ADMIN

Memo

Agenda

Minutes

Priorities

Squalene & Squalane

CIR EXPERT PANEL MEETING JUNE 6-7, 2019

Cosmetic Ingredient Review

Commitment & Credibility since 1976

MEMORANDUM

To: CIR Expert Panel Members and Liaisons
From: Bart Heldreth, Ph.D., Executive Director, Cosmetic Ingredient Review
Subject: 151st Meeting of the CIR Expert Panel — Thursday and Friday, June 6-7, 2019
Date: May 10, 2019

Welcome to the June 2019 CIR Expert Panel Meeting. Enclosed are the agenda and accompanying materials for the 151st CIR Expert Panel Meeting to be held on June 6-7, 2019. The location is the same as the last meeting – The Westin Hotel, Washington, D.C. City Center, 1400 M St NW, Washington, District of Columbia, 20005. Phone: (202) 429-1700.

The meeting agenda includes the consideration of 16 reports advancing in the review process, including 5 final reports, 1 tentative report, 6 draft reports, and 4 re-reviews. Also, on the agenda are a re-review summary and the Draft Final 2020 Priorities.

Schedule and hotel accommodations

We have reserved rooms for the nights of Wednesday, June 5th and Thursday, June 6th at the Westin Hotel. If you encounter travel problems, please contact Monice on her cell phone at 703-801-8156.

Team Meetings

Draft Reports - there are 6 draft reports for review.

1. Caprylhydroxamic Acid – This is the first time that the Panel is seeing this report on 1 chelating ingredient (reported function according to the *Dictionary*). On February 21, 2019, CIR issued the SLR for this ingredient. According to 2019 VCRP survey data and the results of the concentration of use survey conducted by the Council in 2018, Caprylhydroxamic Acid is reported to be used in 227 formulations at maximum leave-on and rinse-off concentrations of 0.25% in body and hand products and 0.3% in bath soaps and detergents, respectively.

   The following unpublished data were received either from the Council or as a direct submission to CIR, and are included in the report: method of manufacture, concentration of use survey, Ames test, in vitro mammalian cell micronucleus assay in human peripheral blood lymphocytes (HPBL), EpiDerm™ skin irritation test, repeated insult patch test of an eyeliner containing 0.105%, repeated insult patch test of a lotion containing 0.15%, repeated insult patch test of W/O thick balm containing 0.15%, repeated insult patch test of a wipe juice containing 0.15%, summary of an HRIPT of a facial cream containing 0.15%, summary of an HRIPT on a brow thickening powder containing 0.195%, repeated insult patch test of a blend containing 5% (tested as a 6% dilution), repeated insult patch test of a blend containing 7.5% (tested as a 4% dilution), repeated insult patch test of a blend containing 10% (tested as a 3% dilution), repeated insult patch test of a blend containing 15% (tested as a 2% dilution), repeated insult patch test of a blend containing 15% (tested as a 2% dilution), repeated insult patch test of undiluted Capryloyl Hydroxamic Acid, Bovine Corneal Opacity and Permeability Test (BCOP) as a 20%, and a MatTek EpiOcularTM MTT Viability Assay.

   The Panel should be aware that in the NICNAS dossier, the following statement was made.

1620 L Street, NW Suite 1200, Washington, DC 20036
(Main) 202-331-0651 (Fax) 202-331-0088
(Email) cirinfo@cir-safety.org (Website) www.cir-safety.org

> Based on the low molecular weight, potential surface activity and irritancy potential, it is likely that [Caprylhydroxamic Acid] will be able to be absorbed into the skin. Hydroxamic acids are known to inhibit certain enzymes such as urease … and therefore have been shown to have protein reactivity, an important factor in skin sensitisation potential. The skin sensitisation potential of [Caprylhydroxamic Acid] cannot be ruled out.

Please comment on whether this statement should be included in the report.

Comments on the SLR that were received from the Council were also addressed. If the data included in this report adequately address the safety of Caprylhydroxamic Acid as used in cosmetics, the Panel should be prepared to formulate a tentative conclusion, provide the rationale to be described in the Discussion, and issue a Tentative Report for public comment. If the data are not sufficient for making a determination of safety, then an Insufficient Data Announcement (IDA) should be issued that provides a listing of the additional data that are needed.

2. Capryloyl Salicylic Acid – This is the first time the Panel has assessed the safety of this ingredient correctly characterized as a ketone. At their April 2019 meeting, the Panel issued a final amended report on the 18 Salicylic Acid esters. Because the definition previously given for Capryloyl Salicylic Acid (previously defined as an ester) is incorrect and it is now correctly defined as a ketone, this ingredient is not included in that final amended report that was issued. Therefore, a separate re-review was initiated for this ingredient, and this draft amended report on Capryloyl Salicylic Acid was prepared for Panel review. According to the *Dictionary*, this ingredient is reported to function as a skin-conditioning agent – miscellaneous.

   According to the 2019 VCRP data, Capryloyl Salicylic Acid is reported to be used in 104 cosmetic products (93 leave-on and 11 rinse-off). The results of a concentration of use survey conducted by the Council in 2018 indicate that Capryloyl Salicylic Acid is used at concentrations up to 0.5% (in moisturizing products, not spray), which is the highest reported maximum use concentration for leave-on formulations. In rinse-off products, Capryloyl Salicylic Acid is reported to be used at concentrations up to 0.4% (in paste masks and mud packs), which is the highest reported maximum use concentration for rinse-off formulations.

   If the data included in this report adequately address the safety of Capryloyl Salicylic Acid, the Panel should be prepared to formulate a tentative conclusion, provide the rationale to be described in the Discussion, and issue a Tentative Amended Report for public comment. If the data are not sufficient for making a determination of safety, then an IDA should be issued that provides a listing of the additional data that are needed.

3. Glycerin Ethoxylates – This is the first time the Panel is reviewing this document. On March 28, 2019, CIR issued the SLR for these ingredients. According to the *Dictionary*, all 8 of these ingredients, which are structurally related as polyethylene glycol ethers of glycerin, are reported to function in cosmetics as skin-conditioning agents; and most are reported to function as viscosity-decreasing agents.

   According to 2019 VCRP survey data, Glycereth-26 has the highest frequency of use, with a total of 379 formulations. The results of the concentration of use survey conducted in 2018 by the Council indicate that Glycereth-26 has the highest maximum concentration of use, and is used at up to 39.5% in skin cleansing products. The concentration reported for this rinse-off use product category is much higher than that reported for other product categories; the highest maximum leave-on use concentration reported is 6% Glycereth-26 in eye lotions.

   Comments on the SLR were received from the Council and have been addressed. The following unpublished data were received and have been incorporated into the document: EpiOcular™ irritation study on a product containing 0.35% Glycereth-12, HRIPT on a product containing 0.35% Glycereth-12, and HRIPT on a product containing 5% Glycereth-26.

   After reviewing these documents, if the available data are deemed sufficient to make a

determination of safety, the Panel should identify matters to be addressed in the Discussion, and then issue a Tentative Report with a safe as used, safe with qualifications, or unsafe conclusion. If, however, the available data are insufficient, the Panel should issue an IDA, specifying the data needs therein.

4. Soy – This is the first time the Panel is seeing this safety assessment of 28 soy-derived ingredients. On March 22, 2019, CIR issued the SLR for these ingredients. According to the *Dictionary*, all but a few of these ingredients are reported to function in cosmetics as skin conditioning agents.

   According to 2019 VCRP data, Glycine Max (Soybean) Seed Extract is reported to be used in 395 formulations, 273 of which are leave-on formulations, and Glycine max (soybean) flour (synonymous with Glycine Soja (Soybean) Flour) is reported to be used in 66 formulations. The results of a 2016 concentration of use survey conducted by the Council indicate Glycine Soja (Soybean) Seed Extract has the highest concentration of use; it is used at up to 2% in face and neck products.

   The following unpublished data were received and are included in the report: use concentration; product specifications, method of manufacturing data, specifications for organic constituents/impurities, and a cellular viability assay on a trade name mixture containing Glycine Soja (Soybean) Phytoplacenta Extract; HRIPT on a leave-on formulation containing 0.3% Glycine Soja (Soybean) Germ Extract; and a 48-hour patch test and in vitro ocular irritation data on a 13% Glycine Soja (Soybean) Seedcake Extract (in water) tested at 4%. Comments provided by Council on the SLR were also received and addressed.

   After reviewing these documents, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a Tentative Report with a safe as used, safe with qualifications, or unsafe conclusion, and Discussion items should be identified. If the available data are insufficient, the Panel should issue an IDA, specifying the data needs therein.

5. MCI/MI – In 1992, the final report on Methylisothiazolinone and Methylchloroisothiazolinone (MCI/MI) was published with the conclusion that this mixture (roughly 3:1 MCI:MI) may be safely used in rinse-off products at a concentration not to exceed 15 ppm and in leave-on cosmetic products at a concentration not to exceed 7.5 ppm.

   At the April 2019 meeting, the Panel voted to re-open this safety assessment to reassess the conclusion based on the numerous sensitization studies and reports that have been published since 1992. The relevant data from these studies have been included in this draft report, along with summary information from the original report (indicated by italics).

   This ingredient combination is reported to function as a preservative in cosmetics. According to 2019 VCRP data, MCI and MI are reported separately and not as a mixture. The total number of uses reported for MCI are 5137; 480 of these are in leave-on products. MI has 6037 reported uses; 1042 of these are in leave-on products. The uses have increased significantly since the original report on MCI/MI was published; the 1986 total number of uses for the ingredient mixture was 381. Currently, the Council has reported the results of their survey that indicate MCI/MI (3:1) is used at up to 7.5 ppm in leave-on products and at up to 15 ppm in rinse-off products. In the original report, the ingredient combination was reported to be used at up to 1% in both leave-on and rinse-off products.

   Comments from the Council on the re-review document have been addressed. Data received since the April meeting include an open HRIPT of 12 ppm MCI/MI in a hand wash, updated concentration of use data, and a QRA 2.0 risk assessment of MCI/MI performed by the CIR Science and Support Committee.

   If no further data are needed to reach a conclusion of safety, the Panel should formulate a Discussion and issue a Tentative Amended Report. However, if additional data are required, the Panel should be prepared to identify those needs and issue an IDA.

6. Vanilla – This is the first time the Panel is seeing this report on 9 *Vanilla*-derived ingredients.

This ingredient family comprises cosmetic ingredients that are derived from two vanilla species, *Vanilla planifolia* and *Vanilla tahitensis*. An SLR was announced on March 28, 2019.

The following unpublished data were received and incorporated into this draft report: use concentration data; method of manufacture and composition data on 2 Vanilla Tahitensis Fruit Extract trade name mixtures (one containing 0.80% and the other containing 1.3% Vanilla Tahitensis Fruit Extract); ocular irritation (in vitro), skin irritation (in vitro and human), skin sensitization (human), and phototoxicity (in vitro) and genotoxicity data (in vitro) on a trade name mixture containing 1.3% Vanilla Tahitensis Fruit Extract. Council's comments on the SLR have also been addressed.

After reviewing these documents, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a Tentative Report with a safe as used, safe with qualifications, or unsafe conclusion, and Discussion items should be identified. If the available data are insufficient, the Panel should issue an IDA, specifying the data needs therein.

Draft Tentative Report – there is 1 draft tentative report.

1. Silicates – At the April 2019 meeting, the Panel tabled the report that contained 40 ingredients in order for CIR staff to reorganize the ingredients into two separate reports: one containing 24 ingredients that are assumed to be synthetically-derived and the other containing 16 ingredients that are assumed to be mined. The data for all of these ingredients were still considered insufficient to determine safety.

   The additional data needs were:
   - The range of particle sizes for all silica and silicate ingredients that are used in spray and powder formulations
   - Chemical characterization, composition, and impurities data for all ingredients, except Silica
   - Method of manufacturing and/or source data for all ingredients, except Silica and Hydrated Silica.

   Since the April Panel meeting, no new unpublished data have been received. Comments provided on the April-draft tentative amended report have been addressed and are included.

   The Panel should review the new grouping of ingredients and the available data in this safety assessment, formulate an updated Discussion, and issue a Tentative Amended Report.

Draft Final Reports - there are 5 draft final reports for consideration (including one amended report). After reviewing these drafts, especially the rationales provided in the Discussion sections, the Panel should issue them as Final Reports, as appropriate.

1. Alkanoyl Lactyl Lactates – This ingredient family comprises the carboxylic acid salts of diesters that are formed between a fatty acid group and two equivalents of lactic acid. A tentative report was issued at the December 2018 meeting, and the Panel's conclusion therein states that the 10 alkanoyl lactyl lactate salts are safe in cosmetics in the present practices of use and concentration described in the safety assessment, when formulated to be non-irritating and non-sensitizing, which may be based on a QRA.

   The Council's comments on the tentative report have been addressed. The draft final report has also been revised to include 2019 FDA VCRP data. When compared to 2018 FDA VCRP data, it should be noted that the new data indicate that Sodium Lauroyl Lactylate is now being used in 34 additional bath soaps and detergents (40 + 34 = 74 products), and that Sodium Stearoyl Lactylate is now being used in 32 additional moisturizing skin care preparations (151 + 32 = 183 products). New product categories relating to ingredient use include 1 reported use of Sodium Caproyl/Lauroyl Lactylate in a moisturizing skin care preparation, and 1 reported use of Sodium Stearoyl Lactylate in the suntan gels, creams, and liquids product category.

The Panel should carefully review the Abstract, Discussion, and Conclusion of this safety assessment. If these are satisfactory, the Panel should issue a Final Report.

2. Alkoxylated Fatty Amides – At the December meeting, the Panel issued a tentative report with a conclusion that the 40 alkoxylated fatty amides named in the document are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-irritating.

   Concentration of use data were received for PEG-3 Lauramide and PEG-20 Cocamide MEA. The data have been included, and the use tables and conclusion have been adjusted accordingly. An exposure assessment submitted by the CIR Science and Support Committee was reviewed at the December meeting; this document was distributed to the Panel the morning of that meeting, but is also included with this submission in case you want to review it again. Comments received from the Council that were received prior to the December 2018 meeting on the draft tentative report, and on the tentative report that was issued following that meeting, have been addressed.

   The Panel should carefully review the Abstract, Discussion, and Conclusion of this safety assessment. If these are satisfactory, a Final Report should be issued.

3. Basic Red 76 – At the December 2018 meeting, the Panel issued a tentative report with the conclusion that this ingredient is safe in cosmetics in the present practices of use and concentration described in the safety assessment.

   At the time the tentative report was issued, Basic Red 76, which according to the *Dictionary* is reported to function as a hair colorant and hair-conditioning agent, only had use in hair coloring formulations. However, according to 2019 VCRP data, this ingredient is now also used in nail polish and enamel; concentration of use data were not reported by industry for this use. The Panel should determine whether the data in the report supports this use, and if it does, formulate language for addition to the Discussion. If the data do not support this use, and additional data are needed to determine safety for this use, then an IDA should be issued to identify those data needs.

   The Panel should carefully review the Abstract, Discussion, and Conclusion of this safety assessment. If these are satisfactory, and the new use type reported in the VCRP does not affect the conclusion, then the Panel should issue a Final Report. If additional data are required, the Panel should be prepared to identify those needs and issue an IDA.

4. Parabens – At the April 2019 meeting, the Draft Final Amended Report on Parabens was tabled in response to correspondence, which included a significant number of articles, received after the meeting documents were in press. The action was taken so that the Panel could adequately address this information.

   Accordingly, this Draft Final Amended Report has been revised to include the new biomonitoring and epidemiological papers that were recently discovered, some of which were published after the April 2019 Panel meeting. New literature is constantly emerging examining the potential impact of paraben exposure on human health. With this in mind, should the Panel consider setting a re-review schedule for this report, which is shorter than the customary 15 years?

   The new studies incorporated into the report address parabens exposure as associated with different types of health outcomes, as compared to health outcomes that were included in the report. However, these findings have not been confirmed by subsequent or previous epidemiologic investigations. Sources of parabens exposure in these studies are broadly from the environment and not specified; more importantly, exposure of the study populations to parabens are always coupled with other suspected active ingredients.

   The Panel should carefully review the newly discovered papers, with particular focus on the negative association of parabens exposure with human health outcomes. The Panel should also determine whether current risk calculations provide adequate safety margins in consideration of the updated biomonitoring and epidemiological data. Also, please carefully review the Abstract,

Discussion, and Conclusion of this safety assessment. If these are satisfactory, and the new data do not affect the conclusion, then the Panel should issue a Final Amended Report.

5. Polyaminopropyl Biguanide – At the December 2017 meeting, the Panel tabled this report. At that meeting, the Panel received a commitment from the cosmetics industry for the completion of a 100-person HRIPT of a product containing Polyaminopropyl Biguanide. This commitment was made in response to one of the data needs listed in the tentative report (insufficient data conclusion) issued at the September 2017 Panel. Updates have been given to the Panel at several meetings (June and December 2018) since the report was first tabled.

   The reason for the insufficient data conclusion that was issued at the September 2017 Panel meeting was two-fold:
   - HRIPT on Polyaminopropyl Biguanide involving a diverse population (i.e., with a range of Fitzpatrick skin types) of 100 subjects tested with a dose of 1000 µg/cm^2 (and a recommendation to test at 500 µg/cm^2 as well)
   - Consumer use data on pump and propellant hair sprays, for use in determining the extent of exposure to Polyaminopropyl Biguanide during product use.

   The CIR has since received a submission including the results of an HRIPT, in which 108 subjects were tested with 0.2% Polyaminopropyl Biguanide (in distilled water; 750 µg/cm^2), but it has not received consumer use data on pump and propellant hair sprays (a remaining insufficiency confirmed by the Panel at the December 2018 meeting). A revised no-expected-sensitization-induction-level (NESIL) that is based on this HRIPT was also provided. Because a revised NESIL has been provided, the QRA worksheet with the NESIL that was received initially is also included so that the Panel can compare the differences.

   The report has also been updated to include 2019 VCRP data. (There were no significant changes in frequency of use.) Additionally, comments that were received from the Council prior to the June 2018 and December 2018 Panel meetings have been addressed.

   After consideration of the data that were submitted as well as the data need that has not been fulfilled, the Panel should determine whether a Final Report with an insufficient data conclusion should be issued at this meeting. The Panel may also consider issuing a split conclusion, based on the data received. (In that case, a Revised Tentative Report should be issued for public comment.) It should be noted that if a Final Report with an insufficient data conclusion is issued at this meeting, interested parties will have 2 years to satisfactorily fill the data gap(s) before the conclusion is categorized as "Use Not Supported by the Data and Information Submitted to the CIR."

Re-Reviews – there are 4 Re-Reviews

1. Acetyl Trialkyl Citrates – The CIR Expert Panel first published the safety assessment of Acetyl Trialkyl Citrates in 2002. The Panel concluded that Acetyl Triethyl Citrate, Acetyl Tributyl Citrate, Acetyl Trioctyl Citrate (now known as Acetyl Triethylhexyl Citrate), and Acetyl Trihexyl Citrate are safe as used in cosmetics, as described in that report. Because it has been at least 15 years since the first report was published, in accordance with CIR Procedures, the Panel should consider whether the safety assessment of Acetyl Trialkyl Citrates should be re-opened. An exhaustive search of the world's literature was performed for studies dated 1996 forward, and a new-data dossier prepared for Panel consideration.

   Current data indicate that only 2 ingredients are in use, and the frequency of use has increased for both ingredients since the final report was issued. According to VCRP data, Acetyl Triethyl Citrate and Acetyl Tributyl Citrate were reported to be used in 9 and 27 formulations, respectively, in 1998. In 2019, the VCRP data indicate that Acetyl Triethyl Citrate is used in 22 formulations, and Acetyl Tributyl Citrate is used in 438 formulations. For Acetyl Triethyl Citrate, the maximum concentration of use was 7% in nail products in 1999; however, according to a recent survey provided by the Council, current use concentration data on this ingredient were not submitted. For Acetyl Tributyl Citrate, the maximum concentrations of use have increased slightly since the original report was issued. In 1999, Acetyl Tributyl Citrate was used at up to 7% in nail products and up to 3% in eye

products (i.e., eyeliners) that resulted in dermal contact; data collected in 2018 indicate that the maximum concentrations of use are now 8.9% in nail products and 7% in eye products that result in dermal contact.

New data that were not included in the original report include: animal dermal sensitization data on Acetyl Triethylhexyl Citrate; animal ocular irritation data on Acetyl Triethylhexyl Citrate; animal carcinogenicity data on triethyl citrate (for potential Acetyl Triethylhexyl Citrate read-across); and other potentially relevant studies on Acetyl Triethyl Citrate, Acetyl Tributyl Citrate, and Acetyl Trihexyl Citrate.

If, upon review of the new studies and updated use data, the Panel determines that a re-review is warranted, a full draft amended report will be presented at an upcoming meeting.

2. BHT – The CIR Expert Panel first published an assessment of butylated hydroxytoluene (BHT) in 2002 with the conclusion, "safe as used in cosmetic formulations." Because it has been at least 15 years since the report was published, in accord with CIR Procedures, the Panel should consider whether the safety assessment of BHT should be re-opened. An exhaustive search of the world's literature was performed for studies dated 1997 forward, and a new-data dossier prepared for Panel consideration.

   Also included for your review are current and historical use data. The frequency of use has increased significantly since the initial review. According to VCRP data, BHT was reported to be used in 1709 formulations in 1998. In 2019, the VCRP data indicate that BHT is now used in 9485 formulations. The current maximum concentration of use in leave-on products (0.5%) is the same as reported in 1999.

   If, upon review of the new studies and updated use data, the Panel determines that a re-review is warranted, a full draft amended report will be presented at an upcoming meeting.

3. EDTA - The CIR Expert Panel first published a safety assessment of ethylene diamine tetraacetic acid (EDTA) and salts in 2002. The Panel concluded that EDTA, Calcium Disodium EDTA, Diammonium EDTA, Dipotassium EDTA, TEA-EDTA, Tetrasodium EDTA, Tripotassium EDTA, Trisodium EDTA, HEDTA, and Trisodium HEDTA are safe as used in cosmetic formulations as described in that report. Because it has been at least 15 years since the report was published, in accord with CIR Procedures, the Panel should consider whether the safety assessment of EDTA and the relating salts should be re-opened. An exhaustive search of the world's literature was performed for studies dated 1997 forward, and a new-data dossier prepared for Panel consideration.

   Also included for your review are current and historical use data. The frequency of use significantly increased for both Disodium and Tetrasodium EDTA. According to VCRP data, Disodium and Tetrasodium EDTA are reported to be used in 12,509 and 7691 formulations, respectively, while in 1998 these were reported to be used in 1165 and 1285 formulations, respectively. In addition, Calcium Disodium EDTA and Tripotassium EDTA are now reported to be in use; these were not reported to be in use in 1998. In 1998, the maximum concentration of use was reported in EDTA (2% in hair products; rinse-off) and Trisodium EDTA (2% in bath soaps and detergents; rinse-off). According to 2019 concentration of use data, the ingredient with the highest maximum concentration of use is now Disodium EDTA, which is used at 3% in "other hair coloring preparations." This ingredient was reported to be used at a maximum of 1% in bath products. Disodium EDTA is reported to have the highest concentration of use in leave-on products (0.85%; hair color sprays) and in products which would come in contact with the skin (0.6%; skin cleansing). All other in-use ingredients are reported to be used in rinse-off formulations at 2% or less.

   If, upon review of the new studies and updated use data, the Panel determines that a re-review is warranted, a full draft amended report will be presented at an upcoming meeting.

4. Imidazolidinyl Urea - Imidazolidinyl Urea was one of the first ingredients reviewed by the CIR Expert Panel, and the final safety assessment was published in 1980 with the conclusion "safe when incorporated in cosmetic products in amounts similar to those presently marketed." In 2001, after considering new studies and updated use data, the Panel determined to not re-open the safety assessment, and affirmed the original conclusion. Because it has been at least 15 years since the first re-review summary was published, in accordance with CIR Procedures, the Panel should again consider whether the safety assessment of Imidazolidinyl Urea should be re-opened. An exhaustive

search of the world's literature was performed for studies dated 1999 forward, and a new-data dossier prepared for Panel consideration.

Also included for your review are current and historical use data. The frequency of use has decreased since the initial re-review was considered. According to VCRP data, Imidazolidinyl Urea was reported to be used in 2025 formulations in 2001. In 2019, the VCRP data indicate that Imidazolidinyl Urea is used in 1558 formulations. The current maximum concentration of use in leave-on products (0.6%) is nearly the same as that reported in 2001 (0.7%). The maximum concentrations of use by exposure type (e.g., eye area, nails) have decreased in most categories.

If, upon review of the new studies and updated use data, the Panel determines that a re-review is warranted, a full draft amended report will be presented at an upcoming meeting.

Administrative Items - there is 1 re-review summary and 1 priorities document

1. Squalane & Squalene - The Panel considered the re-review of Squalane and Squalene at the April 2019 meeting, and determined that the report should not be re-opened. The re-review summary is included for your review.

2. Priorities – The CIR Procedures require preparation of the Draft 2020 Priority List for public comment by June 1, 2019. The Draft 2020 Priority List was issued for public comment earlier (March 2019) in the process to allow more time for the acquisition of data. The list is based on stakeholder requests; frequency of use data (FOU) from FDA's Voluntary Cosmetic Registration Program (VCRP) received from the FDA on February 5, 2018; and on CIR staff and Panel workflow. Comments at the April 2019 Expert Panel meeting have been considered and addressed. The Draft Final Priorities for 2020 are essentially the same as those finalized for 2019; however, this list has been updated with 2019 frequency of use data, a report in progress has been removed from the list, an ingredient (Benzisothiazolinone) was removed for zero frequency of use, and three items were suggested for addition. Most of the ingredients carried forward from the 2019 Priorities List have increased in FOU.

   At the April 2019 Expert Panel meeting, three items were suggested for addition to the 2020 Priorities List, namely, "probiotics," Mica (for uses other than colorant), and Cannabidiol (aka CBD). The CIR is thankful for such suggestions, and always welcomes stakeholder input. According to the CIR Procedures, formation of priority lists and review inclusions/exclusions follow a set series of guidelines. The Panel should consider how, or if, these suggested additions meet those guidelines for inclusion in the 2020 Priority List (or prioritization of 1 or more of these ingredients should be postponed to acquire more information).

Full Panel Meeting

Please remember, the breakfast buffet will open at 8:00 am and the meeting starts at 8:30 am on day 1 and on day 2.

The Panel will consider the 5 reports to be issued as final safety assessments, followed by the remaining reports advancing in the process (including the tentative reports, draft reports, and re-reviews), a re-review summary and priorities. It is likely that the full Panel session will conclude before lunch on day 2; so, plan your travel accordingly.

Have a safe journey!

Agenda
151st Cosmetic Ingredient Review Expert Panel Meeting
June 6th - 7th, 2019

The Westin Hotel
1400 M Street, NW,
Washington, District of Columbia, 20005

Thursday, June 6th

8:00 am	**CONTINENTAL BREAKFAST**	
8:30 am	**WELCOME TO THE 151st EXPERT PANEL TEAM MEETINGS**	**Drs. Bergfeld/Heldreth**
8:45 am	**TEAM MEETINGS**	**Drs. Marks/Belsito**

Dr. Marks' Team*

Admin (BH)	Priorities
RR (CB)	Imidazolidinyl Urea
TAR (CB)	Silicates
DAR (CB)	MI/MCI
FR (PC)	Basic Red 76
RR (PC)	EDTA
FAR (PC)	Parabens
DR (PC)	Soy
RR (AA)	BHT
DR (AA)	Glycerin Ethoxylates
RRsum (MF)	Squalene & Squalane
FR (MF)	Alkoxylated Fatty Amides
DR (MF)	Caprylhydroxamic Acid
FR (WJ)	Alkanoyl Lactyl Lactates
FR (WJ)	Polyaminopropyl Biguanide
RR (WJ)	Acetyl Trialkyl Citrates
DAR (WJ)	Capryloyl Salicylic Acid
DR (WJ)	Vanilla

Dr. Belsito's Team

RRsum (MF)	Squalene & Squalane
FR (MF)	Alkoxylated Fatty Amides
DR (MF)	Caprylhydroxamic Acid
FR (WJ)	Alkanoyl Lactyl Lactates
FR (WJ)	Polyaminopropyl Biguanide
RR (WJ)	Acetyl Trialkyl Citrates
DAR (WJ)	Capryloyl Salicylic Acid
DR (WJ)	Vanilla
RR (CB)	Imidazolidinyl Urea
TAR (CB)	Silicates
DAR (CB)	MI/MCI
FR (PC)	Basic Red 76
RR (PC)	EDTA
FAR (PC)	Parabens
DR (PC)	Soy
RR (AA)	BHT
DR (AA)	Glycerin Ethoxylates
Admin (BH)	Priorities

The purpose of the Cosmetic Ingredient Review is to determine those cosmetic ingredients for which there is a reasonable certainty in the judgment of competent scientists that the ingredients are safe under intended conditions of use.

FR: Final Report // FAR: Final Amended Report // TR: Tentative Report // TAR: Tentative Amended Report // DR: Draft Report // DAR: Draft Amended Report // RR: Re-Review // RRsum: Re-Review Summary // SM: Strategy Memo // Admin: Administrative item

(AA): Alice Akinsulie || (CB): Christina Burnett || (BH) Bart Heldreth || (MF): Monice Fiume || (PC): Priya Cherian || (WJ): Wilbur Johnson

*Team moves to breakout room.

Friday, June 7th			
8:00 am	**CONTINENTAL BREAKFAST**		
8:30 am	**WELCOME TO THE 151st FULL CIR EXPERT PANEL MEETING**		**Dr. Bergfeld**
8:45 am	Admin	**MINUTES OF THE APRIL 2019 EXPERT PANEL MEETING**	**Dr. Bergfeld**
9:00 am	**DIRECTOR'S REPORT**		**Dr. Heldreth**
9:10 am	**FINAL REPORTS, REPORTS ADVANCING TO THE NEXT LEVEL, OTHER ITEMS**		

Final Reports

FAR (PC)	Parabens – *Dr. Belsito Reports*
FR (PC)	Basic Red 76 – *Dr. Marks Reports*
FR (MF)	Alkoxylated Fatty Amides – *Dr. Belsito Reports*
FR (WJ)	Alkanoyl Lactyl Lactates – *Dr. Marks Reports*
FR (WJ)	Polyaminopropyl Biguanide – *Dr. Belsito Reports*

Reports Advancing

DR (WJ)	Vanilla – *Dr. Marks Reports*
DAR (WJ)	Capryloyl Salicylic Acid – *Dr. Belsito Reports*
RR (WJ)	Acetyl Trialkyl Citrates – *Dr. Marks Reports*
DR (AA)	Glycerin Ethoxylates – *Dr. Belsito Reports*
RR (AA)	BHT – *Dr. Marks Reports*
TAR (CB)	Silicates – *Dr. Belsito Reports*
RR (CB)	Imidazolidinyl Urea – *Dr. Marks Reports*
DAR (CB)	MCI/MI – *Dr. Belsito Reports*
RR (PC)	EDTA – *Dr. Marks Reports*
DR (PC)	Soy - *Dr. Belsito Reports*
DR (MF)	Caprylhydroxamic Acid – *Dr. Marks Reports*

Other Items

RRsum (MF)	Squalene & Squalane – *Dr. Belsito Reports*
Admin (BH)	Priorities – *Dr. Marks Reports*

ADJOURN - *Next meeting Monday and Tuesday, September 16-17, 2019, at The Westin Washington, D.C. City Center, 1400 M St NW, Washington, District of Columbia, 20005*

On the basis of all data and information submitted, and after following all of the Procedures (https://www.cir-safety.org/supplementaldoc/cir-procedures), the Expert Panel shall determine whether each ingredient, under each relevant condition of use, is safe, safe with qualifications, unsafe, or there are insufficient data or information to make a determination of safety. Upon making such a determination, the Expert Panel shall issue a conclusion and/or announcement.

FR: Final Report // FAR: Final Amended Report // TR: Tentative Report // TAR: Tentative Amended Report // DR: Draft Report // DAR: Draft Amended Report // RR: Re-Review // RRsum: Re-Review Summary // SM: Strategy Memo // Admin: Administrative item

(AA): Alice Akinsulie || (CB): Christina Burnett || (BH) Bart Heldreth || (MF): Monice Fiume || (PC): Priya Cherian || (WJ): Wilbur Johnson

Commitment & Credibility since 1976

ONE HUNDRED FIFTIETH MEETING

OF THE

EXPERT PANEL

April 8-9, 2019

The Westin Hotel

Washington, D.C.

Expert Panel Members

Wilma F. Bergfeld, M.D., Chair

Donald V. Belsito, M.D.

Ronald A. Hill, Ph.D.

Curtis D. Klaassen, Ph.D.

Daniel C. Liebler, Ph.D.

James G. Marks, Jr., M.D.

Ronald C. Shank, Ph.D. (absent)

Thomas J. Slaga, Ph.D.

Paul W. Snyder, D.V.M., Ph.D.

Liaison Representatives

Consumer

Thomas Gremillion, J.D.

Industry

Alexandra Kowcz, M.B.A.

Government

Linda Katz, MD., M.P.H. (absent)

Adopted (Date)

Wilma F. Bergfeld, M.D.

1620 L Street, N.W., Suite 1200, Washington, DC 20036
(Main) 202-331-0651 (Fax) 202-331-0088
(Email) cirinfo@cir-safety.org (Website) www.cir-safety.org

Others Present at the Meeting

Alice Akinsulie	CIR
Don Bjerke	P & G
Roshil Budhram	Mast
Christina Burnett	CIR
Priya Cherian	CIR
Carol Eisenmann	PCPC
Monice Fiume	CIR
Kevin Fries	CIR
Bart Heldreth	CIR
Carla Jackson	CIR
Wilbur Johnson, Jr.	CIR
Brett Jurd	SASSI
Linda Loretz	PCPC
Ryan Nelson	HBW Insight
Nakissa Sadrieh	FDA
Teresa Washington	FDA
Keith Wyatt	FDA

MINUTES FROM THE 150th CIR EXPERT PANEL MEETING

CHAIRMAN'S OPENING REMARKS

Dr. Bergfeld welcomed the attendees to the 150th meeting of the Cosmetic Ingredient Review (CIR) Expert Panel. On a sad note, she then offered condolences for one of the former members of the Expert Panel, Dr. Arnold Schroeter, who passed away a few months ago. Dr. Bergfeld recalled that Dr. Schroeter was a great addition to the Panel, having served for many years.

