

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210365Orig1s000

PRODUCT QUALITY REVIEW(S)

The attached pages from the redacted Product Quality Review section of the Drug Approval Package for NDA 210365 posted on Drugs@FDA were unredacted in June 2020 to release information that is publicly available in Drug Enforcement Administration Docket No. DEA-486.

Impurity Qualification:

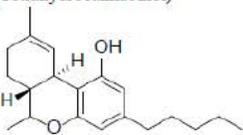
For the specified impurities, the sponsor states: “Toxicity studies have been carried out for these specified impurities ([see Module 4, section 4.2.3.7.6](#)) and the proposed limits have been qualified.” The process history of these impurities is shown below:

Table 3.2.S.4.5-3 Summary - Specified Cannabinoids Results (% w/w)	
Data (n=32)	(b) (4) THC (% w/w) (b) (4)
Average	
SD	
Minimum	
Maximum	
Average + 3xSD	
Proposed Specification limit	NMT 0.10 % w/w



(b) (4)

Summary of Potential Organic Impurities:

Table 3.2.S.3.2-1 Known and Potential Cannabinoid Impurities			
Name/Structure	Origin	Reduction	Control Point / Specification Limit
(b) (4)			
THC (Tetrahydrocannabinol) 	(b) (4)		(b) (4) CBD specification NMT 0.10% w/w
(b) (4)			

S.4 Control of Drug Substance

Table 3.2.S.4.1-1 Drug Substance Specification		
Test	Test Method	Specification
(b) (4)		
Impurities (other cannabinoids):	In-house	(b) (4)
- THC		NMT 0.10% w/w (b) (4)
(b) (4)		

(b) (4)

(b) (4)

**Reviewer's Assessment: Adequate**

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

THC is controlled in the drug substance with a limit of no more than 0.10% w/w.

(b) (4)

(b) (4)



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PRODUCT QUALITY REVIEW(S)

memo

To: NDA 210365 Administrative Record
From: Wendy Wilson-Lee, Branch Chief, OPQ/ONDP
CC: Stephanie Parncutt, RPM, DNP
Date: June 4, 2018
Re: Quality Information Request Response dated May 23, 2018

In a joint information request (IR) dated May 3, 2018, Office of Pharmaceutical Quality (OPQ) and Controlled Substances Staff (CSS) asked for a revision to the proposed drug substance specification limit for tetrahydrocannabinol (THC) from (b) (4)% to (b) (4)%. The Applicant, GW Research Ltd, provided a preliminary response on May 14, 2018 to facilitate a teleconference between FDA and the Applicant regarding this issue (teleconference held May 17, 2018). The Applicant submitted a final, formal response to the IR on May 23, 2018 as an amendment to the NDA.

As noted during the teleconference and as outlined in the formal response, the Applicant opposes the requested revision to the THC content limit in the drug substance specification for the reasons summarized below:

- The (b) (4)% limit for THC content complies with ICH Q6A guidance

(b) (4)

- The Applicant's interpretation of the Human Abuse Potential Study results finds that there is no apparent relationship between plasma level of THC and the occurrence of abuse related events

Based on the data provided in the submission and in response to the IR, OPQ agrees that a limit of (b) (4)% is adequate to control the THC content in the final drug substance, from a product quality perspective. This proposed limit is considered qualified (b) (4)

(b) (4)

. OPQ defers to CSS and the clinical division regarding the Applicant's assertion that changes in THC plasma levels do not correlate with abuse related events.

OPQ continues to recommend of APPROVAL of NDA 210365 for Cannabidiol Oral Solution as noted in the OPQ IQA Combined Review dated April 16, 2018.



Wendy
Wilson- Lee

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Recommendation: APPROVAL

**NDA 210365
Review #1**

Drug Name/Dosage Form	Cannabidiol Oral Solution
Strength	100 mg/mL
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	GW Research Ltd
US agent, if applicable	Greenwich Biosciences Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original – Part 1	23-JUN-2017
Original – Part 2	27-OCT-2017
Amendment	17-NOV-2017
Amendment	21-DEC-2017
Amendment	08-JAN-2018
Amendment	16-JAN-2018
Amendment	19-JAN-2018
Amendment	27-FEB-2018
Amendment	09-MAR-2018
Amendment	28-MAR-2018
Amendment	06-APR-2018

