peer review, five experts were selected by Versar, Inc. 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 those findings or of any specific product .

In Section II of this peer review response report, we list the charge questions given to the reviewers regarding the objective of the peer review and specific advice sought through the peer review. In Section III of this peer review response report, we provide a summary of the peer reviewers' comments followed by either a description of any changes made to the literature review in response to peer reviewer comments or an explanation of our decision to not make suggested changes. The individual peer reviewer comments are provided in tabular format in Appendix I.

Below are the names and affiliations of the peer reviewers:

Maria Roberta Cilio, M.D., Ph.D.
University of Louvain School of Medicine, Belgium
Saint-Luc University Hospital

Tyler E. Gaston, M.D.
The University of Alabama at Birmingham

Cecilie Johannessen Landmark, Ph.D.
Oslo Metropolitan University, Norway
Oslo University Hospital

Simona Pisanti, Ph.D.
University of Salerno, Italy

Kenneth Sommerville, M.D.
Sommerville Consulting LLC

II. Charge to Reviewers

FDA is a science-based public health and regulatory agency within the Department of Health and Human Services (HHS), responsible for protecting and promoting public health. This includes ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation.

In recent years, FDA has seen a growing interest in the development of therapies and other FDA-regulated consumer products derived from cannabis (Cannabis sativa L.) and its components, including cannabidiol (CBD). This interest spans the range of product categories that the agency regulates. Interest in these products increased when Congress passed the Agriculture Improvement Act of 2018 (the 2018 Farm Bill). Among other things, this law established a new category of cannabis classified as "hemp" – defined as cannabis and cannabis derivatives with extremely low (no more than 0.3 percent on a dry weight basis) concentrations of the psychoactive compound delta-9-tetrahydrocannabinol (THC). The 2018 Farm Bill removed hemp from the definition of marihuana (marijuana) in the Controlled Substances Act, and hemp is no longer a controlled substance under federal law.

At the same time, Congress explicitly preserved FDA's current authority to regulate products containing cannabis or cannabis-derived compounds under the Federal Food, Drug, and Cosmetic Act (FD&C Act) and section 351 of the Public Health Service Act. In doing so, Congress recognized the agency's important public health role with respect to all the products it regulates. This allows 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.

FDA treats products containing cannabis or cannabis-derived compounds as we do any other FDA-regulated products. Among other things, the FD&C Act requires a cannabis product (hemp-derived or otherwise) that is intended to diagnose, cure, mitigate, treat or prevent disease to either be approved by FDA for its intended use, or, for certain over-the-counter (OTC) drugs, meet specific requirements in the FD&C Act, before it may be introduced into interstate commerce. Articles (other than food) that are intended to affect the structure or function of the body of humans or animals are also required to be approved by FDA or meet the requirements for certain OTC drugs. Additionally, it is unlawful to introduce food containing added CBD, or the psychoactive compound THC, into interstate commerce, or to market CBD or THC products as dietary supplements. This is in part because CBD and THC are active ingredients in FDA-approved drug products and were the subject of substantial clinical investigations before they were marketed as food. In such situations, with certain exceptions that are not applicable here, the only path that the FD&C Act allows for such substances to be added to foods or marketed as dietary supplements is if the Secretary of HHS first issues a regulation, through notice-and-comment rulemaking, allowing such use.

There are many unanswered questions about the science, safety, and quality of products containing CBD. As part of FDA's effort to evaluate potential regulatory pathways for FDA-regulated consumer products containing CBD, FDA continues to stay apprised of emerging available scientific information about the safety of CBD. This effort has resulted in the development of a document, Safety Risks of CBD Products to Humans – A Literature Review. 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 approval of Epidiolex, which is currently the only approved drug containing CBD. The literature review is a compilation of published scientific findings within a specific timeframe on CBD's safety risks, not an analysis or evaluation of those findings.

Charge Questions

1. Are the procedures and criteria used in the inclusion of clinical and animal studies in the literature review appropriate for the purpose of identifying scientific data that informs our understanding of CBD's safety profile in humans? For example, are there additional studies that should be included in the literature review based on the current search criteria, and should different search criteria be used to identify additional studies?

2. For the studies currently included in the literature review: are the safety findings presented clearly and comprehensively?

3. We note at the beginning of the literature review that the review is a compilation of published scientific findings on CBD's safety, not an analysis of those findings. Are the scientific findings presented in a way consistent with this approach?

4. Are the limitations of oral CBD clinical trials accurately described in section 2.1d?

III. Summary of Peer Reviewer Comments and FDA Response

Summary of General Impressions:

Overall, the reviewers expressed satisfaction with the breadth and thoroughness of the literature review and agree that the information provided is accurate, and that each relevant aspect about CBD safety has been taken into consideration and described properly. They also agreed that the structure of the document is well-organized, and the process by which the studies were identified for inclusion in the literature review (e.g., inclusion/exclusion criteria, search parameters) is clear. The reviewers confirmed that there is no judgment about the quality of the studies.

In response to this request for general impression of the literature review, reviewers highlighted several suggestions to improve clarity and flow of some sections of the document, including suggestions on reference format. Further, some reviewers requested clarifying or additional information to be added to the literature review, such as additional description of the number of participants in each arm of the trial and the various CBD products used in the identified studies. While the goal of the literature review was to provide a compilation of published scientific findings on CBD's safety risks (as of December 12, 2019) and not an analysis of those findings, some reviewers suggested the document include an analysis of the study data and corresponding conclusions.

FDA Response:

We appreciate the reviewers' responses and suggestions to improve upon the clarity and flow of the literature review. In response, we reformatted the literature review to use a bibliography that corresponds to each section in the literature review and modified the literature review to present the safety findings, as described in the identified studies in a more straightforward manner.

Regarding the recommendation to provide an analysis of the scientific data presented in this literature review, we note that this was not in scope for the purposes of this document as indicated by FDA asking the reviewers to assess the unbiased presentation of data per Charge Question #3. Additionally, while some reviewers suggested inclusion of additional studies, we note that many of the recommended studies fell outside of the December 12, 2019, cut-off date for inclusion in this literature review document.