Dr. Bergfeld noted that very robust discussions on a number of ingredients took place during Day 1 Team meetings. The CIR Draft Priority List and the following 11 ingredient reports were reviewed: 4 draft reports, 1 draft tentative report, and 6 draft final reports. She then stated that the Panel is moving in the direction of using other tools for evaluating sensitization potential, namely, quantitative risk assessment (QRA) and the direct peptide reactivity assay (DPRA). Furthermore, on the subject of sensitization, she noted that a caveat stating that products containing ingredients with sensitization potential should be formulated to be non-sensitizing has appeared in some CIR report conclusions.

APPROVAL OF MINUTES

The minutes of the December 3-4, 2018 (149th) CIR Expert Panel meeting were approved.

DIRECTOR'S REPORT

Dr. Heldreth expressed gratitude for the Panel's and other stakeholders' continued support of the Cosmetic Ingredient Review program. He also reported on the presentations covering the CIR process and utility of the Panel's reports. Specifically, Dr. Bergfeld presented at the meeting of Mexican Academy of Dermatology in March and Dr. Heldreth presented at the Society of Cosmetic Chemists 72nd Annual Scientific Meeting in December.

Based on Panel feedback, Dr. Heldreth also commented on coming changes to transmission of late received information to the Panel. Specifically, for future meetings, supplemental information transmission would not be limited to data only.

Final Safety Assessments

Fatty Acids & Fatty Acid Salts

The Panel issued a final report with the conclusion that the following 102 ingredients are safe in the present practices of use and concentration described in the safety assessment when formulated to be non-irritating and non-sensitizing, which may be based on a quantitative risk assessment (QRA).

Aluminum Distearate
Aluminum Isostearate*
Aluminum Isostearates/Palmitates*
Aluminum Isostearates/Stearates*
Aluminum Isostearates/Laurates/Palmitates*
Aluminum Isostearates/Laurates/Stearates*
Aluminum Lanolate*
Aluminum Stearate
Aluminum Stearates
Aluminum Tristearate
Ammonium Isostearate*
Ammonium Oleate*
Ammonium Stearate*
Arachidic Acid
Beeswax Acid*
Behenic Acid
C14-28 Alkyl Acid
C10-40 Isoalkyl Acid
C14-28 Isoalkyl Acid
C32-36 Isoalkyl Acid*
Calcium Behenate
Calcium Laurate*
Calcium Stearate
Calcium Undecylenate*
Capric Acid
Caproic Acid
Caprylic Acid
Dilinoleic Acid
Dierucic Acid*
Eicosatrienoic Acid*
Erucic Acid*
Hydroxycapric Acid
Hydroxycaprylic Acid
10-Hydroxydecanoic Acid
Hydroxylauric Acid*
Hydroxystearic Acid
10-Hydroxystearic Acid*
Isomerized Linoleic Acid
Isomerized Safflower Acid*
Isostearic Acid
Lauric Acid
Linoleic Acid
Linolenic Acid
Lithium Stearate

Magnesium Lanolate*
Magnesium Laurate
Magnesium Palmitate*
Magnesium Stearate
Magnesium Tallowate*
Myristic Acid
Methyl Myristic Acid*
Oleic Acid
Palmitic Acid
Potassium Behenate
Potassium Borageate*
Potassium Camelliate*
Potassium Caprate*
Potassium Caprylate*
Potassium Caprylate/Caprate*
Potassium Castorate
Potassium Hydrogenated Tallowate
Potassium Hydroxystearate*
Potassium Isostearate
Potassium Lanolate*
Potassium Laurate
Potassium Linoleate*
Potassium Linseedate*
Potassium Oleate
Potassium Olivate/Sunflowerseedate*
Potassium Palmitate
Potassium Stearate
Potassium Sunflowerseedate*
Potassium Tallate
Potassium Tallowate
Potassium Undecylenate*
Sodium Arganate*
Sodium Beeswax*
Sodium Behenate
Sodium Camellia Japonica Seedate*
Sodium Caprate*
Sodium Caprylate*
Sodium Castorate
Sodium Dilinoleate*
Sodium Hydrogenated Tallowate*
Sodium Hydroxystearate*
Sodium Isostearate
Sodium Lanolate*
Sodium Lardate*
Sodium Laurate
Sodium Laurate/Linoleate/Oleate/Palmitate
Sodium Linoleate*
Sodium Oleate
Sodium Palmitate
Sodium Stearate
Sodium Tallowate
Sodium Tamanuseedate*
Sodium Undecylenate*
Stearic Acid
Trilinoleic Acid
Undecanoic Acid
Undecylenic Acid

**Not reported to be in current use. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.*

Ingredients denoted in blue were previously reviewed by the Panel; this conclusion supersedes the previous conclusion.

The Expert Panel recognized that these ingredients, particularly Myristic Acid, Oleic Acid, and Sodium Caprate, can enhance the penetration of other ingredients through the skin. The Panel cautioned that care should be taken in formulating cosmetic products that may contain these ingredients in combination with any ingredients whose safety was based on their lack of dermal absorption data, or when dermal absorption was otherwise a concern.

The Panel was concerned that the potential exists for dermal irritation with the use of products formulated using fatty acids and fatty acid salts. The Panel specified that products containing fatty acids and fatty acid salts must be formulated to be non-irritating. The Panel was also concerned about the potential for polyunsaturated fatty acids to undergo oxidation during the formulation, or storage of cosmetic products, that may produce compounds that are dermal sensitizers. The Panel advises industry to limit oxidative products in formulations containing fatty acids and fatty acid salts, and to utilize accepted methodologies, such as a QRA, to ensure formulations are non-sensitizing.

Titanium Complexes

The Panel issued a final report with a split conclusion:

Isopropyl Titanium Triisostearate is safe in cosmetics in the present practices of use and concentration described in the safety assessment, when used as a surface modifier. The data are insufficient to determine the safety of the following 4 ingredients: Titanium Citrate, Titanium Ethoxide, Titanium Isostearates, and Titanium Salicylate. These 4 ingredients are not reported to be in current use in cosmetic formulations.

The Panel determined that the following data are needed to assess the safety of these 4 ingredients:

- Maximum use concentrations

- Methods of manufacture
- Impurities
- 28-day dermal toxicity data
    - Depending on the results of these studies, various systemic toxicity data may also be needed
- Genotoxicity data
- Skin irritation and sensitization data at maximum cosmetic use concentrations, except for Titanium Citrate

Skin irritation and sensitization data on Titanium Citrate previously requested are no longer needed because the Panel determined that results of a study on 37 patients (all suspected of having titanium allergy) patch tested with 0.16% and 0.32% Titanium Citrate were sufficient for evaluating these endpoints.

According to data received from the US Food and Drug Administration's (FDA) Voluntary Cosmetic Registration Program (VCRP) in 2019, Isopropyl Titanium Triisostearate is reported to be used in 513 cosmetic products (506 leave-on and 7 rinse-off products). The results of a concentration of use survey conducted by the Personal Care Products Council (Council) in 2017 indicate that Isopropyl Titanium Triisostearate is used at concentrations up to 1.4% in leave-on products (eye shadows) and at concentrations up to 0.3% in rinse-off products (eye make-up removers).

Confirmation that Isopropyl Titanium Triisostearate is only being used as a surface modifier was received. Submitted method of manufacture data demonstrate that as a surface modifier in cosmetic products, Isopropyl Titanium Triisostearate is covalently bound to a pigment. Thus, the presence of any residual or unreacted Isopropyl Titanium Triisostearate in the product formulation would be considered an impurity. In relation to the bound form of Isopropyl Titanium Triisostearate (i.e., use as a surface modifier), data indicating that surface modification does not result in any appreciable residual Isopropyl Titanium Triisostearate in the final product were not provided. However, it was agreed that appreciable residual Isopropyl Titanium Triisostearate in the final product is not a concern, considering that Isopropyl Titanium Triisostearate is produced by reacting isopropyl tris(isostearoyl) titanate with a colorant particle (e.g., black iron oxide).

Salicylic Acid and Salicylates

The Panel issued a final amended report with the conclusion that Salicylic Acid and the 17 salicylate ingredients listed below are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-irritating and non-sensitizing, which may be based on a QRA.

Butyloctyl Salicylate
Calcium Salicylate*
C12-15 Alkyl Salicylate*
Ethylhexyl Salicylate
Hexyldodecyl Salicylate*
Isocetyl Salicylate*
Isodecyl Salicylate
Magnesium Salicylate
Methyl Salicylate
Myristyl Salicylate*
Potassium Salicylate*
Salicylic Acid
Sodium Salicylate
TEA-Salicylate
Tridecyl Salicylate
Amyl Salicylate
Hexyl Salicylate
Isotridecyl Salicylate*

**Not reported to be in current use. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group*.

Ingredients identified by green text were not included in the original safety assessment.

The Panel originally published a Safety Assessment of Salicylic Acid and 16 salicylates in 2003 with the conclusion that Salicylic Acid; the salts, Calcium Salicylate, Magnesium Salicylate, MEA-Salicylate, Potassium Salicylate, Sodium Salicylate, and TEA-Salicylate; the esters, Capryloyl Salicylic Acid, C12-15 Alkyl Salicylate, Isocetyl Salicylate, Isodecyl Salicylate, Methyl Salicylate, Myristyl Salicylate, Ethylhexyl Salicylate, and Tridecyl Salicylate; and the compounds, Butyloctyl Salicylate and Hexyldodecyl Salicylate, are safe as used when formulated to avoid skin irritation and when formulated to avoid increasing the skin's sun sensitivity, or, when increased sun sensitivity would be expected, directions for use include the daily use of sun protection.

However, Capryloyl Salicylic Acid has since been deleted from this grouping because it was determined that this ingredient was erroneously defined as an ester in the International Cosmetic Ingredient Dictionary and Handbook, but is now correctly identified as a ketone. A separate rereview document on this ingredient is under development.

The qualification relating to formulating products to avoid increasing the skin's sun sensitivity that was included in the original conclusion is now omitted, based on results from a National Toxicology Program (NTP) photocarcinogenicity study indicating that Salicylic Acid had some protective effect at lower light intensities. In the NTP study, the effects of synthetic solar light on the skin of hairless mice that had been treated with creams containing 2% or 4% Salicylic Acid were evaluated. Creams containing Salicylic Acid decreased the incidence of skin tumors in mice receiving the lower of the two light intensities.

Regarding margin of safety (MOS) calculations the Panel agreed that 100% absorption is a more accurate assumption for mucous membrane exposure, and that the MOS calculations regarding lipstick use should be based on this absorption level only. The report was revised accordingly.

According to 2019 VCRP data, the ingredient in this report with the greatest use frequency of is Ethylhexyl Salicylate (3974 uses), followed by Salicylic Acid (1429 uses). The results of a concentration of use survey conducted by the Council in 2018 indicate that Butyloctyl Salicylate is used at concentrations up to 35.9% in leave-on products (lipstick), which is the highest maximum use concentration reported for ingredients reviewed in this safety assessment.

Benzyl Salicylate

The Panel issued a final report with a conclusion that Benzyl Salicylate is safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-irritating and non-sensitizing, which may be based on a QRA.

The Panel recognized several positive sensitization studies as well as the outcome of a QRA for dermal sensitization. Consequently, the Panel noted that the potential for induction of skin sensitization varies depending on a number of factors, including site of exposure, formulation, frequency of use, and duration of exposure. The Panel noted that manufacturers should evaluate their final product formulations for the potential for induction of skin sensitization using a QRA or other accepted methodologies. The Panel was also concerned that the potential exists for dermal irritation with the use of products formulated using Benzyl Salicylate, and thus specified that products containing Benzyl Salicylate should be formulated to be non-irritating.

According to 2019 VCRP data, Benzyl Salicylate is reported to be used in 3079 formulations. The results of a concentration of use survey conducted by the Council in 2018 indicate that Benzyl Salicylate is used at concentrations up to 0.5% in skin cleansing preparations; and the greatest leave-on use concentration for this ingredient is 0.15% in "other makeup preparations."

Tentative Safety Assessment

Brown Algae

The Panel issued a revised tentative report for public comment with the conclusion that 32 of the 82 distinct brown algae-derived ingredients reviewed are safe in the present practices of use and concentration described in the safety assessment. The Panel determined there was insufficient data to determine the safety of the remaining 50 ingredients. The insufficiencies include a lack of systemic toxicity data and/or sensitization data. The Panel also suggested the consideration of sufficient composition data in lieu of sensitization data for some of these ingredients. As for those ingredients that are formulated differently, but are derived from the same genus and species and would be similar in composition (ex. Laminaria Digitata Extract and Laminaria Digitata Powder), the Panel stated that if there is sufficient data to support the safety of one of these ingredients, all related ingredients of the same genus and species would be considered safe as well. In addition, the Panel noted the concern of arachidonic acid in several of these brown algae ingredients and determined that the concern can be mitigated as the final concentration of this material would be minimal in cosmetics. The Panel also expressed concern regarding pesticide residues and heavy metals that may be present in botanical ingredients, and stressed that the cosmetics industry should continue to use the necessary procedures to limit these impurities in the ingredient before blending into cosmetic formulations.

Alaria Esculenta Extract
Ascophyllum Nodosum*
Ascophyllum Nodosum Extract
Ascophyllum Nodosum Powder
Fucus Spiralis Extract*
Fucus Vesiculosus
Fucus Vesiculosus Extract
Fucus Vesiculosus Powder
Himanthalia Elongata Extract
Himanthalia Elongata Powder*
Hydrolyzed Fucus Vesiculosus Extract*
Hydrolyzed Fucus Vesiculosus Protein*
Laminaria Diabolica Extract*
Laminaria Digitata Extract
Laminaria Digitata Powder Laminaria Japonica Extract
Laminaria Japonica Powder*
Laminaria Ochroleuca Extract
Laminaria Saccharina Extract
Macrocystis Pyrifera (Kelp)
Macrocystis Pyrifera (Kelp) Blade/Pneumatocyst/Stipe Juice Extract*
Macrocystis Pyrifera (Kelp) Extract
Macrocystis Pyrifera (Kelp) Juice*
Macrocystis Pyrifera (Kelp) Protein
Saccharina Japonica Extract*
Sargassum Filipendula Extract Sargassum Muticum Extract
Undaria Pinnatifida Extract
Undaria Pinnatifida Cell Culture Extract*
Undaria Pinnatifida Leaf/Stem Extract*
Undaria Pinnatifida Powder
Undaria Pinnatifida Root Powder*
Agarum Cribrosum Extract
Cladosiphon Novae-Caledoniae Extract*
Cladosiphon Okamuranus Extract
Cystoseira Amentacea/Caespitosa/Branchycarpa Extract*
Cystoseira Baccata Extract*
Cystoseira Balearica Extract*
Cystoseira Caespitosa Extract*
Cystoseira Compressa Extract*
Cystoseira Compressa Powder*
Cystoseira Tamariscifolia Extract*
Dictyopteris Polypodioides Extract
Dictyota Coriacea Extract*
Durvillaea Antarctica Extract
Ecklonia Cava Extract*
Ecklonia Cava Water*
Ecklonia Kurome Extract*
Ecklonia Kurome Powder*
Ecklonia/Laminaria Extract*
Ecklonia Maxima Extract*
Ecklonia Maxima Powder*
Ecklonia Radiata Extract
Eisenia Arborea Extract*
Fucus Serratus Extract
Halidrys Siliquosa Extract
Halopteris Scoparia Extract*
Hizikia Fusiforme Extract*
Hizikia Fusiformis Water*
Hizikia Fusiformis Callus Culture Extract*
Hydrolyzed Ecklonia Cava Extract*
Laminaria Cloustoni Extract
Laminaria Hyperborea Extract
Laminaria Longissima Extract*
Lessonia Nigrescens Extract
Lessonia Nigrescens Powder*
Nereocystis Luetkeana Extract
Pelvetia Canaliculata Extract
Pelvetia Siliquosa Extract*
Phyllacantha Fibrosa Extract*
Saccharina Angustata Extract*
Saccharina Longicruris Extract
Sargassum Fulvellum Extract
Sargassum Fusiforme Extract
Sargassum Glaucescens Extract*
Sargassum Horneri Extract*
Sargassum Pallidum Extract*
Sargassum Siliquastrum Extract*
Sargassum Thunbergii Extract*
Sargassum Vulgare Extract
Sphacelaria Scoparia Extract
Undaria Peterseniana Extract*

**Not reported to be in current use. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.*

Ingredients in black type were considered safe as used.
Ingredients in green type were considered insufficient for sensitization data or composition data.
Ingredients in blue type were considered insufficient for systemic toxicity data.
Ingredients in red type were considered insufficient in both systemic toxicity and sensitization data.

According to 2019 VCRP data, Laminaria Digitata Extract, Fucus Vesiculosus Extract, Macrocystis Pyrifera (Kelp) Extract, and Ascophyllum Nodosum Extract are used in 310, 291, 199, and 140 formulations, respectively. Concentration of use surveys conducted by Council in 2015 and 2016 indicate Laminaria Digitata Powder has the highest reported maximum concentration of use; it is used at up to 40% in face and neck products. Macrocystis Pyrifera (Kelp) Extract is reported to be used at up to 36.4% in eye lotions.

Insufficient Data Announcements

Alkyl Amides MIPA

The Panel issued an insufficient data announcement (IDA) for the following 14 Alkyl Amide MIPA ingredients evaluated in this safety assessment:

Cocamide MIPA
Coconut Oil MIPA Amides
Hydroxyethyl Stearamide-MIPA
Isostearamide MIPA
Lauramide MIPA
Linoleamide MIPA
Oleamide MIPA
MIPA- Myristate
Myristamide MIPA
Palmamide MIPA
Palm Kernelamide MIPA
Peanutamide MIPA
Ricinoleamide MIPA
Stearamide MIPA

The Panel issued an IDA with the following data request:

- Skin sensitization data for Cocamide MIPA at maximum cosmetic use concentrations
- 28-Day dermal toxicity studies
- Dermal sensitization data at maximum use concentrations

All but a few of these ingredients are reported to function in cosmetics as a surfactant or viscosity increasing agent. According to 2019 VCRP, the alkyl amide MIPA ingredients are primarily used in rinse-off formulations, with use in a few leave-on formulations. Most of the reported uses are in some type of hair or skin cleansing formulation. Lauramide MIPA has the highest frequency of use, with a total of 485 formulations and Cocamide MIPA is reported to have is reported to have 335 uses, 324 of which are in rinse-off formulations.

The results of the concentration of use survey conducted in 2017 by the Council indicate that Cocamide MIPA has the highest maximum concentration of use, and is used at up to 12% in hair bleaches. The next highest reported maximum concentration of use is 4.8% Lauramide MIPA in bath soaps and detergents (rinse- offs). The highest concentration of use reported for products resulting in leave-on dermal exposure is 1% Cocamide MIPA in body and hand preparations.

The Panel also noted that these ingredients may potentially contain residual amine impurities. Thus, the Panel cautioned that these ingredients should not be used in cosmetic products in which *N*-nitroso compounds may be formed.

Palm Tree-Derived Ingredients

The Panel issued an IDA for the following 8 ingredients:

Euterpe Edulis Fruit Extract
Euterpe Edulis Juice Extract
Euterpe Oleracea Fruit Extract
Euterpe Oleracea Juice
Euterpe Oleracea Palm Heart Extract
Euterpe Oleracea Pulp Powder
Euterpe Oleracea Seed Powder
Hydrolyzed Euterpe Oleracea Fruit

The data requests are as follows:

For all of the ingredients above

- 28-day dermal toxicity

Euterpe Edulis Fruit Extract and Euterpe Edulis Juice Extract

- Method of manufacture
- Skin sensitization data at maximum use concentrations
- Genotoxicity
- Confirmation that these ingredients are foods

Euterpe Oleracea Seed Powder and Hydrolyzed Euterpe Oleracea Fruit

- Method of Manufacture

Euterpe Oleracea Palm Heart Extract

- Skin irritation and sensitization data at maximum use concentrations

According to 2019 VCRP data, Euterpe Oleracea Fruit Extract is reported to be used in 430 cosmetic products (297 leave-on products, 129 rinse-off products, 4 products that are diluted for (bath) use). Of the ingredients reviewed in this safety assessment, this is the greatest reported ingredient frequency of use. Results from a concentration of use survey conducted by the Council in 2017 indicate that Euterpe Oleracea Pulp Powder is used at maximum use concentrations up to 3% in leave-on products (face and neck products [not spray]) and maximum use concentrations up to 0.6% in rinse-off products (moisturizing products [not spray] and paste masks [mud packs]). These are the greatest leave-on and rinse-off concentrations that reported for the palm-tree derived ingredients.

Punica Granatum Ingredients

The common name for *Punica granatum* is pomegranate. The Panel issued an IDA for the following ingredients:

Punica Granatum Extract†
Punica Granatum Bark Extract
Punica Granatum Bark/Fruit Extract
Punica Granatum Callus Culture Extract
Punica Granatum Flower Extract
Punica Granatum Fruit Extract
Punica Granatum Fruit Juice
Punica Granatum Fruit/Root/Stem Powder
Punica Granatum Fruit/Sucrose Ferment Filtrate
Punica Granatum Fruit Water
Punica Granatum Juice Extract
Punica Granatum Leaf Cell Extract
Punica Granatum Peel Extract
Punica Granatum Pericarp Extract
Punica Granatum Seed
Punica Granatum Seed Cell Culture Lysate
Punica Granatum Seed Extract
Punica Granatum Seed

†Recently deleted from the INCI Dictionary, but still has reported uses reported in the VCRP database.

The additional data needed for these cosmetic ingredients are:

- Dermal irritation and sensitization data at maximum leave-on use concentrations for all ingredients, except Punica Granatum Pericarp Extract
- A no-observed-effect-level (NOEL) for skin lightening effects
- The generally recognized as safe (GRAS) status for the pomegranate plant parts not usually consumed (e.g., the bark, flower, root, stem, and leaf)
- Method of manufacturing for the extracts, especially with regard to solvent-type used
- Composition and impurities data for Punica Granatum Bark Extract, Punica Granatum Bark/Fruit Extract, Punica Granatum Callus Culture Extract, Punica Granatum Flower Extract, Punica Granatum Fruit/Root Stem Powder, and Punica Granatum Leaf Cell Extract.

Mannitol, Sorbitol, and Xylitol

The Panel issued an IDA for this ingredient group comprising Mannitol, Sorbitol, and Xylitol. (This group was previously referred to as Penta/Hexahydric Alcohols.) The Panel requested sensitization and irritation data at maximum use concentrations for all three ingredients. In addition, the Panel noted the positive phototoxicity study on Xylitol (10%), and requested additional data to evaluate the phototoxic potential of these ingredients at leave-on concentrations.

According to 2019 VCRP Data, Sorbitol, Xylitol, and Mannitol are used in 1976, 472, and 404 formulations, respectively. The results of the concentration of use survey conducted by the Council indicate Sorbitol has the highest concentration of use; it is used at up to 70% in dentifrices. The highest concentration of use reported for products resulting in leave-on dermal exposure is 60.5% Mannitol in other skin care preparations.

Tabled Assessments

Silica and Silicates

Activated Clay
Aluminum Calcium Sodium Silicate
Aluminum Iron Calcium Magnesium Germanium Silicates
Aluminum Iron Calcium Magnesium Zirconium Silicates
Aluminum Iron Silicates
Aluminum Silicate
Ammonium Silver Zinc Aluminum Silicate
Ammonium Silver Zeolite
Attapulgite
Bentonite
Calcium Magnesium Silicate
Calcium Silicate
Fuller's Earth
Gold Zeolite
Hectorite
Hydrated Silica
Kaolin
Lithium Magnesium Silicate
Lithium Magnesium Sodium Silicate
Magnesium Aluminometasilicate
Magnesium Aluminum Silicate
Magnesium Silicate
Magnesium Trisilicate
Montmorillonite
Potassium Silicate
Pyrophyllite
Silica
Silver Copper Zeolite
Sodium Magnesium Aluminum Silicate
Sodium Magnesium Silicate
Sodium Metasilicate
Sodium Potassium Aluminum Silicate
Sodium Silicate
Sodium Silver Aluminum Silicate
Titanium Zeolite
Tromethamine Magnesium Aluminum Silicate
Zeolite
Zinc Silicate
Zinc Zeolite
Zirconium Silicate

Ingredients in blue were previously reviewed by the Panel.

CIR staff will reorganize these ingredients into 2 separate reports with the first report to be reviewed to include Silica, Hydrated Silica, and silicate ingredients, with a focus on ingredients that are synthetically derived. The second report will be comprised of the ingredients that are determined to be naturally sourced (i.e. mined), including clay materials, zeolites, and any other ingredients in the above list that are mined.

The data on all these ingredients are still considered insufficient to determine the conclusion on safety. The additional data needed for the two safety assessments of these cosmetic ingredients comprise:

- The mean and range of particle sizes for all silica and silicate ingredients (and corresponding sizes of final formulation particles) that are used in spray and powder formulations
- Chemical characterization, composition, and impurities data for all ingredients, except Silica
- Method of manufacturing and/or source data for all ingredients, except Silica and Hydrated Silica.

Parabens

The Panel tabled discussion on the following 21 ingredients for consideration of an updated data profile:

Benzylparaben*
Butylparaben
Calcium Paraben*
Ethylparaben
Isobutylparaben
Isopropylparaben
Methylparaben
Potassium Butylparaben*
Potassium Ethylparaben*
Potassium Methylparaben*
Potassium Paraben*
Potassium Propylparaben*
Propylparaben
Sodium Butylparaben
Sodium Ethylparaben
Sodium Isobutylparaben
Sodium Isopropylparaben*
Sodium Methylparaben
Sodium Paraben
Sodium Propylparaben
4-Hydroxybenzoic Acid

**Not reported to be in use according to 2019 VCRP data and the 2016 Concentration of Use survey.*

A significant quantity of data and a number of comments were received after these documents were in press. Thus, the Panel decided to table this report in order to adequately address this information.

According to VCRP survey data received in 2019, Methylparaben and Propylparaben were reported to be used in 11,739 and 9034 formulations, respectively. The results of the concentration of use survey conducted by the Council in 2016 indicate Methylparaben had the highest reported maximum concentration of use; it is used at up to 0.9% in shampoos. The highest maximum concentration of use reported for products resulting in leave-on exposure is 0.8% Methylparaben in a mascara, and for leave-on dermal exposure is 0.65% Ethylparaben in eye shadows.

Rereviews

Squalane and Squalene

The CIR Expert Panel first reviewed the safety of Squalane and Squalene in 1982, concluding that "both Squalane and Squalene are safe as cosmetic ingredients in the present practices of use and concentration," as described in that report. In 2001, after considering new studies and updated use data on these two ingredients, the Panel determined to not re-open the safety assessment. Because it has been at least 15 years since the first re-review summary was published, in accord with CIR Procedures, the Panel again considered whether the safety assessment of Squalane and Squalene should be re-opened.

The Panel reviewed data that have been published since the last re-review, as well as updated frequency and concentration of use data. The frequency of use of both of these ingredients has increased significantly. The Panel noted that, although additional studies indicated there may be some potential for sensitization, significant clinical evidence suggests these ingredients are not sensitizers. Additionally, the lack of case reports in spite of the increased use supports this fact. Therefore, the Panel reaffirmed the original conclusion, and did not re-open this safety assessment.

MCI/MI

In 1992, the final report on MCI/MI was published with the conclusion that this mixture may be safely used in rinse-off products at a concentration not to exceed 15 ppm and in leave-on cosmetic products at a concentration not to exceed 7.5 ppm. Based on the multiple reported incidences of sensitization reported globally since the original report was published and the large number of uses being reported to the VCRP database, the Panel re-opened the safety assessment on MCI/MI to amend the current conclusion. Prior to determining the new conclusion, however, the Panel is awaiting the results of a second-generation quantitative risk assessment (QRA 2.0) calculation to be performed by industry stakeholders.

Draft 2020 Priorities

Interested parties are invited to comment on the inclusion of the ingredients listed in the 2020 CIR Draft Priorities. The selection of these ingredients was based on those elected for cause, and those on the list of ingredients that have not yet been reviewed by the CIR Expert Panel that have the greatest number of uses reported to the VCRP in 2018, and updated in 2019. While the number of proposed new reports below is fewer than usual, a number of re-reviews and previously prioritized report projects are likely to be carried forward into 2020. Comments are also being sought on the grouping of each ingredient family. Proposed ingredients and families may be found starting at pdf page 26 in the document available at the following url: https://www.cir- safety.org/sites/default/files/Admin_4.pdf.

Of note, Benzisothiazolinone was proposed for deletion from the priorities, as it has not been reported to be in use since 2016. The liaison from the FDA proposed the addition of Mica (when not used as a colorant), Cannabidiol, and probiotics (no specific ingredients proposed). CIR plans to finalize the proposed 2020 Priority List at the June 2019 Panel meeting.

Commitment & Credibility since 1976

Memorandum

Date: May 10th, 2019

From: Bart Heldreth, Ph.D., Executive Director, Cosmetic Ingredient Review

To: All stakeholders

Re: Draft Final 2020 Priority List

The CIR Procedures require preparation of the Draft 2020 Priority List for public comment by June 1, 2019. The Draft 2020 Priority List was issued for public comment earlier (March 2019) in the process to allow more time for the acquisition of data. The list is based on stakeholder requests; frequency of use data (FOU) from FDA's Voluntary Cosmetic Registration Program (VCRP) received from the FDA on February 5, 2018; and on CIR staff and Panel workflow. Comments at the April 2019 Expert Panel meeting have been considered and are addressed below. The Draft Final Priorities for 2020 are essentially the same as those finalized for 2019; however, this list has been updated with 2019 frequency of use data, a report in progress has been removed from the list, an ingredient (Benzisothiazolinone) was removed for zero frequency of use, and three items were suggested for addition. Most of the ingredients herein have increased in FOU.

At the April 2019 Expert Panel meeting, three items were suggested for addition to the 2020 Priorities List, namely, "probiotics," Mica (for uses other than colorant), and Cannabidiol (aka CBD). The CIR is thankful for such suggestions, and always welcomes stakeholder input. According to the CIR Procedures, formation of priority lists and review inclusions/exclusions follow a set series of guidelines. With regard to the request for the review of "probiotics," no specific ingredients have been named for review. While "probiotics" is an interesting area for review, the purview of the Expert Panel is to assess the safety of individual ingredients as used in cosmetics. Are any specific ingredients nominated for prioritization? Additionally, the study of probiotics in skin care appears to yet be in its infancy. If/when any specific ingredient is named, should an expert in this emerging field provide an overview of the issues with this biotechnology, prior to prioritization?

Concerning the suggestion for the assessment of Mica, there are yet some issues that require clarification, precluding addition to the 2020 Priorities List. In the US, Mica is used in cosmetics as a color additive, which is typically excluded from Expert Panel assessment because its safety is determined under 21 CFR Part 71. However, the suggestion for CIR review of this ingredient was

accompanied with the assertion that it is being used for a function other than colorant (e.g., absorbent). While such other uses are not necessarily excluded from CIR review, 21 CFR Part 70.3(g) states that:

> For a material otherwise meeting the definition of color additive to be exempt from section 721 of the act, on the basis that it is used (or intended to be used) solely for a purpose or purposes other than coloring, the material must be used in a way that any color imparted is clearly unimportant insofar as the appearance, value, marketability, or consumer acceptability is concerned. (It is not enough to warrant exemption if conditions are such that the primary purpose of the material is other than to impart color.)

Thus, the question remains, is the safety assessment of Mica, even for other uses, still not the purview of FDA colorant regulators? In the event that the answer is unequivocally no, to minimize duplication of effort, the inclusion and priority of cosmetic ingredients which are also subject to other existing FDA safety reviews, should be based in whole, or at least in part, on that existing review. Would FDA be willing and able to provide such data, prior to the prioritization of this ingredient?

The use of hemp-derived chemicals is certainly of great public interest. However, it is unclear how such chemicals are currently used in cosmetics. According to the FDA's VCRP data we received earlier this year, Cannabidiol is not reported to be used in cosmetics. Typically, when no uses are reported, use concentrations are also not available. Data on frequency, categories, and concentration of use would be of paramount importance to evaluating risk. Would FDA be willing and able to provide such data, if the Expert Panel were to agree to the prioritization of this ingredient?

Furthermore, in evaluating a cosmetic ingredient which is also used as an inactive or active ingredient in an over-the-counter (OTC) or prescription drug for which the FDA has at any time approved a New Drug Application (NDA), the Expert Panel shall review all related documents which the FDA makes available to determine whether all safety information relevant to cosmetic use of the ingredient was available to the FDA, and whether the cosmetic use of the ingredient presents any additional safety considerations not adequately covered by the FDA action on the NDA. The Expert Panel shall adopt those conclusions of the FDA action which it concludes adequately cover cosmetic use of the ingredient, and shall conduct its own evaluation of those cosmetic uses not adequately covered by the FDA action. On June 25, 2018, the FDA Center for Drug Evaluation and Research (CDER) approved such an NDA for Epidiolex (cannabidiol) 100 mg/mL oral solution for the treatment of seizures associated with Lennox Gastaut syndrome or Dravet syndrome in patients two years of age and older. Summary information regarding this NDA approval, is provided herein (*NDAletter, NDAsummary_review*) for the Expert Panel's consideration (additional components of the NDA approval package may be accessed at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210365Orig1s000TOC.cfm).

Moreover, the FDA issued a scientific data call in the Federal Register on April 3, 2019 (*Federal_Register_04032019*). The docket for responses to this call closes July 2, 2019. Therein, is a specific call for information regarding exposure to Cannabidiol via cosmetic use. Accordingly,

should not the consideration of prioritizing Cannabidiol be postponed at least until the results of such a data call are made available?

While this Draft Final Priority list includes only the lead ingredients, groupings are provided for each on the following pages of this document. There are 24 reports covering 187 ingredients on the Draft Final 2020 Priorities List. Reports previously prioritized and on the CIR docket at the end of 2019, as well as a number of re-reviews of previous assessments, will supplement the total number of ingredients to be assessed in 2020. Should the Expert Panel conclude that any of the above suggested additions be included in the 2020 Priorities, such will be added to these numbers.

Interested parties are encouraged to submit pertinent data to the CIR, as soon as possible, for use in the development of the Scientific Literature Reviews for these ingredients. Although the specific data needs vary for each safety assessment, the following are typical data that the Panel reviews for each safety assessment.