Quality Review Team

DISCIPLINE	PRIMARY/SECONDARY REVIEWER	OPQ OFFICE
Drug Substance	Rajan Pragani/Charles Jewell	ONDP
Drug Product	Andrei Ponta/Wendy Wilson-Lee	ONDP
Process	Sydney Choi/Nallaperumal Chidambaram	OPF
Microbiology	Yeissa Chabrier Rosello/Marla Stevens-Riley	OPF
Facility	Christina Capacci-Daniel/Derek Smith	OPF
Regulatory Business Process Manager	Dahlia Walters	DHP
Application Technical Lead	Wendy Wilson-Lee	ONDP
Environmental	Raanan Bloom/Scott Furness	ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Review Date	Comments
(b) (4)	Type II		(b) (4)	Adequate	n/a	Adequate information provided in the NDA
	Type III			Adequate	n/a	Adequate information provided in the NDA
	Type III			Adequate	n/a	Adequate information provided in the NDA
	Type III			Adequate	n/a	Adequate information provided in the NDA

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	120055	Cannabidiol

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Botanical Review Team	Complete	Approve	29-MAR-2018	Cassandra Taylor/Charles Wu

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends approval of NDA 210365 for Cannabidiol Oral Solution, 100 mg/mL.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	<i>Adjunctive treatment of seizures associated with Dravet Syndrome and Lennox-Gastaut Syndrome in patients 2 years and older</i>
Duration of Treatment	<i>Chronic; Twice daily dosing</i>
Maximum Daily Dose	<i>20 mg/kg/day</i>
Alternative Methods of Administration	<i>None</i>

B. Quality Assessment Overview

GW Research Ltd is filing a 505(b)(1) for a drug product containing cannabidiol (CBD) for adjunctive treatment of seizures associated with Dravet syndrome or Lennox Gastaut syndrome in patients 2 years and older. The Applicant received orphan designation for development of this drug product. The drug substance is a (b) (4) yellow, crystalline (b) (4), produced from an extract of Cannabis sativa L. plants. 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. A secondary carton containing 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 adapter co-packaged with the drug product is a Tier 1 device and is considered low risk. No additional information is needed from the applicant as there are minimal 21 CFR 820 expectations for Tier 1 devices. Therefore, no CDRH ODE or OC consults were sent given the low risk of the device component.

The Applicant has demonstrated the consistent production of cannabidiol drug substance with adequate quality and control. Sufficient release and stability data were provided for drug substance originating from (b) (4) the purified cannabidiol drug substance. The nonclinical reviewer was consulted on the specified impurity limits. The nonclinical reviewer determined the limits were acceptable based on the qualification studies.

Over the course of the review, it was determined that cannabidiol drug substance in this process is best described as a highly-purified drug substance from a plant source. The drug substance is neither a botanical drug substance nor considered (b) (4). The regulatory starting material is the (b) (4). (b) (4). Because the drug substance comes from a plant source, the applicant demonstrated a conformance to the principles of USP<561> Articles of Botanical Origin.

A comparability protocol was submitted for review in the NDA. Regarding drug substance manufacture, the applicant had suggested (b) (4). We disagreed and requested that they switch to a reporting category of “CBE-30” supplement for each change, which was agreed to by the Applicant. The NDA was revised, accordingly.

The drug product manufacturing process can be described (b) (4). Drug product release results for 129 drug product batches have been provided, all of which indicated that the drug product met specifications. The Applicant has proposed a 24-month shelf life at USP controlled room temperature for the drug product. The data provided (24 months of supportive stability and (b) (4) of primary stability) to date supports the proposed shelf life.

During development, the Applicant monitored drug product (b) (4) but these attributes are currently not monitored on release and stability. Data provided support the omission of these tests; however, if there are major changes in the manufacturing process, drug product formulation, or raw material these drug product attributes should be reevaluated to ensure drug product quality is maintained.

The information and results provided in support of the microbial quality of the API and of the drug product, which included microbial enumeration, AET testing and (b) (4) determination are deemed adequate. The data for microbial enumeration testing of 129 drug product batches showed that the drug product does not support microbial proliferation. AET studies, conducted as per USP <51>, showed a > 4 log reduction at time points 14 days and 28 days for the compendial organisms, suggesting that the drug product might have inherent antimicrobial activity. (b) (4)

(b) (4). Additionally, the results for microbial enumeration of 10 API batches showed no microbial proliferation.