The peer reviewers included helpful comments that were outside of the scope of the peer review, some of which may be considered in the future (e.g., drug-drug interaction data, which is lacking in human clinical trials but there are some animal data available). Therefore, we have limited our following responses to the information requested in the charge questions.

Summary of Charge Question Comments

1. Are the procedures and criteria used in the inclusion of clinical and animal studies in the literature review appropriate for the purpose of identifying scientific data that informs our understanding of CBD's safety profile in humans? For example, are there additional studies that should be included in the literature review based on the current search criteria, and should different search criteria be used to identify additional studies?

Summary of the Comments:

The reviewers agreed that the search procedure and inclusion criteria are well defined and appropriate, with one reviewer noting that, in particular for the cannabinoid space, it is important to appropriately define search procedures given the large amounts of poor levels of evidence (i.e., surveys). Further, reviewers agreed and stated that the most relevant current safety data from animal and human studies were captured, and animal studies were included only where evidence from humans were not available, i.e., male reproductive toxicity and developmental toxicity. There were some recommendations to include additional studies. For example, one reviewer suggested inclusion of drug-drug interaction data, but acknowledged this would be out of scope for the purposes of this literature review given the paucity of data in humans. Another reviewer suggested inclusion of additional search criterion "GWP42003" as it yielded additional human studies for consideration.

FDA Response:

FDA thanks the reviewers for their thoughtful comments and for agreement that the search criteria applied are well defined and appropriate. Regarding the specific peer reviewer recommendations (human drug-drug interaction data, gender differences, additional search criterion), FDA will take these into consideration, and respond appropriately, should the literature review be updated in the future.

2. For the studies currently included in the literature review: are the safety findings presented clearly and comprehensively?

Summary of the Comments:

The studies are comprehensively presented and grouped into single- or multiple dosing, healthy volunteers vs. patients, and route of administration. Reviewers appreciated the acknowledgment of safety related to special populations. Some reviewers requested FDA update the literature review to include additional description of the CBD evaluated the respective study, e.g., pharmaceutical-grade, highly purified, synthetic, CBD and other components, etc. Additionally, one reviewer requested FDA include additional detail on the elevation of hepatic enzymes, including a discussion of Hy's Law as it relates to hepatotoxicity.

FDA Response:

Should FDA decide to update this literature review, we will consider revising study descriptions to include more details regarding coadministration of CBD, product type and formulation, and presentation of long-term exposure study details (e.g., Hy's law, physical addition, and weight gain). We note that additional information was added to the section titled "Safety Related to Inhalation" to provide more clarity around these data.

3. We note at the beginning of the literature review that the review is a compilation of published scientific findings on CBD's safety, not an analysis of those findings. Are the scientific findings presented in a way consistent with this approach?

Summary of Comments:

Overall, the reviewers state that the document presents study data agnostic to analysis. In its present form, the review provides a clear compilation of relevant published literature (through December 12, 2019) covering safety aspects of CBD in humans, but with no evaluation or grading of evidence. Peer reviewers agreed that throughout the literature review, data are reported and do not appear to be interpreted or analyzed. One reviewer noted that the review is important for further research purposes as it clearly identifies data gaps. Additionally, a reviewer suggested that any conclusory statements from the study reports be put in quotations to avoid the perception that these statements represent FDA's views.

FDA Response:

We appreciate the reviewer feedback that the FDA presented findings in an accurate manner and the recommendations to consider use of quotations for conclusory statements made by the study investigators be included in the summary. To this end, we've included a statement in the summary to clearly indicate that summaries of scientific findings are non-conclusory and have added quotations where appropriate per the recommendation of the peer reviewers to clearly indicate direct quotes from studies.

4. Are the limitations of oral CBD clinical trials accurately described in section 2.1d?

Summary of Comments:

In general, reviewers stated that the limitations of oral CBD clinical trials are accurately described and that evidence from long-term studies are scarce. Reviewers provided some considerations for updates to this section:

- One reviewer stated that there are sufficient repeated dosing studies for safety and the single-dose studies are adequately complemented by the longer term data and suggested removing the limitation regarding lack of long-term data to address the safety of repeated and single dosing.
- One reviewer recommended inclusion of additional studies that may address the limitation on the lack of long-term data in epilepsy.
- Other reviewers recommended acknowledging additional limitations such as the variability of pure oral oil CBD preparations and formulations, and that this may influence the safety profile.
- Another reviewer recommended assessment of safety findings in the context of whether a protocol administered CBD or co-administered CBD as this may discern side effects attributed to CBD and that all safety findings may not necessarily be extrapolated to apply to all products.

FDA Response:

We thank the reviewers for their feedback regarding the FDA's presentation of the limitations of oral CBD clinical trials. We note that section 2.1d of the literature review as sent to the peer reviewers can now be found in section 3 under the heading of "Safety Related to Ingestion". This section includes the limitation regarding lack of long-term exposure in health and at-risk populations, which one reviewer recommended removing. While the FDA appreciates this recommendation, the Agency will maintain this presentation of facts because it is not clear whether these safety findings would be generalizable to the users of non-drug CBD products, which may include both healthy adults and children, as well as adults and children with comorbidities other than epilepsy. FDA agrees with the reviewer regarding long-term data to address the safety of repeated and single dosing and FDA has updated the section to remove the

limitation related to acute adverse effect of single doses not reflecting safety related to chronic exposure to CBD. It is also noted that other reviewers agree with inclusion of this limitation. Regarding the recommendations to address the limitations associated with lack of long-term data in epilepsy and assessment of side effects based on administration of CBD alone versus co-administration of CBD, should the Agency decide to update this literature review, these studies and others that may address these limitations will be reviewed. We thank the reviewers for the recommendation regarding limitations of study data due to the inherent inter- and intra- CBD preparation and formulation variability and that not all safety findings may necessarily be extrapolated to apply to all products and have included a modification in the limitations outlined in the "Summary of Safety Findings" section.