- Chemistry, impurities, and method of manufacture
- Toxicokinetics data, specifically dermal absorption and/or penetration
- Repeated-dose toxicity data
- Inhalation toxicity data, if the ingredient is used in a product that can be incidentally inhaled
- Reproductive/developmental toxicity data
- Genotoxicity data; if positive, carcinogenicity data may be needed
- Dermal irritation and sensitization data

For the review of botanical ingredients, the additional data needed include: species, plant part, extraction method, solvent, and data on component chemical characterization. It is important that these data are specific to the cosmetic ingredient(s).

Draft Final 2020 Priorities List

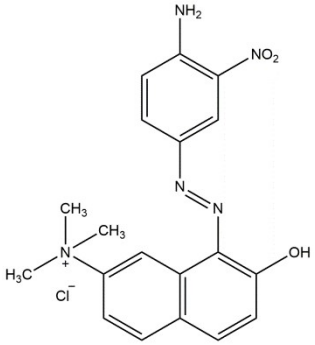
Ingredients	Frequency of Use (FOU) Data	
	Year 2018	Year 2019
For cause		
BASIC BROWN 17 – a hair dye	45	51↑
Per FOU		
HONEY	949	1002↑
SACCHARUM OFFICINARIUM (SUGARCANE) EXTRACT	406	447↑
EQUISETUM ARVENSE EXTRACT	369	338↓
SACCHARIDE ISOMERATE	365	455↑
PORTULACA OLERACEA (PURSLANE) EXTRACT	363	481↑
UBIQUINONE	343	374↑
DIATOMACEOUS EARTH	337	213↓
SODIUM LEVULINATE	331	390↑
GLUCONOLACTONE	329	369↑
ACETYL HEXAPEPTIDE-8	318	379↑
CALCIUM SULFATE	317	178↓
HONEY EXTRACT	306	359↑
CHONDRUS CRISPUS EXTRACT	299	350↑
ROSA DAMASCENA FLOWER OIL	298	328↑
SALVIA OFFICINALIS (SAGE) LEAF EXTRACT	292	325↑
ROSA DAMASCENA FLOWER WATER	289	331↑
DICAPRYLYL ETHER	288	344↑
PEG/PPG-8/3 DIISOSTEARATE	277	290↑
POLYQUATERNIUM-51	274	310↑
DIACETONE ALCOHOL	268	223↓
ACETYL GLUCOSAMINE	265	276↑
POLYQUATERNIUM-6	265	280↑
OLEA EUROPAEA (OLIVE) LEAF EXTRACT	257	279↑

Draft 2020 Priorities Groupings for New Reports

Proposed 2020 Report – per cause

Basic Brown 17 *– per PCPC HCTC* **FOU = 51**

Definition: Basic Brown 17 is the monoazo color that conforms to the formula:



Reported **Function**: Hair Colorant

Notes: *Since FOU might not be a very accurate surrogate for exposure, with regard to hair dyes, the PCPC HCTC proposes one hair dye ingredient annually for CIR review.*

Grouping proposal: None

Proposed 2020 Reports – per FOU (all 2019 data)

Honey **FOU = 1002**

Definition: Honey is a saccharic secretion gathered and stored by honey bees of the species, *Apis mellifera*, *Tetragonisca angustula*, *Scaptotrigona pectoralis*, or *Melipona Becheii.*

Reported **Functions**: Flavoring Agents; Humectants; Skin-Conditioning Agents - Humectant; Solvents

Notes: *Primarily saccharides, but a complex mixture of proteins, amino acids, vitamins, minerals, etc.*

Grouping proposal: *Honey Ingredients (7 ingredients; 1,373 combined FOU)*

Honey (FOU priority ingredient)	**1002**
Honey Extract	**359**
Hydrogenated Honey (mix of saccharides)	**6**
Hydrolyzed Honey (mix of saccharides)	**-**
Honey Cocoates	**-**
Honey Powder	**6**
Hydrolyzed Honey Protein	**-**

Saccharum Officinarum (Sugarcane) Extract

FOU = 447

Definition: Saccharum Officinarum (Sugarcane) Extract is the extract of the sugar cane, *Saccharum officinarum.*

Reported **Functions**: Exfoliants; Skin-Conditioning Agents - Miscellaneous; Solvents

Notes: *Sugarcane wax is used as a commercial source of long chain fatty alcohols, acids, esters, aldehydes, and ketones. Policosanols and D-003 along with some steroids and terpenoids have also been identified and isolated from sugarcane wax. Policosanols are a mixture of long chain primary aliphatic alcohols (1 - 8) ranging from 2.5 - 80%. Octacosanol constitutes 50 - 80% of the total policosanoles. Other major pharmacologically active components of sugarcane wax are long chain aliphatic fatty acids (9 - 18) present at lower concentrations. Although fatty acid and fatty alcohol are reported as major constituents various phytosterols, steroids, and higher terpenoids have also been reported in sugarcane wax.* *Pharmacognosy Reviews*. 2015;9(17):45-54

Grouping proposal: *Saccharum officinarum-Derived Ingredients (2 ingredients; 447 combined FOU)*

Saccharum Officinarum (Sugarcane) Extract (FOU priority ingredient)	**447**
Saccharum Officinarum (Sugarcane) Wax	**-**

Equisetum Arvense Extract

FOU = 338

Definition: Equisetum Arvense Extract is the extract of the whole herb, *Equisetum arvense*.

Reported **Functions**: Skin-Conditioning Agents - Miscellaneous

Notes:

Grouping proposal: *Horsetail Ingredients (6 ingredients, 368 combined FOU)*

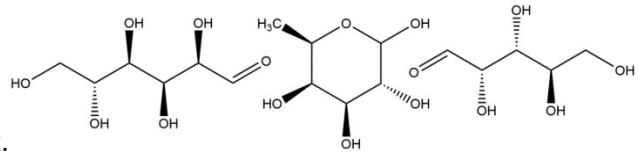
Equisetum Arvense Extract (FOU priority ingredient)	**338**
Equisetum Arvense Juice	**-**
Equisetum Arvense Leaf Extract	**8**
Equisetum Arvense Leaf Powder	**-**
Equisetum Arvense Powder	**1**
Horsetail (Equisetum Arvense) – not in INCI; VCRP only	21

Saccharide Isomerate

FOU = 455

Definition: Saccharide Isomerate is a carbohydrate complex formed from a base catalyzed rearrangement of a mixture of saccharides.

Ex.



***Reported* Functions**: Skin-Conditioning Agents - Humectant

Notes: *Many of the saccharide ingredients used as humectants in cosmetic formulation have been previously assessed for safety (e.g., calcium gluconate, fructose, fucose galactose, galactosyl fructose, galacturonic acid, gluconic acid, glucose, isomalt, kefiran, lactitol lactose, lactulose, maltose, mannose, melibiose, potassium gluconate, rhamnose, ribose, sodium gluconate, sucralose, sucrose, trehalose, xylobiose, and xylose were found safe as used in 2014* (Final Report)).

Grouping proposal: *Saccharide Humectants (7 ingredients, 636 combined FOU)*

Saccharide Isomerate (FOU priority ingredient)	**455**
Saccharide Hydrolysate (mix of saccharides)	**30**
Anhydrogalactose	**-**
Anhydroglucitol	**-**
Anhydroxylitol	**151**
Arabinose	**-**
Psicose	**-**

Portulaca Oleracea Extract

FOU = 481

Definition: Portulaca Oleracea Extract is the extract of the whole plant, *Portulaca oleracea*.

***Reported* Functions**: Skin-Conditioning Agents - Humectant

Notes: *Common name, Purslane*

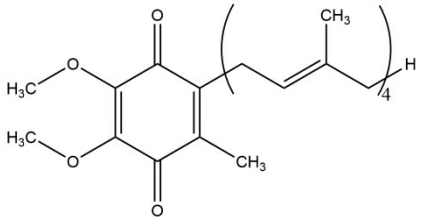
Grouping proposal: *Portulaca oleracea-Derived Ingredients (4 ingredients, 481 combined FOU)*

Portulaca Oleracea Extract (FOU priority ingredient)	**481**
Portulaca Oleracea Flower/Leaf/Stem Extract	**-**
Portulaca Oleracea Juice	**-**
Portulaca Oleracea Water	**-**

Ubiquinone

FOU = 374

Definition: Ubiquinone is the organic compound that conforms to the formula:



***Reported* Functions**: Antioxidants; Skin-Conditioning Agents – Miscellaneous

Notes: *Common name is Coenzyme Q10*

Grouping proposal: *Ubiquinone Ingredients (3 ingredients, 381 combined FOU)*

Ubiquinone (FOU priority ingredient)	**374**
Disodium Ubiquinone (salt for of Ubiquinone)	**-**
Hydroxydecyl Ubiquinone (93% structural similarity to Ubiquinone)	**7**

Diatomaceous Earth

FOU = 213

Definition: Diatomaceous Earth is a mineral material consisting chiefly of the siliceous frustules and fragments of various species of diatoms, which may or may not be calcined.

***Reported* Functions**: Antiacne Agents; Chelating Agents; Skin-Conditioning Agents - Miscellaneous

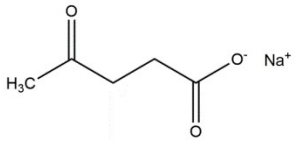
Notes:

Grouping proposal: None

Sodium Levulinate

FOU = 390

Definition: Sodium Levulinate is the sodium salt of Levulinic Acid



***Reported* Functions**: Skin-Conditioning Agents - Miscellaneous

Notes: *These are "keto acids," alkyl moieties with a ketone and carboxylic acid functional group.*

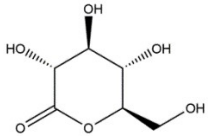
Grouping proposal: *Levulinic Acid and Sodium Levulinate (2 ingredients, 516 combined FOU)*

Sodium Levulinate (FOU priority ingredient)	**390**
Levulinic Acid	**126**

Gluconolactone

FOU = 369

Definition: Gluconolactone is the lactone that conforms to the formula:



***Reported* Functions**: Antiacne Agents; Chelating Agents; Skin-Conditioning Agents - Miscellaneous

Notes: *5 such oxidized monosaccharides are found in the Dictionary.*

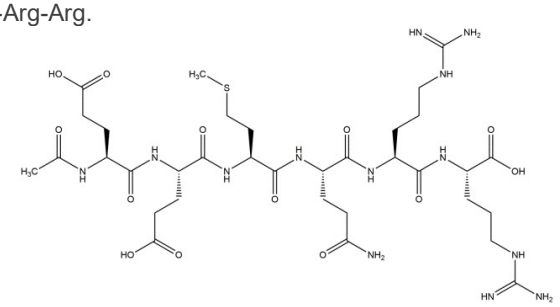
Grouping proposal: *Glycolactones (5 ingredients, 369 combined FOU)*

Gluconolactone (FOU priority ingredient)	**369**
Galactonolactone	**-**
Glucarolactone	**-**
Glucoheptonolactone	**-**
Ribonolactone	**-**

Acetyl Hexapeptide-8

FOU = 379

Definition: Acetyl Hexapeptide-8 is product obtained by the acetylation of Hexapeptide-8. Hexapeptide-8 is a synthetic peptide containing arginine, glutamic acid, glutamine and methionine. The specific sequence is Ac-Glu-Glu-Met-Gln-Arg-Arg.



***Reported* Functions**: Skin-Conditioning Agents - Humectant

Notes: *These two ingredients share the same sequence and only differ at the C-terminus*

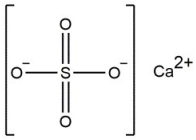
Grouping proposal: *Acetyl Hexapeptide-8 and its Amide (2 ingredients, 379 combined FOU)*

Acetyl Hexapeptide-8 (FOU priority ingredient)	**379**
Acetyl Hexapeptide-8 Amide	**-**

Calcium Sulfate

FOU = 178

Definition: Calcium Sulfate is the inorganic salt that conforms to the formula:



***Reported* Functions**: Abrasives; Bulking Agents; Opacifying Agents

Notes:

Grouping proposal: *Calcium Sulfate and its hydrate (2 ingredients, 183 combined FOU)*

Calcium Sulfate (FOU priority ingredient)	**178**
Calcium Sulfate Hydrate	**5**

Chondrus Crispus Extract

FOU = 350

Definition: Chondrus Crispus Extract is the extract of the ~~whole plant~~ [red alga], *Chondrus crispus*.

***Reported* Functions**: Skin-Conditioning Agents - Miscellaneous

Notes:

-most are from the complex cell wall

-source of stabilizers and thickeners used in: salad dressing, soft serve ice cream, puddings, icings, sauces, creamed soups, laxatives, lotions, creams, etc.

-source of Agar (safe as used by CIR (Final Report))

Grouping proposal: *Red Alga (73 ingredients, combined 865 FOU)*

Chondrus Crispus Extract (FOU priority ingredient)	**350**
Chondrus Crispus (aka "irish moss" in VCRP)	**6**
Chondrus Crispus Powder	**42**
Hydrolyzed Chondrus Crispus Extract	**2**
Ahnfeltiopsis Concinna Extract (aka AHNFELTIA CONCINNA EXTRACT)	**15**
Asparagopsis Armata Extract	**40**
Betaphycus Gelatinum Extract	**-**
Botryocladia Occidentalis Extract	**-**
Calliblepharis Ciliata Extract	**-**
Calliblepharis Jubata Extract	**-**
Ceramium Kondoi Extract	**-**
Ceramium Rubrum Extract	**-**
Chondracanthus Teedei Powder	**-**
Chondracanthus Tenellus Extract	**-**
Chondracanthus Tenellus/Saccharina Angustata/Ulva Linza Extract	**-**
Chondrus Elatus Extract	**-**
Chondrus Elatus/Saccharina Angustata/Monostroma Nitidum Thallus Extract	**-**
Corallina Officinalis Extract	**79**
Corallina Officinalis Powder	**-**
Digenea Simplex Extract	**1**
Dilsea Carnosa Extract	**-**
Eucheuma Serra Extract	**-**
Eucheuma Serra/Grateloupia Sparsa/Saccharina Angustata/Ulva Linza/Undaria Pinnatifida Extract	**-**
Eucheuma Serra/Saccharina Angustata/Ulva Linza Extract	**-**
Furcellaria Lumbricalis Extract	**-**
Galaxaura Rugosa Extract	**-**

Galaxaura Rugosa/Sargassum Pacificum/Turbinaria Ornata Extract	**-**
Gelidiella Acerosa Extract	**17**
Gelidium Amansii Extract	**-**
Gelidium Cartilagineum Extract	**27**
Gelidium Sesquipedale Extract	**-**
Gigartina Skottsbergii Extract	**-**
Gigartina Stellata Extract	**9**
Gigartina Stellata/Kappaphycus Alvarezii Extract	**-**
Gloiopeltis Furcata Extract	**-**
Gloiopeltis Tenax Extract	**-**
Gloiopeltis Tenax Powder	**-**
Gracilaria Vermiculophylla Extract	**-**
Gracilaria Verrucosa Extract	**-**
Gracilariopsis Chorda Extract	**-**
Grateloupia Elliptica Extract	**-**
Grateloupia Livida Powder	**-**
Grateloupia Sparsa Extract	**-**
Hydrolyzed Asparagopsis Armata Extract	**-**
Hydrolyzed Corallina Officinalis	**-**
Hydrolyzed Corallina Officinalis Extract	**5**
Hydrolyzed Gracilariopsis Chiangii Extract	**-**
Hydrolyzed Porphyra Yezoensis	**-**
Hydrolyzed Rhodophyceae Extract	**-**
Hypnea Musciformis Extract	**133**
Kappaphycus Alvarezii Extract	**9**
Lithothamnion Calcareum Extract	**-**
Lithothamnion Calcareum Powder	**-**
Lithothamnion Corallioides Powder	**-**
Mesophyllum Lichenoides Extract	**-**
Palmaria Palmata Extract	**78**
Palmaria Palmata Powder	**-**
Phymatolithon Calcareum Extract	**-**
Pikea Robusta Extract	**-**
Polysiphonia Brodiei Extract	**-**
Polysiphonia Elongata Extract	**-**
Polysiphonia Lanosa Extract	**-**
Porphyra Columbina Extract	**-**
Porphyra Linearis Powder	**-**
Porphyra Tenera Extract	**-**
Porphyra Umbilicalis Extract	**42**
Porphyra Umbilicalis Powder	**-**
Porphyra Yezoensis Extract	**10**
Porphyra Yezoensis Powder	**-**
Rhodymenia Palmata Extract (synonym for Palmaria Palmata Extract?)	**-**
Rissoella Verruculosa Extract	**-**
Sarcodiotheca Gaudichaudii Extract	**-**
Sodium Porphyra Yezoensis Extract	**-**

Rosa Damascena Flower Oil

FOU = 328

Definition: Rosa Damascena Flower Oil is the volatile oil obtained from the flowers of *Rosa damascena.*

Reported **Functions**: Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous

Notes: *ROSA DAMASCENA (DAMASK ROSE) FLOWER OIL according to the VCRP.*

Grouping proposal: *Rosa damascene-Derived Ingredients (10 ingredients, 888 combined FOU)*

Rosa Damascena Flower Oil (FOU priority ingredient)	**328**
Hydrolyzed Rosa Damascena Flower Extract	**-**
Rosa Damascena Bud Extract	**-**
Rosa Damascena Extract	**49**
Rosa Damascena Flower	**4**
Rosa Damascena Flower Extract	**153**
Rosa Damascena Flower Powder	**1**
Rosa Damascena Flower Water	**331**
Rosa Damascena Flower Water Extract	**-**
Rosa Damascena Flower Wax	**22**

Salvia Officinalis (Sage) Leaf Extract

FOU = 325

Definition: Salvia Officinalis (Sage) Leaf Extract is the extract of the leaves of *Salvia officinalis*.

Reported **Functions**: Oral Care Agents; Skin-Conditioning Agents - Miscellaneous

Notes:

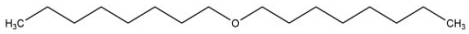
Grouping proposal: *Salvia officinalis-Derived Ingredients (8 ingredients, 423 combined FOU)*

Salvia Officinalis (Sage) Leaf Extract (FOU priority ingredient)	**325**
Salvia Officinalis (Sage) Extract	**83**
Salvia Officinalis (Sage) Flower/Leaf/Stem Extract	**-**
Salvia Officinalis (Sage) Flower/Leaf/Stem Juice	**-**
Salvia Officinalis (Sage) Flower/Leaf/Stem Water	**1**
Salvia Officinalis (Sage) Leaf	**8**
Salvia Officinalis (Sage) Leaf Water	**6**
Salvia Officinalis (Sage) Root Extract	**-**

Dicaprylyl Ether

FOU = 344

Definition: Dicaprylyl Ether is the ether that conforms to the structure:



Reported **Functions**: Skin-Conditioning Agents - Emollient

Notes: *These ingredients are all simple alkyl ethers.*

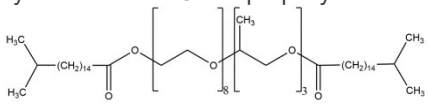
Grouping proposal: *Fatty Ethers (8 ingredients, 360 combined FOU)*

Dicaprylyl Ether (FOU priority ingredient)	**344**
Dicetyl Ether	**-**
Didecyl Ether	**-**
Diisononyl Ether	**-**
Dilauryl Ether	**-**
Dimyristyl Ether	**-**
Distearyl Ether	**16**
Cetyl Dimethylbutyl Ether	**-**

PEG/PPG-8/3 Diisostearate

FOU = 290

Definition: PEG/PPG-8/3 Diisostearate is the polyethylene glycol ether of the propoxylated diester of isostearic acid containing an average ethoxylation value of 8 and propoxylation value of 3.



Reported **Functions**: Surfactants - Emulsifying Agents

Notes: *Glycereth-7 Diisononanoate ("Glycereth" means a glyceryl PEG ether) previously assessed* (Published Report). *These ingredients are linear alkoxyl chains, capped at both ends with stearyl esters.*

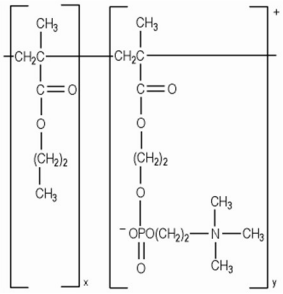
Grouping proposal: *Fatty Ester End-Capped Alkoxylates (13 ingredients, 313 combined FOU)*

PEG/PPG-8/3 Diisostearate (FOU priority ingredient)	**290**
PEG-15 Butylene Glycol Diisostearate	**-**
PEG-10 Glyceryl Diisostearate	**-**
PEG-20 Glyceryl Diisostearate	**-**
PEG-30 Glyceryl Diisostearate	**-**
PEG-60 Glyceryl Diisostearate	**-**
PEG-12 Glyceryl Dimyristate	**18**
PEG-12 Glyceryl Dioleate	**-**
[PEG-3 Glyceryl Distearate] (VCRP listing only)	**1**
PEG-4 Glyceryl Distearate	**-**
PEG-12 Glyceryl Distearate	**4**
PEG-23 Glyceryl Distearate	**-**
PEG-4 Polyglyceryl-2 Distearate	**-**

Polyquaternium-51

FOU = 310

Definition: Polyquaternium-51 is the polymeric quaternary ammonium salt that conforms generally to the formula:



Reported **Functions**: Film Formers; Skin-Conditioning Agents - Humectant

Notes: *All of these ingredients share a acryloyloxyethyl phosphorylcholine monomer in common*

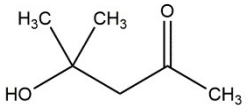
Grouping proposal: *Acryloyloxyethyl Phosphorylcholine Polymers (8 ingredients, 341 combined FOU)*

Polyquaternium-51 (FOU priority ingredient)	**310**
Polyquaternium-61	**9**
Polyphosphorylcholine Glycol Acrylate	**22**
Acrylic Acid/Phosphorylcholine Glycol Acrylate Crosspolymer	**-**
C4-18 Alkyl Methacrylate/Methacryloyloxyethyl Phosphorylcholine Copolymer	**-**
Hydroxyethylcellulose/Phosphorylcholine Glycol Acrylate Copolymer	**-**
Phosphorylcholine Glycol Methacrylate/PEG-10 Dimethacrylate Crosspolymer	**-**
Polyquaternium-10/Phosphorylcholine Glycol Acrylate Copolymer	**-**

Diacetone Alcohol

FOU = 223

Diacetone Alcohol is the ketone that conforms to the formula:



Reported **Functions**: Fragrance Ingredients; Solvents

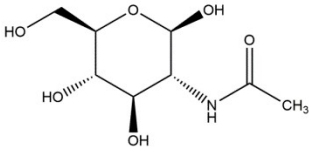
Notes:

Grouping proposal: None

Acetyl Glucosamine

FOU = 276

Definition: Acetyl Glucosamine is the organic compound that conforms to the formula:



Reported **Functions**: Skin-Conditioning Agents – Miscellaneous

Notes:

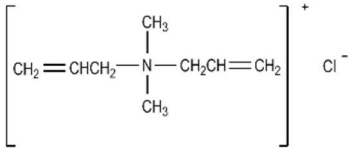
Grouping proposal: *Glucosamine and Acetyl Glucosamine (3 ingredients, 416 combined FOU)*

Acetyl Glucosamine (FOU priority ingredient)	**276**
Glucosamine	**9**
Glucosamine HCl	**131**

Polyquaternium-6

FOU = 280

Definition: Polyquaternium-6 is a polymeric quaternary ammonium salt of Diallyldimethyl Ammonium Chloride (DADMAC)

DADMAC: 

***Reported* Functions**: Antistatic Agents; Film Formers; Hair Fixatives

Notes: *homopolymer*

Grouping proposal: *None*

Olea Europaea (Olive) Leaf Extract

FOU = 279

Definition: Olea Europaea (Olive) Leaf Extract is the extract of the leaves of *Olea europaea.*

***Reported* Functions**: Skin-Conditioning Agents – Miscellaneous

Notes: *Olea Europaea (Olive) Fruit Oil has been previously assessed by CIR* (Published Report)

Grouping proposal: *Olea europaea-Derived Ingredients (20 ingredients, 743 combined FOU)*

Olea Europaea (Olive) Leaf Extract (FOU priority ingredient)	**279**
Olea Europaea (Olive) Bark Extract	**-**
Olea Europaea (Olive) Branch Extract	**-**
Olea Europaea (Olive) Bud Extract	**-**
Olea Europaea (Olive) Flower Extract	**186**
Olea Europaea (Olive) Flower Water	**-**
Olea Europaea (Olive) Fruit	**19**
Olea Europaea (Olive) Fruit Extract	**202**
Olea Europaea (Olive) Fruit Juice	**-**
Olea Europaea (Olive) Fruit Oil Ethyl Ester	**-**
Olea Europaea (Olive) Fruit Unsaponifiables	**40**
Olea Europaea (Olive) Fruit Water	**-**
Olea Europaea (Olive) Husk Powder	**-**
Olea Europaea (Olive) Leaf	**-**
Olea Europaea (Olive) Leaf Powder	**3**
Olea Europaea (Olive) Leaf Water	**-**
Olea Europaea (Olive) Sap Extract	**-**
Olea Europaea (Olive) Seed	**-**
Olea Europaea (Olive) Seed Powder	**14**
Olea Europaea (Olive) Wood Extract	**-**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210365Orig1s000

APPROVAL LETTER

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

210365Orig1s000

Trade Name:	Epidiolex (cannabidiol) 100 mg/mL oral solution
Generic or Proper Name:	Cannabidiol
Sponsor:	GW Research, Ltd.
Approval Date:	June 25, 2018
Indication:	For the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients two years of age and older.

CENTER FOR DRUG EVALUATION AND RESEARCH

210365Orig1s000

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Summary Review	**X**
Officer/Employee List	**X**
Office Director Memo	
Cross Discipline Team Leader Review	
Clinical Review(s)	**X**
Product Quality Review(s)	**X**
Non-Clinical Review(s)	**X**
Statistical Review(s)	**X**
Clinical Microbiology / Virology Review(s)	
Clinical Pharmacology Review(s)	**X**
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	**X**
Proprietary Name Review(s)	**X**
Administrative/Correspondence Document(s)	**X**

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 210365

NDA APPROVAL

GW Research, Ltd.
Attention: Catherine Maher, Ph.D., RAC
Head of U.S. Regulatory Affairs
68 T.W. Alexander Drive, P.O. Box 13628
Research Triangle Park, NC 27709

Dear Dr. Maher:

Please refer to your New Drug Application (NDA), dated and received October 27, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Epidiolex (cannabidiol) 100 mg/mL oral solution.

This new drug application provides for the use of Epidiolex (cannabidiol) 100 mg/mL oral solution for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients two years of age and older.

We have completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTROLLED SUBSTANCE SCHEDULING

The drug substance, cannabidiol, is currently controlled in Schedule I under the Controlled Substances Act (CSA). A scheduling recommendation has been transmitted to the Drug Enforcement Administration (DEA) but your drug product, Epidiolex, remains a Schedule I controlled substance and may not be marketed until the DEA has made a final scheduling decision in accordance with the CSA (21 U.S.C. 811). We further note that, when a final scheduling decision has been published in the Federal Register, you will need to make appropriate revisions to the package insert, Medication Guide, and the carton and container labels through supplementation of your NDA. For changes to the prescribing information, Medication Guide, and carton and immediate-container labels of Epidiolex, you may submit a Changes Being Effected supplement described in 21 CFR 314.70(c)(6). Permission to use a Changes Being Effected supplement for this purpose reflects a waiver by the Agency, pursuant to 21 CFR 314.90, of the requirement to submit a Prior Approval Supplement for changes to reflect the scheduling to the Highlights section of the prescribing information for Epidiolex described in 21 CFR 314.70(b)(2)(v)(C) and changes to the Medication Guide described in 21 CFR 314.70(b)(2)(v)(B).

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the prescribing information and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the carton and immediate container labels submitted on June 20, 2018, except with the revisions listed below, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3). For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 210365**." Approval of this submission by FDA is not required before the labeling is used.

- The product carton and container labels should not have the same NDC numbers. The carton label should state NDC 70127-100-10. The bottle label should state NDC 70127-100-01. The package insert should include both NDC numbers.

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a rare pediatric disease priority review voucher, as provided under section 529 of the FDCA. This priority review voucher (PRV) has been assigned a tracking number, PRV NDA 210365. All correspondences related to this voucher should refer to this tracking number.

This voucher entitles you to designate a single human drug application submitted under section 505(b)(l) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. The list below describes the sponsor responsibilities and the parameters for using and transferring a rare pediatric disease priority review voucher:

- The sponsor who redeems the priority review voucher must notify FDA of its intent to submit an application with a priority review voucher at least 90 days before submission of the application, and must include the date the sponsor intends to submit the application. This notification should be prominently marked, "Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Review Voucher."
- This priority review voucher may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. There is no limit on the number of times that the priority review voucher may be transferred, but each person to whom the priority review voucher is transferred must notify FDA of the change in ownership of the voucher not later than 30 days after the transfer. If you retain and redeem this priority review voucher, you should refer to this letter as an official record of the voucher. If the priority review voucher is transferred, the sponsor to whom the priority review voucher has been transferred should include a copy of this letter (which will be posted on our Web site as are all approval letters) and proof that the priority review voucher was transferred.
- FDA may revoke the priority review voucher if the rare pediatric disease product for which the priority review voucher was awarded is not marketed in the U.S. within 1 year following the date of approval.
- The sponsor of an approved rare pediatric disease product application who is awarded a priority review voucher must submit a report to FDA no later than 5 years after approval that addresses, for each of the first 4 post-approval years:
  - the estimated population in the U.S. suffering from the rare pediatric disease for which the product was approved (both the entire population and the population aged 0 through 18 years),
  - the estimated demand in the U.S. for the product, and
  - the actual amount of product distributed in the U.S.
- You may also review the requirements related to this program at http://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf1 (see Section 908 of FDASIA on pages 1094-1098, which amends the FD&C Act by adding Section 529). Formal guidance about this program will be published in the future.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of liver injury, to assess a signal of a serious risk of increased serum creatinine, or to identify the following unexpected serious risks: adverse maternal, fetal, or infant outcomes resulting from the use of Epidiolex; adverse effects of the 7-COOH metabolite on embryofetal development or pre- and postnatal growth and development; or the carcinogenic potential of cannabidiol or its 7-COOH metabolite.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

3429-1 An embryofetal development study of 7-COOH-cannabidiol in rat.

The timetable you submitted on June 13, 2018, states that you will conduct this study according to the following schedule:

Draft protocol submission:	02/2019
Final protocol submission:	04/2019
Study completion:	12/2019
Final report submission:	04/2020

3429-2 A pre- and postnatal development study of 7-COOH-cannabidiol in rat.

The timetable you submitted on June 13, 2018, states that you will conduct this study according to the following schedule:

Draft protocol submission:	02/2019
Final protocol submission:	04/2019
Study completion:	12/2019
Final report submission:	04/2020

3429-3 A juvenile animal toxicology study of 7-COOH-cannabidiol in rat.

The timetable you submitted on June 13, 2018, states that you will conduct this study according to the following schedule:

Draft protocol submission:	02/2019
Final protocol submission:	04/2019
Study completion:	12/2019
Final report submission:	04/2020

3429-4 A 2-year carcinogenicity study of cannabidiol in mouse.

The timetable you submitted on June 18, 2018, states that you will conduct this study according to the following schedule:

Draft protocol submission:	09/2017
Final protocol submission:	07/2018
Study completion:	04/2020
Final report submission:	08/2020

3429-5 A 2-year carcinogenicity study of cannabidiol and 7-COOH-cannabidiol, both directly administered, in rat.

The timetable you submitted on June 19, 2018, states that you will conduct this study according to the following schedule:

Draft protocol submission:	06/2019
Final protocol submission:	08/2019
Study completion:	08/2022
Final report submission:	02/2023

3429-6 Assess whether the effect of Epidiolex on serum creatinine reflects an effect on glomerular filtration rate.

The timetable you submitted on June 8, 2018, states that you will conduct this study according to the following schedule:

Draft protocol submission:	09/2018
Final protocol submission:	03/2019
Study completion:	09/2019
Final report submission:	03/2020

3429-7 Assess the potential for chronic liver injury with Epidiolex, with evaluation including physical exam, serum/blood biomarkers, and other noninvasive measures of liver fibrosis, such as MRI or ultrasound-based elastography. Patients should be evaluated yearly for five years.

The timetable you submitted on June 8, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	11/2018
Final Protocol Submission:	05/2019

Study/Trial Completion:	05/2027
Final Report Submission:	11/2027

3429-8 Conduct a pregnancy outcomes study using a different study design than provided for in the North American Antiepileptic Drug (NAAED) Pregnancy Registry (for example, a retrospective cohort study using claims or electronic medical record data or a case-control study) to assess major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in women exposed to Epidiolex (cannabidiol) during pregnancy compared to an unexposed control population.

The timetable you submitted on June 13, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	03/2019
Final Protocol Submission:	01/2020
Study/Trial Completion:	03/2027
Final Report Submission:	03/2028

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of drug-drug interactions or QT interval prolongation.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

3429-9 A drug-drug interaction trial to evaluate the effects of Epidiolex on the pharmacokinetics of caffeine in healthy volunteers. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies —Study Design, Data Analysis, and Clinical Implications."

The timetable you submitted on June 8, 2018, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	08/2018
Final Protocol Submission:	01/2019
Trial Completion:	06/2019
Final Report Submission:	12/2019

3429-10 A drug-drug interaction trial to evaluate the effects of Epidiolex on the pharmacokinetics of a sensitive CYP2B6 substrate in healthy volunteers. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies —Study Design, Data Analysis, and Clinical Implications."

The timetable you submitted on June 8, 2018, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	10/2018
Final Protocol Submission:	04/2019
Trial Completion:	09/2019
Final Report Submission:	03/2020

3429-11 A drug-drug interaction trial to evaluate the effects of Epidiolex on the pharmacokinetics of a sensitive CYP2C9 substrate in healthy volunteers. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies —Study Design, Data Analysis, and Clinical Implications."

The timetable you submitted on June 8, 2018, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	10/2018
Final Protocol Submission:	04/2019
Trial Completion:	09/2019
Final Report Submission:	03/2020

3429-12 Submit the complete results for the ongoing drug-drug interaction trial to evaluate the effects of a strong CYP2C19 inhibitor on the pharmacokinetics of Epidiolex in healthy volunteers.

The timetable you submitted on June 8, 2018, states that you will conduct this trial according to the following schedule:

Trial Completion:	09/2018
Final Report Submission:	02/2019

3429-13 Submit the complete results for the ongoing drug-drug interaction trial to evaluate the effects of a strong CYP3A inhibitor on the pharmacokinetics of Epidiolex in healthy volunteers.