The risk assessment conducted for the overall drug product manufacturing, which included potential sources of microbial contamination, shows that the risk of microbial contamination is very low. Based on the information and results provided in support of the microbiology quality of the drug product, the firm agreed to perform skip-lot testing on every 10th lot for microbial enumeration tests as per USP <61> and USP <62> and added microbial limits testing to the drug product release specification, as requested by

the Agency. The specification for USP <61> and USP <62> testing meets the recommendations in USP <1111> for a non-sterile, non-aqueous oral solution.

Following a review of the application, inspectional documents, and initial pre-approval inspection results, there are no significant, outstanding manufacturing or facility risks that prevent approval of this application. The manufacturing facilities for NDA 210365 are found to be acceptable.

The applicant has submitted a claim of categorical exclusion under 21CFR 25.31(b) and a statement of “no extraordinary circumstances.” Based on the estimated concentration of the CBD at the point of entry into the aquatic environment, the application meets the criteria for the cited categorical exclusion. Significant impact to the environment due to approval of this application is not anticipated. Available information supports a statement of “no extraordinary circumstances.” The applicant’s claim of categorical exclusion under 21 CFR 25.31(b) and statement of no extraordinary circumstance are acceptable.

C. Special Product Quality Labeling Recommendations (NDA only)

None.

D. Final Risk Assessment (see Attachment)

ATTACHMENT I: Final Risk Assessment

A. Final Risk Assessment - NDA

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Assay	Formulation Container Closure Raw Materials Process/Scale/Equipment Site	Low	End product testing	Acceptable	
(b) (4)	Formulation Raw Materials Process/Scale/Equipment Site	Low		Acceptable	
	Formulation Raw Materials Process/Scale/Equipment Site	Low	One known polymorph	Acceptable	
Dosing Accuracy	Formulation Container Closure Dosing Device Raw Materials Process/Scale/Equipment Site	Low	End product testing	Acceptable	
Palatability	Formulation Raw Materials	Medium	Formulated with	Acceptable	



QUALITY ASSESSMENT



	Process/Scale/Equipment Site		(b) (4)		
Microbial Limits	Formulation Container Closure Raw Materials Process/Scale/Equipment Site	Low	End product testing	Acceptable	
Leachables	Formulation Container Closure Process/Scale/Equipment Site	Low	Toxicological assessment	Acceptable	
(b) (4)					
Viscosity	Formulation Container Closure Raw Materials Process/Scale/Equipment Site	Low	In-process testing	Acceptable	
(b) (4)					



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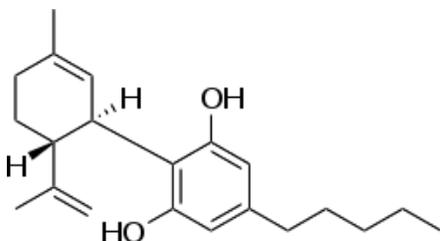
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ENVIRONMENTAL

R Regional Information

Cannabidiol (CBD) is a new molecular entity developed for the adjunctive treatment of seizures associated with Dravet and Lennox Gastaut syndromes.

The drug substance, CBD, is a 21-carbon terpenophenolic compound (b) (4) (b) (4) plants of *Cannabis sativa* L, with defined chemical profiles and containing consistent levels of CBD as the major cannabinoid and a low level of delta-9-tetrahydrocannabinol (THC).



The applicant has submitted a claim of categorical exclusion under 21CFR 25.31(b) and a statement of “no extraordinary circumstances”. The applicant provided additional information to support the claim for an exclusion. In addition, the applicant provided the Environmental Risk Assessment submitted in a Marketing Authorization Application to the EMA.

Based on the estimated concentration of the CBD at the point of entry into the aquatic environment (EIC) of < 1ug/L (ppb), the application meets the criteria for the cited categorical exclusion. This review then evaluates the “extraordinary circumstances” statement to determine if available data establish that, at the expected level of exposure, there is the potential for serious harm to the environment (21 CFR 25.21a).