Appendix I – Individual Peer Reviewer Comments

I. General Impressions	
REVIEWER	**COMMENT**
Reviewer #1	The report was a comprehensive review of the published safety literature concerning the safety of CBD in humans. It provided an exhaustive list of studies of varying size and across a number of medical conditions as well as data from healthy adult volunteers. The data are well-presented and reasonably organized although the extensive number of trials included are daunting. There is no judgment about the quality of the studies. A greater emphasis on the four epilepsy studies that formed the basis for approval in Dravet and LGS would be helpful to the reader since these are probably the best clinical data done with FDA guidance and including adults and children. There is no section that separately treats the extension study 1415 which documents the safety over months and includes the patients from the four key epilepsy studies. The 1415 study could be presented in the same section as data from the Expanded Access Program (EAP) as a complement to the long-term open-label data from the clinical trials. The EAP studies included epilepsy syndromes other than Dravet and LGS and are important as safety data outside the approved syndromes. These data are again probably the best long-term data and should be treated with special emphasis. There are also data from posters presented by Greenwich Biosciences at the 2019 meeting of the American Epilepsy Society (AES) in Baltimore that can be made available to FDA. There is the most recent safety data of the 1415 study presented for both Dravet and LGS. There is also a poster with the preliminary data from the adequate and well-controlled study of Tuberous Sclerosis that compared 25 and 50 mg/kg for CBD versus placebo.
Reviewer #1	Other additions that should be considered are more detail on the hepatic enzyme elevations including data on what happened to the elevations after stopping, revising doses, or continuing on CBD. If actual measures of weight would be helpful for assessment of the reported weight loss are available, those data could also be presented with the four controlled epilepsy trials.
Reviewer #1	Lastly, data on the completed abrupt withdrawal study recently presented in Epilepsy and Behavior (March 2020) may be of interest given concerns about abuse and addiction with cannabinoids although these data are outside the cut-off date of December 15, 2019. Another brief review of the deaths in the clinical trials would also be helpful although the NDA covered this very well and it may or may not be needed.
Reviewer #2	The overall impression of the review is that it is clearly written based on comprehensive searches on published studies. The review is up to date, until December 2019. *Accuracy* The title of the review is "Safety of CBD in Humans". This includes various aspects, as short- and long-

I. General Impressions	
REVIEWER	**COMMENT**
	term exposure of CBD in healthy volunteers as well as in patients. Various patient groups in a range of age groups are included from the studies that have been performed. Also, different CBD-products were used in some of the studies, and the routes of administration cover different ways in which CBD cause exposure to the human body. To collect data on certain areas where human studies have not been performed, animal studies were provided, i.e., male reproductive toxicity and developmental toxicity and even in vitro studies. Thus, the title covers these aspects but are broader than one could assume.
Reviewer #2	*Clarity* The outline is rather general, as the content is divided into only two main chapters: 1) Background, which is a short introduction of pharmacodynamics and -kinetics, and the main part 2) Safety in humans, which is sub-divided into six sections of safety related to ingestion, topical use, inhalation and other routes of administration (short parts, where all these three could be described under "other routes of administration" than the oral route), interactions with food, other drugs and THC (extensive part, could be divided into separate sections), and safety related to special patient populations, also including preclinical studies (extensive part, could as well be divided into specific sections). Thus, the headings would reflect the content even more clearly. In addition, there are more than 25 pages of appendices of the various studies as an appendix. First there is a summary and description of literature searches, which could be included in the list of contents for improved overview of the report.
Reviewer #2	*Conclusions* There are some clear comments made by the FDA and further post marketing studies that will be performed. The main summary in short is provided before the total report and could also be included in the contents. It does not seem, however, that the review includes any conclusions, as the approach is only to provide the data and not to analyze or evaluate this. In my opinion, it would be more clinically relevant for the readers if some conclusions were stated.

I. General Impressions	
REVIEWER	**COMMENT**
Reviewer #3	Overall the information provided is accurate, each relevant aspect about CBD safety has been taken into consideration and described properly. The data underlying both clinical trials and preclinical studies are reported in detail even if their description can be further improved by using the same consistent format both throughout the main document and in the Appendices, in order to increase the readability and allow the correct identification of the references. The compilation of the safety findings leads to verifiable and sound conclusions, not affected by interpretation biases or by speculations.
Reviewer #3	In my opinion, the main issue about the clarity of presentation regards the way the references to clinical trials and relevant publications are cited in the text. The fact that the same reference is mentioned in the footnotes with a different number each time it is cited in the text (sometimes even in consecutive pages) only creates a lot of confusion to the reader. Moreover, it is very difficult to link the findings described in the main document to the corresponding clinical trial listed in the Appendices, because the study is not unambiguously identified. For these reasons, it would be far more preferable and clearer for the reader to use a unique notation with a reference number that is always the same for the single reference in the main document and the appendix, moving the reference list/Bibliography to a proper section at the end of the document and using the footnotes only for relevant annotations and explanations. Instead of using the citation of references by number, the First Author Year notation could be used, as in fact already done in some cases in the document. In any case, I suggest always using the same style (number or First Author Year) throughout the document and the Appendices. It would also be useful identifying the clinical trials in the Appendix with their Identifier and linked publications, adding two columns (Clinical Trial Number, References) to the tables.
Reviewer #3	Furthermore, always using the same way to describe clinical trials data would make them clearer and easier to interpret. For example, the number of participants in each arm of the trial analyzed, should always be reported not only in the Appendices but also in the main document with the notation (n=X).
Reviewer #3	As regards the organization of the main document's contents, the Summary is too repetitive and written in a way too similar to the main text, so it is a little bit confusing and it is difficult to understand why the same concepts are repeated a few pages apart. Maybe it would be better to organize the Summary in a more concise, non-repetitive, schematic way.
Reviewer #4	The document reviewed, "Safety of CBD in Humans – A Literature Review", is a comprehensive compilation of the available data to date on the safety of CBD in humans. A majority of this data come from placebo-controlled and other clinical trials of Epidiolex, a highly purified pharmaceutical grade CBD that is now FDA approved in the treatment of seizures associated with Lennox Gastaut and Dravet Syndromes, but other clinical trials of other CBD products were also included. Overall, the data presented are accurate. The structure of the document is well-organized, and the process by which the studies presented were obtained (e.g., inclusion/exclusion criteria, search parameters) is clear.
Reviewer #4	However, there are some concerns regarding the completeness of the description of the various CBD products (other than Epidiolex) used in the other presented studies. The rationale for this and recommendations on how to improve this are in the response for charge question 2.
Reviewer #4	The document itself, when viewed as a whole, is somewhat choppy in its flow and appears that possibly different writing styles are at least in part responsible for this. The review does not appear to draw specific conclusions with the data presented or provide recommendations based on the presented data- it merely reports the available safety data within the defined criteria without analysis or interpretation of those data. This appears to have been the objective of this compilation.