The timetable you submitted on June 8, 2018, states that you will conduct this trial according to the following schedule:

Trial Completion:	09/2018
Final Report Submission:	02/2019

3429-14 Submit the complete results for the ongoing drug-drug interaction trial to evaluate the effects of rifampin on the pharmacokinetics of Epidiolex in healthy volunteers.

The timetable you submitted on June 8, 2018, states that you will conduct this trial according to the following schedule:

Trial Completion:	08/2018
Final Report Submission:	04/2019

3429-15 A drug-drug interaction trial to evaluate the effects of Epidiolex on the pharmacokinetics of a sensitive UGT1A9 substrate in healthy volunteers. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies —Study Design, Data Analysis, and Clinical Implications."

The timetable you submitted on June 8, 2018, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	11/2018
Final Protocol Submission:	05/2019
Trial Completion:	09/2019
Final Report Submission:	03/2020

3429-16 A drug-drug interaction trial to evaluate the effects of Epidiolex on the pharmacokinetics of a sensitive UGTB7 substrate in healthy volunteers. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies —Study Design, Data Analysis, and Clinical Implications."

The timetable you submitted on June 8, 2018, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	11/2018
Final Protocol Submission:	05/2019
Trial Completion:	09/2019
Final Report Submission:	03/2020

3429-17 A thorough QT trial at the maximum tolerable dose of Epidiolex that is feasible (e.g., dosing in the fed state), with appropriate controls (i.e., placebo and positive control).

The timetable you submitted on June 8, 2018, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission	08/2018

Final Protocol Submission:	01/2019
Trial Completion:	07/2019
Final Report Submission:	01/2020

Submit clinical protocol(s) to your IND with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312 or FDA's regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards).

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

REQUESTED PHARMACOVIGILANCE

We request that you perform postmarketing surveillance for liver toxicity after exposure to Epidiolex. Submit 15-day expedited reports to the Division of Neurology Products and to the NDA with sufficient data to assess causality including duration of Epidiolex administration, symptoms, whether the patient was hospitalized, or had organ dysfunction, failure, transplant, or death. Include comprehensive summaries and analyses of these events, including incidence, quarterly as part of your required postmarketing safety reports (e.g., periodic safety update reports [PSURs]). In the analysis of each case, provide an assessment of causality, with documentation of risk factors and results of all assessments that support the diagnosis or the

causality, along with duration of Epidiolex therapy, concomitant therapies, treatment given for the event, range of severity, and outcome of each event.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the prescribing information, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the prescribing information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

REPORTING REQUIREMENTS

You must comply with the reporting requirements described in 21 CFR 314.80(c)(1) (e.g., 15-day alert reports) beginning on the date of **this** letter. The due dates for the periodic (including quarterly) adverse drug experience reports described in 21 CFR 314.80(c)(2) should be calculated from the date of this letter. Annual reports described in 21 CFR 314.81(b)(2) are due within 60 days of the anniversary of the date of approval in accordance with 21 U.S.C. 355(x).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, contact Stephanie N. Parncutt, M.H.A., Senior Regulatory Health Project Manager, at (301) 796-4098 or Stephanie.Parncutt@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Robert Temple, MD
Deputy Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure(s):
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELLIS F UNGER on behalf of ROBERT TEMPLE
06/25/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210365Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	June 22, 2018
From	Teresa Buracchio, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	210365
Applicant	GW Pharma
Date of Submission	October 27, 2018
PDUFA Goal Date	June 27, 2018
Proprietary Name	Epidiolex
Established or Proper Name	Cannabidiol
Dosage Form(s)	100 mg/mL oral solution
Applicant Proposed Indication(s)/Population(s)	Adjunctive treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older
Applicant Proposed Dosing Regimen(s)	The recommended starting dose of EPIDIOLEX is 2.5 mg/kg taken twice daily (5 mg/kg/day) for 1 week. After one week's treatment, each dose should be increased weekly by 2.5 mg/kg administered twice daily (5 mg/kg/day) to a therapeutic dose of 5 mg/kg twice daily (10 mg/kg/day). Based on individual clinical response and tolerability, each dose can be further increased in weekly increments of 2.5 mg/kg administered twice daily (5 mg/kg/day) to 10 mg/kg twice daily (20 mg/kg/day).
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older
Recommended Dosing Regimen(s) (if applicable)	The starting dosage is 2.5 mg/kg twice daily (5 mg/kg/day). After one week, increase to a maintenance dosage of 5 mg/kg twice daily (10

	mg/kg/day). Patients who are tolerating EPIDIOLEX at 5 mg/kg twice daily and require further reduction of seizures may benefit from a dosage increase to a maximum recommended dosage of 10 mg/kg twice daily (20 mg/kg/day), in weekly increments of 2.5 mg/kg twice daily (5 mg/kg/day), as tolerated.

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

This application provides data to support the efficacy and safety of cannabidiol (GWP43003-P) for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS) in patients 2 years of age and older. Cannabidiol (CBD) is a cannabinoid prepared from the *Cannabis sativa* L. plant administered as a 100mg/ml oral solution. It is a new molecular entity and it is structurally unrelated to other drugs approved for the treatment of seizures.

Both LGS and DS are rare, severe, refractory epilepsy syndromes with onset in early childhood. The syndromes are categorized as developmental and epileptic encephalopathies, in which the epileptic activity is thought to contribute to developmental delay and behavioral abnormalities beyond the pathology of the underlying disease. The syndromes are characterized by multiple seizure types that are generally refractory to many of the drugs typically used for the treatment of seizures. Both syndromes are associated with higher rates of mortality than in the general epilepsy population, primarily due to status epilepticus and sudden unexpected death in epilepsy patients (SUDEP).

In addition to drugs approved for the general treatment of seizures, six drugs are approved specifically for the treatment of seizures in patients with LGS: clobazam, rufinamide, topiramate, lamotrigine, felbamate, and clonazepam. There are currently no drugs approved specifically for the treatment of seizures in DS.

Clinically meaningful and statistically significant reductions in seizure frequency were demonstrated in three adequate and well-controlled trials in LGS and DS. In Study 1414 in LGS, the median percentage change from baseline in drop seizure (atonic, tonic, or tonic-clonic seizures that could have led to a fall) frequency per 28 days was 37.2 in the 10 mg/kg/day group and 41.9 in the 20 mg/kg group CBD groups compared to 17.2 in the placebo group (p=0.002 and p=0.005, respectively). In Study 1423 in LGS, the median percentage change from baseline in drop seizure frequency per 28 days 43.9 in the 20 mg/kg/day CBD group and 21.8 in the placebo group (p=0.014). In Study 1332B in DS, the median percentage change from baseline in convulsive seizure (tonic, clonic, tonic–clonic, or atonic) frequency per 28 days was 38.9 in the CBD group and 13.3 in the placebo group (p=0.012). The results from these three adequate and well-controlled studies provide substantial evidence of the effectiveness of CBD for the treatment of seizures associated with LGS and DS.

The most commonly observed adverse events in the controlled clinical trials conducted with CBD that occurred with a greater incidence in CBD-treated patients than on placebo were in the following categories: central nervous system (e.g., somnolence and sedation), gastrointestinal (e.g., decreased appetite and diarrhea), hepatic (e.g., transaminase elevations) and infections (e.g., pneumonia). These events were generally mild to moderate in severity. Serious and/or severe adverse events were generally related to transaminase elevations, somnolence and lethargy, and infections.

A signal for drug-induced liver toxicity was identified in the controlled trials and in the Expanded Access Program. Frequencies of adverse events of transaminase elevations were 8% in the CBD 10 mg/kg/day group, 16% in the CBD 20 mg/kg/day group, and 3% in the placebo group. Some events of transaminase elevation were serious or severe; however, there were no Hy's law cases and no events of liver failure or death related to liver injury. All transaminase elevations resolved, with some resolving during continued treatment with CBD.

The applicant proposes the same dosing regimen for both the LGS and DS populations: a titration up to 10 mg/kg/day as a maintenance dose, with further titration up to 20 mg/kg/day, as needed. All three studies assessed a 20 mg/kg/day dose of CBD; however, only Study 1414 in LGS assessed a dose of 10 mg/kg/day. In Study 1414, the 10 mg/kg/day dose of CBD showed an estimated median difference from placebo of 19.2% while the 20 mg/kg/day dose showed a difference of 21.6%. The difference in safety between the two doses showed a more notable difference in dose-response, with the 20 mg/kg/day group showing markedly higher rates of adverse events than the 10 mg/kg/day, particularly transaminase elevations. The dose-response seen with adverse events supports the use of a lower dose as a maintenance dose if efficacy can be supported. Given that the seizure types were similar between the two disease populations and an overall reduction in all seizure types was seen with CBD for both populations, it is reasonable to assume that the 10 mg/kg/day dose that was shown to be efficacious in an LGS population will also be effective in a DS population. Therefore, the proposed maintenance dose of CBD of 10 mg/kg/day with a maximum dose of 20 mg/kg/day is acceptable.

There was an inadequate assessment of the 7-COOH-CBD metabolite in nonclinical studies; however, there are adequate safety data from the clinical development program to support the safety of CBD for approval. Additional nonclinical studies to assess the major metabolite, 7-COOH-CBD, should be conducted as PMR studies.

The risks associated with CBD treatment are acceptable, particularly given the findings of clinical efficacy in LGS and DS, which are serious, debilitating, and life-threatening disorders. Although the risk of liver injury has the potential to be serious, the observed risk can be appropriately managed with inclusion of relevant language in labeling, education of prescribers regarding the risk of transaminase elevation and need for monitoring of liver enzyme levels, and further characterization of the risk in the postmarket setting. The risk-benefit profile established by the data in the application support the approval of CBD for the treatment of seizures associated with LGS and DS.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<u>Lennox-Gastaut Syndrome</u> • Lennox-Gastaut syndrome (LGS) is a severe form of epilepsy that presents during childhood. LGS is a developmental and/or epileptic encephalopathy, in which the seizures and the epileptic activity are thought to contribute to developmental delay and behavioral abnormalities. Onset of LGS typically occurs between ages 3 and 5 years. Some patients (20-60%) have evidence of delayed intellectual development at the time of diagnosis, and the severity of patients' cognitive and	Lennox-Gastaut syndrome and Dravet syndrome are both severe epilepsy syndromes that are associated with refractory seizures, cognitive impairment, and increased risk of mortality related to seizures.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	behavior impairments varies from minimally affected (rare) to profoundly impaired. Drop attacks are the most disabling of the seizure types (seen in >50% of LGS patients). A drop attack is a seizure that leads to a fall or would have caused a fall, thus frequently leading to injury. Non-convulsive status epilepticus (continuous seizure activity) is seen in 50-70% of patients. Seizure freedom is essentially never seen in patients with LGS, regardless of antiepileptic drugs (AEDs) or other epilepsy treatments. Children and adolescents with LGS have a higher mortality rate than the general epilepsy population. Common reported proximate causes of death in patients with LGS are SUDEP, status epilepticus, or seizures. <u>Dravet Syndrome</u> • Dravet syndrome (DS) is a severe form of childhood epilepsy that is characterized by early onset of refractory seizures of multiple types, frequent episodes of status epilepticus, and developmental arrest or regression. Patients typically present prior to 2 years of age with a variety of disabling seizure types and developmental delay. The cognitive impairment is considered to be, at least in part, caused by the seizures. Although the diagnosis of DS is made by clinical criteria, most (80%) of patients with DS have mutations in the SCN1A gene, but the individual mutations vary widely. Seizures in patients with DS are generally refractory to AEDs. Seizure-freedom almost never occurs, but many patients experience fewer seizures in late adolescence and adulthood. SUDEP and status epilepticus are more common in patients with DS than most other childhood epilepsy syndromes, and DS patients' increased mortality compared to the general population is, in part, due to these seizure-related events.	
Current Treatment Options	<u>Lennox-Gastaut Syndrome</u> • Six drugs are approved by FDA for reduction of seizures in patients with LGS: clobazam, rufinamide, topiramate, lamotrigine, felbamate, and clonazepam. Many other drugs are used to treat seizures in patients with LGS, especially valproic acid (which is generally considered a first-line agent) and levetiracetam. • There is potential for severe adverse drug reactions with many of the approved and/or frequently used drugs to treat seizures in LGS, such as hepatic failure (felbamate, lamotrigine, and valproic acid), serious skin reactions (lamotrigine,	<u>Lennox-Gastaut Syndrome</u> Six drugs are approved by FDA for reduction of seizures in patients with LGS. Despite the availability of approved therapies, most patients continue to have poorly-controlled seizures. Additionally, some drugs are poorly tolerated or have the potential for serious adverse events.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	clobazam, rufinamide), and hematologic abnormalities (felbamate, lamotrigine, topiramate, rufinamide). <u>Dravet Syndrome</u> • There are no approved treatments of seizures in patients with DS.	There remains a need for efficacious therapies for the treatment of seizures in LGS. <u>Dravet Syndrome</u> There is a high unmet need for effective treatments for Dravet syndrome as there are no approved treatments for this condition.
Benefit	<u>Lennox-Gastaut Syndrome</u> • Two randomized, double-blind, placebo-controlled studies were conducted with CBD in LGS. In Study 1414 in LGS, the median percentage change from baseline in drop seizure frequency per 28 days was 37.2 in the 10 mg/kg/day group and 41.9 in the 20 mg/kg group CBD groups compared to 17.2 in the placebo group (p=0.002 and p=0.005, respectively). In Study 1423 in LGS, the median percentage change from baseline in drop seizure frequency per 28 days was 43.9 in the 20 mg/kg/day CBD group and 21.8 in the placebo group (p=0.014). <u>Dravet Syndrome</u> • A single randomized, double-blind, placebo-controlled studies were conducted with CBD in DS. In Study 1332B in DS, the median percentage change from baseline in convulsive seizure frequency per 28 days was 38.9 in the CBD group and 13.3 in the placebo group (p=0.012).	These well-controlled clinical trials have established that CBD is effective for the treatment of seizures in LGS and DS.
Risk and Risk Management	• Transaminase elevations were identified as a safety issue of concern. Transaminase elevations were reported as an adverse event in 8% of patients in the CBD 10 mg/kg/day group, 16% of patients in the CBD 20 mg/kg/day group, and 3% of patients in the placebo group. Some events of transaminase elevation were serious or severe; however, there were no Hy's law cases and no events of liver failure or death related to liver injury. All transaminase elevations resolved, with some resolving during continued treatment with CBD. Concomitant use of valproic acid and a higher (20 mg/kg/day) dose of CBD led to an increased risk of transaminase elevations. Concomitant use of clobazam also increased the	The risks associated with CBD are acceptable. Although the risk of liver injury has the potential to be serious, the observed risk can be appropriately managed with inclusion of relevant language in labeling, education of prescribers regarding the risk of transaminase elevation and need for monitoring of liver enzyme levels, encouraging initial use of 10 mg/kg/day dose as an initial maintenance dose, and further characterization of the risk in the post-market setting.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	incidence of transaminase elevations, although to a lesser extent than valproic acid. • Somnolence, sedation, and lethargy occurred in a large number of patients (32% and 11% in CBD-treated and placebo subjects, respectively). Somolence, sedation, and lethargy were somewhat dose-related, with rates of 34% of patients taking CBD 20 mg/kg/day, and 27% in patients taking CBD 10 mg/kg/day. The rate was considerably higher in patients on concomitant clobazam (44% in CBD-treated patients taking clobazam compared with 13% in CBD-treated patients not taking clobazam or valproic acid) • Other potential risks identified during the review include: o GI adverse effects: diarrhea, nausea, decreased appetite, abdominal pain o Rash o Infections: pneumonia o Decreased weight o Decrease hemoglobin/hematocrit o Increases in creatinine A dose-response was observed for gastrointestinal adverse events and rash, with higher incidences observed at the 20 mg/kg/day dose of CBD.	The following risk mitigation measures are recommended: • WARNINGS and PRECAUTIONS should be included in labeling to describe the risks of transaminase elevations; somnolence and sedation; and hypersensitivity reactions. Warnings for suicidal behavior and withdrawal of seizure medications are to be included as class warnings for seizure medications. • Enhanced pharmacovigilance for liver toxicity. • PMR to characterize the effects of CBD on the liver with long-term use. • PMR to characterize the acute changes in creatinine with CBD. • PMRs to characterize drug-drug interactions. • PMRs to assess the effects of 7-COOH-CBD in a battery of nonclinical studies.

2. Background

This application provides data intended to support the effectiveness and safety of cannabidiol (CBD) (investigational product name GWP43003-P) for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS) in patients 2 years of age and older. CBD is a cannabinoid prepared from the *Cannabis sativa* L. plant and administered as a 100mg/ml oral solution. It is a new molecular entity and it is structurally unrelated to other drugs approved for the treatment of seizures. The precise mechanism(s) by which Epidiolex exerts its anticonvulsant effect in humans is unknown. In addition to drugs approved for the general treatment of seizures, six drugs are approved specifically for the treatment of seizures in patients with LGS: clobazam, rufinamide, topiramate, lamotrigine, felbamate, and clonazepam. There are currently no drugs approved specifically for the treatment of seizures associated with DS.

Both LGS and DS are rare, severe, refractory epilepsy syndromes, with onset in early childhood. The syndromes are categorized as developmental and epileptic encephalopathies, in which the epileptic activity is thought to contribute to developmental delay and behavioral abnormalities beyond the pathology of the underlying disease. The syndromes are characterized by multiple seizure types that are generally refractory to many of the drugs typically used for the treatment of seizures. Both syndromes are associated with higher rates of mortality than are seen in the general epilepsy population, primarily because of status epilepticus and sudden unexpected death in epilepsy (SUDEP).

LGS is characterized by a triad of findings: multiple seizure types, developmental delay, and an interictal electroencephalography (EEG) pattern of diffuse, slow spike-wave complexes. Onset of LGS typically occurs before 8 years of age, with peak presentation occurring between 3 and 5 years of age. Etiologies can be identified in approximately 2/3 of patients with LGS, and include a wide variety of causes, such as hypoxic-ischemic insults (most common), tuberous sclerosis complex, brain malformations, and traumatic brain injuries. An initial diagnosis of infantile spasms may also be associated with a later diagnosis of LGS. A variety of genetic anomalies have been reported in patients with the diagnosis of LGS, including variants or mutations in the SCN1A, FOXG1, DNM1, and CHD2 genes.

DS (previously known as severe myoclonic epilepsy of infancy) is characterized by refractory epilepsy with multiple seizure types, febrile seizures, frequent episodes of status epilepticus, and developmental arrest or regression. Onset of DS is typically before 2 years of age, and occurs with an initial presentation of seizures and developmental delay. Most patients with the clinical syndrome have a gene mutation affecting the sodium channel (SCN1A).

This application provides efficacy and safety data from the following three randomized, double-blind, placebo-controlled trials:

- Study 1414 and Study 1423 – two 14-week, multicenter, randomized, double-blind, placebo-controlled trials in patients with LGS

- Study 1332B – a 14-week, multicenter, randomized, double-blind, placebo-controlled trial in patients with DS

Additional safety data were provided from the following sources:

- Study 1332A – a 3-week, randomized, double-blind, placebo-controlled dose-finding study in patients with DS
- Study 1415 – an open-label extension study in patients with LGS and DS
- Expanded access programs (EAPs) in refractory epilepsy populations

A detailed summary of the regulatory history of CBD is provided in the combined clinical and statistical review by the clinical reviewer, Dr. Natalie Getzoff.

3. Product Quality

The technical lead on the Office of Product Quality (OPQ) review was Dr. Wendy Wilson. Dr. Wilson's review lists the entire OPQ team that was involved with the review of this application. Please refer to the OPQ review for details of the product quality assessment.

The drug substance is a (b) (4) yellow, crystalline (b) (4), produced from an extract of *Cannabis sativa* L. plants. OPQ determined that the drug substance is best described as a highly-purified drug substance from a plant source. The drug product is a 100 mg/mL, non-sterile, non-preserved, non-aqueous oral solution of CBD dissolved in sesame oil, (b) (4), and flavoring agent. The drug product is packaged in a 105 mL amber glass bottle. Two 5-mL syringes and a bottle adapter are co-packaged with the drug product. As these components are co-packaged, this drug product is classified as a combination product. The oral syringe and the adapter co-packaged with the drug product are Tier 1 devices and considered low risk.

Stability and release testing were found to be acceptable. The specified impurity limits were found to be acceptable based on the qualification studies. The microbial quality of the API and drug product were found to be adequate. There were no outstanding issues identified in the OPQ review, and all manufacturing facilities for this product were found to be acceptable.

OPQ recommends approval of this NDA.

4. Nonclinical Pharmacology/Toxicology

The nonclinical reviewer for this application is Dr. Ed Fisher, with Dr. Lois Freed performing a secondary review.

CBD is metabolized to form 7-hydroxy-cannabidiol (7-OH-CBD), which circulates in human plasma at levels of approximately 50% of the parent, making it a major human metabolite. 7-

OH-CBD is further metabolized to 7-carboxy-cannabidiol (7-COOH-CBD). 7-COOH-CBD circulates at levels far exceeding (approximately 40-fold higher) those of the parent in humans, representing at least 90% of all drug-related material measured in plasma, and is a major human metabolite. Compared to humans, the toxicology species do not produce the two major human metabolites to a comparable extent, and Dr. Fisher has determined that there is inadequate coverage for 7-COOH-CBD in the toxicology studies.

The following additional important findings were noted in the nonclinical reviews:

- In the pivotal oral toxicity studies (26-week in Wistar rat, 39-week in Beagle dog), the primary target organ was the liver in both species. Findings in both species included hepatocellular hypertrophy accompanied by increases in ALT and ALP.
- A carcinogenicity study was conducted using CBD botanical drug substance (BDS), (b) (4) (b) (4) it is considered inadequate because of uncertain exposures and potential interactions with impurities. The applicant is conducting a carcinogenicity in mice using purified CBD that will be completed in the postmarketing setting.
- There was no evidence of genotoxicity with CBD in a standard battery of in vitro and in vivo tests.
- A full battery of oral reproductive and developmental studies was conducted using purified CBD in rats and rabbits. Total litter loss at the high dose (250 mg/kg) was observed in the embryofetal development study in rats. In the pre- and postnatal development study in rats, adverse effects were observed on body weight, attainment of developmental landmarks, learning and memory, and reproductive structure and, possibly, function, primarily at the medium and high doses (150 mg/kg and 250 mg/kg).
- A juvenile toxicity study was conducted in rats. Findings included neurobehavioral deficits and delayed sexual maturation in males.

Although the toxicity evaluation of the parent compound can be considered adequate, the assessment of the 7-COOH-CBD metabolite was inadequate. Based on this finding, Dr. Fisher has concluded that the nonclinical studies do not support approval because of the lack of adequate nonclinical safety assessment of the major human metabolite 7-COOH-CBD.

Dr. Freed notes in her secondary review, however, that “because of the seriousness of the indications and the unmet medical need, if the clinical team concludes that the clinical data are sufficient to support approval, the nonclinical studies needed to address the inadequate assessment of the major human metabolite, 7-COOH-CBD, may be conducted as postmarketing requirements.”

Based on the available clinical data, and after discussions with the clinical review team, we believe that there are adequate safety data from the clinical development program to support the safety of CBD for approval. Additional nonclinical studies to assess the major metabolite, 7-COOH-CBD, should be conducted as PMR studies.

5. Clinical Pharmacology

An integrated Office of Clinical Pharmacology (OCP) review was written by Dr. Jagan Parepally (clinical pharmacology reviewer), Dr. Angela Men (clinical pharmacology team leader), Dr. Michael Bewernitz (pharmacometrics reviewer), Dr. Kevin Krudys (pharmacometrics team leader), Dr. Manuela Grimstein, and Dr. Yuching Yang. The primary conclusions of the OCP review are summarized below. Please refer to the OCP review for a more detailed discussion of these findings.

The following summary of the general pharmacokinetic (PK) findings with CBD is extracted from the OCP review.

- Absorption: Cannabidiol exposure exhibits a nonlinear increase with dose up to 6000 mg under fasting conditions. The median cannabidiol T_{max} ranged from 2.5 to 5 hours. Absolute bioavailability has not been determined.
    - With a high-fat meal, the C_{max} and AUC of cannabidiol increased by approximately 5-fold and 4-fold respectively.
- Distribution: The estimated volume of distribution in healthy volunteers was 20963 L to 42849 L. High plasma protein binding (i.e., >94 %) was observed for cannabidiol and its metabolites (7-COOH-CBD,7-OH-CBD and 6-OH-CBD).
- Metabolism: Cannabidiol is extensively metabolized in liver and gut, primarily by CYP2C19, CYP3A4, and UGT1A7, UGT1A9, and UGT2B7 enzymes. The major circulating metabolites include 7-carboxy-cannabidiol (7-COOH-CBD), which was approximately 40-fold higher than the parent, 7-hydroxy-cannabidiol (7-OH-CBD), which was approximately 38% of the parent based on AUC of cannabidiol, and 6-hydroxy-cannabidiol (6-OH-CBD), a minor metabolite (< 10% of CBD). Cannabidiol and 7-OH-CBD were found to be equipotent and active. 7-COOH-CBD was found to be inactive in nonclinical animal models of epilepsy.
- Elimination: The mean elimination half-life of CBD ranged from 56 to 61 hours following twice-daily dosing for 7 days in healthy volunteers. Following a single oral dose of ^{14}C-CBD at 5 mg/kg, radioactivity was excreted predominantly via the fecal route (84%), and smaller proportions of administered radioactivity was recovered in the urine (8%). The total recovery after 168 hours was 94%.

The food effects are large for CBD, with a 4- to 5-fold increase in exposure following a high-fat meal. In the clinical studies, CBD was not administered consistently in the fed or fasted state, and consequently, exposure levels were found to be highly variable. The sponsor is proposing to state in the prescribing information (PI) that CBD (b) (4) could have been taken with or without food. OCP recommends that the PI recommend that CBD be administered consistently in either the fed or fasting state. As the dose-response between the 10 and 20 mg dose is not steep, intermittent food-related differences should not have a major impact on efficacy. Also, effectiveness was established in studies with the drug administered without any restriction related to the timing of food intake. The drug also has a long half-life, and the natural variability of dosing with respect to food intake should maintain

a relatively constant long-term steady state exposure despite acute superimposed alterations in exposure due to individual doses. Therefore, labeling will not include any specific recommendation to take the drug in a fed or fasted state.

Drug-drug interaction

Dedicated drug-interaction trials evaluating concomitant administration of CYP2C19 and CYP3A inhibitors or inducers were not conducted. Co-administration with moderate or strong inhibitors of CYP3A4 or CYP2C19 is predicted to increase CBD plasma concentrations. Co-administration with moderate or strong inducers of CYP3A4 or CYP2C19 is predicted to increase CBD plasma concentrations.

In vitro Assessments

In vitro studies suggest that CBD inhibits (IC50 <10 µM) CYP1A2, CYP2B6, CYP2C8, CYP2C19, and CYP3A4. CBD is also a time-dependent inhibitor of CYP3A4, CYP1A2 *in vitro*. CBD is a strong inhibitor of UGT1A9 and UGT2B7 in human liver microsomes.

Cannabidiol induces CYP1A2, CYP2B6, and CYP3A4 in vitro at clinically relevant concentrations.

In vivo Assessments

CBD did not demonstrate significant CYP3A4 inhibition in a dedicated drug-drug interaction study (GWEP17028) with midazolam (a sensitive CYP3A4 substrate).

A dedicated drug-drug interaction study was conducted to evaluate the effect of multiple-dose administration of CBD on steady-state plasma concentrations of CLB and N-desmethylclobazam (N-CLB), stiripentol (STP), or valproate (VPA) in healthy male and female subjects. There was no significant increase in CLB levels; however, there was a 3-fold increase in N-CLB levels. When CBD was combined with STP, there was a minor increase in STP levels (1.28-fold increase in Cmax and 1.55-fold increase in AUCtau). There was no effect of concomitant CBD administration on VPA exposure.

Hepatic impairment

The effect of hepatic impairment on the PK of CBD was evaluated in a dedicated study. The geometric mean AUC (0-∞) for total CBD increased 2.45- and 5.15-fold, respectively, in patients with moderate or severe hepatic impairment, and by about 50% in patients with mild hepatic impairment, compared with subjects with normal hepatic function. Based on these findings, OCP recommends a 50% lower starting dose and 50% lower maintenance dose in patients with moderate hepatic impairment, and a slow dose titration with a 80% lower starting dose and a 80% lower maintenance dose in patients with severe hepatic impairment.

Renal impairment

A dedicated renal impairment trial was conducted to evaluate the effect of renal impairment on PK of CBD in subjects with mild, moderate, or severe renal impairment. No trends toward

increases in exposure were observed in patients with various degrees of renal impairment; therefore, no dose adjustments are recommended for patients with renal impairment.

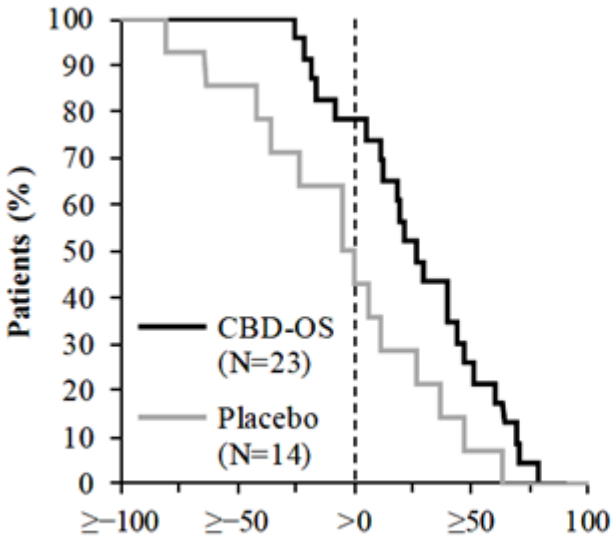
Exposure-response

As previously noted, there are large food effects with CBD. Moreover, CBD was not administered consistently in the fed or fasted state in clinical studies; consequently, exposure levels were found to be highly variable. Food diaries were not obtained during the study to help understand the variability in exposures in relation to food. Because of the large food effect seen with CBD and variability in exposures in the Phase 3 trials, the population PK (PPK) models for the DS and LGS populations were not found to be reliable. Exposure-response analyses could not be used to support the efficacy or safety of CBD.

Interaction with clobazam and stiripentol

Clobazam (CLB) is metabolized by CYP3A4, and to a lesser extent by CYP2C19 and CYP2B6, to the active metabolite norclobazam (N-CLB), which is thought to have 1/3 to 1/5 the activity of clobazam. N-CLB is metabolized by CYP2C19. CBD is known to inhibit the CYP2C19 enzyme and is therefore predicted to increase CLB and N-CLB levels. No increase in CLB levels was observed in clinical trials, but exposures to N-CLB were found to be up to 300% higher in the CBD arm compared to the placebo arm in the controlled trials. Based on this increase in N-CLB levels, the applicant explored the potential impact of clobazam use and N-CLB levels on the efficacy findings; that is, whether changes in N-CLB levels could explain some or all of the effect of CBD. The applicant conducted a number of subgroup analyses in the pivotal studies for LGS and DS. OCP determined that because of the small numbers of patients in the subgroups and variability in the data, the analyses were not adequately powered to allow reliable evaluation of the effects of CBD independent of clobazam. Additionally, the large number of concomitant medications used by patients made it difficult to analyze the effects of clobazam alone. In an attempt to futher explore this issue, the applicant conducted an analysis of concomitant stiripentol (STP) use in Study 1332B. STP was used by a subset of patients in Study 1332B for DS (STP was not used in the LGS studies). STP, like CBD, inhibits the CYP2C19 enzyme. Patients who were taking clobazam and STP at baseline did not did not show a further increase of N-CLB levels following the initiation of CBD, but did have improved seizure control. The applicant hypothesizes that CLB and N-CLB levels were already maximally increased by STP-induced inhibition of CYP2C19, and patients did not appear to experience further augmentation of the CYP2C19 inhibition with the initiation of CBD. An analysis of the patients taking clobazam and STP showed that CBD was superior to placebo, with 80% of patients showing a reduction in seizures, vs. 50% on placebo. This is shown in Figure 1 below (CBD-OS in Figure 1 is cannabidiol oral solution).

Figure 1: Cumulative Distribution of Seizure Reduction by Treatment Arm in Study 1332B (Patients taking clobazam and STP)



Source: summary-clin-efficacy-dravet-syn.pdf, page 83 of 122

The OCP review team believes that this observation supports the applicant's claim that CBD has an effect on seizures that is independent of its ability to increase N-CLB. As STP was not used in the LGS studies, this analysis could not be conducted in the LGS population.

Valproate Interaction

There was no effect of concomitant CBD administration on valproate (VPA) exposures in the clinical trials. Although increased rates of transaminase elevation were observed in the clinical trials with concomitant VPA use, this does not appear to be mediated by a PK interaction. Please refer to the safety section of this memo for further discussion.

Dosing/Titration regimen

Maintenance dosing

The OCP review notes that the 20 mg/kg/day dose used in the controlled studies for both LGS and DS demonstrated efficacy, but that the 10 mg/kg/day dose was studied only in the LGS population, where it also demonstrated efficacy. As previously noted, the exposure-response analysis was not found to be sufficiently reliable to support recommendations for dosing. Based on the efficacy seen in the LGS studies, OCP supports labeling for 10 to 20 mg/kg/day as target maintenance dose range in LGS patients. Based on discussions with the clinical team regarding the similarity of the disease populations, concerns regarding the dose-response observed with adverse events, and the desire for flexibility in dosing based on efficacy and tolerability, OCP also supports 10 to 20 mg/kg/day as the target maintenance dose range in DS patients. Please see the efficacy section of this memo for further discussion of the rationale for recommending the same maintenance dosing for LGS and DS.

The applicant has proposed that CBD be labeled for (b) (4) use, as this is how the drug was studied in clinical trials; however, it does not appear that the efficacy of CBD depends on concomitant use of other particular seizure drugs. Therefore, the recommended use of CBD does not need to be explicitly restricted to the (b) (4) setting. The proposed label will include recommendations for dosing adjustments when CBD is used with strong CYP3A4 and CYP2C19 inhibitors/inducers.

Titration regimen
The regimen used in the clinical trials was a 2.5 mg/kg/day initiation dose, to be increased by 2.5 mg/kg/day increments every 2 days until a dosage of 10 mg/kg/day was reached. If patients were titrated to the 20 mg/kg/day dosage level, starting from the 10 mg/kg/day dosage level, dosage was increased by 5 mg/kg/day increments every 2 days until the 20 mg/kg/day dosage level was reached.