Environmental

FDA utilized the fish plasma model (FPM; per Nallani et al., 2016 and Huggett et al., 2003) to help screen for CBD aquatic environmental risk. The following inputs were used: human C_{max} (b) (4) (from Clinical Overview), a predicted log D value of (b) (4) (www.chemspider.com), and expected introductory concentration (EIC) into surface water concentration of (b) (4) ug/L (round up from predicted EIC of (b) (4) ug/L). The result indicates some potential ecotoxicological concern for this substance driven by the lipophilic nature of the molecule. However, due to the partitioning characteristics of CBD (CBD is lipophilic and practically insoluble in water and aqueous media), preferential partitioning to biosolids in wastewater treatment plants and to sediments would be predicted. This would lower the predicted EIC and subsequent surface water exposure concentrations. The EIC calculation also tends to overestimate exposure concentrations since it assumes no metabolism, biodegradation or retention of the drug

substance in sewage treatment plant sediments and solids and represents effluent and not surface water concentrations. The iSTREEM® model (<https://www.cleaninginstitute.org/istreem/>) a free, web-based GIS-model, was used to further estimate the concentration of CBD in the effluents and surface waters (a conservative assumption of (b) (4) % removal in activated sludge was utilized and an input value of (b) (4) CBD/capita/day based on marketing estimated). The following surface water concentration results indicate low exposure concentrations.

Surface water results

Percentile	Conc (µg/L)
10	(b) (4)
25	(b) (4)
50	(b) (4)
75	(b) (4)
90	(b) (4)
95	(b) (4)
99	(b) (4)

Accordingly, the FPM model appears to overestimate potential ecotoxicological concern. A search of the literature did not find information on the ecotoxicological effects of CBD. A study of CBD concentrations in effluents and effluents were <LOD. No CBD was measured at low µg/L levels (Alexandros, et al., 2017). The FDA will survey the literature periodically to determine possible impacts due to the use of CBD.

We also evaluated interaction with the estrogen receptor using CERAPP: Collaborative Estrogen Receptor Activity Prediction Project (Mansouri et al., 2016). Although some interaction is predicted, published studies indicate that CBD has interactions only at very high concentrations (Sauer et al., 1983). Ruh et al. (1997) tested the hypothesis that cannabinoid compounds produce a direct activation of estrogen receptors. They concluded that psychoactive or inactive compounds of the cannabinoid structural class fail to behave as agonists in appropriate assays of estrogen receptor responses in vitro.

In addition, according to information in the 2017 EMA Environmental Risk Assessment no effect on embryonic development was observed. In animal reproduction studies, there was no maternal toxicity when rats were administered orally up to 250 mg/kg/day CBD. No adverse effects on fertility and early embryonic development in rat following dosing of maternal rats up to a dose of 250 mg/kg/day were observed, and no adverse effects were observed on offspring up to a dose of 75 mg/kg/day in a pre-and post-natal rat study. With dosing up to the no observed adverse effect level of 250 mg/kg/day in rat, there were no effects on male or female reproductive indices, no effect on female oestrus cycling, no effect on reproductive ability of males and females, and no effect on survivability or on the fertility of the subsequent generation. No effect was seen on embryonic development/teratogenicity in rat up to the no observed effect level of 150 mg/kg/day.

CBD, therefore, does not appear to present a reproductive risk. The levels in aquatic environments would be significantly lower than the NOAELs used in the repro studies, thus lowering concern for aquatic effects.

A third consideration when evaluating this application is whether therapeutic CBD use will significantly increase levels of CBD in the environment. Based on patient population, indications and chemical characteristics, limited CBD is expected to enter US waterways due to use of this product. When compared to CBD levels found in the (b) (4) cultivated plants of *Cannabis sativa* L. that could enter US waterways, the increase would not appear to be significant. Cannabis is used throughout the United States, is approved for medicinal and recreational use in several states and is used illicitly in wide-spread locales. Cannabis is available in a variety of delivery forms include leaf, tinctures, oils, edibles, lozenges, drinking products and topical applications. CBD is also found in hemp (a variety of the *Cannabis sativa* plant species that is grown specifically for the industrial with non-or limited psychoactive properties). In fact, as summarized by Andre *et al* (2016), hemp seed, hemp stem, hemp leaf and hemp flower contain up to 244, 18090, 20000, and 8590 µg CBD per gram dry weight, respectively. These levels would be expected to be higher in psychoactive forms. CBD from oral use of *Cannabis sativa* L products would be excreted and enter US waters in a manner similar to CBD from the present drug application.