I. General Impressions

REVIEWER	COMMENT
Reviewer #5	I have one concern related to the fact that, in the literature, the terms "CBD" and "Cannabidiol" may encompass a large number of products, i.e., CBD-bases with different composition. It should be stated in the section on Clinical data – procedures and criteria on page 1, whether only trials using pharmaceutical-grade, highly purified, or pure synthetic CBD were included. Otherwise, the composition of the investigational product for each study should be listed together with the other study details in the Appendices.
Reviewer #5	As noted in the Review, many studies do not include any safety data; most studies reporting safety findings conclude that CBD is well tolerated, despite a very high incidence of AEs. This is worrisome and should be considered if safety is evaluated.

II. Charge Questions

CHARGE QUESTION 1. Are the procedures and criteria used in the inclusion of clinical and animal studies in the literature review appropriate for the purpose of identifying scientific data that informs our understanding of CBD's safety profile in humans? For example, are there additional studies that should be included in the literature review based on the current search criteria, and should different search criteria be used to identify additional studies?

REVIEWER	COMMENT
Reviewer #1	The search procedure seems reasonable and captured the most important safety data. There are two posters from the 2019 AES (December 2019 in Baltimore) presented by Greenwich Biosciences that may be helpful. Please see Question #4 comments. Although a bit later than December 15, 2019, the study of abrupt withdrawal to test for a withdrawal syndrome was published in Epilepsy and Behavior in the March 2020 edition by Lesley Taylor et al. This publication is a report on a randomized and placebo-controlled trial examining whether there is a withdrawal syndrome with Epidiolex. This may be of interest given the concern if there are any data to support physical addiction with CBD. The study showed no evidence of a withdrawal syndrome.
Reviewer #2	Up to date evaluation on safety aspects of CBD. Animal data and human studies included. Animal studies have been included only where evidence from humans were not available, i.e., male reproductive toxicity and developmental toxicity.
Reviewer #2	The searches with a stepwise process is clear from identification, searches and inclusion/exclusion. To illustrate the process, a flow chart could be of benefit to the readers. The search criteria are well defined, only pure CBD, Epidiolex, included from PubMed and clinicaltrials.gov, whereas other preparations with CBD/THC and reviews were excluded. It is stated that exclusion criteria were cannabis, marijuana, THC, CBD+THC and CBD-products.
Reviewer #2	However, in older studies not only pure CBD, but also CBD-based products or CBD+ other components in cannabis are included in the review. This is important to emphasize regarding safety aspects and actual exposure of CBD. Some in vitro studies were also searched for, as with caffeine, and a poster presentation

CHARGE QUESTION 1. Are the procedures and criteria used in the inclusion of clinical and animal studies in the literature review appropriate for the purpose of identifying scientific data that informs our understanding of CBD's safety profile in humans? For example, are there additional studies that should be included in the literature review based on the current search criteria, and should different search criteria be used to identify additional studies?	
REVIEWER	**COMMENT**
	is the only source of evidence for topical use of CBD. The evidence included refers to studies from in vitro, to case reports, posters, uncontrolled studies to randomized controlled clinical studies. This range of sources could be commented. As far as I am aware, all pharmacological studies of interactions are included and up to date.
Reviewer #3	The criteria used in the inclusion of clinical and animal studies from Pubmed literature or from clinicaltrials.gov database are appropriate and the relevant studies have been selected, even if it is difficult to trace them because the studies are not identified in univocal correspondence in the main text and in the Appendices. Sometimes there are inconsistencies in reporting the number of the studies analyzed in each section (e.g., page 10, the trials are 94 or 96?).
Reviewer #3	As an additional search criterion, I suggest using GWP42003 (CBD botanical extract) that is the former name for Epidiolex, used in the title of some clinical trials. For example, I found the NCT01562314 trial on ulcerative colitis (results published by Irving et al., Infl Bowel Diseases 2018) which reports relevant safety profile and adverse events.
Reviewer #3	There is a clinical trial NCT01605539 not considered in the compilation 'Acute and short-term effects of CBD in drug-abstinent heroin dependent humans' that reports relevant adverse events.
Reviewer #3	I don't understand why all the preclinical studies on anesthetized animals were excluded independently of the endpoint. Relevant information about pharmacokinetic, adverse events and toxicity could be obtained also from studies on anesthetized animals. Maybe an explanation on this exclusion criterion in the footnote would be helpful.
Reviewer #3	I would move the Animal data paragraph from page 9 (where it actually breaks the discussion on clinical data) to the end of document, so that all safety and toxicity data derived from preclinical studies are grouped in one place. For animal data I would extend the search criteria including the keywords: "safety", "toxicology", "genotoxicity", "mutagenicity", "adverse or side effects/events/reactions", "complications", "organ failure", "organ impairment". As regard animal studies, relevant reviews could be helpful: Bergamaschi et al., Curr Drug Saf. 2011 Sep 1; 6(4):237- 49; Iffland & Grotenhermen Cannabis Cannabinoid Res. 2017; 2(1):139-154; Huestis et al., Curr Neuropharmacol. 2019 Oct; 17(10): 974–989.
Reviewer #3	There are relevant animal studies, not cited in the document, reporting adverse events and toxicities in acute following high doses or after chronic administration. Rosenkrantz and Hayden, 1981 observed tremors, central nervous system inhibition, convulsions, bradycardia, hypopnea, cardiac failure, liver weight increase in monkeys beyond decreases in testicular weights. Garberg et al., 2017 reported hypotension and cardiac arrest in piglets. Marx et al., 2018 observed decreased mean body weight gain, food consumption and feed efficiency in rats with associated changes in the absolute and relative weights of liver, thymus, spleen, and adrenal glands at high doses. Ewing et al., 2019 reported that CBD caused hepatotoxicity in acute in mice, with significant increases in liver-to-body weight (LBW) ratios, plasma alanine transaminase (ALT), aspartate transaminase (AST), and total bilirubin. As regard genotoxicity, Zimmerman and Raj (1980) found evidence of increased rates of chromosomal aberrations (CA) in bone marrow cells of mice and observed induction of micronuclei, which are formed as a consequence of structural and numerical chromosomal aberrations.
Reviewer #4	Overall, yes. The inclusion and exclusion criteria are important, particularly for this subject matter given the large amounts of poor levels of evidence (i.e., surveys) in the cannabinoid space. Further, there is