For labeling, the applicant proposed an alternate titration regimen, with initial dosage of 5 mg/kg/day, with increases of 5 mg/kg/day every week to a maximum dosage of 20 mg/kg/day. The applicant's rationale for this new titration regimen was that it would be simpler and could improve tolerability. The applicant also reported that this regimen has been used in the EAPs and has been well-tolerated.

To support this alternate regimen, the applicant submitted a simulated PK profile for the original titration regimen that was compared with the simulated PK profile for the alternate titration regimen (based on a PPK model developed for DS). Given the previously stated concerns regarding the PPK model from the patient population, the pharmacometrics reviewer utilized the simulated PPK model from the healthy subject dataset to address the acceptability of the new regimen. This model is shown in Figure 2 below. The upper line represents the original titration regimen, and the lower line represents the proposed alternate titration regimen.

Figure 2: Simulated PK Profile for Original Titration Regimen used in Clinical Trials and Proposed Alternate Regimen up to 20 mg/kg/day

(b) (6)

The model shows that the alternate titration regimen would provide slightly higher exposures until Day 4 following the initiation of the 5 mg/kg/day dose, but the remaining exposures would be generally lower than (within the first 3 weeks) or within the range of the current titration regimen.

Although the applicant did not provide safety data from the EAPs to specifically support the 5 mg/kg/day initiation dosage, the clinical review team has not identified any safety issues uniquely associated with this initiation dosage used in the EAPs. Additionally, safety data for the 5 mg/kg/day dosage in Study 1332A shows a safety profile comparable to placebo (see safety section of this review). (b) (4) it is reasonable to recommend a slower titration based on the dose-response that was observed with regard to adverse events, particularly transaminase elevations. The titration regimen appears acceptable from a safety perspective and OCP and the clinical review team agree that it is acceptable for labeling. However, the clinical review team also noted that the regimen used in the controlled trials was acceptably tolerated, and there may be some situations (such as a patient with a particularly high seizure burden) where a prescriber may desire a faster titration to the 20 mg/kg/day dosage. Therefore, labeling will also include a statement that dosing may be increased from 10 mg/kg/day to 20 mg/kg/day by increments of 5 mg/kg/day no more frequently than every 2 days for situations where faster titration is warranted.

QT study
The applicant conducted a thorough QT (TQT) study, GWEP1451, which was reviewed by the Interdisciplinary Review Team for QT Studies (IRT-QT). The IRT-QT team found the study to be inadequate to support the QT risk assessment for the proposed dosing in the current indication. The exposures achieved in the QT study are substantially lower than the therapeutic exposures of the parent and the 7-COOH-CBD metabolite because there are substantial food effects observed with CBD (4- to 5- fold increase in exposure) and the QT study was conducted in the fasted state. The QT-IRT team recommends that the applicant conduct another TQT study with appropriate dosing (e.g., in the fed state) to adequately characterize this risk of QTc prolongation.

The OCP review team recommends approval of the NDA. The OCP team proposes a variety of PMRs to further evaluate drug-drug interactions, as outlined in Section 13 of this review. A TQT study with appropriate dosing will also be required as a PMR.

6. Clinical Microbiology

N/A

7. Clinical/Statistical- Efficacy

Dr. Natalie Getzoff was the clinical reviewer for this application. Dr. Xiang Ling was the biometrics reviewer and Dr. Kun Jin was the biometrics team leader for this application.

The applicant conducted three randomized, double-blind, placebo-controlled trials in LGS (2 studies) and DS (1 study), which served as the basis for this application:

- Study 1414 and Study 1423 – two 14-week, multicenter, randomized, double-blind, placebo-controlled trials in patients with LGS
- Study 1332B – a 14-week, multicenter, randomized, double-blind, placebo-controlled trial in patients with DS

All three studies had a similar study design, with a 28-day baseline period followed by a 14-week treatment period that included a 7- or 11-day titration period.

The results of these studies will be described below. A detailed analysis of the studies can be found in the combined clinical and statistical review by Dr. Getzoff and Dr. Ling.

Study 1414 in LGS
Study 1414 was a 14-week, multicenter, randomized, double-blind, placebo-controlled trial in patients with LGS. There were 225 patients randomized in a 1:1:1 ratio to either CBD 10

mg/kg/day (divided twice daily), CBD 20 mg/kg/day (divided twice daily), or placebo. CBD (or the equivalent volume of placebo) was started at a dosage of 2.5 mg/kg/day, and increased by 2.5 mg/kg/day increments every other day, over a 7-day period, to a dosage of 10 mg/kg/day. Patients were then further titrated by 5 mg/kg/day increments every other day to a dosage of 20 mg/kg/day (or matching placebo), for a total of 11 days of titration. Randomization was stratified by age group (2-5 years, 6-11 years, 12-17 years, and 18-55 years). Patients were required to meet the following enrollment criteria: have a clinical diagnosis of LGS (including documentation of having met EEG diagnostic criteria) not completely controlled by AEDs, experience ≥ 2 drop seizures per week during a 28-day baseline period, be taking one or more AEDs at a stable dose, and be between 2 and 55 years of age. Concomitant AEDs and doses were to remain constant during the treatment period. The study was conducted in the United States (US), United Kingdom (UK), France, and Spain.

The primary endpoint for Study 1414 was the percentage change from baseline in drop seizure frequency (average per 28 days) during the 14-week treatment period. A drop seizure was defined as *"an attack or spell (atonic, tonic or tonic-clonic) involving the entire body, trunk, or head that led or could have led to a fall, injury, slumping in a chair or hitting the patient's head on a surface."* Non-drop seizures were defined as *"all other countable seizures, except drop attacks, and [included] atypical absence, focal [seizures] with or without loss of consciousness, and any seizure that would not result in a fall."* Patients or caregivers recorded the number and type of drop seizures (atonic, tonic, or tonic-clonic) and non-drop seizures (myoclonic, partial, or absence) each day using an interactive voice response system (IVRS) telephone diary during the 28-day baseline period and during the entire treatment period until completion of dosing.

Secondary "key" endpoints controlled for multiplicity were:

- Number of patients considered treatment responders, defined as those with a ≥ 50% reduction in drop seizure frequency from baseline during the treatment period
- Percentage change from baseline in number of total seizures (average per 28 days)
- Subject/Caregiver Global Impression of Change (S/CGIC) [in the patient's overall condition]: the S/CGIC was rated using a 7-point scale (1 = very much improved; 7 = very much worse) and compared the patient's status at the last visit with baseline.

Exploratory endpoint
The sponsor assessed "drop seizure free days" as an exploratory endpoint.

The primary analyses used the intention-to-treat (ITT) analysis set, which included all patients randomized to treatment who received at least 1 dose of the investigational treatment and who had any post-baseline efficacy data. All statistical tests were 2-sided and used the 5% significance level. The Type-I error was controlled by use of a hierarchical gate-keeping procedure, as presented in the sequence listed in Table 1 below.

Table 1: Study 1414, Hierarchical Testing for Endpoints

Test	Endpoint	Treatment Comparison
1	Primary endpoint	20 mg/kg/day CBD vs. Placebo
2	Primary endpoint	10 mg/kg/day CBD vs. Placebo
3	1st key secondary endpoint	20 mg/kg/day CBD vs. Placebo
4	2nd key secondary endpoint	20 mg/kg/day CBD vs. Placebo
5	3rd key secondary endpoint	20 mg/kg/day CBD vs. Placebo
6	1st key secondary endpoint	10 mg/kg/day CBD vs. Placebo
7	2nd key secondary endpoint	10 mg/kg/day CBD vs. Placebo
8	3rd key secondary endpoint	10 mg/kg/day CBD vs. Placebo

The primary endpoint of percent change from baseline in seizure frequency was analyzed using a Wilcoxon rank-sum test. Seizure frequency was calculated as a 28-day frequency. Estimates of the median differences between CBD and placebo and the approximate 95% confidence intervals (CI) were calculated using the Hodges-Lehmann approach.

The proportion of responders was analyzed using a Cochran-Mantel-Haenszel (CMH) test stratified by age group. Analyses of total seizures were performed with the same analysis method used for the primary endpoint. For the analysis of S/CGIC scores, the CGIC was used, except in the situation where only a SGIC was completed, in which case the SGIC was to be used. The 7-point scale scores at the end of treatment visit and last visit (if different from the end of treatment) were analyzed using ordinal logistic regression. However, Dr. Ling notes that the analysis of S/CGIC score at the end of treatment visit is essentially a completer analysis. This analysis is considered valid only under the assumption of missing completely at random, which is unlikely to be true. Therefore, Dr. Ling considered the analysis of S/CGIC score at the last visit as the main analysis, and the analysis of the end of treatment visit a sensitivity analysis.

Results

Primary Endpoint

The primary efficacy analysis population comprised a total of 225 patients: 76 patients in the 20 mg/kg/day CBD group, 73 patients in the 10 mg/kg/day CBD group, and 76 patients in the placebo group. The overall discontinuation rate in the study was low (5.8%); however, discontinuations were greater in the 20 mg/kg/day CBD groups (11.8% in the 20 mg/kg/day group compared to 2.7% in the 10 mg/kg/day group and 2.6% in the placebo group). The majority of discontinuations in the CBD group were due to adverse events. Demographic variables were well balanced across the three treatment groups. The study population was predominantly White/Caucasian (88%). Other racial groups consisted of Black/African-American, Asian, and other. There is no indication of differences in the phenotype of LGS by race/ethnicity to suggest a differential response to treatment. Therefore, the findings of these studies should be applicable to the general LGS population.

The treatment groups were reasonably well matched for baseline drop seizure counts. Patients took a median of 3 concomitant AEDs in all treatment groups. Approximately 50% of patients took concomitant clobazam, and approximately 40% of patients took concomitant valproic acid. Other frequently used AEDs included lamotrigine, levetiracetam, and rufinamide.

There were statistically significant differences between each CBD group (20 mg/kg/day and 10 mg/kg/day) compared to the placebo group in the percent change from baseline in drop seizure frequency in favor of CBD (p=0.005 and p=0.002, respectively). **Table 2**, from the clinical study report (CSR), and confirmed by the FDA statistical reviewer, presents the results of the analysis of the primary endpoint.

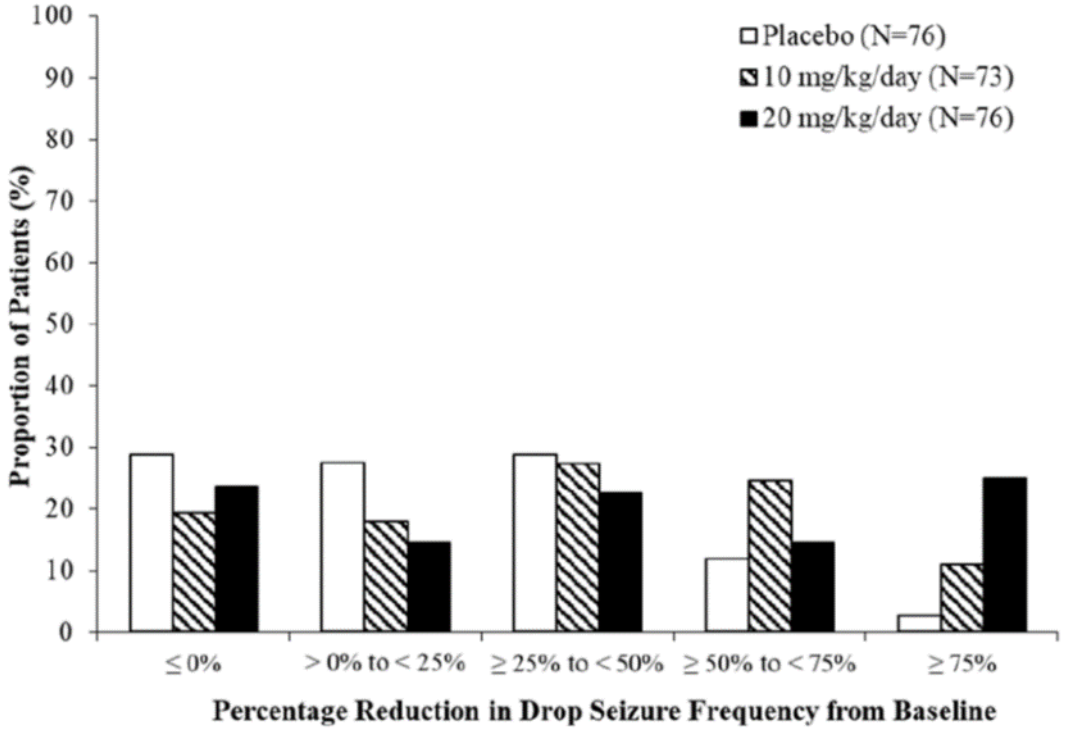
Table 2: Primary Endpoint Analysis Results from Study 1414 (LGS)

Drop Seizure Frequency (per 28 Days)	20 mg/kg/day (N=76)	10 mg/kg/day (N=73)	Placebo (N=76)
Baseline Period Median	85.5	86.9	80.3
Treatment Period Median	44.9	50.0	72.7
Median Percentage Change During Treatment, Interquartile range (Q1, Q3)	−41.9 (−72.4, −1.3)	−37.2 (−63.8, −5.6)	−17.2 (−37.1, 0.9)
Comparison over Placebo			
Estimated Median Difference (CI)*	−21.6 (−34.8, −6.7)	−19.2 (−31.2, −7.7)	
p-value by Wilcoxon rank-sum test	0.0047	0.0016	

Source: CSR Table 8.4.1.1-1, confirmed by FDA statistical reviewer
*based on Hodges-Lehmann estimator

Overall, the study results show a statistically significant seizure reduction in both the 10 mg/kg/day and 20 mg/kg/day CBD groups, compared to placebo. The distribution of responders, shown in Figure 3, suggests that the efficacy findings may be largely driven by a subset of patients who show a large (>50%) reduction in seizures.

Figure 3: Study 1414, Proportion of Patients by Category of Seizure Response



Source: Applicant submission, May 3, 2018.

Sensitivity analyses using ANCOVA on ranked data and log-transformed data yielded results similar to the primary analysis. Consistent results were seen for the maintenance period and each 4-week period of the maintenance period (Table 3).

Table 3: Study 1414, Sensitivity Analyses of Time Periods, Primary Efficacy Endpoint

Analysis Period	Treatment	n	Median	Q1 Q3	Estimated Median Difference[b] (95% CI)	p-value[c]
Maintenance Period	10 mg/kg (N=73)	73	-39.99	-67.4, -2.2	-19.54 (-32.22, -6.50)	0.0033
	20 mg/kg (N=76)	76	-47.15	-78.8, 1.7	-21.23 (-36.40, -6.24)	0.0067
	Placebo (N=76)	76	-18.73	-40.6, -1.2		
Maintenance Period (Week 1 to 4)[a]	10 mg/kg (N=73)	73	-41.74	-61.1, -10.0	-20.40 (-31.78, -8.29)	0.0017
	20 mg/kg (N=76)	75	-39.73	-85.6, -0.5	-25.19 (-40.94, -8.97)	0.0015
	Placebo (N=76)	75	-19.97	-37.1, 0.0		
Maintenance Period (Week 5 to 8) [a]	10 mg/kg (N=73)	72	-44.13	-71.9, -0.4	-17.10 (-31.72, -1.79)	0.0255
	20 mg/kg (N=76)	68	-53.54	-89.9, -5.4	-29.11 (-43.59, -12.93)	0.0008
	Placebo (N=76)	75	-22.16	-45.6, -1.9		
Maintenance Period (Week 9 to 12) [a]	10 mg/kg (N=73)	71	-49.01	-79.6, -6.3	-21.95 (-35.60, -6.61)	0.0068
	20 mg/kg (N=76)	67	-36.44	-76.6, 10.1	-14.80 (-32.05, 2.11)	0.0848
	Placebo (N=76)	74	-22.80	-46.0, 0.0		

Source: Study 1414, Unblinded Final Tables, Table 8.1.1

[a] Patients with at least 7 days of seizure data within the corresponding 4 week period

[b] based on Hodges-Lehmann estimator

[c] by Wilcoxon Rank Sum Test

There were few missing data (2%); therefore, results of sensitivity analyses for missing data were generally similar to the primary analysis. Dr. Liang performed an additional sensitivity analysis using multiple imputation to account for missing data because of dropouts, because of an imbalance in discontinuation rates between the 20 mg/kg/day CBD group and placebo. Although the resulting estimated difference between the two groups was smaller (-15.6% vs. -21.6%), the difference still favored treatment with CBD.

There were 6 protocol amendments during the study. Dr. Getzoff notes that Amendment 6 increased the planned sample size from 120 patients to 150 patients, based on a review of published clinical trial literature that showed a greater placebo response rate than was previously used in the initial sample size calculation. Although this justification was found to be acceptable by the clinical reviewer, Dr. Getzoff notes that the final enrollment of the study was 225 subjects, without further justification for the increase above 150. Dr. Ling conducted an analysis of the primary endpoint on the first 150 randomized patients. The results showed similar treatment effects as the primary analysis on the ITT set.

Subgroup analyses were performed on the primary efficacy endpoint for age group, sex, region, clobazam use, valproic acid use, lamotrigine use, and rufinamide use for both the 20 mg/kg and 10 mg/kg groups, as shown below (Table 4, Table 5). The results of the subgroup analyses generally favored CBD for both doses in all groups.

Table 4: Study 1414, Subgroup Analysis of the Primary Endpoint (Demographics)

Subgroup Item	Treatment	N	Median	Median Difference (95%CI)*	
Male	10 mg/kg	40	-36.08	-16.86	(-31.34, -0.32)
	20 mg/kg	45	-39.62	-22.09	(-39.78, -3.89)
	Placebo	44	-17.17		
Female	10 mg/kg	33	-49.33	-22.04	(-41.29, -5.75)
	20 mg/kg	31	-43.65	-19.75	(-42.63, 6.35)
	Placebo	32	-17.85		
White/ Caucasian	10 mg/kg	62	-36.69	-16.81	(-28.46, -5.18)
	20 mg/kg	67	-39.62	-15.74	(-29.81, -1.30)
	Placebo	69	-19.13		
Other	10 mg/kg	11	-49.65	-43.02	(-109.51, 19.09)
	20 mg/kg	9	-85.08	-67.37	(-123.15, 1.68)
	Placebo	7	1.30		
2-5 years	10 mg/kg	8	-39.69	-22.68	(-56.60, 19.18)
	20 mg/kg	9	-29.55	-10.58	(-62.35, 35.11)
	Placebo	9	-13.37		
6-11 years	10 mg/kg	24	-49.41	-28.92	(-49.07, -2.19)
	20 mg/kg	25	-25.74	-15.16	(-41.19, 10.06)
	Placebo	24	-17.17		
12-17 years	10 mg/kg	19	-46.74	-26.44	(-44.30, -7.62)
	20 mg/kg	20	-50.18	-27.05	(-51.09, 3.47)
	Placebo	20	-26.94		
18-55 years	10 mg/kg	22	-18.16	-2.31	(-22.90, 17.98)
	20 mg/kg	22	-44.65	-29.35	(-50.30, -0.99)
	Placebo	23	-8.90		

Source: FDA statistical reviewer
*based on Hodges-Lehmann estimator

Table 5: Study 1414, Subgroup Analysis of the Primary Endpoint (Concomitant AEDs)

Subgroup/Item	Treatment	N	Median	Median Difference (95% CI)*	
Clobazam Use					
Yes	10 mg/kg	37	-43.43	-17.55	(-36.84, -1.27)
	20 mg/kg	36	-56.85	-33.97	(-51.78, -15.57)
	Placebo	37	-26.54		
No	10 mg/kg	36	-35.19	-20.29	(-35.28, -5.18)
	20 mg/kg	40	-23.18	-4.63	(-25.68, 12.85)
	Placebo	39	-9.63		
Valproic Acid Use					
Yes	10 mg/kg	27	-34.44	-18.35	(-34.96, 1.77)
	20 mg/kg	28	-39.87	-14.57	(-39.49, 9.96)
	Placebo	30	-15.31		
No	10 mg/kg	46	-40.30	-19.88	(-36.18, -4.57)
	20 mg/kg	48	-41.86	-25.02	(-41.49, -6.36)
	Placebo	46	-18.11		
Lamotrigine Use					
Yes	10 mg/kg	22	-40.30	-13.32	(-34.96, 10.31)
	20 mg/kg	20	-44.65	-22.01	(-49.84, 8.18)
	Placebo	25	-30.30		
No	10 mg/kg	51	-36.44	-22.59	(-36.88, -8.12)
	20 mg/kg	56	-39.42	-22.83	(-38.70, -5.65)
	Placebo	51	-13.33		
Levetiracetam Use					
Yes	10 mg/kg	22	-46.82	-16.55	(-41.59, 11.97)
	20 mg/kg	24	-37.27	-9.85	(-35.31, 17.13)
	Placebo	23	-28.23		
No	10 mg/kg	51	-36.44	-22.14	(-33.99, -8.55)
	20 mg/kg	52	-44.65	-25.52	(-42.44, -8.33)
	Placebo	53	-9.63		
Rufinamide Use					
Yes	10 mg/kg	19	-34.44	-15.95	(-41.46, 7.79)
	20 mg/kg	26	-25.55	-17.70	(-40.52, 3.55)
	Placebo	20	-17.17		
No	10 mg/kg	54	-45.91	-19.75	(-33.99, -7.18)
	20 mg/kg	50	-46.21	-24.68	(-41.81, -4.62)
	Placebo	56	-19.76		

Source: Table 9.20.1, Study 1414 CSR
*based on Hodges-Lehmann estimator

Secondary Endpoints

The analysis of the secondary endpoint of ≥50% reduction in convulsive seizures from baseline demonstrated a greater reduction in the 20 mg/kg/day and 10 mg/kg/day CBD groups (39.5% and 35.6% respectively), compared with the placebo group (14.5%). The odds ratios (ORs) were statistically significant for both the 20 mg/kg/day group (OR =3.9; *p*=0.001) and the 10 mg/kg/day group (OR =3.3; *p* = 0.003).

A greater median reduction in total seizure frequency (28-day average) during the treatment period was observed in both the 20 mg/kg/day and 10 mg/kg/day CBD groups (-38.4% and -36.4%, respectively), compared with the placebo group (-18.5%). The difference between each CBD group and placebo was statistically significant (*p*=0.009 and *p*=0.002, respectively).

For the analysis of S/CGIC score, the 7-point scale scores (1 = very much improved; 7 = very much worse) at the last visit (if different than the end of treatment) were analyzed using ordinal logistic regression. The mean S/CGIC score at last visit was 3.0 in the 20 mg/kg/day CBD group and 3.2 in the 10 mg/kg/day CBD group (corresponding to "slightly improved"), compared with 3.6 (most closely associated with "no change") in the placebo group. The treatment differences were in favor of the 20 mg/kg/day and 10 mg/kg/day CBD groups (OR=1.8 and OR=2.6, respectively) and were both statistically significant (*p*=0.044 and *p*=0.002, respectively).

The results of the secondary endpoints of ≥50% reduction in convulsive seizures and total seizure frequency were generally consistent with effects on seizure reduction seen on the primary endpoint. The reduction in total seizure frequency suggests that the efficacy of CBD is not limited to drop attacks. The changes on the S/CGIC provide additional support for the clinical meaningfulness of the effects on seizure reduction.

Exploratory Endpoint

There were 3 patients in the CBD 10 mg/kg/day group, 5 patients in the CBD 20 mg/kg/day group, and 1 patient in the placebo group who completed the study and reported no drop seizures during the maintenance period. Although this was an exploratory endpoint, there appears to be a clinically meaningful difference between the treatment and placebo groups.

Study 1423 in LGS

Study 1423 was a 14-week, multicenter, randomized, double-blind, placebo-controlled trial in patients with LGS. The study design and study population was identical to Study 1414 with the exception that Study 1423 included only a 20 mg/kg/day CBD dose arm. Please refer to the description of Study 1414 above for details of the study design and population. There were 171 patients randomized in a 1:1 ratio to CBD 20 mg/kg/day (divided twice daily) or placebo. The study was conducted in the US, Poland, and the Netherlands.

As with Study 1414, the primary endpoint for Study 1423 was the percent change from baseline in drop seizure frequency (average per 28 days) during the treatment period. Please refer to the definition of drop seizures described under Study 1414 above.

The statistical analysis of the primary endpoint was identical to that described for Study 1414. The study contained the same secondary endpoints as Study 1414. It was inconsistently stated in the in the statistical analysis plan (SAP) whether there was pre-specified hierarchal testing of secondary endpoints in the United States (US) SAP; however, the applicant provided a clarification that the secondary endpoints were pre-specified for hierarchical testing and that a sentence in the SAP stating that secondary endpoints were only pre-specified for hierarchical testing in the EU was an error. However, this is difficult to verify. All statistical tests were 2-sided and used the 5% significance level.

The sponsor also assessed "drop seizure free days" as an additional secondary endpoint that was not tested hierarchically.

Results

Primary Endpoint

The primary efficacy analysis population comprised a total of 171 patients: 86 patients in the 20 mg/kg/day CBD group and 85 patients in the placebo group. Discontinuations were 16.3% in the CBD group vs. 1.2% in the placebo group. The majority of discontinuations in the CBD group were due to adverse events. Demographic variables were well balanced across the three treatment groups. As with Study 1414, the study population was predominantly White/Caucasian (approximately 90%). Other racial groups consisted of Black/African-American, Asian and other.

Baseline seizure count and concomitant AED use were similar to those observed in Study 1414. The treatment groups were reasonably well matched for baseline drop seizure counts. Patients took a median of 3 concomitant AEDs in all treatment groups. Approximately 50% of patients took concomitant clobazam, and approximately 40% of patients used concomitant valproic acid. Other frequently used AEDs include lamotrigine, levetiracetam, and rufinamide.

There was a statistically significant difference between the groups in the percent change from baseline in drop seizure frequency during the treatment period, in favor of CBD treatment (p=0.014). **Table 6**, from the CSR, and confirmed by the FDA statistical reviewer, presents the results of the analysis of the primary endpoint:

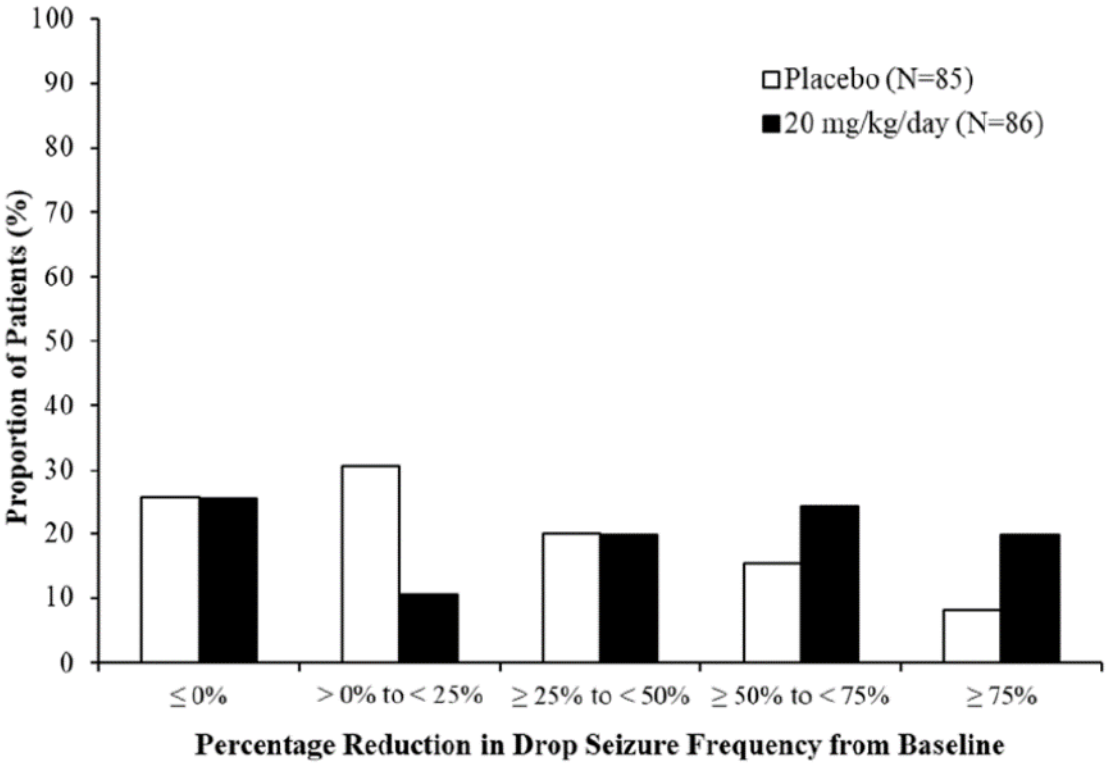
Table 6: Primary Endpoint Analysis Results from Study 1423(LGS)

Drop Seizure Frequency (per 28 Days)	CBD 20 mg/kg/day (N=86)	Placebo (N=85)
Baseline Period Median	71.4	74.7
Treatment Period Median	31.4	56.3
Median Percentage Change from Baseline (Q1, Q3)	−43.9 (−69.6, −1.9)	−21.8 (−45.7, 1.7)
Estimated Median Difference (CI)*	−17.2 (−30.3, −4.1)	
p-value by Wilcoxon rank-sum test	0.0135	

Source: CSR Table 8.4.1.1-1, confirmed by FDA statistical reviewer
*based on Hodges-Lehmann estimator

The study results were generally consistent with those of Study 1414, showing a statistically significant seizure reduction in the 20 mg/kg/day CBD groups compared to placebo. As with Study 1414, the distribution of responders, shown in Figure 4, suggests that the efficacy findings may be largely driven by a subset of patients who show a large (>50%) reduction in seizure frequency.

Figure 4: Study 1423, Proportion of Patients by Category of Seizure Response



Source: Applicant submission, May 3, 2018.

Sensitivity analyses using ANCOVA on ranked data and log-transformed data yielded similar results to the primary analysis. Consistent results were seen for the maintenance period and each 4-week period of the maintenance period (Table 7).

Table 7: Study 1423, Sensitivity Analyses of Time Periods, Primary Efficacy Endpoint

Analysis Period	Treatment	n	Median	Q1, Q3	Estimated Median Difference[b] (95% CI)	p-value[c]
Maintenance Period	20 mg/kg (N=86)	85	-48.77	-74.6, 2.2	-19.45 (-33.05, -4.68)	0.0096
	Placebo (N=85)	85	-20.45	-48.5, -0.2		
Maintenance Period (Week 1 to 4)[a]	20 mg/kg (N=86)	82	-51.30	-81.5, -21.4	-23.63 (-37.19, -11.03)	0.0005
	Placebo (N=85)	85	-23.33	-51.9, 0.0		
Maintenance Period (Week 5 to 8)[a]	20 mg/kg (N=86)	73	-45.36	-70.8, -17.4	-16.77 (-30.87, -2.56)	0.0205
	Placebo (N=85)	84	-23.46	-53.8, 0.0		
Maintenance Period (Week 9 to 12)[a]	20 mg/kg (N=86)	72	-52.56	-77.9, -13.1	-23.58 (-38.42, -6.76)	0.0062
	Placebo (N=85)	84	-26.99	-46.9, 5.1		

Source: Study 1423, Unblinded Final Tables, Table 8.1.1

[a] Patients with at least 7 days of seizure data within the corresponding 4 week period

[b] based on Hodges-Lehmann estimator

[c] by Wilcoxon Rank Sum Test

There were few missing data (2%); therefore, results of sensitivity analyses for missing data were generally similar to the primary analysis. Dr. Liang performed an additional sensitivity analysis using multiple imputation to account for missing data because of dropouts due to the imbalance in discontinuation rates between the 20 mg/kg/day CBD group and placebo. Although the resulting estimated difference between the two groups was smaller (-5.5% vs. -17.2%), the difference still favored treatment with CBD.

There were 3 protocol amendments during the study. Amendment 3 increased the planned sample size from 80 patients to 100 patients, based on a review of published clinical trial literature that showed a greater placebo response rate than was previously used in the initial sample size calculation. However, the final enrollment for the study was 171 subjects. To explore the impact of the over-enrollment, Dr. Liang conducted an analysis on the first 100 patients enrolled into Study 1423. The placebo group had a higher drop seizure frequency at baseline in this subset. The results showed a smaller median treatment difference of -8.6%, which was not statistically significant. A query was sent to the applicant to understand the reason for the over-enrollment. The following description from the clinical/statistical provides the rationale for the over-enrollment:

> *"…the over-enrollment was not in response to any interim analyses. It was primarily due to many patients having been pre-identified by investigators prior to completion of the*

site initiation, a prolonged site initiation process (need for Schedule 1 DEA license), and the required 28-day time lag between screening and randomization. One-third of the 24 sites opened for screening during the final 5 weeks of study enrollment, and 37 patients were screened in the final week of open enrollment. It was decided that all patients who had been screened and were randomizable, could continue participation even though the study had been over enrolled."

As the over-enrollment was not based on any interim analysis, Dr. Liang felt that analysis of the entire ITT dataset was appropriate for the primary endpoint.

Subgroup analyses were performed on the primary efficacy endpoint for age group, sex, region, and concomitant AED use (Table 8, Table 9). The results generally favored CBD over placebo in the subgroups.