References:

- Huggett, D. B., J. C. Cook, J. F. Ericson and R. T. Williams (2003). A theoretical model for utilizing mammalian pharmacology and safety data to prioritize potential impacts of human pharmaceuticals to fish. *Human and Ecological Risk Assessment: An International Journal*, 9(7):1789-1799.
- Nallani G., Venables B., Constantine L., Huggett D. 2016. Comparison of measured and predicted bioconcentration estimates of pharmaceuticals in fish plasma and prediction of chronic risk. *Bulletin of Environmental Contamination and Toxicology*, 96(5):580-584.
- Ruh F., Mary & A. Taylor, Julia & Howlett, Allyn & Welshons, Wade. (1997). Failure of cannabinoid compounds to stimulate estrogen receptors. *Biochemical Pharmacology*. 53. 35-41. 10.1016/S0006-2952(96)00659-4.
- Andre C.M., Hausman J. F., Guerriero G. *Cannabis sativa*: The plant of the thousand and one molecules. *Plant Science* 2016; 7 (19): 1-17.
- Sauer, M.A., S.M. Rifka, R.L. Hawks, G.B. Cutler and D.L. Loriaux. Marijuana: Interaction with the Estrogen Receptor. *Journal of Pharmacology and Experimental Therapeutics* February 1983, 224 (2) 404-407.

Mansouri, K., Abdelaziz, A., Rybacka, A., Roncaglioni, A., Tropsha, A., Varnek, A., et al. CERAPP: Collaborative Estrogen Receptor Activity Prediction Project. *Environ Health Perspect.* 2016;124(7):1023-33. doi: 10.1289/ehp.1510267.

Alexandros G. Asimakopoulos, Pranav Kannan, Sean Higgins, Kurunthachalam Kannan. Determination of 89 drugs and other micropollutants in unfiltered wastewater and freshwater by LC-MS/MS: an alternative sample preparation approach. *Anal Bioanal Chem* (2017) 409:6205–6225.

Reviewer's Assessment: *Adequate*

The applicant has submitted a claim of categorical exclusion under 21CFR 25.31(b) and a statement of “no extraordinary circumstances.” Based on the estimated concentration of the CBD at the point of entry into the aquatic environment, the application meets the criteria for the cited categorical exclusion. Serious harm to the environment due to approval of this application is not anticipated. Available information supports a statement of “no extraordinary circumstances.”

The applicant's claim of claim of categorical exclusion under 21 CFR 25.31(b) and statement of no extraordinary circumstance is acceptable

Primary Environmental Reviewer: Raanan A. Bloom, Ph.D.

Secondary Reviewer: Scott Furness, Ph.D.



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Bloom

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Michael
Furness

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LABELING

I. Package Insert

1. Highlights of Prescribing Information



(b) (4)

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	(b) (4) (Cannabidiol) Oral solution
Dosage form, route of administration	Oral solution, oral
Controlled drug substance symbol (if applicable)	(b) (4)
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Oral solution: 100 mg/mL

Is the information accurate? Yes No

2. Section 2 Dosage and Administration

2.2 Administration Instructions

(b) (4)



Item	Information Provided in NDA
(Refer to Labeling Review Tool and	21 CFR 201.57(c)(12))
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	The drug product is to be administered by measuring the dosage with an oral dosing syringe

Is the information accurate? Yes No

3. Section 3 Dosage Forms and Strengths

3 DOSAGE FORMS AND STRENGTHS

Oral Solution: 100 mg/mL for oral administration. Each bottle contains 100 mL of a clear, colorless to yellow solution. [Module 3, 3.2.P.5.1 Specification; [Module 5, CSR GWEPI448, Section 5.4.2](#)]

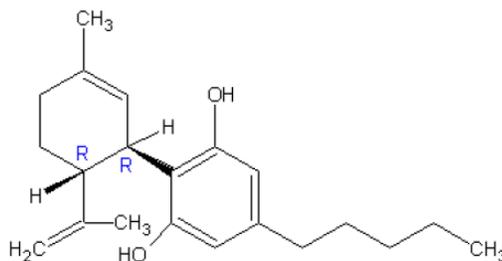
Item	Information Provided in NDA
(Refer to Labeling Review Tool and	21 CFR 201.57(c)(4))
Available dosage forms	Oral Solution
Strengths: in metric system	100 mg/mL
Active moiety expression of strength with equivalence statement (if applicable)	Cannabidiol
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	A clear, colorless to yellow solution