CHARGE QUESTION 1. Are the procedures and criteria used in the inclusion of clinical and animal studies in the literature review appropriate for the purpose of identifying scientific data that informs our understanding of CBD's safety profile in humans? For example, are there additional studies that should be included in the literature review based on the current search criteria, and should different search criteria be used to identify additional studies?	
REVIEWER	**COMMENT**
	often a poor description or high variance of particular product(s) being studied in many of these publications. This will be discussed again in my response to question 2. One area of research that overall is lacking to date is drug-drug interaction data, particularly in humans. While it is appreciated that the objective of this literature review was to report on the safety findings in humans, given the interaction data are overall lacking, it could be considered to include some animal data in this section. This may be outside of the FDA's desired scope for this review, however, and may be more appropriately mentioned in the limitations section.
Reviewer #4	In regards to the cutoff date, this is a rapidly evolving field, and a review will be somewhat outdated at the time of publication no matter when the cutoff occurs.
Reviewer #5	Overall, while the keywords used in the search are appropriate, it is not clear whether the search took into account the qualitative and quantitative composition of the compound labeled in the literature as "CBD" or "cannabidiol", i.e., pharmaceutical grade, highly purified. This should be specified.

CHARGE QUESTION 2. For the studies currently included in the literature review: are the safety findings presented clearly and comprehensively?	
REVIEWER	**COMMENT**
Reviewer #1	The studies are comprehensively presented but more detail on the elevation of hepatic enzymes should be included. The NDA discussed the issue with reference to Hy's Law as a measure of liver damage. This was not discussed but it was a critical part of the section on hepatic safety in the label. A description of Hy's Law is needed and a statement that no instances of meeting Hy's Law is important to include. It would also be helpful to describe what happened to the patients with hepatic enzyme elevations since some continued while others discontinued and the elevations resolved in all cases. This would not be an analysis but a further description of the safety profile so far. One other area to consider is weight loss. If there are actual measurements of weight available, it would be helpful to summarize.
Reviewer #2	The clinical studies are well described and grouped into single- or multiple dosing, healthy volunteers vs. patients and route of administration. Dosing ranges are well described, but unfortunately there is a lack of evidence of actual exposure, i.e., serum concentration measurements were not available in many studies. Some details are elaborated upon below. The risk summary of pregnancy and fetal growth on page 40, in a separate box is clearly described as a warning, as clinical data are lacking.
Reviewer #2	*Adverse effects:* It would be an advantage to divide the deported adverse effects in children and adults regarding safety, e.g., lack of appetite, diarrhea, weight loss as well as possible cognitive effects, that may have a greater impact in developing children than in adults.
Reviewer #2	*CYP2C19: Interactions with drugs and genes* Regarding drug interactions due to inhibition of CYP2C19, it is well-known that this may cause signs of toxicity with N-desmethylclobazam or CBD. It should also be noted the possible similar phenotype in patients with a poor metabolizer (PM) genotype in some patients. The impact of pharmacogenetics in CYP2C19 PMs is poorly investigated but could be a source of variability leading to toxicity in susceptible patients. In the phase 1 study of interactions by Morrison et al., 2019 there was only one PM patient out of