Table 8: Study 1423, Subgroup Analysis of the Primary Endpoint (Demographics)

Subgroup Item	Treatment	N	Median	Median Difference (95% CI)*	
Male	20 mg/kg	45	-46.43	-10.29	(-30.52, 9.26)
	Placebo	43	-21.66		
Female	20 mg/kg	41	-42.00	-21.57	(-39.51, -5.24)
	Placebo	42	-21.93		
White/Caucasian	20 mg/kg	75	-42.00	-17.92	(-32.25, -3.81)
	Placebo	79	-21.66		
Other	20 mg/kg	11	-49.91	-3.36	(-47.41, 45.20)
	Placebo	6	-45.75		
2-5 years	20 mg/kg	11	-50.68	-8.55	(-49.19, 42.37)
	Placebo	12	-28.29		
6-11 years	20 mg/kg	26	-40.73	-22.16	(-50.49, 2.02)
	Placebo	27	-14.04		
12-17 years	20 mg/kg	19	-45.81	-27.28	(-59.50, 5.15)
	Placebo	18	-26.54		
18-55 years	20 mg/kg	30	-39.89	-13.32	(-32.04, 13.74)
	Placebo	28	-22.35		
USA	20 mg/kg	62	-40.80	-18.91	(-33.71, -4.22)
	Placebo	66	-21.81		
Rest of the World	20 mg/kg	24	-48.52	-10.76	(-42.85, 25.80)
	Placebo	19	-9.49		

Source: FDA statistical reviewer
*based on Hodges-Lehmann estimator

Table 9: Study 1423, Subgroup Analysis of the Primary Endpoint (Concomitant AEDs)

Subgroup/Item	Treatment	N	Median	Median Difference (95% CI)*	
Clobazam Use					
Yes	20 mg/kg	42	-59.60	-28.17	(-46.12, -10.05)
	Placebo	42	-22.91		
No	20 mg/kg	44	-28.61	-6.04	(-25.25, 15.46)
	Placebo	43	-21.66		
Valproic Acid Use					
Yes	20 mg/kg	36	-53.88	-28.51	(-44.24, -5.76)
	Placebo	33	-21.80		
No	20 mg/kg	50	-36.98	-12.15	(-28.89, 6.37)
	Placebo	52	-21.74		
Lamotrigine Use					
Yes	20 mg/kg	33	-29.79	-9.32	(-32.94, 15.99)
	Placebo	31	-11.68		
No	20 mg/kg	53	-50.68	-22.16	(-37.80, -6.18)
	Placebo	54	-27.12		
Levetiracetam Use					
Yes	20 mg/kg	23	-42.00	-16.39	(-37.93, 7.42)
	Placebo	35	-32.32		
No	20 mg/kg	63	-45.81	-21.36	(-37.24, -3.23)
	Placebo	50	-19.80		
Rufinamide Use					
Yes	20 mg/kg	25	-29.79	-19.42	(-44.64, 6.69)
	Placebo	21	-15.42		
No	20 mg/kg	61	-46.43	-17.03	(-32.25, -0.72)
	Placebo	64	-21.93		

Source: Table 9.20.1, Study 1423 CSR
*based on Hodges-Lehmann estimator

Secondary endpoints

Hierarchical testing of the secondary endpoints was not specified in the EU SAP, but not in the US SAP. A descriptive summary of selected secondary endpoints is provided.

- During the treatment period, the proportion of patients with a reduction of 50% or more in their baseline drop seizure frequency was greater in the CBD group (44.2%), compared with the placebo group (23.5%). The nominal p value was 0.004.
- A greater median reduction in total seizure frequency (28-day average) during the treatment period was seen in the CBD group (44.2%), compared with the placebo group (23.5%). The nominal *p*-value was 0.001.
- For the analysis of S/CGIC score, the 7-point scale scores (1 = very much improved; 7 = very much worse) at the last visit were analyzed using ordinal logistic regression. The mean S/CGIC score at last visit was 3.0 (corresponding to “slightly improved”) in the

CBD group, compared with 3.7 (most closely associated with "no change") in the placebo group. The treatment difference was in favor of the CBD group (OR=2.5) and nominally statistically significant (*p*=0.001).

- 3 of 86 (3%) patients in the EPIDIOLEX 20 mg/kg/day group reported no drop seizures during the maintenance period, compared to 0 patients in the placebo group.

The secondary endpoints results were generally consistent with the results of the primary endpoint.

Study 1332B in DS

Study 1332B was a 14-week, multicenter, randomized, double-blind, placebo-controlled trial in patients with DS. The study consisted of a baseline period, a treatment period (titration plus maintenance), and a taper period (alternatively, patients could be enrolled in an open-label, long-term extension study). There were 120 patients randomized in a 1:1 ratio to either CBD 20 mg/kg/day (divided twice daily) or placebo. The study drug (or the equivalent volume of placebo) was started at 2.5 mg/kg/day and increased by 2.5 mg/kg/day increments every other day to 10 mg/kg/day, and then increased by 5 mg/kg/day increments every other day to 20 mg/kg/day. Randomization was stratified by age group (2-5 years, 6-12 years, and 13-18 years). Subjects were required to meet the following enrollment criteria: have a documented history of DS not completely controlled by current AEDs, experience ≥ 4 convulsive seizures during a 28-day baseline period, be taking one or more AEDs at a stable dose, and be between 2 and 18 years of age. Concomitant AEDs and doses were to remain constant during the treatment period. The study was conducted in the US, UK, France, and Poland.

The primary endpoint was the percent change from the baseline in total convulsive seizure frequency during the entire treatment period of the study. Convulsive seizures were defined as tonic, clonic, tonic-clonic, or atonic. Patients or caregivers recorded the number and type of convulsive seizures and non-convulsive seizures (myoclonic, partial, or absence) each day using an IVRS telephone diary during a 28-day baseline period and during the entire treatment period (titration and maintenance periods) until completion of dosing.

The number of patients considered treatment responders, defined as those with a ≥50% reduction in convulsive seizures from baseline during the treatment period, was designated as a "key" secondary endpoint; however, there was no pre-specified hierarchical analysis in the US SAP. Other secondary endpoints included: convulsive seizure treatment responders and convulsive seizure freedom, status epilepticus, non-convulsive seizures, individual seizure types and total seizures, use of rescue medication, the Quality of Life in Childhood Epilepsy scale, and Caregiver Global Impression of Change (CGIC).

The primary analyses used the intention to treat (ITT) analysis set, which included all patients randomized to treatment who received at least 1 dose of the investigational treatment and had any post-baseline efficacy data. All statistical tests were 2-sided and used the 5% significance level.

The primary endpoint of percentage change from baseline in seizure frequencies was analyzed using a Wilcoxon rank-sum test. Seizure frequency was calculated as a 28-day frequency. Estimates of the median differences between CBD and placebo and the approximate 95% confidence intervals (CI) were calculated using the Hodges-Lehmann approach.

Results

Primary Endpoint

The primary efficacy analysis population comprised a total of 120 patients: 61 patients in the CBD group and 59 patients in the placebo group.

Discontinuations were 14.8% in the CBD group vs. 5.1% in the placebo group. All of the discontinuations in the CBD group were due to adverse events. Demographic variables were well balanced across the three treatment groups. The study population was predominantly White/Caucasian (approximately 78%). Other racial groups consisted of Black/African-American, Asian and other. There were 14% of patients who were classified as "not applicable" due to country-specific data protection laws. As with LGS, there is no indication of a variation in the phenotype of DS by race/ethnicity to suggest a differential response to treatment. Therefore, the findings from the study should apply to the broad DS population.

The treatment groups were reasonably well matched for baseline drop seizure counts. Patients took a median of 3 concomitant AEDs in both treatment groups. Approximately 65% of patients took concomitant clobazam, approximately 55% of patients used valproic acid, and approximately 43% of patients were taking concomitant stiripentol.

There was a statistically significant difference between the groups in the percent change from baseline in total convulsive seizure frequency, in favor of CBD treatment (p=0.012). **Table 10**, adapted from the CSR, and confirmed by the FDA statistical reviewer, presents the results of the analysis of the primary endpoint:

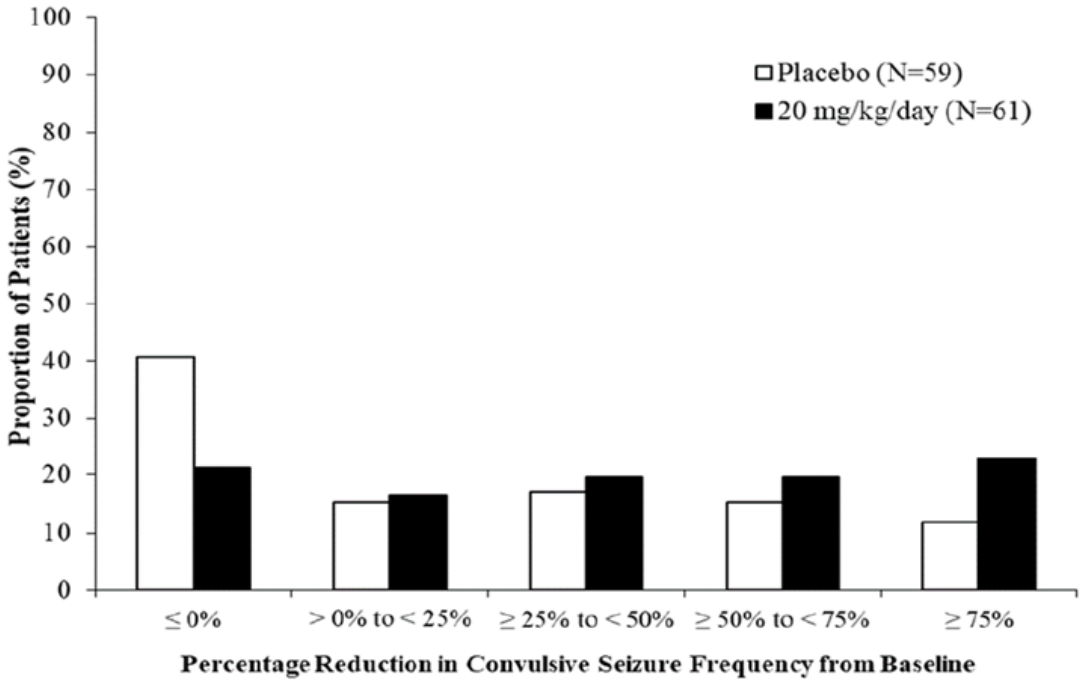
Table 10: Primary Endpoint Analysis Results from Study 1332B (DS)

Total Convulsive Seizure Frequency (per 28 Days)	CBD (N=61)	Placebo (N=59)
Baseline Period Median	12.4	14.9
Treatment Period Median	5.9	14.1
Median Percentage Change from Baseline (Q1, Q3)	−38.9 (−69.5, −4.8)	−13.3 (−52.5, 20.2)
Estimated Median Difference (CI)*	−22.8 (−41.1, −5.4)	
p-value by Wilcoxon rank-sum test	0.0123	

Source: CSR Table 8.4.1.1-1, confirmed by statistical reviewer
*based on Hodges-Lehmann estimator

The study results show a statistically significant reduction in seizures, with treatment effects comparable to those seen in the LGS studies. The distribution of responders, shown in Figure 5, shows a consistent response across the responder categories; however, as with the LGS studies, it does appear that the numerically greater difference is in patients with a large reduction in seizures (>75%).

Figure 5:Study 1332B, Proportion of Patients by Category of Seizure Response



Source: Applicant submission, May 3, 2018.

Sensitivity analyses using ANCOVA on ranked data and log-transformed data yielded similar results to the primary analysis. Consistent results were seen for the maintenance period and each 4-week period of the maintenance period (Table 11).

Table 11: Study 1332B, Sensitivity Analyses of Time Periods, Primary Efficacy Endpoint

Analysis Period	Treatment	n	Median	Q1, Q3	Estimated Median Difference[b] (95% CI)	p-value[c]
Maintenance Period	20 mg/kg (N=61)	60	-40.67	-79.9, -10.9	-26.06 (-45.07, -8.24)	0.0052
	Placebo (N=59)	59	-15.95	-54.9, 21.0		
Maintenance Period (Week 1 to 4)[a]	20 mg/kg (N=61)	57	-58.17	-80.0, -19.0	-29.69 (-48.75, -11.23)	0.0020
	Placebo (N=59)	58	-24.70	-53.6, 29.5		
Maintenance Period (Week 5 to 8) [a]	20 mg/kg (N=61)	54	-49.20	-82.3, -15.2	-25.21 (-44.76, -8.33)	0.0055
	Placebo (N=59)	56	-25.00	-56.4, 5.9		
Maintenance Period (Week 9 to 12) [a]	20 mg/kg (N=61)	52	-41.40	-87.9, 7.3	-19.96 (-40.74, 1.25)	0.0756
	Placebo (N=59)	55	-21.74	-64.1, 21.7		

[a] Patients with at least 7 days of seizure data within the corresponding 4 week period

[b] based on Hodges-Lehmann estimator

[c] by Wilcoxon Rank Sum Test

There was little missing data (4%); therefore, sensitivity analyses for missing data were generally similar to the primary analysis. Dr. Liang performed an additional sensitivity analysis using multiple imputation to account for missing data due to dropouts due to the imbalance in discontinuation rates between the 20 mg/kg/day CBD group and placebo. Although the resulting estimated difference between the two groups was smaller (-14.1% vs. -22.8%), the difference still favored treatment with CBD.

Subgroup analyses were performed on the primary efficacy endpoint for age group, sex, and region in CBD and placebo groups. The sample sizes for each subgroup are small, making it difficult to derive any substantive conclusions of efficacy in a specific subgroup; however, all results trended in favor of CBD, compared to placebo (Table 12).

Subgroup analyses were also performed on the primary efficacy endpoint for concomitant drugs of interest, specifically clobazam, valproic acid, and stiripentol (Table 13). Concomitant use of any of these AEDs with CBD was associated with better results than without these drugs; however, the results favored CBD over placebo for all AED subgroups.

Table 12: Study 1332B, Primary Efficacy Endpoint Analysis by Subgroups

Subgroup Item	Treatment	N	Median	Median Difference (95% CI)*	
Sex					
Male	20 mg/kg	35	-37.14	-19.63	(-41.85, 4.89)
	Placebo	27	-9.52		
Female	20 mg/kg	26	-42.97	-24.87	(-53.97, -0.30)
	Placebo	32	-20.60		
Race					
White/Caucasian	20 mg/kg	44	-38.57	-21.52	(-41.46, -0.31)
	Placebo	50	-20.60		
Other	20 mg/kg	17	-39.52	-45.44	(-89.64, 5.61)
	Placebo	9	10.71		
Age					
2-5 years	20 mg/kg	18	-54.86	-29.58	(-60.63, 8.96)
	Placebo	17	-39.37		
6-12 years	20 mg/kg	23	-28.57	-29.86	(-63.48, 6.02)
	Placebo	24	12.43		
13-18 years	20 mg/kg	20	-49.33	-18.19	(-40.48, 13.82)
	Placebo	18	-24.73		
Region					
USA	20 mg/kg	35	-55.15	-24.67	(-50.50, -3.19)
	Placebo	37	-22.58		
Rest of the World	20 mg/kg	26	-33.79	-19.75	(-48.88, 6.53)
	Placebo	22	-7.43		

Source: FDA statistical reviewer
*based on Hodges-Lehmann estimator

Table 13: Study 1332B, Primary Efficacy Endpoint Analysis by Concomitant Drugs of Interest

Concomitant Drug Y/N	Treatment	N	Median	Median Difference (95% CI)*
Clobazam				
Yes	20 mg/kg	40	-45.0	-31.8 (-55.9, -10.2)
	Placebo	38	-9.9	
No	20 mg/kg	21	-28.6	-6.3 (-36.5, 23.7)
	Placebo	21	-18.6	
Valproic Acid				
Yes	20 mg/kg	36	-39.6	-26.2 (-51.6, -0.8)
	Placebo	32	-11.8	
No	20 mg/kg	25	-38.3	-20.32 (-47.7, 7.4)
	Placebo	27	-18.6	
Stiripentol				
Yes	20 mg/kg	30	-28.1	-32.7 (-57.1, -9.0)
	Placebo	21	5.4	
No	20 mg/kg	31	-56.8	-20.8 (-45.6, 1.4)
	Placebo	38	-32.0	

Source: Study 1332B, CSR Table 9.15.1B
*based on Hodges-Lehmann estimator

Secondary endpoints

Hierarchical testing of the secondary endpoints was specified in the EU SAP, but not in the US SAP. A descriptive summary of selected secondary endpoints is provided.

- There were 26 (42.6%) patients on CBD versus 16 (27.1%) patients on placebo who showed a ≥50% reduction from baseline in convulsive seizures. The nominal *p*-value was 0.078.
- The median percentage change from baseline in total seizure frequency during the treatment period was −28.57 in the CBD group compared with −9.00 in the placebo group. The estimated median difference was −19.20 (−39.25, −1.17), favoring CBD over placebo.
- There were 4 patients treated with CBD 20 mg/kg/day who reported no convulsive seizures during the maintenance period, compared to 0 patients in the placebo group.

The secondary endpoints results were generally consistent with the results of the primary endpoint.

Efficacy Discussion:

The applicant submitted data from three randomized, double-blind, placebo-controlled trials conducted in patients with LGS (2 studies) and DS (1 study). The studies compared the change in seizure frequency (primary endpoints assessed drop seizures for LGS and convulsive seizures for DS; total seizure counts were also assessed), as assessed by seizure diaries, between the 14-week treatment period and a 28-day baseline period. The studies all utilized a similar design that is typical for trials that assess drugs to treat seizures. The

primary endpoint for the LGS studies was the change in "drop seizures", and the primary endpoint for the DS study was the change in "convulsive seizures". Both endpoints were agreed upon with the Agency prior to the initiation of the studies. The studies were generally well-conducted, with little missing data, and no concerns with study integrity were identified. It is noted that both LGS studies were over-enrolled; however, Dr. Getzoff and Dr. Ling reviewed the reasons for over-enrollment, performed sensitivity analyses to assess the impact of the over-enrollment, and concluded that the over-enrollment did not impact the overall interpretation of the study results. Overall, the three studies showed an approximate 20% decrease in seizure frequency in CBD-treated patients, compared to placebo-treated patients. The secondary endpoints in the studies also generally favored CBD. The study results were both clinically meaningful and statistically significant, and support the effectiveness of CBD for both the LGS and DS patient populations. There was a demonstrated effect of CBD alone and when added to clobazam, but the effect was consistently greater in the latter group, perhaps because of increased levels of clobazam's active metabolite.

The applicant is seeking an indication for the treatment of seizures associated with LGS and DS. The primary endpoint for the LGS studies was change in "drop seizures", which was defined as atonic, tonic or tonic-clonic seizures that led or could have led to fall or injury. The primary endpoint for the DS study was the change in "convulsive seizures", which were defined as atonic, tonic, clonic, or tonic-clonic seizures. This endpoint is similar to "drop seizures", but includes clonic seizures, and does not require that the seizures led or could have led to a fall or injury. Although the seizure definitions were not identical, it is reasonable to assume that the studies were measuring seizure types of similar character and severity. Additionally, both studies demonstrated positive effects on total seizure counts, which included other seizure types (e.g., absence, focal seizures) that did not meet the definition of drop or convulsive seizures. Given that the seizure types were similar between the two disease populations and an overall reduction in all seizure types was seen with CBD for both populations, we believe the study findings support an indication for the treatment of seizures associated with both LGS and DS.

The applicant is also proposing the same dosing regimen for both the LGS and DS populations: a titration up to 10 mg/kg/day as a maintenance dosage, with further titration up to 20 mg/kg/day, as needed. All three studies assessed a 20 mg/kg/day dosage of CBD; however, only Study 1414 in LGS assessed a dosage of 10 mg/kg/day. In Study 1414, the 10 mg/kg/day dosage of CBD showed an estimated median difference from placebo of 19.2%, while the 20 mg/kg/day dosage showed a difference of 21.6%. The difference in safety between the two dosages showed a more notable difference in dose-response, with the 20 mg/kg/day group showing markedly higher rates of adverse events than the 10 mg/kg/day, particularly transaminase elevations (see safety section of this review). The dose-response seen with adverse events supports initial use of lower effective dosages with higher dosages being reserved for patients with inadequate seizure control at the initial dose. As noted above, given that the seizure types were similar between the two disease populations, and as an overall reduction in all seizure types was seen with CBD for both populations, it is reasonable to assume that the 10 mg/kg/day dosage that was shown to be effective in LGS

will also be effective in DS. Although there was a marginal difference in efficacy between the 10 mg/kg/day dosage and the 20 mg/kg/day dosage in Study 1414, there are some patients who may show additional benefit from higher doses. The ability to titrate CBD to 20 mg/kg/day based on clinical response and tolerability allows prescribers to use a higher dose if that is warranted for their patient. Therefore, the applicant's proposal for dosing is reasonable. Please refer to the Clinical Pharmacology section of this review for a discussion of the potential impact of concomitant clobazam use on the efficacy findings for CBD.

Efficacy conclusions
The applicant has provided positive results from three randomized, double-blind, placebo-controlled trials conducted in patients with LGS and DS. The design of the studies and primary endpoints are consistent with other studies that have been used to support drug approvals for epilepsy indications, including LGS. The studies are adequate and well-controlled. The statistically significant and clinically meaningful results from these three adequate and well-controlled studies in two similar diseases with comparable study endpoints provide substantial evidence of the effectiveness of CBD for the treatment of seizures associated with LGS and DS. In both diseases, there were more patients on active treatment with substantial effects on seizure frequency (50-75% reduction). Despite the uncertainty of the effect of food on blood levels, the overall difference between 10 and 20 mg is a necessary indicator that dose-response is not steep and should not be greatly affected by intermittent food-related differences.

8. Safety

Dr. Ellis Unger performed the safety review.

The primary safety analysis was conducted using the controlled safety database, derived from the following sources:

- Study 1414 and Study 1423 – two 14-week, multicenter, randomized, double-blind, placebo-controlled trials in patients with LGS
- Study 1332B – a 14-week, multicenter, randomized, double-blind, placebo-controlled trial in patients with DS
- Study 1332A – a 3-week, randomized, double-blind, placebo-controlled dose-finding study in patients with DS

Additional uncontrolled safety data were analyzed on the uncontrolled safety database, derived from the following sources:

- Study 1415- an ongoing open-label extension study in LGS and DS patients expanded access programs and compassionate access schemes at 38 sites in the US and Australia for patients with drug-resistant epilepsy.

The 120-day safety update submitted on February 21, 2018, included additional adverse events from these studies and these events were included in the uncontrolled safety database. These data provided a secondary role in the safety analysis.

Additionally, Study 1424 is an ongoing 14-week, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of CBD in DS. The study remains blinded, and only limited safety data were submitted from this study, i.e., CIOMS forms for deaths, discontinuations, pregnancies, and serious adverse events.

Safety data were pooled for patients with LGS and DS because the diseases are similar, and study designs and CBD doses were comparable for the studies.

Exposures and Adequacy of the Safety Database

As defined, the safety population included all subjects who received ≥ 1 dose of CBD or placebo, and subjects were categorized by actual drug (or placebo) received.

Table 14, copied from Dr. Unger's review, describes the exposures with CBD and the sources that comprise the safety data to support this application. These exposures include data from the 120-day safety update.

Table 14: Overall Cannabidiol Exposure in the Clinical Development Program

All subjects exposed to cannabidiol	**1808**		
Subjects with epilepsy	**1419**		
Controlled trials	323		
DS (Study 1332, Parts A and B)		88	
LGS (Studies 1414 and 1423)		235	
Extension trial* (Study 1415)	644		366 unique
DS		278	209 unique
LGS		366	157 unique
Expanded access for refractory epilepsy	684		
DS		64	
LGS		97	
other seizure disorders		523	
Other epilepsy	46		not in ISS
Subjects without epilepsy	**389**		
Phase 1 clinical pharmacology (healthy subjects and special patient populations)	346		
Other conditions (schizophrenia, diabetes, fatter liver disease)	43		not in ISS

*Includes unique patients who had received placebo in controlled studies
Adapted from Table 5-1 of applicant's 120-Day Updated ISS

Of these 1808 individual exposures, there are 291 patients with DS and LGS and 158 patients with drug-resistant epilepsy in EAP who have been exposed to CBD for over 1 year. As noted in the efficacy section of this memo, the baseline demographics in the controlled safety population were generally well-balanced across the treatment groups. Approximately 80% of subjects in the controlled safety database were from the US. As previously noted, the safety population was predominantly white/Caucasian (approximately 85%); however, there is no indication that the phenotype of LGS or DS varies with race/ethnicity to suggest a differential response to treatment or susceptibility to drug toxicity. Therefore, the safety findings should be generalizable to the indicated US patient population. Dr. Unger has determined that the patient exposures are adequate to support an assessment of safety in the application.

The methods for assessing and collecting safety data appear to be adequate. Dr. Unger performed an independent analysis of the safety data. He reviewed the translation of verbatim terms to preferred terms for completeness and accuracy. Dr. Unger identified some inaccuracies and changes or additions were made, as indicated. Grouping of related adverse event terms was performed by the applicant and was found to be inconsistent, and underestimated the magnitude of safety signals in some cases. Dr. Unger performed his own analysis with grouping of related preferred terms, as appropriate. In addition to assessing change in mean values over time, critical laboratory parameters were visually inspected in scatter plots.

Deaths

There were 21 deaths reported in the development program. One death was reported in the controlled trials in a patient taking CBD 20 mg/kg/day. There were seven deaths reported in the open-label extension trial and 13 deaths in the EAP. Dr. Unger reviewed the causes of death. For the majority of cases, the causes of death appeared to be related to the underlying disease. These patients were generally very ill, with multiple comorbidities and complex disease courses. Dr. Unger notes that: “It is not possible to attribute the deaths to cannabidiol; conversely, it is not possible to be confident that the drug was not in some way contributory…the proximate causes of death were typical for these patient populations; there was no suggestion that an off-target drug effect was responsible.”

Serious and Significant Adverse Events

Table 15 below, from the safety review, shows the serious adverse events (SAEs) that were reported in at least two more patients treated with CBD than in patients on placebo. Transaminase elevations are notable and will be described further below. There were two reports of “hepatic failure”; however, neither patient had elevations of bilirubin or INR consistent with generally accepted criteria for liver failure. They are more accurately considered as transaminase elevations. Infections and seizures are common in this population and do not appear to be markedly different from placebo. Respiratory failure does not appear to be markedly different from placebo.

Table 15: Serious Adverse Events in the controlled LGS/DS population

	Cannabidiol				Placebo	RR	Δ Risk (%)
Cannabidiol dose (mg/kg/d)	5	10	20	All			
N =	10	75	238	323	227		
Transaminases ↑, hepatic failure	(0%)	2 (3%)	10 (4%)	12 (4%)	(0%)	-	3
Somnolence, lethargy	(0%)	(0%)	7 (3%)	7 (2%)	(0%)	-	2
Lethargy	(0%)	(0%)	3 (1%)	3 (1%)	(0%)	-	0
Infection, all	(0%)	5 (7%)	17 (7%)	22 (7%)	5 (2%)	3.1	5
Pneumonia	(0%)	4 (5%)	9 (4%)	13 (4%)	1 (0%)	9.1	4
Infection, viral	(0%)	1 (1%)	6 (3%)	7 (2%)	1 (0%)	4.9	2
Infection, bacterial	(0%)	1 (1%)	1 (0%)	2 (1%)	(0%)	-	1
Sepsis	(0%)	1 (1%)	1 (0%)	2 (1%)	(0%)	-	1
Sleep apnea	(0%)	1 (1%)	1 (0%)	2 (1%)	(0%)	-	1
Fatigue, asthenia	(0%)	(0%)	2 (1%)	2 (1%)	(0%)	-	1
Bleeding	(0%)	(0%)	2 (1%)	2 (1%)	(0%)	-	1
Constipation	(0%)	(0%)	2 (1%)	2 (1%)	(0%)	-	1
Fever	(0%)	2 (3%)	1 (0%)	3 (1%)	1 (0%)	2.1	0
Seizure	1 (10%)	8 (11%)	14 (6%)	23 (7%)	10 (4%)	1.6	3
Respiratory failure	(0%)	1 (1%)	4 (2%)	5 (2%)	3 (1%)	1.2	0

Dr. Unger reviewed SAEs in the uncontrolled safety population. Transaminase elevations and infections were also observed most frequently in this population. No new signals were identified.

Dr. Unger also reviewed severe adverse events. Severe adverse events were generally similar to the serious adverse events in character. There were 2 severe cases of rash and 3 severe cases of decreased appetite in the CBD group that were not seen in the serious adverse events.

Discontinuations Due to Adverse Events

In the controlled safety database, discontinuations due to adverse events were reported in 2.7% of patients taking CBD 10 mg/kg/day, 11.8% of patients taking CBD 20 mg/kg/day, and 1.3% in patients on placebo. As with the SAEs, adverse events leading to discontinuation are most notable for transaminase elevations and somnolence.

Treatment-Emergent Adverse Events (TEAEs) of All Severities

Table 16, copied from Dr. Unger's review, shows all TEAEs in the controlled safety database that occurred in ≥2% of CBD-treated patients and more frequently than in the placebo group. The most commonly observed adverse events in controlled clinical trials that occurred with a greater incidence in CBD-treated patients than on placebo were in the following categories: central nervous system (e.g., somnolence and sedation), gastrointestinal (e.g., decreased appetite and diarrhea), hepatic (e.g., transaminase elevations) and infections (e.g., pneumonia). These events were generally mild to moderate in severity. There was some trend towards higher rates at the 20 mg dose, but this was not consistent and differences were generally small.

Table 16: All TEAEs in the Controlled Safety Database

	Cannabidiol (mg/kg/day)				Placebo	RR	95% CI	Δ Risk (%)
	5	10	20	10 + 20				
N:	10	75	238	313	227			
Hepatic								
Transaminases elevated	1 (10%)	6 (8%)	37 (15.5%)	43 (13.7%)	6 (2.6%)	5.2	(2.3, 12)	11.2
Other gastrointestinal								
Decreased appetite	(0%)	12 (16%)	53 (22.3%)	65 (20.8%)	11 (4.8%)	4.3	(2.3, 7.9)	16.1
Weight decreased	(0%)	2 (2.7%)	11 (4.6%)	13 (4.2%)	3 (1.3%)	3.1	(0.9, 10.9)	2.9
Abdominal pain, discomfort	(0%)	2 (2.7%)	7 (2.9%)	9 (2.9%)	2 (0.9%)	3.3	(0.7, 15)	2.0
Gastroenteritis	1 (10%)	(0%)	10 (4.2%)	10 (3.2%)	3 (1.3%)	2.4	(0.7, 8.7)	1.9
Diarrhea	(0%)	7 (9.3%)	47 (19.7%)	54 (17.3%)	20 (8.8%)	2.0	(1.2, 3.2)	8.8
Central nervous system								
Irritability, agitation	(0%)	7 (9.3%)	12 (5%)	19 (6.1%)	4 (1.8%)	3.4	(1.2, 10)	4.4
Somnolence, sedation, lethargy	4 (40%)	20 (26.7%)	81 (34%)	101 (32.3%)	26 (11.5%)	2.8	(1.9, 4.2)	21.3
Somnolence	2 (20%)	17 (22.7%)	60 (25.2%)	77 (24.6%)	19 (8.4%)	2.9	(1.8, 4.7)	16.6
Sedation	2 (20%)	2 (2.7%)	14 (5.9%)	16 (5.1%)	2 (0.9%)	5.8	(1.3, 25)	4.3
Lethargy	0 (0%)	3 (4%)	18 (7.6%)	21 (6.7%)	5 (2.2%)	3.0	(1.2, 8)	4.6
Fatigue, malaise, asthenia	(0%)	8 (10.7%)	28 (11.8%)	36 (11.5%)	9 (4%)	2.9	(1.4, 5.9)	7.7
Fatigue	(0%)	5 (6.7%)	26 (10.9%)	31 (9.9%)	8 (3.5%)	2.8	(1.3, 6)	6.5
Ataxia, coordination abnormal	2 (20%)	1 (1.3%)	5 (2.1%)	6 (1.9%)	(0%)	-	-	1.9
Tremor	(0%)	1 (1.3%)	4 (1.7%)	5 (1.6%)	(0%)	-	-	1.6
Aggression, anger	(0%)	2 (2.7%)	11 (4.6%)	13 (4.2%)	1 (0.4%)	9.4	(1.2, 71.6)	3.7
Drooling, salivary hypersecretion	(0%)	1 (1.3%)	10 (4.2%)	11 (3.5%)	1 (0.4%)	8.0	(1, 61.4)	3.1
Insomnia, sleep disorder, poor quality sleep	1 (10%)	8 (10.7%)	12 (5%)	20 (6.4%)	10 (4.4%)	1.5	(0.7, 3)	2.2
Insomnia	(0%)	4 (5.3%)	9 (3.8%)	13 (4.2%)	5 (2.2%)	1.9	(0.7, 5.2)	2.1
Gait disturbance	(0%)	2 (2.7%)	4 (1.7%)	6 (1.9%)	1 (0.4%)	4.4	(0.5, 35.9)	1.5
Infectious								
Infection, all	4 (40%)	31 (41.3%)	96 (40.3%)	127 (40.6%)	70 (30.8%)	1.3	(1, 1.7)	11.2
Infection, viral	2 (20%)	5 (6.7%)	25 (10.5%)	30 (9.6%)	13 (5.7%)	1.7	(0.9, 3.1)	4.1
Pneumonia	(0%)	6 (8%)	12 (5%)	18 (5.8%)	2 (0.9%)	6.5	(1.5, 27.9)	4.9
Infection, fungal	(0%)	1 (1.3%)	6 (2.5%)	7 (2.2%)	(0%)	-	-	2.2
Other								
Rash	1 (10%)	5 (6.7%)	30 (12.6%)	35 (11.2%)	7 (3.1%)	3.6	(1.6, 8)	8.2
Hypoxia, respiratory failure	(0%)	2 (2.7%)	8 (3.4%)	10 (3.2%)	3 (1.3%)	2.4	(0.7, 8.7)	1.9

Dr. Unger also explored TEAEs in the uncontrolled patient population and did not identify any new safety signals.

Laboratory Findings

There were notable changes in hemoglobin/hematocrit, creatinine clearance, and liver function tests that are described further below. There were no notable changes in other hematology or chemistry laboratory values.

Decreases in hemoglobin and hematocrit

There was a small decrease in hemoglobin and hematocrit, with normal red blood cell indices, that was seen in patients taking CBD, but not those on placebo. The change is small; however, Dr. Unger recommends that it be described in labeling so that prescribers can be aware of the potential for anemia and manage patients appropriately.

Creatinine Clearance

The applicant calculated creatinine clearance using the Schwartz formula for subjects under the age of 18, and using the Cockcroft-Gault equation for older subjects. Decreases in creatinine clearance were identified in Table 17 below. There were no notable changes in BUN.

Table 17: Renal parameters in the controlled safety dataset

		Cannabidiol n=323	Placebo n=227
Creatinine Jaffe (mean ± SD) µmol/L	Baseline	42.4 ± 15.8 (n=323)	44.1 ± 19.1 (n=227)
	Δ from baseline to end-of-treatment	3.5 ± 8.5 (n=293)	1.5 ± 8.4 (n=210)
BUN (mean ± SD) µmol/L	Baseline	4.6 ± 1.6 (n=323)	4.7 ± 1.6 (n=227)
	Δ from baseline to end-of-treatment	0.1 ± 1.5 (n=293)	0.0 ± 1.1 (n=210)
Creatinine clearance Schwartz (mean ± SD) mL/min/1.73 m^2	Baseline	139.0 ± 38.8 (n=248)	139.9 ± 40.4 (n=174)
	Δ from baseline to end-of-treatment	−10.0 ± 26.7 (n=223)	−4.3 ± 26.9 (n=163)
Creatinine clearance Cockroft-Gault (mean ± SD) mL/min/1.73 m^2	Baseline	156.6 ± 52.9 (n=75)	143.6 ± 47.2 (n=53)
	Δ from baseline to end-of-treatment	−14.1 ± 20.7 (n=70)	−1.2 ± 19.7 (n=47)

Source: Applicant's ISS, Table 9.1.2.1.3.2-1

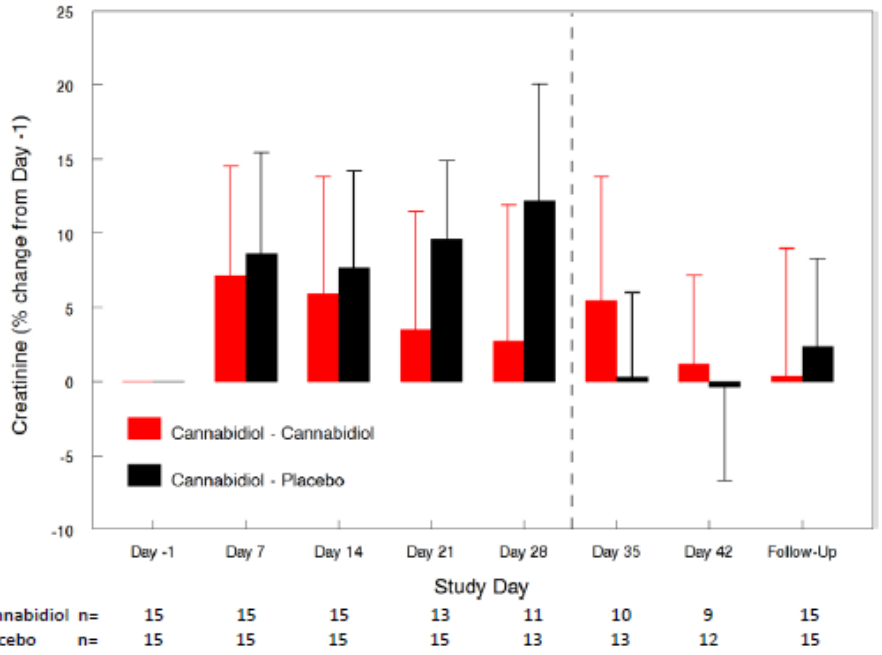
In the ISS, the applicant identified the changes, but noted that the majority of patients remained within normal range for creatinine clearance, so they felt that the finding was not clinically significant and should not be described in labeling.

To further investigate the signal, Dr. Unger performed an analysis of data from Study 1542, a double-blind randomized withdrawal study conducted in healthy adult subjects, to evaluate potential adverse effects of CBD withdrawal. Thirty (30) subjects received CBD 750 mg twice daily for 4 weeks, followed by a randomized withdrawal where 15 subjects were continued on CBD for 2 weeks, and 15 subjects were switched abruptly to placebo. As can be seen in

Figure 6, creatinine levels increase by approximately 8% within one week of starting CBD, and rapidly decrease following withdrawal of CBD after day 28. Those who continued to receive CBD also showed reduction in creatinine over time. This demonstrates that the effects on creatinine appear to be reversible.

The current laboratory findings appear to represent an acute change that is reversible and do not indicate a nephrotoxic process. Additionally, Dr. Unger reviewed renal adverse events and did not identify any events that suggest a direct toxicity to the kidneys.

Figure 6: Study 1542- Changes in Creatinine with treatment and withdrawal of cannabidiol



A consultation was requested from the Division of Cardiovascular and Renal Products to evaluate these findings. The consultants noted some concerns with the creatinine clearance values; however, the applicant confirmed the validity of the findings. Nonetheless, there does appear to be a real trend of increase in creatinine levels and findings of reversibility noted in the analysis above. The consultants felt that this could represent a hemodynamic effect or possibly an effect of CBD on tubular secretion. Although the clinical significance of these findings is unclear, the consultants recommended that this effect be described in the PI so that prescribers can be aware of these effects and manage patients appropriately. They also suggested conducting a PMR study in healthy adults that includes measurements of GFR (b) (4) to help elucidate the underlying mechanism of this change. Dr. Unger and I agree with the recommendation for a PMR study and inclusion of the description of change in creatinine levels in labeling.

Transaminase elevations

A signal for transaminase elevations was identified during the development program. During a pre-submission meeting, the Agency requested that the applicant have an external expert in liver disease evaluate the liver data for the NDA submission. A liver safety evaluation was conducted by Dr. Paul Watkins and an extensive Liver Safety Report was included in the submission. Dr. Lara Dimick of the Division of Gastroenterology and Inborn Errors Products (DGIEP) and Dr. Mark Avigan of the Office of Surveillance and Epidemiology (OSE) provided a consultation on the liver safety findings during the review. Additionally, an information request was sent to the applicant during the NDA review to request additional information on the management of transaminase elevations during the studies and the applicant submitted a response on February 23, 2018, that was reviewed by the liver consultants.

According to Dr. Unger's review, transaminase elevations were reported as adverse events in 2.6% of patients on placebo, 8% of patients taking CBD 10 mg/kg/day and 15.5% of patients taking CBD 20 mg/kg/day. Some of the elevations were serious [assessed as medically significant or led to hospitalization)(4% in CBD-treated patients vs 0% on placebo), and some were severe (2% in CBD-treated patients vs 0% on placebo)]; however, there were no cases of liver failure, and no deaths due to liver injury. As previously noted in the section on SAEs, there were two cases that were reported as hepatic failure; however, the cases did not have elevations of bilirubin or INR consistent with standard definitions of liver failure.

Review of the laboratory data showed that elevations of ALT were greater than elevations of AST, suggesting that the liver was the source of the transaminase elevations. The majority of ALT elevations were less than 5 times the upper limit of normal (ULN); however, ALT elevations up to 10 times ULN were observed. Although there were small increases from baseline values in bilirubin levels reported in a few cases, the bilirubin levels generally remained within normal limits. No cases met Hy's law criteria (ALT ≥ 3X ULN and bilirubin > 2X ULN). Given the modest overall exposure, it remains possible that there will be patients who could develop such elevations in a post-approval setting.

Table 18 shows Dr. Unger's analysis of ALT elevations by subgroup. The incidence of transaminase elevations was highest in patients taking concomitant VPA and in patients taking the 20 mg/kg/day dosage of CBD. Concomitant use of clobazam was also associated with a higher incidence of transaminase elevations, although to a lesser extent than that seen with VPA. In CBD-treated patients, the incidence of ALT elevations greater than 3 times the ULN was 20% in patients taking concomitant valproic acid (without clobazam), 5% in patients taking concomitant clobazam (without valproic acid), 29% in patients taking both drugs, and 3% in patients taking neither drug.

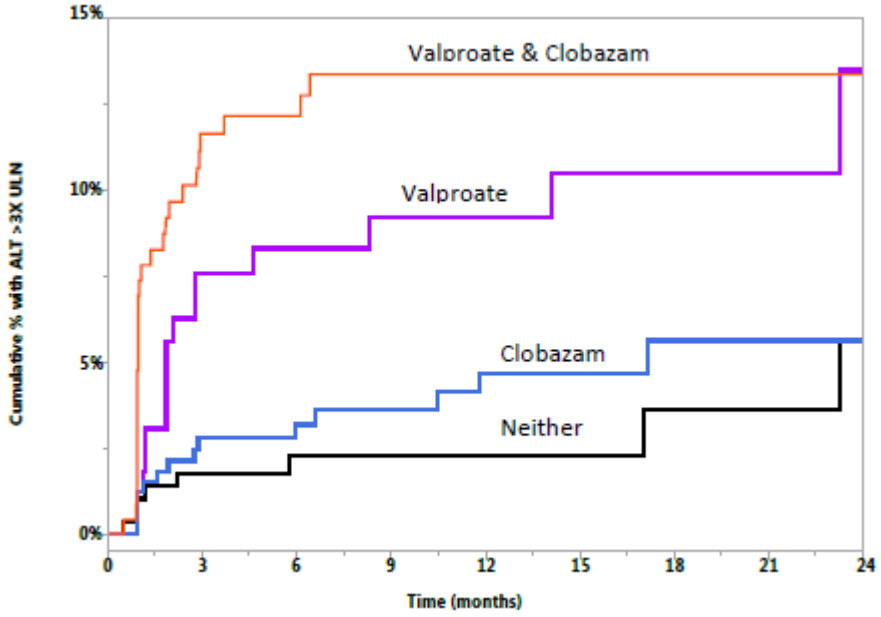
Table 188: ALT Elevation in the Controlled Trial Database by Subgroup

		% of subjects	↑ ALT > 3X ULN CBD	↑ ALT > 3X ULN Placebo	RR	↑ ALT > 5X ULN CBD	↑ ALT > 5X ULN Placebo	RR
All		100%	13%	1%	15.1	7%	1%	7.4
Disease	Dravet	28%	14%	2%	9.0	6%	2%	3.8
	Lennox-Gastaut	72%	13%	1%	21.2	7%	1%	11.0
Age group	2-5 years	16%	14%	3%	5.2	4%	3%	1.5
	6-11 years	36%	15%	0%	-	9%	0%	-
	12-17 years	25%	11%	2%	6.4	8%	2%	4.3
	>= 18 years	23%	13%	1%	15.1	6%	1%	7.4
Sex	Male	54%	16%	0%	-	7%	0%	-
	Female	46%	10%	2%	5.1	5%	2%	2.9
Race	White	85%	14%	1%	13.8	7%	1%	6.7
	Black	4%	7%	0%	-	0%	0%	-
	Asian	2%	0%	0%	-	0%	0%	-
	Other	8%	16%	0%	-	9%	0%	-
Dose	5 mg	3%	10%	1%	11.4	10%	1%	11.4
	10 mg	23%	1%	1%	1.5	1%	1%	1.5
	20 mg	74%	17%	1%	19.6	8%	1%	9.1
Weight quartile*	1	25%	14%	2%	7.3	6%	2%	3.0
	2	25%	10%	0%	-	5%	0%	-
	3	25%	13%	0%	-	7%	0%	-
	4	25%	17%	2%	11.0	8%	2%	5.5
Other AEDs	Valproate (Yes)	45%	24%	1%	23.9	12%	1%	12.0
	Valproate (No)	55%	4%	1%	5.1	2%	1%	2.2
	Clobazem (Yes)	54%	15%	2%	8.9	9%	2%	5.4
	Clobazem (No)	46%	12%	0%	-	4%	0%	-
	On Both	21%	29%	2%	13.4	19%	2%	8.7
	On Neither	23%	3%	0%	-	1%	0%	-

* weight quartiles: <23.23; 23.23 to <34.45; 34.45 to <53.15; >=53.15 kg

In the controlled studies, transaminase elevations were typically seen in the first 2 months of treatment. The open-label extension study and the EAP experience provide information on the occurrence of transaminase elevations with longer durations of treatment. Dr. Unger performed a Kaplan-Meier analysis of the data in Figure 7 that shows that elevations were seen up to 18 months after initiation of therapy, particularly in patients taking VPA.

Figure 7: Time-to-initial ALT Elevation >3X ULN in Uncontrolled studies



The DGIEP/OSE consultation and liver safety report submitted by the applicant were concordant with the findings described in Dr. Unger's review. There was agreement in all reviews that the transaminase elevations appeared to be causally related to CBD, and that higher doses of CBD, concomitant VPA, and possibly concomitant use of clobazam, appear to be risk factors for transaminase elevations. Baseline liver function tests > ULN was also identified as a risk factor for transaminase elevations. The liver consult provided additional assessment of recovery times, management of CBD, and concomitant AEDs in response to transaminase elevations, and rechallenge with CBD that is described below.

In the pivotal studies, liver function tests were generally assessed after 2, 4, 8, and 12 weeks of treatment. Liver function tests were also assessed after 24, 36, and 48 weeks of treatment in the open-label extension study. Patients were withdrawn from the studies for the following criteria:

- ALT or AST > 3 × ULN with (or the appearance of) fatigue, nausea,
- vomiting, right upper quadrant pain or tenderness, fever, rash, and/or
- eosinophilia > 5%.
- ALT or AST > 8 × ULN.
- ALT or AST > 5 × ULN for or more than 2 weeks.
- ALT or AST > 3 × ULN and bilirubin > 2 × ULN or INR > 1.5.

However, it is noted that these criteria were inconsistently applied in the EAP.

In general, most patients "recovered" from the transaminase elevations within two weeks; however, recovery is defined as ALT elevation < 3X ULN, and does not indicate a complete

return to baseline. Of 37 patients in the controlled trials who experienced a ALT elevation > 5X ULN, 17 (45.9%) recovered from the ALT elevation without, or prior to, stopping CBD. Of these, 12 patients recovered without any dose reduction of CBD, and 5 patients recovered after dose reduction or during the taper of CBD. A total of 6 patients had their valproate reduced after such an ALT elevation.

There were 11 patients in the EAP who were rechallenged with CBD following a transaminase elevation that led to discontinuation of CBD for more than two days. Of these, 4 patients experienced a recurrence of the transaminase elevation of similar severity to the preceding event, and 7 patients experienced no recurrence.

There does not appear to be a PK interaction between CBD and VPA, so the mechanism by which VPA increases the risk for transaminase elevations is unclear. However, the liver consult notes the following:

> "…in vitro data suggest that 7-COOH-CBD could cause serum ALT elevations via direct action on hepatic mitochondria at concentrations achieved in vivo. Furthermore, the commonly used antiepileptic drug (AED), valproate, and its metabolite 4-ene-valproic acid, have been implicated as ETC inhibitors. Therefore, a potential interaction effect between CBD and valproate at the level of the mitochondria could underlie observations in the clinical data. This hypothesis is currently being investigated further via additional data collection and simulations in collaboration with (b) (4)

The liver consultants have provided the following recommendations for further evaluation and risk management of the transaminase elevations:

- The indication should be limited to the studied population of patients with LGS or DS (although restricted distribution is not necessary).
- The lowest effective dosage of CBD (10 mg/kg/day) should be used, when possible.
- Product labeling should provide specific recommendations for monitoring transaminases, similar to those used in the clinical studies.
- Labeling should indicate increased risk for transaminase elevations with VPA (Dr. Unger also recommends labeling for increased risk with clobazam.)
- Labeling should include recommendations for dose modification or interruption of treatment with CBD.
- Enhanced pharmacovigilance should be initiated.
- A post-marketing requirement (PMR) for a non-invasive study (e.g., liver ultrasound, biomarkers of liver injury) in CBD users to assess the long-term effects of CBD on the liver should be considered.

Dr. Unger and I agree with these recommendations.

Vital Signs

There were no notable differences in heart rate, blood pressure, or temperature. The frequency of weight decreases (≥ 5%) was 9.3%, 18.5% and 8.4% in the CBD 10 mg/kg/day,

CBD 20 mg/kg/day, and placebo groups, respectively. A similar trend was also noted for body mass index (BMI) decrease. Per Dr. Unger's review, there appeared to be some concordance with patients who reported decreased appetite and decreased weight as an adverse event, as seen in Table 16.

ECG/QT

There were no significant mean effects on the mean QTcB (corrected QT; Bazett's formula), PR, or QRS intervals. Please refer to the Clinical Pharmacology section for a discussion of the TQT study.

Subgroup analyses

Dr. Unger performed an assessment of important safety signals by demographic characteristics, baseline weight, dose, and use/non-use of VPA and clobazam. Diarrhea, weight loss, somnolence/sedation/lethargy, and ALT elevations were all dose-related. Somnolence, sedation, and lethargy occurred more frequently with concomitant clobazam use (44% in patients taking clobazam only compared to 13% in patients taking neither clobazam or VPA).

Other Events of Interest

Hypersensitivity reactions

There were two reports of hypersensitivity reactions in studies with CBD. One case occurred in Study 1414 in an 8 year-old patient with a limited description of the event. The patient continued the study drug and the symptoms resolved. The second case occurred in a healthy adult in the abuse liability study. The subject experienced swelling of the cheeks, generalized redness, and pruritus, all of which were moderate in severity, and occurred approximately 3 hours after receiving CBD. The subject was treated with diphenhydramine. The second case appears consistent with a hypersensitivity reaction. Dr. Unger recommends that "hypersensitivity reactions" be described in the PI. The sponsor has proposed that hypersensitivity reactions be listed as a contraindication in the label.

Suicidal behavior/ideation

The Columbia-Suicide Severity Rating Scale (C-SSRS) was included in the controlled studies. Analysis of the scales did not identify a signal for suicidal ideation or behavior; however, there were two serious adverse events of suicidal ideation or behavior in the EAP.

The applicant has included a warning for suicidal behavior and ideation in the proposed product label, which is a class warning for all drugs for the treatment of seizures. Dr. Unger supports the inclusion of this warning in labeling and I agree.

Abuse Potential

Since CBD is derived from the *Cannabis sativa* plant and is currently a Schedule I drug, a thorough evaluation of the abuse potential was conducted. Dr. Katherine Bonson from the Controlled Substances Staff performed the review of the data to evaluate abuse potential.

Please refer to Dr. Bonson's review for a detailed discussion of the assessment of abuse potential of CBD.

Following are the key findings from Dr. Bonson's review:

- In receptor binding studies with CBD, there was no significant affinity of CBD of cannabinoid (CB1 or CB2) sites or other sites associated with abuse potential (e.g., mu, kappa, or delta).
- Based on the nonclinical studies evaluating general behavior, similarity to THC (tetrad test and drug discrimination study) and ability to produce rewarding effects (self-administration studies), CBD did not demonstrate meaningful abuse-related signals
- In Phase 1 clinical studies, there were no euphoria-related AEs or other abuse-related AEs. Phase 2/3 studies in LGS and DS patients could not be evaluated for abuse-related signals due to the concomitant use of other seizure drugs and the limited capacity of the patients.
- A Phase 1 human abuse potential (HAP) study assessed CBD (750, 1500, and 4500 mg) compared to dronabinol (THC; 10 and 30 mg), alprazolam 2 mg, and placebo.
    - Randomized, double-blind, placebo-controlled, crossover design in healthy recreational polydrug users (n = 40, with 35 completers)
    - CBD at the lower therapeutic dose (750 mg) produced a mean Drug Liking score that did not differentiate statistically from placebo on Drug Liking and was within the acceptable placebo range
    - CBD at 1500 and 4500 mg produced very small increases in mean Drug Liking scores that were statistically significantly different from placebo; however, the mean scores bordered on the placebo range and were substantially lower than the two positive drug controls, THC and alprazolam
    - CBD was not identified as THC or any substance
- A human physical dependence study showed that CBD does not produce withdrawal signs or symptoms three days after drug discontinuation following chronic administration.

Although the HAP study showed that the higher therapeutic dose (1500 mg) and supratherapeutic dose (4500 mg) of CBD produced marginal signals of abuse potential from subjective measures and AEs, Dr. Bonson concluded that the overall evidence suggests that there is little evidence that CBD has meaningful abuse potential.

Pediatric and Assessment of Effects on Growth

Decreased weight was identified as a safety finding, as described above. No other adverse effects on growth and development were identified.

Human Factors

The applicant submitted a Human Factors (HF) Validation Study to assess the use of the 5 ml syringes and an adapter that are co-packaged with the product. The report was reviewed by Dr. Briana Rider in the Division of Medication Error Prevention and Analysis (DMEPA). Please refer to Dr. Rider's review for a detailed discussion of the human factors assessment.

The most concerning failure in the HF study was use errors associated with a critical dose measurement task. The majority of use errors associated with the dose measurement task resulted in ten-fold overdoses and the remainder of the use errors contributed to failure to clear air bubbles, resulting in minor underdose. DMEPA noted that users typically made errors on the first attempt, and were able to learn and correct the mistake on subsequent attempts. DMEPA provided a recommendation to change the language in the instructions for use for more clarity. Based on the applicant's assessment of the root causes, the subjective feedback, the information provided by the review team, and the learning effect demonstrated in the study, DMEPA found the residual risk to be acceptable for this product.

For all other failures, the applicant provided an assessment of each of the use errors observed with essential tasks, including the subjective feedback, root cause analysis, and the proposed mitigations. DMEPA agreed with the mitigation strategies.

It was also identified during the review that the 5 ml syringe that will be co-packaged with CBD will not be capable of measuring the small doses (<1 ml) that may be required for low-weight patients with moderate to severe hepatic impairment. As CBD will be distributed through a specialty pharmacy, the applicant proposes that the specialty pharmacy will distribute 1 ml syringes with the CBD if the prescribed dose is < 1 ml. The applicant provided updated labeling to address this issue. DMEPA agreed with this proposal.

DMEPA recommends approval of the supplement.

Safety Conclusions

Safety data were derived primarily from four controlled trials in LGS and DS, with the open-label extension trial and EAP providing additional supportive data. There was adequate exposure to allow for an assessment of safety. The most commonly observed adverse events in controlled clinical trials that occurred with a greater incidence in CBD-treated patients than on placebo were in the following categories: central nervous system (e.g., somnolence and sedation), gastrointestinal (e.g., decreased appetite and diarrhea), hepatic (e.g., transaminase elevations), and infections (e.g., pneumonia). These events were generally mild to moderate in severity. Serious and/or severe adverse events were generally related to transaminase elevations, somnolence and lethargy, and infections. Discontinuations were greater in CBD-treated patients (9.3%) than on placebo (1.3%), with most of the discontinuations related to transaminase elevations or somnolence. There were 21 deaths in the development program; however, as the patients were generally ill with multiple comorbidities, none of the deaths could be attributed to CBD.

A signal for drug-induced liver toxicity was identified in the controlled trials and in the Expanded Access Program. Frequencies of adverse events of transaminase elevations were 14% and 3% in CBD-treated and placebo subjects, respectively. Some events of transaminase elevation were serious or severe; however, there were no events of liver failure or death related to liver injury. All transaminase elevations resolved, with some resolving during continued treatment with CBD.

Safety Conclusion
The risks associated with CBD are acceptable. Although the risk of liver injury has the potential to be serious, the observed risk can be appropriately managed with inclusion of relevant language in labeling, education of prescribers regarding the risk of transaminase elevation and need for monitoring of liver enzyme levels, and further characterization of the risk in the post-market setting.

9. Advisory Committee Meeting

The Peripheral and Central Nervous System Drugs (PCNS) Advisory Committee met on April 19, 2018, to discuss the efficacy and safety findings from the NDA submission for CBD.

The committee was asked to vote on the following question:

"Is the benefit-risk profile of cannabidiol favorable for the treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome in patients 2 years of age and older?"

The committee voted unanimously (13 Yes, 0 No) that the risk-benefit profile was favorable for CBD for the treatment of seizures associated with LGS and DS.

10. Pediatrics

The studies in LGS and DS were conducted in a pediatric population down to 2 years of age. Issues specific to the pediatric population are discussed within the review. Because the product has orphan designation for both LGS and DS, the Pediatric Research Equity Act (PREA) is not triggered.

11. Other Relevant Regulatory Issues

- No Good Clinical Practice (GCP) issues were identified in Dr. Getzoff's review.
- Dr. Getzoff concludes that the applicant has adequately disclosed financial interests/arrangements with clinical investigators. Dr. Getzoff noted that some of the remunerations to investigators were large; however, there was no evidence that that this influenced data integrity.
- The Office of Scientific Investigations (OSI) has inspected six clinical sites and the applicant. Regulatory compliance violations were noted at two sites; however, OSI feels that the findings are unlikely to impact data reliability. The applicant inspection revealed issues consistent with inadequate oversight and monitoring by the applicant for the three pivotal studies. The applicant and the two sites received a compliance

classification of Voluntary Action Indicated (VAI). Despite these findings, OSI states that "the studies appear to have been conducted adequately and the data generated by these sites and submitted by the applicant appear acceptable in support of the respective indications."

12. Labeling

Labeling negotiations with the sponsor have been completed and the sponsor has accepted all recommended changes.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)
The Division of Risk Management (DRISK) reviewer for this application is Dr. Yasmeen Abou-Sayed. Dr. Abou-Sayed concludes that a risk evaluation and mitigation strategy (REMS) is not necessary for CBD.

Postmarketing Requirements (PMRs) and Commitments (PMCs)
The following studies are recommended as PMRs:

- An embryofetal development study of 7-COOH-cannabidiol in rat.
- A pre- and postnatal development study of 7-COOH-cannabidiol in rat.
- A juvenile animal toxicology study of 7-COOH-cannabidiol in rat.
- A 2-year carcinogenicity study of cannabidiol in mouse.
- A 2-year carcinogenicity study of cannabidiol and 7-COOH-cannabidiol, both directly administered, in rat.
- Assess whether the effect of Epidiolex on serum creatinine reflects an effect on glomerular filtration rate.
- Assess the potential for chronic liver injury with Epidiolex, with evaluation including physical exam, serum/blood biomarkers and other noninvasive measures of liver fibrosis, such as MRI or ultrasound based elastography. Patients should be evaluated yearly for five years.
- Conduct a pregnancy outcomes study using a different study design than provided for in the North American Antiepileptic Drug (NAAED) Pregnancy Registry (for example, a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in women exposed to Epidiolex during pregnancy compared to an unexposed control population.
- A drug-drug interaction trial to evaluate the effects of Epidiolex on the pharmacokinetics of caffeine in healthy volunteers.
- A drug-drug interaction trial to evaluate the effects of Epidiolex on the pharmacokinetics of a sensitive CYP2B6 substrate in healthy volunteers.

- A drug-drug interaction trial to evaluate the effects of Epidiolex on the pharmacokinetics of a sensitive CYP2C9 substrate in healthy volunteers.
- Submit the complete results for the ongoing drug-drug interaction trial to evaluate the effects of a strong CYP2C19 inhibitor on the pharmacokinetics of Epidiolex in healthy volunteers.
- Submit the complete results for the ongoing drug-drug interaction trial to evaluate the effects of a strong CYP3A inhibitor on the pharmacokinetics of Epidiolex in healthy volunteers.
- Submit the complete results for the ongoing drug-drug interaction trial to evaluate the effects of rifampin on the pharmacokinetics of Epidiolex in healthy volunteers.
- A drug-drug interaction trial to evaluate the effects of Epidiolex on the pharmacokinetics of a sensitive UGT1A9 substrate in healthy volunteers.
- A drug-drug interaction trial to evaluate the effects of Epidiolex on the pharmacokinetics of a sensitive UGTB7 substrate in healthy volunteers.
- A thorough QT trial at the maximum tolerable dose of Epidiolex that is feasible (e.g. dosing in the fed state), with appropriate controls (i.e., placebo and positive control).

Additional comments will be conveyed to the applicant regarding recommended enhanced postmarketing pharmacovigilance, as described in Section 14 of this review.

14. Recommended Comments to the Applicant

We request that you perform postmarketing surveillance for liver toxicity after exposure to Epidiolex. Submit 15-day expedited reports to the Division of Neurology Products and to the NDA with sufficient data to assess causality including duration of Epidiolex administration, symptoms, whether the patient was hospitalized or had organ dysfunction, failure, transplant, or death. Include comprehensive summaries and analyses of these events quarterly as part of your required postmarketing safety reports [e.g., periodic safety update reports (PSURs)]. In the analysis of each case, provide an assessment of causality, with documentation of risk factors and results of all assessments that support the diagnosis or the causality, along with duration of Epidiolex therapy, concomitant therapies, treatment given for the event, range of severity, and of each event, and incidence.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TERESA J BURACCHIO
06/25/2018

WILLIAM H Dunn
06/25/2018

ELLIS F UNGER on behalf of ROBERT TEMPLE
06/25/2018

IV. Notice of Hearing Under 21 CFR Part 15

The Commissioner of Food and Drugs is announcing that the public hearing will be held in accordance with part 15 (21 CFR part 15). The hearing will be conducted by a presiding officer, who will be accompanied by FDA senior management from the Office of the Commissioner, the Center for Devices and Radiological Health, the Center for Drug Evaluation and Research, and the Office of the Chief Counsel. Under § 15.30(f) (21 CFR 15.30(f)), the hearing is informal, and the rules of evidence do not apply. No participant may interrupt the presentation of another participant. Public hearings under part 15 are subject to FDA's policy and procedures for electronic media coverage of FDA's public administrative proceedings (21 CFR part 10, subpart C). Under 21 CFR 10.205, representatives of the media may be permitted, subject to certain limitations, to videotape, film, or otherwise record FDA's public administrative proceedings, including presentations by participants. Persons attending FDA's hearings are advised that the Agency is not responsible for providing access to electrical outlets. The hearing will be transcribed as stipulated in § 15.30(b) (see *Transcripts*). To the extent that the conditions for the hearing, as described in this notification, conflict with any provisions set out in part 15, this notification acts as a waiver of those provisions as specified in § 15.30(h).

Dated: March 28, 2019.

Lowell J. Schiller,

Acting Associate Commissioner for Policy.

[FR Doc. 2019–06438 Filed 4–2–19; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 15

[Docket No. FDA–2019–N–1482]

Scientific Data and Information About Products Containing Cannabis or Cannabis-Derived Compounds; Public Hearing; Request for Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of public hearing; request for comments.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is announcing a public hearing to obtain scientific data and information about the safety, manufacturing, product quality, marketing, labeling, and sale of products containing cannabis or cannabis-derived compounds.

DATES: The public hearing will be held on May 31, 2019, from 8 a.m. to 6 p.m. Submit requests to make oral presentations and comments at the public hearing by May 10, 2019. Electronic or written comments will be accepted until July 2, 2019. See the **SUPPLEMENTARY INFORMATION** section for registration and information.

ADDRESSES: The public hearing will be held at FDA White Oak Campus,10903 New Hampshire Ave., Building 31 Conference Center, the Great Room (Rm. 1503), Silver Spring, MD 20993. Entrance for the public hearing participants (non-FDA employees) is through Building 1, where routine security check procedures will be performed. For parking and security information, please refer to *https://www.fda.gov/AboutFDA/WorkingatFDA/BuildingsandFacilities/WhiteOakCampusInformation/ucm241740.htm*.

FDA is establishing a docket for public comment on this hearing. The docket number is FDA–2019–N–1482. The docket will close on July 2, 2019. Submit either electronic or written comments on this public hearing by July 2, 2019. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before July 2, 2019. The *https://www.regulations.gov* electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of July 2, 2019. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal: https://www.regulations.gov.* Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to *https://www.regulations.gov* will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on *https://www.regulations.gov.*
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- *Mail/Hand delivery/Courier (for written/paper submissions):* Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA–2019–N–1482 for "Scientific Data and Information about Products Containing Cannabis or Cannabis-Derived Compounds; Public Hearing; Request for Comments." Received comments, those filed in a timely manner (see **ADDRESSES**), will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at *https://www.regulations.gov* or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in our consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on *https://www.regulations.gov.* Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked

as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: *https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf.*

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to *https://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Beth F. Fritsch, Food and Drug Administration, 10903 New Hampshire Ave. Bldg. 32, Rm. 5308, Silver Spring, MD 20993, 301–796–8451, *StakeholderEngagement@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION:

I. Background and Purpose of Hearing

Cannabis is a plant of the Cannabaceae family and contains more than 80 biologically active chemical compounds. The most commonly known compounds are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Parts of the *Cannabis sativa* plant have been controlled under the Federal Controlled Substances Act (CSA) since 1970 under the drug class "Marihuana" (21 U.S.C. 802(16)).[1] "Marihuana" is listed in Schedule I of the CSA due to its high potential for abuse, which is attributable in large part to the psychoactive effects of THC, and the absence of a currently accepted medical use for marijuana in the United States. Cannabis and cannabis-derived products have been the subject of increasing interest by consumers, industry, researchers, the public, and regulators. Regulatory oversight of products containing cannabis or cannabis-derived compounds is complex and involves multiple Federal and State agencies.

The legality of cannabis has been changing over time at both the State and Federal levels. Currently, 33 States and Washington, DC, allow "medical" use of marijuana under State law and 14 additional States have State law "medical" programs that are limited to CBD products. In addition, 10 States and Washington, DC, have legalized marijuana for recreational use under State law, and 13 additional States have decriminalized recreational marijuana possession under State law in some form.

At the Federal level, the Agriculture Improvement Act of 2018, Public Law 115–334 (the 2018 Farm Bill), was signed into law on December 20, 2018. Among other things, this new law changes certain Federal authorities relating to the production and marketing of hemp, defined as the plant *Cannabis sativa L.* and any part of that plant, including the seeds thereof and all derivatives, extracts, cannabinoids, isomers, acids, salts, and salts of isomers, whether growing or not, with a delta-9 tetrahydrocannabinol concentration of not more than 0.3 percent on a dry weight basis. These changes include removing hemp from the CSA, which means that cannabis plants and derivatives that contain no more than 0.3 percent THC on a dry weight basis are no longer controlled substances under Federal law.

The 2018 Farm Bill explicitly preserved FDA's 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.[2] In doing so, Congress recognized FDA's important public health role with respect to all the products it regulates. Therefore, because the 2018 Farm Bill did not change FDA's authorities, cannabis and cannabis-derived products are subject to the same authorities and requirements as FDA-regulated products containing any other substance, regardless of whether the products fall within the definition of "hemp" under the 2018 Farm Bill.

FDA is aware that some companies are marketing products containing cannabis and cannabis-derived compounds in ways that violate the FD&C Act. FDA has taken action against companies illegally selling cannabis and cannabis-derived products that put the health and safety of consumers at risk. For example, FDA has issued warning letters[3] to companies illegally selling CBD products that were intended to prevent, diagnose, mitigate, treat, or cure serious diseases, such as cancer, and that had not obtained new drug approvals. Selling unapproved drug products with unsubstantiated therapeutic claims is not only a violation of the law, but also can put patients at risk as the marketing of unproven treatments raises significant public health concerns. Patients and other consumers may be influenced not to use approved therapies to treat serious and even fatal diseases.

FDA's warning letters also cited food products to which CBD had been added and CBD products marketed as dietary supplements. As discussed below, under current law, such products violate the FD&C Act because CBD is an active ingredient in an approved drug and has been the subject of substantial clinical investigations. Allowing drug ingredients in foods can undermine the drug approval process and diminish commercial incentives for further clinical study of the relevant drug substance. It also raises questions about the safety to consumers of exposure from broader consumption of such ingredients.