CHARGE QUESTION 2. For the studies currently included in the literature review: are the safety findings presented clearly and comprehensively?	
REVIEWER	**COMMENT**
	a total number of 77, and the authors conclude that this could not be assessed. As the prevalence of CYP2C19 PMs is up to 30% in the South-east Asian population, this should be evaluated further in a safety study. I have not observed any other studies discussing this so far.
Reviewer #2	Food: It is of great clinical importance that a high fat-rich meal increases the exposure of CBD 4-5-fold and it should be emphasized that all patients should be encouraged to follow to increase the poor bioavailability, be more efficacious and more cost-effective. It is stated in the product label and is of relevance for clinicians and patients.
Reviewer #2	P. 30: Alcohol: Product label claims "EPIDIOLEX can cause serious side effects," includes this statement: "EPIDIOLEX may cause you to feel sleepy, which may get better over time. Other medicines (e.g., clobazam) or alcohol may increase sleepiness". Two old studies found contradictory findings on blood levels at different doses. Comment: This interaction may be moderate and mainly a pharmacodynamic interaction.
Reviewer #2	Caffeine: In vitro studies were not found. Clinical study ongoing. Data are lacking.
Reviewer #2	THC: Pharmacodynamic interaction with drugs potentiating CNS-effects, various studies and results performed at a large time span from the 1970s and may be difficult to compare.
Reviewer #2	Other drugs: PK interactions that could be bi-directional. Inducers/inhibitors on CYP3A4/2C19 on CBD, while CBD on drugs metabolized by UGT1A9, 2B7,1A2,2B6,2C8,2C9/19. Liver toxicity with valproate is also described and is an important clinical finding with implications for treatment. The studies are case reports or clinical studies including a few patients and should be interpreted with caution.
Reviewer #2	*Other ways of administration:* Topical use: No adverse effects reported, one study with a transdermal gel well tolerated, one poster presentation is the only evidence. Inhalation: Two studies, 150 mg/kg no toxicity, 400 mg /kg? acute toxicity. One from 1970s and one more recent study, where limited clinical data is available. Other: i.v. injection (n=6) 1970s, sublingual drops (n=33), given to volunteers Comment: What about bioavailability in these studies (inhalation and i.v.), which is expected to be much higher, perhaps up to 40-50%?? It is difficult to compare and evaluate the exposure of these cases and studies.
Reviewer #3	Overall, while safety findings are presented in the Appendices in a consistent format that is the same for each clinical trial, in the main document sometimes it uses a narrative/descriptive format, other times a more schematic/itemized format, also through tables. For the sake of clarity, it would be better to always use the same format as used in the main document.
Reviewer #3	It is not always clear, both in the document and in the Appendices, in which studies there is a coadministration of CBD with other drugs and which drug it is. In the main document this argument is treated in the paragraph 'Interactions with other drugs' that recapitulates the main observations subdivided for drug classes. However, in the description of trials in the other paragraphs or in the Appendix, the information about the drug eventually co-administered with CBD is always lacking with few exceptions. It is therefore difficult to discern how much the side effects are actually attributable to CBD or may be due to the co-administered drug or the combination therapy itself.
Reviewer #3	In general, reporting the % of side effects only for the CBD-treated group without showing the % for the placebo or the control group of the study as it was done, for example, at pages 19-20 for epilepsy studies,

CHARGE QUESTION 2. For the studies currently included in the literature review: are the safety findings presented clearly and comprehensively?	
REVIEWER	**COMMENT**
	gives a partial information, since in many studies the incidence rate of side effects is similar between the CBD group and placebo or control group, if not in some cases higher in the placebo or control group.
Reviewer #3	The document never talks about gender differences, which is an important and extremely topical aspect to evaluate in relation to CBD safety. Are there no clinical studies on CBD or publications that consider gender differences in the assessment of safety or side effects?
Reviewer #4	In general, yes. However, there are a few concerns. First and foremost, the description of the CBD products in the studies in this literature review is limited (with the exception of the Epidiolex studies), and I would recommend this be expanded. It appears from the inclusion/exclusion criteria for the review that the products intended to be included were CBD only. However, it is important that this review be as specific as possible when describing the CBD products used in the different studies. In some instances, it appeared that Epidiolex was the product used in the study, but was reported as "CBD" in the literature review. As I am familiar with the literature, I am aware that this varies in terms how specific the authors are in describing the products, but the more specific the description of the particular products (as much information as the papers provide), the better. This would include terms such as "pharmaceutical grade", "purified CBD", etc. In addition, the formulation of the products should also be included, beyond delivery (oral, inhaled, transdermal, etc). It could be that some safety issues could be related to the formulation (i.e., oil oral solution, etc.)- though I am aware this is not the scope of this review. One very common misconception I have experienced in the clinical setting when counseling patients about products is that Epidiolex data can simply be applied/extrapolated to all CBD products, including things like gummies, gas station products, etc. I have also experienced this when discussing with other physicians who have less experience in the cannabinoid space. Therefore, the more specific the description of the products used in this literature review will make it clearer that all the data cannot necessarily be conglomerated or extrapolated to apply to all products.
Reviewer #4	Another comment ties into the comments above. It is noted that there are some articles included in the review of synthetic CBD that are included. It is recommended that this is clearly stated in the description of the studies, and it may benefit to include a statement in the process of identifying articles in the search criteria that studies of synthetic products were allowed and clearly marked in the literature review when one of these products/studies is described.
Reviewer #4	Finally, one minor stylistic comment is that it appears that there is some variance throughout the document in how references are presented. Some sections have very clearly marked references, which allowed for easy reading and lookup of papers, with other sections referencing the appendices, making it somewhat more cumbersome to identify the exact reference being described.
Reviewer #5	It should be noted that some safety findings including weight loss cannot be fully assessed in short-term studies (i.e., less than 6 months). Therefore, it should be considered that weight loss frequently occurs as a direct and expected consequence of appetite loss, diarrhea, and vomiting. In addition, appetite loss, diarrhea, vomiting, and weight loss have a different significance in children compared with adults. In the pediatric age, insufficient weight gain and inappropriate weight loss are considered failure to thrive.

CHARGE QUESTION 3. We note at the beginning of the literature review that the review is a compilation of published scientific findings on CBD's safety, not an analysis of those findings. Are the scientific findings presented in a way consistent with this approach?	
REVIEWER	**COMMENT**
Reviewer #1	Yes, the data are presented without analysis but a better presentation of the long-term exposure studies, Hy's Law, physical addiction, and possibly weight gain should be included. Please see Question #4 below and previous comments.
Reviewer #2	It is an unusual approach not to end a comprehensive review by an evaluation of the evidence provided and a conclusion with clinical implications and a guide to further patient management. A conclusion would be of benefit for the reader. Even if the review is provided by the FDA, it would be possible to give an objective evaluation of all the efforts during the preparation of this review. In its present form, the review provides a clear and updated summary of relevant published literature covering safety aspects of CBD in humans, but with no evaluation or grading of evidence. The review is important for further research purposes, as the review points to where FDA has requested further studies to be performed.
Reviewer #3	Yes, they are.
Reviewer #4	This task was accomplished by the document. In the process of the thorough review, in all sections the data are reported and do appear to be interpreted or analyzed in any way. The only suggestion is that, if allowed, for the conclusory statements that are included in the summary such as "CBD was well tolerated", if these are direct quotes from the papers that the statements be put in quotations. This would further avoid any perceived analysis or interpretation of the data by readers.
Reviewer #5	Yes, they do.