While the use of cannabis and cannabis-derived products, including hemp and hemp-derived products, has increased dramatically in recent years, questions remain regarding the safety considerations raised by the widespread use of these products. These questions could impact the approaches we consider taking in regulating the development and marketing of products. For example, a 2017 report by the National Academies of Sciences, Engineering, and Medicine[4] reviewed the scientific literature published since 1999 about what is known about the health impacts of cannabis and cannabis-derived products and identified the need for additional research. In addition, during its review of the marketing application for EPIDIOLEX, a CBD oral solution indicated for the treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome in patients 2 years of age and older that was approved in 2018, FDA identified certain safety concerns (see FDA's drug approval package at: *https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210365Orig1s000TOC.cfm*). Specifically, at doses of 20

[1] Under the CSA, 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 a term does not include hemp or 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.

[2] For a discussion of FDA's legal authorities, see section IV of this notice.

[3] *https://www.fda.gov/NewsEvents/PublicHealthFocus/ucm484109.htm.*

[4] *http://www.nationalacademies.org/hmd/Reports/2017/health-effects-of-cannabis-and-cannabinoids.aspx.*

milligrams per kilogram of body weight per day (mg/kg/day) of EPIDIOLEX in clinical trials, there was a potential for liver injury, evidenced by elevated transaminase levels. This is a potentially serious risk that can be managed when the product is taken under medical supervision in accordance with the FDA approved labeling for the product, but it is less clear how this risk might be managed if this substance is used far more widely, without medical supervision, and not in accordance with FDA-approved labeling. Other serious treatment-emergent adverse events reported in clinical studies of EPIDIOLEX included somnolence and lethargy; and hypersensitivity reactions. Common adverse reactions included decreased appetite, diarrhea, and sleep disorders.

Given the substantial interest in this topic and Congressional interest in fostering the development of appropriate hemp products under the 2018 Farm Bill, while also preserving FDA's ability to protect the public health, FDA is holding a public hearing. The goal of the hearing is to obtain additional scientific data and other information related to cannabis and cannabis-derived compounds, both from botanical and synthetic sources, to inform our regulatory oversight of these products. FDA does not intend for this hearing to produce any decisions or new positions on specific regulatory questions, but this hearing is expected to be an important step in our continued evaluation of cannabis and cannabis-derived compounds in FDA-regulated products.

II. Participating in the Public Hearing

Registration: To register to attend the public hearing, either in person or by webcast, on "Scientific Data and Information about Products Containing Cannabis or Cannabis-Derived Compounds" please register at *https://www.fda.gov/NewsEvents/MeetingsConferencesWorkshops/ucm634550.htm*. Please provide complete contact information for each attendee, including name, title, affiliation, address, email, and telephone and whether you want to attend in person or by webcast.

Request for Presentations: During online registration, you may indicate if you wish to make a formal presentation (with accompanying slide deck) or present oral comments during the public hearing session (with no slide deck) and which topic(s) you would like to address. FDA will do its best to accommodate requests to make public presentations. We are seeking to have a broad representation of ideas and issues presented at the meeting. Individuals and organizations with common interests are urged to consolidate or coordinate their presentations. Following the close of registration, FDA will determine the amount of time allotted to each presenter and the approximate time each presentation is to begin and will select and notify participants by May 21, 2019. All requests to make presentations must be received by the close of registration on May 10, 2019, Eastern Time.

If selected for a formal oral presentation (with a slide deck), each presenter must submit an electronic copy of their presentation (PowerPoint or PDF) to *Stakeholderengagement@fda.hhs.gov* with the subject line "Scientific Data and Information about Products Containing Cannabis or Cannabis-Derived Compounds" on or before May 28, 2019. No commercial or promotional material will be permitted to be presented or distributed at the public hearing.

Persons notified that they will be presenters are encouraged to arrive at the hearing room early and check in at the onsite registration table to confirm their designated presentation time. Actual presentation times may vary based on how the meeting progresses in real time. An agenda for the hearing and any other background materials will be made available 5 days before the hearing at *https://www.fda.gov/NewsEvents/MeetingsConferencesWorkshops/ucm634550.htm*.

Those without internet or email access can register and/or request to participate by contacting Beth F. Fritsch by the above dates (see **FOR FURTHER INFORMATION CONTACT**).

Streaming Webcast of the Public Hearing: For those unable to attend in person, FDA will provide a live webcast of the hearing. To join the hearing via the webcast, please go to *https://collaboration.fda.gov/cannabispart15*.

Transcripts: Please be advised that as soon as a transcript is available, it will be accessible at *https://www.fda.gov/NewsEvents/MeetingsConferencesWorkshops/ucm634550.htm*. It may be viewed at the Dockets Management Staff (see **ADDRESSES**) and also will be available at *https://www.regulations.gov*.

III. Issues for Consideration and Request for Data and Information

We encourage public comments and presentations at the public hearing. In submitting comments, data, and information to the docket, please identify available references for the data and information, as well as the general category area and specific question number listed below.

A. Health and Safety Risks

As noted above, there are many unanswered questions about the safety of cannabis and cannabis-derived products. To inform FDA's regulatory oversight of these products, especially as we consider whether it is appropriate to exercise our authority to allow the use of CBD in dietary supplements and other foods, we are interested in obtaining information, including data and studies, on, among other things:

1. Based on what is known about the safety of products containing cannabis and cannabis-derived compounds, are there particular safety concerns that FDA should consider regarding its regulatory oversight and monitoring of these products? For example:
   - What levels of cannabis and cannabis-derived compounds cause safety concerns?
   - How does the mode of delivery (*e.g.*, ingestion, absorption, inhalation) affect the safety and exposure to cannabis and cannabis-derived compounds?
   - How do cannabis and cannabis-derived compounds interact with other substances (*e.g.*, drug ingredients)?
2. Are there special human populations (*e.g.*, children, adolescents, pregnant and lactating women) or animal populations (*e.g.* species, breed, or class) that should be considered when assessing the safety of products containing cannabis and cannabis-derived compounds?
3. What are the characteristics of a successful system to collect representative safety information at the national or State level about products containing cannabis and cannabis-derived compounds?
   - Are there systems that currently exist for the collection of this information (other than FDA's systems)?
   - Are there particular safety concerns related to the overlap of therapeutic dose levels from approved drug products, with potential exposure from other uses (*e.g.*, from food, dietary supplements, cosmetics)? Please identify any safety concerns and include relevant data or studies.
4. What endpoints or outcomes would define a maximal acceptable daily intake from all products?
   - What margin of exposure would represent an appropriate and safe level from anticipated cumulative exposure? Does that margin of exposure vary based on the form of consumption (*e.g.*, from ingestion, absorption, inhalation)? Please explain your reasoning and include relevant data or studies.

- What mechanisms would be available to help ensure that this margin of exposure was maintained at a level sufficiently protective of public health?

5. Are there any data known that would support the safe use of cannabis and cannabis-related compounds in general food use (including dietary supplements), including data regarding exposure levels to cannabis and cannabis-related compounds in foods (including dietary supplements) that would be acceptable from a food safety perspective?

- What data are available about residues of cannabis-derived compounds in human foods (*e.g.*, meat, milk, or eggs) that come from animals that consume cannabis or cannabis-derived compounds? Are there residue levels that should be tolerated in these foods? Please provide data or other information to support your reasoning.

6. How does the existing commercial availability of food products containing cannabis-derived compounds such as CBD (which may in some cases be lawful at the State level but not the Federal level) affect the incentives for, and the feasibility of, drug-development programs involving such compounds?

- How would the incentives for, and the feasibility of, drug development be affected if food products containing cannabis-derived compounds, such as CBD, were to become widely commercially available? How would this change if FDA established thresholds on acceptable levels of cannabinoids, including CBD, in the non-drug products it regulates? What else could FDA do to support drug development from cannabinoids?

B. Manufacturing and Product Quality

Please provide data and information on how products containing cannabis or cannabis-derived compounds (other than those marketed as drugs in compliance with the FD&C Act) are currently manufactured, including information about methods for ensuring product quality and consistency. More specifically, we are interested in obtaining information on, among other things:

1. Are there particular standards needed to address any safety issues related to the manufacturing, processing, and holding of products containing cannabis and cannabis-derived compounds (*e.g.*, genotoxic impurities, degradation of active compounds)? Please identify or describe those standards.

2. Are there particular standards or processes needed to ensure manufacturing quality and consistency of products containing cannabis or cannabis-derived compounds, including standards applied to evaluate product quality? Please identify or describe those standards.

3. What validated analytical testing is needed to support the manufacturing of safe and consistent products?

4. Are there any currently used standardized definitions for the ingredients in cannabis products (*e.g.*, "hemp oil")? If standardized definitions would be helpful, what terms should be defined and what should the definition(s) be?

5. What are the functional purposes of adding cannabis-derived compounds, such as CBD, to foods (*e.g.*, nutritive value, technical effect), both in terms of manufacturer intent and consumer perceptions and/or expectations? To the extent a compound is added to food to achieve a particular functional purpose, what evidentiary support is available to demonstrate that the addition of such compound has the intended or perceived effect?

C. Marketing/Labeling/Sales

FDA is interested in information about how products containing cannabis or cannabis-derived compounds, other than drug products approved by FDA for human or animal use, are marketed, labeled, and sold. More specifically, we seek information on, among other things:

1. How should consumers be informed about the risks associated with such products (*e.g.*, directions for use, warnings)? What specific risks should consumers be informed about? Are there any subpopulations for which additional warnings or restrictions are appropriate? Please explain your reasoning.

2. What conditions, restrictions, or other limitations on the manufacturing and distribution of these products have been put in place under State or local law, particularly with respect to food products containing cannabis-derived compounds such as CBD (which may, in some cases, be lawful at the State level but not the Federal level)? What other conditions, restrictions, or other limitations might be appropriate to ensure adequate consumer information and to protect the public health?

3. What statutory or regulatory restrictions are in place under State or local law to warn about the use of these products by certain vulnerable human populations (*e.g.*, children, adolescents, pregnant and lactating women) or animal populations (*e.g.* species, breed, or class)? Are there other steps that should be taken to warn about use by vulnerable populations? Please identify such steps and how they would apply to a particular subpopulation.

4. What other information should FDA consider in the labeling of specific product categories of cannabis and cannabis-derived products?

IV. FDA Legal Authorities

There are FD&C Act provisions that are relevant to the legality of cannabis or cannabis-derived products. To help in understanding the context of the public hearing and current FDA actions, a synopsis of FDA legal authorities is provided below.

A. Human Drugs

A drug is an article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals (section 201(g) of the FD&C Act (21 U.S.C. 321(g)). A drug is also defined as an article (other than food) intended to affect the structure or any function of the body of man or other animals. Thus, the determination of whether a product is a drug turns in part on the "intended use" of the product.

By statute, it is a prohibited act to introduce a new drug into interstate commerce unless it has an approved marketing application (New Drug Application (NDA) or Abbreviated New Drug Application (ANDA)) (section 301(d) of the FD&C Act (21 U.S.C. 331(d)). FDA reviews the data submitted in a marketing application to evaluate whether a drug product meets the statutory standards for approval. To conduct clinical research that can lead to an approved new drug, including research using materials from plants such as cannabis, researchers submit an Investigational New Drug (IND) application to FDA, as described in 21 CFR part 312.

FDA has approved several drug products that contain compounds found in cannabis. Most recently, FDA has approved EPIDIOLEX,[5] which contains the purified drug substance CBD for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older. We also have approved MARINOL and SYNDROS for therapeutic uses in the United States, including for the treatment of anorexia associated with weight loss in AIDS patients. MARINOL and SYNDROS include the active ingredient dronabinol, a synthetic THC which is considered the psychoactive component of marijuana. Another FDA-approved drug, CESAMET, contains the active ingredient nabilone, which has a

[5] *https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210365Orig1s000TOC.cfm.*

chemical structure similar to THC and is synthetically derived.

B. Human Foods/Dietary Supplements

By statute, any substance intentionally added to food is a food additive, and therefore subject to premarket review and approval by FDA, unless the substance is generally recognized as safe (GRAS) by qualified experts under the conditions of its intended use, or the use of the substance is otherwise excepted from the definition of a food additive (sections 201(s) and 409 of the FD&C Act (21 U.S.C. 321(s) and 348)). Three hemp seed ingredients—hulled hemp seeds, hemp seed protein, and hemp seed oil—have gone through the FDA GRAS process and can be legally marketed in human foods for certain uses without food additive approval, provided they comply with all other requirements. More specifically, these three ingredients were the subject of a GRAS notice in which the submitter concluded that the ingredients were GRAS for specific uses in human foods. FDA evaluated these notices and had no questions [6] regarding the submitter's conclusions.

No other cannabis-derived compounds have been the subject of a food additive petition, an evaluated GRAS petition, or have otherwise been approved for use in food by FDA. Food companies that wish to use cannabis or cannabis-derived compounds in their foods are subject to the relevant laws and regulations that relate to the food additive [7] and GRAS [8] processes.

In addition, it is prohibited by statute to introduce or deliver for introduction into interstate commerce any food (including any animal food) to which has been added a substance which is an active ingredient in a drug product approved under section 505 of the FD&C Act (21 U.S.C. 355) or a drug for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public (section 301(*ll*) of the FD&C Act (21 U.S.C. 331(*ll*)). There are exceptions, including when the drug was marketed in food before the drug was approved or before the substantial clinical investigations involving the drug had been instituted or, in the case of animal food, that the drug is a new animal drug approved for use in animal food and used according to the approved labeling. Based on available evidence, FDA has concluded [9] that it is a prohibited act to introduce or deliver for introduction into interstate commerce any food (including any animal food) to which THC or CBD has been added. When this statutory prohibition applies to a substance, the substance cannot be added to any food that is sold into interstate commerce unless the Secretary of the Department of Health and Human Services (the Secretary),[10] in the Secretary's discretion, has issued a regulation approving the use of the substance in the food (section 301(*ll*)(2) of the FD&C Act. To date, no such regulation has been issued for any substance.

For similar reasons, FDA has determined that products that contain THC or CBD cannot be marketed as dietary supplements.[11] By statute, if an ingredient is approved as a new drug under section 505 of the FD&C Act or has been authorized for investigation as a new drug for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, then products containing that substance are excluded from the statutory definition of a dietary supplement (sections 201(ff)(3)(B)(i) and (ii) of the FD&C Act. There is an exception if the substance was "marketed as" a dietary supplement or as a food before the new drug investigations were authorized. Based on available evidence, FDA has concluded that this is not the case for THC or CBD. There is also an exception if FDA has issued a regulation finding that the article would be lawful under the FD&C Act (section 201(ff)(3)(B) of the FD&C Act). At this time, no such regulation has been issued.

Some ingredients are derived from parts of the cannabis plant that may not contain THC or CBD, in which case those ingredients might fall outside the scope of this exclusion, and therefore might be able to be marketed as dietary supplements. However, the product must still comply with all other applicable laws and regulations governing dietary supplement products. For example, manufacturers and distributors who wish to market dietary supplements that contain "new dietary ingredients" (*i.e.*, dietary ingredients that were not marketed in the United States in a dietary supplement before October 15, 1994) generally must notify FDA [12] about these ingredients (section 413(d) of the FD&C Act (21 U.S.C. 350b(d)). Generally, the notification must include information demonstrating that a dietary supplement containing a new dietary ingredient will reasonably be expected to be safe under the conditions of use recommended or suggested in the labeling. A dietary supplement is adulterated if it contains a new dietary ingredient for which there is inadequate information to provide reasonable assurance that the ingredient does not present a significant or unreasonable risk of illness or injury (section 402(f)(1)(B) of the FD&C Act (21 U.S.C. 342(f)(1)(B)).

Numerous other legal requirements apply to food and dietary supplement products, including requirements relating to CGMPs, labeling, allergens, and various provisions of the FDA Food Safety Modernization Act. Information about these requirements, and about FDA requirements across all product areas, can be found on FDA's website, *https://www.fda.gov.*

C. Animal Food and Drugs

FDA regulates animal food in a variety of ways, including by approving safe food additives and establishing standards for animal food contaminants. FDA has not reviewed any food additive petitions for cannabis-derived animal feed, nor have any cannabis-derived feed ingredients been the subject of a GRAS determination by FDA, a GRAS notice that underwent FDA evaluation and received a "no questions" response, or otherwise been approved for use in animal feed by FDA. Animal food companies that wish to use cannabis or cannabis-derived compounds in their animal food products are subject to the relevant laws and regulations that relate to the food additive and GRAS processes. With respect to THC and CBD specifically, as discussed above, it is a prohibited act under section 301(*ll*) of the FD&C Act, to introduce or deliver for introduction into interstate commerce any animal food to which THC or CBD has been added.

As stated above, a drug is an article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals (section 201(g) of the FD&C Act. A drug is also defined as an article (other than food) intended to affect the structure or any function of the body of man or other animals. Thus, the determination of whether a product is a drug turns in part on the "intended use" of the product.

[6] *https://www.fda.gov/Food/NewsEvents/ConstituentUpdates/ucm628910.htm.*

[7] *https://www.fda.gov/Food/IngredientsPackagingLabeling/FoodAdditivesIngredients/default.htm.*

[8] *https://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/.*

[9] *https://www.fda.gov/newsevents/publichealthfocus/ucm421168.htm#legal.*

[10] The authority to make this determination has been delegated to FDA.

[11] *https://www.fda.gov/newsevents/publichealthfocus/ucm421168.htm#dietary_supplements.*

[12] *https://www.fda.gov/Food/DietarySupplements/NewDietaryIngredientsNotificationProcess/ucm109764.htm.*

Currently, there are no legally marketed new animal drugs that contain cannabis or cannabis-derived compounds. A new animal drug is deemed "unsafe" under section 512(a) of the FD&C Act (21 U.S.C. 360b(a)), and may not be sold into interstate commerce under section 301(a) of the FD&C Act), unless it has an approved new animal drug application (NADA), abbreviated NADA (ANADA), conditional approval (CNADA) or index listing. FDA reviews the data submitted in a marketing application to evaluate whether an animal drug product meets the statutory standards for approval. To conduct clinical research that can lead to an approved new animal drug, including research using materials from plants such as cannabis, researchers establish an Investigational New Animal Drug (INAD) file with FDA, and comply with the requirements described in 21 CFR part 511.

D. Cosmetics

Under the FD&C Act, cosmetic products and ingredients are not subject to premarket approval by FDA, except for most color additives. Certain cosmetic ingredients are prohibited or restricted by regulation,[13] but currently that is not the case for any cannabis or cannabis-derived ingredients. Ingredients not specifically addressed by regulation must nonetheless comply with all applicable requirements, and no ingredient—including a cannabis or cannabis-derived ingredient—can be used in a cosmetic if it causes the product to be adulterated or misbranded in any way. A cosmetic generally is adulterated if it bears or contains any poisonous or deleterious substance which may render it injurious to users under the conditions of use prescribed in the labeling, or under such conditions of use as are customary or usual (section 601(a) of the FD&C Act (21 U.S.C. 361(a)).

E. Tobacco Products

The Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) (Pub. L. 111–31) was enacted on June 22, 2009, amending the FD&C Act and providing FDA with the authority to regulate tobacco products. Specifically, the Tobacco Control Act amends the FD&C Act by adding a new chapter that provides FDA with authority over tobacco products. Section 901(b) of the FD&C Act (21 U.S.C. 387a(b)), as amended by the Tobacco Control Act, states that the new chapter in the FD&C Act (chapter IX—Tobacco Products) (21 U.S.C. 387 through 387u) applies to all cigarettes, cigarette tobacco, roll-your-own tobacco, smokeless tobacco, and any other tobacco products that the Secretary by regulation deems to be subject to chapter IX. In the **Federal Register** of May 10, 2016 (81 FR 28973), FDA issued a final rule deeming all products that meet the statutory definition of "tobacco product" in section 201(rr) of the FD&C Act (21 U.S.C. 321(rr)), except accessories of deemed tobacco products, to be subject to FDA's tobacco product authority (the deeming rule). The products now subject to FDA's tobacco product authority include electronic nicotine delivery systems (sometimes referred to as vapes, vaporizers, or electronic cigarettes, among other terms), cigars, waterpipes (hookah), pipe tobacco, nicotine gels, dissolvables that were not already subject to the FD&C Act, and other tobacco products that meet the statutory definition of "tobacco product" (other than accessories) that may be developed in the future. The term "tobacco product" means any product made or derived from tobacco that is intended for human consumption, including any component, part, or accessory of a tobacco product (except for raw materials other than tobacco used in manufacturing a component, part, or accessory of a tobacco product) (section 201(rr)(1) of the FD&C Act. For example, an e-liquid mixture that contains both a cannabis-derived ingredient and nicotine made or derived from tobacco, and that is intended for human consumption, would likely be subject to FDA's chapter IX authorities.

Numerous legal requirements apply to tobacco products, including legal requirements that relate to new tobacco products that are to be introduced, or delivered for introduction into interstate commerce. Other requirements relate to registration and listing, and sales and distribution, among other things. For more information on these topics, including the statutory standards that must be met for FDA to permit new tobacco products to be marketed, we encourage interested parties to go to the Center for Tobacco Products' web page at *https://www.fda.gov/TobaccoProducts/Labeling/RulesRegulationsGuidance/ucm246129.htm.*

F. Medical Devices

An article is a device if it is an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar related article which is intended for use in the diagnosis of disease or other conditions, or in the cure mitigation, treatment, or prevention of disease, or is intended to affect the structure or any function of the body of man (section 201(h) of the FD&C Act). A device is also defined as not achieving its primary intended purposes through chemical action in or on the body of man and which is not dependent upon being metabolized for the achievement of its primary intended purpose (Id.). For example, an article that is used to aid intake of a product that contains cannabis or a cannabis-derived compound could be properly classified as a device if it meets all aspects of the above definition.

The FD&C Act establishes a comprehensive system for the regulation of medical devices intended for human use. The FD&C Act categorizes medical devices into one of three classes based on their risks and the extent of the regulatory controls needed to provide reasonable assurance of their safety and effectiveness (see section 513 of the FD&C Act (21 U.S.C. 360c)). The three categories of devices are class I (general controls), class II (special controls), and class III (premarket approval). Class I devices generally pose the lowest risk to the patient and/or user and class III devices pose the highest risk.

The class to which a device is assigned determines, among other things, the type of premarket submission required for FDA authorization to market. In general, if a device is classified as class I or II, and if it is not exempt, manufacturers must obtain FDA clearance of a premarket notification (also referred to as a 510(k) submission) (see sections 510(k) and 513(i) of the FD&C Act (21 U.S.C. 360(k) and 360c(i))). For class III devices, manufacturers generally must obtain FDA approval of a premarket approval application (PMA) (see section 515 of the FD&C Act (21 U.S.C. 360e)). It is a prohibited act to market a device without its requisite premarket approval (see section 501(f)(1) of the FD&C Act (21 U.S.C. 351)).

V. Notice of Hearing Under 21 CFR Part 15

The Commissioner of Food and Drugs is announcing that this public hearing will be held in accordance with part 15 (21 CFR part 15). The hearing will be conducted by a presiding officer, who will be accompanied by FDA senior management from relevant program areas. Under § 15.30(f), the hearing is informal and the rules of evidence do not apply. No participant may interrupt the presentation of another participant. Only the presiding officer and panel members can pose questions; they can question any person during or at the

[13] *https://www.fda.gov/Cosmetics/GuidanceRegulation/LawsRegulations/ucm127406.htm.*

conclusion of each presentation. Public hearings under part 15 are subject to FDA's policy and procedures for electronic media coverage of FDA's public administrative proceedings (21 CFR part 10, subpart C).

Under § 10.205, representatives of the media may be permitted, subject to certain limitations, to videotape, film, or otherwise record FDA's public administrative proceedings, including presentations by participants. Persons attending FDA's public hearings are advised that FDA is not responsible for providing access to electrical outlets.

The hearing will be transcribed as stipulated in § 15.30(b) (see **SUPPLEMENTARY INFORMATION**). To the extent that the conditions for the hearing, as described in this notice, conflict with any provisions set out in part 15, this notice acts as a waiver of those provisions as specified in § 15.30(h).

Dated: March 28, 2019.

Lowell J. Schiller,

Acting Associate Commissioner for Policy.

[FR Doc. 2019-06436 Filed 4-2-19; 8:45 am]

BILLING CODE 4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 165

[Docket No. FDA-2018-N-1815]

RIN 0910-AI03

Beverages: Bottled Water

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA or we) is proposing to revise the quality standard for bottled water to specify that bottled water to which fluoride is added by the manufacturer may not contain fluoride in excess of 0.7 milligrams per liter (mg/L). This action, if finalized, will revise the current allowable levels for fluoride in domestically packaged and imported bottled water to which fluoride is added. We are taking this action to make the quality standard regulation for fluoride added to bottled water consistent with the recommendation by the U.S. Public Health Service (PHS) for community water systems that add fluoride for the prevention of dental caries. This action, if finalized, will not affect the allowable levels for fluoride in bottled water to which fluoride is not added by the manufacturer (such bottled water may contain fluoride from its source water).

DATES: Submit either electronic or written comments on the proposed rule by June 3, 2019.

ADDRESSES: You may submit comments as follows: Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before June 3, 2019. The *https://www.regulations.gov* electronic filing system will accept comments until midnight Eastern Time at the end of June 3, 2019. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal: https://www.regulations.gov.* Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to *https://www.regulations.gov* will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on *https://www.regulations.gov.*
- If you want to submit a comment with confidential information that you do not wish to be made available to the public submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions.")

Written/Paper Submissions

Submit written/paper submissions as follows:

- *Mail/Hand delivery/Courier (for written/paper submissions):* Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2018-N-1815 for "Beverages: Bottled Water." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at *https://www.regulations.gov* or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions—To submit a comment with confidential information that you do not wish to be made publicly available submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." We will review this copy, including the claimed confidential information, in our consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on *https://www.regulations.gov.* Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: *https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf.*

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to *https://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Yinqing Ma, Center for Food Safety and Applied Nutrition (HFS-317), Food and Drug Administration, 5001 Campus Dr., College Park, MD 20740, 240-402-2479.

SUPPLEMENTARY INFORMATION:

Table of Contents

I. Executive Summary
A. Purpose of the Proposed Rule

SQUALANE and SQUALENE

CONCLUSION: The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) first published the Final Report on the Safety Assessment of Squalane and Squalene in 1982.[1] The Panel concluded that "both Squalane and Squalene are safe as cosmetic ingredients in the present practices of use and concentration," as described in that report. In 2001, after considering new studies and updated use data on these two ingredients, the Panel determined to not re-open the safety assessment.[2] Data identified in the published literature[3-13] that have become available since the 2001 re-review was issued, support the conclusion reached by the Panel in the original review. The Panel also reviewed updated information regarding product types and ingredient use frequencies as reported in the US Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP) database,[14] and the maximum use concentrations provided by the Personal Care Products Council.[15] The Panel determined to not reopen this safety assessment and reaffirmed the original conclusion that Squalane and Squalene are safe as cosmetic ingredients in the present practices of use and concentration, as given in Table 1.

DISCUSSION: The reported frequency of use has increased significantly for both ingredients since the initial re-review was considered. According to VCRP data, Squalane and Squalene were reported to be used in 595 and 29 formulations, respectively, in 2001.[2] In 2019, the VCRP indicates that Squalane is used in 2785 formulations, and Squalene is used in 527 formulations.[14] For Squalane, the current maximum concentration of use (96.8%)[14] is the same as that reported in 2001 (97%);[2] however, the maximum concentrations of use by exposure type (e.g., eye area, nails) have increased for some categories. The opposite is true for Squalene; the maximum concentration of use has decreased since the previous re-review. In 2001, Squalene was used at up to 10%;[2] data received in 2018 report that the maximum concentration of use is 1.2%.[15]

Squalane and Squalene are natural components of human sebum. Although new studies indicated there could be sensitization potential, there is no significant clinical evidence of sensitization. The Panel stated the lack of case reports, in spite of the increased frequency of use, and the Panel's clinical experience with these ingredients support the safety of these ingredients for use in cosmetics.

Table 1. Current and historical frequency and concentration of use of Squalane and Squalene according to duration and exposure

	# of Uses		*Max Conc of Use (%)*	
	2019[14]	**2001[2]**	**2018[15]**	**2001[2]**
	SQUALANE			
Totals*	**2785**	**595**	**0.0001-96.8**	**0.01 – 97**
Duration of Use				
Leave-On	*2608*	*541*	*0.0001 - 96.8*	*0.01 – 97*
Rinse-Off	*171*	*54*	*0.0001 - 34.9*	*0.1 – 5*
Diluted for (Bath) Use	*6*	*NR*	*0.14*	*NR*
Exposure Type				
Eye Area	366	42	0.0001 – 38	0.01 – 15
Incidental Ingestion	253	52	0.001 – 22.8	3 – 17
Incidental Inhalation-Spray	spray: 12 possible: 772[a]; 656[b]	spray: 12 possible: 170[a]; 68[b]	spray: 0.048 – 0.15 possible: 0.005 – 12[a]	possible: 0.3 – 36[a]; 0.1 – 97[b]
Incidental Inhalation-Powder	powder: 107 possible: 656[b]; 11[c]	powder: 28 possible: 68[b]; 2[c]	powder: 1 – 3.4 possible: 0.01 – 40.1	powder: 3 – 9 possible: 0.1 – 97[b]
Dermal Contact	2447	510	0.0001 – 85.4	0.1 – 97
Deodorant (underarm)	3[a]	NR	0.18 – 4	NR
Hair - Non-Coloring	69	17	0.001 – 2.3	0.8 – 5
Hair-Coloring	NR	NR	NR	NR
Nail	4	6	0.0001 – 96.8	NR
Mucous Membrane	277	63	0.001 – 22.8	0.1 – 17
Baby Products	11	2	0.03 - 2	NR
	SQUALENE			
Totals*	**527**	**29**	**0.004 – 1.2**	**0.01 – 10**
Duration of Use				
Leave-On	*300*	*26*	*0.0045 – 0.7*	*0.02 – 10*
Rinse-Off	*215*	*2*	*0.004 – 1.2*	*0.01 – 0.5*
Diluted for (Bath) Use	*12*	*1*	*NR*	*0.2*
Exposure Type				
Eye Area	19	NR	0.0046 – 0.07	0.5 – 0.7
Incidental Ingestion	71	NR	0.0045 – 0.09	0.7
Incidental Inhalation-Spray	spray: 1 possible: 102[a]; 67[b]	possible: 9[a]; 13[b]	possible: 0.07[a]	possible: 0.06 – 0.5[a]; 0.08 – 0.5[b]
Incidental Inhalation-Powder	powder: 2 possible: 67[b]; 2[a]	possible: 13[b]	possible: 0.05 – 0.7	powder: 10 possible: 0.08 – 0.5[b]
Dermal Contact	453	29	0.004 – 0.7	0.02 – 10
Deodorant (underarm)	NR	NR	0.06	NR
Hair - Non-Coloring	3	NR	0.07 – 1.2	0.01
Hair-Coloring	NR	NR	0.2	NR
Nail	NR	NR	NR	NR
Mucous Membrane	288	1	0.004 – 0.09	0.2 – 0.7
Baby Products	2	NR	NR	NR

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.
[b] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, there fore the information is captured in both categories
[c] It is possible these products are powders, but it is not specified whether the reported uses are powders.
NR – not reported

REFERENCES

1. Elder R.L. (ed). Final Report on the Safey Assessment of Squalane and Squalene. *J Am Coll Toxicol* 1982;1(2):37-56.

2. Andersen F.A. (ed). Squalene and Squalane. *Int J Toxicol* 2003;22:27-31.

3. Chiba K, Yoshizawa K, Makino I, Kawakami K, Onoue M. Comedogenicity of squalene monohydroperoxide in the skin after topical application. *J Toxicol Sci* 2000;25(2):77-83.

4. Filipovic M, Gledovic A, Lukic M, et al. Alp Rose stem cells, olive oil squalene and a natural alkyl polyglucoside emulsifier: Are they appropriate ingredients of skin moisturizers - in vivo efficacy on normal and sodium lauryl sulfate - irritated skin? *Vojnosanit Pregl* 2016;73(11):991-1002.

5. Kreiling R, Hollnagel HM, Hareng L, et al. Comparison of the skin sensitizing potential of unsaturated compounds as assessed by the murine local lymph node assay (LLNA) and the guinea pig maximization test (GPMT). *Food Chem Toxicol* 2008;46(6):1896-1904.

6. McPhee D, Pin A, Kizer L, Perelman L. Deriving renewable squalane from sugarcane. *Cosemtics & Toiletries Magazine* 2014;129(6).

7. Mi T, Dong Y, Santhanam U, Huang N. Niacinamide and 12-hydroxystearic acid prevented benzo(a)pyrene and squalene peroxides induced hyperpigmentation in skin equivalent. . *Exp Dermatol* 2018;[Epub ahead of print].

8. Narayan BH, Tatewaki N, Giridharan VV, Nishida H, Konishi T. Modulation of doxorubicin-induced genotoxicity by squalene in Balb/c mice. *Food Funct* 2010;1(2):174-179.

9. Nikitakis J, Kowcz A. Web-Based International Cosmetic Ingredient Dictionary and Handbook. http://webdictionary.personalcarecouncil.org/jsp/Home.jsp. Washington, DC: Personal Care Products Council. Last Updated: 2019. Accessed: 02/08/2019.

10. Rao CV, Newmark HL, Reddy BS. Chemopreventive effect of squalene on colon cancer. *Carcinogenesis* 1998;19(2):287-290.

11. Ryu A, Arakane K, Koide C, Arai H, Nagano T. Squalene as a target molecule in skin hyperpigmentation caused by singlet oxygen. *Biol Pharm Bull* 2009;32(9):1504-1509.

12. Smith TJ, Yang GY, Seril DN, Liao J, Kim S. Inhibition of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced lung tumorigenesis by dietary olive oil and squalene. *Carcinogenesis* 1998;19(4):703-706.

13. Yuzbasioglu D, Unal F, Koc F, et al. Genotoxicity assessment of vaccine adjuvant squalene. *Food Chem Toxicol* 2013;56:240-246.

14. US Food and Drug Administration (FDA) Center for Food Safety & Applied Nutrition (CFSAN). 2019. Voluntary Cosmetic Registration Program (VCRP) - Frequency of Use of Cosmetic Ingredients. College Park, MD (Obtained under the Freedom of Information Act from CFSAN; requested as "Frequency of Use Data" January 3 2019; received February 13, 2019.)

15. Personal Care Products Council. 2018. Council Concentration of Use by FDA Product Category: Squalane and Squalene. (Unpublished data submitted by the Personal Care Products Council on June 1, 2018.)