CHARGE QUESTION 4. Are the limitations of oral CBD clinical trials accurately described in section 2.1d?	
REVIEWER	**COMMENT**
Reviewer #1	The first bullet can be deleted since there is sufficient long-term data to address the safety of repeated and single dosing.
Reviewer #1	The paragraph on the lack of long-term data in epilepsy is not completely accurate. There were two large safety studies with data in hundreds of patients in the original NDA. The studies were 1415, the extension of the major epilepsy studies, and the Expanded Access (EAP-a type of compassionate use) data that treated patients long-term with multiple types of resistant seizures. The median exposure in these trials was one year. It may be possible to find updated data on these trials. An additional section with focus on these studies should address this concern. There were two posters presented by Greenwich Biosciences on the long-term data in 1415 for both Dravet and LGS patients that can be made available to the FDA. They were presented at the 2019 AES (December 2019) in Baltimore.
Reviewer #2	The clinical studies included are well described, with a total number of included studies of 60. Oral: Intake of CBD, repeated doses, in healthy volunteers (6 trials) and patients with epilepsy (/with other seizures) (30 trials), other disorders (20 trials), dosing range of 5, 10, and 20 mg/kg. Also, single-dose studies in healthy volunteers (5 studies) and patients (5 trials) are included. The randomized, controlled studies in Dravet syndrome and Lennox-Gastaut syndrome that were included for the approval of CBD are well described, as these studies possibly provide the best clinically relevant data on safety of CBD in patients with severe epilepsy. Evidence from long-term studies are still scarce but is important to evaluate possible long-term effects on the developing brain in children.
Reviewer #2	The limitations that are listed in the text include the following: • "Acute adverse effect of single doses may not reflect safety related to chronic exposure to CBD."

CHARGE QUESTION 4. Are the limitations of oral CBD clinical trials accurately described in section 2.1d?	
REVIEWER	**COMMENT**
	○ I agree that this is emphasized. It should also be noted that the extensive inter- and intra-individual variability of pure oral oil CBD-preparation give rise to unpredictable exposure in the single patient. More studies of exposure vs. efficacy and tolerability should be warranted.
Reviewer #2	• "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". ○ I strongly agree that this is commented upon and is clinically relevant.
Reviewer #2	• "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 the users of non-drug CBD products, which may include both healthy adults and children, as well as adults and children with comorbidities other than epilepsy". ○ I agree. Are various serious conditions comparable when it comes to exposure and evaluation of CBD? What about clinically relevant doses, where there is different experience in epilepsy vs e.g., spasms (lower daily doses used).
Reviewer #3	I have the following observations about the limitations of oral CBD clinical trials. • It is reported that '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.' This is true, as it is also a matter of fact that CBD is largely used in non-drug settings through the consumption of CBD-based products (foods or dietary supplements) like CBD oil or CBD capsules, at doses that can be equivalent to those used in these clinical studies and taken for longer times. Pending clinical trials on long-term exposure to oral CBD, a monitoring system on consumers of CBD-based products could be put in place to obtain valuable information about CBD adverse events and safety issues.
Reviewer #3	• In many clinical trials conducted on CBD through oral route, the placebo group had a much lower number of participants than the treated group. For this reason, it is difficult to compare the % relative to the real incidence of side effects. Furthermore, in many studies with similarly sized treatment groups, the incidence rate of side effects is similar between the CBD group and placebo, if not in some cases higher in the placebo group.
Reviewer #4	The limitations presented are accurately described; however, there are other limitations that may also need to be included. First, in reference to the issues above in describing multiple different CBD products in these studies- it is not known if any of these data on these products can be extrapolated to apply to other products. It seems that this is what is being described in bullet point 3 of the limitations, but this is not entirely clear in its wording. Secondly, the botanical/plant-based products vs. synthetic product difference should also be mentioned here.
Reviewer #4	Another limitation that was not seen, and was also mentioned above in section 2- to some degree, it is somewhat unknown what safety findings/adverse effects can be attributed to CBD alone vs. its formulation (oil, capsule, etc.). Given these delivery systems are necessary in order for the CBD to be absorbed in the GI tract, this will be difficult or impossible to parse out.
Reviewer #5	Yes, they are.

III. Specific Observations on "Safety of CBD in Humans – A Literature Review"

REVIEWER	Page	Paragraph/ Line	Comment
Reviewer #1	4	2, line 2	"severe liver injury" is unclear. Was it only enzyme elevation that improved? Is this the risk of severe liver damage although there were no actual cases?
Reviewer #1	4	3, line 9	Should comment on whether placebo also had adverse events and how collected in this trial, if known.
Reviewer #1	4	4, line 3	How does the 400 mg dose compare with 150 mcg/kg mentioned earlier in the paragraph. It is hard to compare them.
Reviewer #1	5	3, line 4	Describe the toxicity if possible.
Reviewer #1	10	Table	Define "at risk" with a footnote
Reviewer #1	17	2, line 1	Consider a separate section for the 1415 trial which included long-term patients from the epilepsy trials of Dravet and LGS for approval. Another separate section with the data from the Expanded Access Program (EAP) provides long-term data from patients with other epileptic syndromes.
Reviewer #1	17	5, line 2	Make it clear these four trials are not the four trials for approval in epilepsy.
Reviewer #1	18	4, line 2	This was a major multicenter trial and the second major trial in Dravet. The FDA agreed it could be submitted when completed and would not be in the original NDA.
Reviewer #1	18	4, line 5	Take out the "%" sign. It is confusing for the reader and the percentages are included with the numbers.
Reviewer #1	19	1, line 2	The instances of higher aggression with CBD are not consistent. Would just state the incidences.
Reviewer #1	19	2, line 5	The range of time in the trials would be helpful here.
Reviewer #1	19	3, line 5	It may be helpful to mention the total n for the trials is 1451. This may help provide context for the adverse events in the next paragraph.
Reviewer #1	21	3, line 1	Insert "multiple dose" to describe the 20 trials outside of epilepsy.
Reviewer #1	21	5, line 8	Isn't it 8 trials?
Reviewer #1	23	3, line 4	This paragraph is not completely accurate. The SBA has safety data on two major safety trials that exposed patients for a median of one year with hundreds of patients from the major epilepsy studies and the expanded access (EAP) programs. Would include the data from these studies, updated from the SBA in this summary. Some of the open-label studies may have been published with data from single sites.
Reviewer #1	23	2, line 2	There is sufficient repeated dosing studies for safety. The single-dose studies are adequately complemented by the longer term data. Would remove this bullet point.
Reviewer #1	41	1, line 2	Children with epilepsy may not substantially differ from children without epilepsy so stating there is insufficient data among children without epilepsy may make more sense.
Reviewer #1	57	Study 1 in the second table	This study was part of the EAP program. Note there is exposure up to 96 weeks. Several of these trials were from the EAP program.

III. Specific Observations on "Safety of CBD in Humans – A Literature Review"

REVIEWER	Page	Paragraph/ Line	Comment
Reviewer #2	30	2nd paragraph	Alcohol: Product label claims "EPIDIOLEX can cause serious side effects," includes this statement: "EPIDIOLEX may cause you to feel sleepy, which may get better over time. Other medicines (e.g., clobazam) or alcohol may increase sleepiness". Comment: This interaction may be moderate and mainly a pharmacodynamic interaction
Reviewer #2	31	2nd paragraph	The reference is an unpublished study? #63: 63 The 19 antiepileptic drugs included in the analysis were: clobazam, valproate, levetiracetam, phenobarbital, clonazepam, phenytoin, carbamazepine, lamotrigine, oxcarbazepine, ethosuximide, topiramate, vigabatrin, zonisamide, eslicarbazepine, ezogabine, pregabalin, perampanel, rufinamide, and lacosamide.
Reviewer #2	32	Last paragraph	In relation to the pharmacokinetic interactions, as inhibition of CYP2C19 that may cause signs of toxicity with N-desmethylclobazam or CBD, it should also be noted the possible similar phenotype in patients with a poor metabolizer (PM) genotype in some patients. It is shortly noted that this has not been evaluated in reference #67, but mechanistically it is expected: 67 Morrison G, Crockett J, Blakey G, et al. A Phase 1, open-label, pharmacokinetic trial to investigate possible drug-drug interactions between clobazam, stiripentol, or valproate and cannabidiol in healthy subjects. Clin Pharmacol Drug Dev, 2019 Nov;8(8):1009-1031.
Reviewer #3	i		The Summary is not included in the Index
Reviewer #3	3	Par. 3-5	The number of participants is lacking (n=?)
Reviewer #3	4	Par. 1, 3, 4	The number of participants is lacking (n=?)
Reviewer #3	9	Line 2	Correct 12/12/19
Reviewer #3	10	Par. 2	94 or 96 trials?
Reviewer #3	13	Par. 4	(n=6) instead of 6 per dose group
Reviewer #3	13	Last line	Broken table. Move the first line of the table to the next page
Reviewer #3	14		The number of participants is lacking (n=?)
Reviewer #3	17	Par 6	The range of the tested doses is calculated only for adult participants (average 70 kg) even if 16/30 trials were in pediatric patients. The doses range used in pediatric patients should be also reported
Reviewer #3	26	2.3b	I would move this paragraph about animal data in the animal data section
Reviewer #3	30	Line 5	(diazepam and hexobarbital)
Reviewer #3	33	Last line	N is lacking for headache
Reviewer #4	5		Would it be possible to include references in the summary pages also?

III. Specific Observations on "Safety of CBD in Humans – A Literature Review"			
REVIEWER	**Page**	**Paragraph/ Line**	**Comment**
Reviewer #4	5	Bullet point 4 on this page	Surveys on animal use of "CBD" products- while it is clear that surveys were not utilized in this literature review, it is not clear why quotes were used in this instance. Does this imply that the type of product was not clearly described in the papers? If so, would add "not otherwise defined" to this criterion.
Reviewer #4	9	1	Would recommend the word "exploited" be changed
Reviewer #4	23	3	In section ii, there is a description of a trial that was excluded due to sample size. It does not appear in the inclusion/exclusion criteria that there was a cutoff for sample size. Would recommend clarifying this one way or the other.
Reviewer #4	23	3, line 6	The statement "only a handful of patients reported…"- it is unclear if this is a direct quote from the paper or writing from the author of the review. In keeping with the purpose of the review to be a compilation and not an analysis, if this is a quote from the paper, would utilize quotation marks, and if not, would recommend including more specific data (number of patients)
Reviewer #5	19	Second bullet point	The terms "Seizure" and "Convulsion" indicate the same event, i.e., an epileptic seizure. Reporting epileptic seizures as an AE in trials evaluating CBD for the treatment of seizures in patients with epilepsy in is a non-sense. In the trials described in this Review, the presence of a certain number of seizure/month is the main inclusion criteria. In contrast, the occurrence of status epilepticus – a rare complication in epilepsy – should be viewed with concern when evaluating safety of an anti-seizure medication.
Reviewer #5	34	Last paragraph	This is an extremely important point as everolimus is approved for use in patients with Tuberous Sclerosis for the treatment of seizures, subependimal giant cell astrocytoma, and renal angiomyolipoma. The Review includes the single case report showing that CBD strongly affects the serum concentration of everolimus. It should be noted the lack of data in this regard in published studies on Epidiolex and Tuberous Sclerosis (Hess EJ et al. Epilepsia 2016), where everolimus is not mentioned.