Is the information accurate? Yes No

4. Section 11 Description

11 DESCRIPTION

(b) (4) Cannabidiol is a cannabinoid designated chemically as 2-[(1R,6R)-3-Methyl-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-pentyl-1,3-benzenediol (IUPAC/CAS). Its empirical formula is $C_{21}H_{30}O_2$ and its molecular weight is 314.46. The chemical structure is:



Cannabidiol, the active ingredient in (b) (4) is a (b) (4) cannabinoid that naturally occurs in the *Cannabis sativa* L. plant.

Cannabidiol is a white to pale yellow crystalline solid. It is insoluble in water and is soluble in organic solvents. [Module 3, Section 3.2.P.2.1]

(b) (4) is a clear colorless to yellow liquid containing cannabidiol at a concentration of 100 mg/mL.

Inactive ingredients include (b) (4) sesame oil, (b) (4) sucralose, and strawberry flavor.

[Module 2, 2.7.1 Summary of Biopharmaceutical Studies and Associated Analytical Methods, Section 1 & 2; Module 2, 2.7.2 Clinical Pharmacology Summary, Section 1.1; Module 3, Section 3.2.P.2.1]

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	(b) (4) (cannabidiol) oral solution (not included in label)
Dosage form and route of administration	Oral solution (not included)
Active moiety expression of strength with equivalence statement (if applicable)	Cannabidiol
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Not applicable
Statement of being sterile (if applicable)	Not applicable
Pharmacological/ therapeutic class	Antiepileptic
Chemical name, structural formula, molecular weight	Included and accurate
If radioactive, statement of important nuclear characteristics.	Not Applicable
Other important chemical or physical properties (such as pKa or pH)	Insoluble in water

Is the information accurate? Yes No

5. Section 16 How Supplied/Storage and Handling

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

(b) (4) is a strawberry flavored clear, colorless to yellow solution supplied in a (b) (4) mL amber glass bottle with child-resistant closure (NDC 70127-100-01). Each mL contains 100 mg of cannabidiol. [Module 3, Section 3.2.P.2.1, Section 3.2.P.2.1.1.1, Table 3.2.P.2.2.1-1 and 3.2.P.2.2.1-2]. (b) (4) is packaged in a carton with two 5 mL calibrated oral dosing syringes and a bottle adapter (NDC-70127-100-10). [Module 1.14.1.1; Module 5.3.5.4, 16-188-R1, Section 3.1; Module 3, 3.2-P-8.1]

(b) (4)

16.2 Storage and Handling

Store (b) (4) in its original bottle in an upright position at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature]. Use within 12 weeks of first opening the bottle, then discard any remainder. [Module 1.14.1.3 16-188-R1; Section 3.1; Module 3, 3.2-P-8.1]

Item	Information Provided in NDA
(Refer to Labeling Review Tool and	21 CFR 201.57(c)(17))
Strength of dosage form	Oral Solution (100 mg/mL)
Available units (e.g., bottles of 100 tablets)	(b) (4)
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	A clear, colorless to yellow solution
Special handling (e.g., protect from light)	Use within 12 weeks of opening the bottle, then discard any remainder
Storage conditions	USP controlled room temperature
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Not included

Reviewer’s Assessment of Package Insert: Adequate

Revisions identified and will be communicated to the Applicant as part of DNP labeling negotiations. The PI is adequate assuming Applicant accepts edits.

II. Labels:

1. Container and Carton Labels

(b) (4)



List of Deficiencies:

- *Under the Dosage Forms and Strength section, include the active moiety (CBD)*
- *In the Description section:*
 - *Include oral solution after (b) (4) (cannabidiol)*
 - *Include the dosage form in the description*
 - *Remove (b) (4) from the first sentence*
- *The label indicates that the drug product is provided in a (b) (4) bottle. The proposed commercial container closure system is a 105 mL bottle. Update the label accordingly.*
- *Ensure the manufacturers name is included in the How Supplied/Storage and Handling Section*

- Change ^{(b) (4)} sesame oil to sesame oil in the description and the container label
- Include the following statements in the *Storage and Handling* section:
 - Do not refrigerate or freeze
 - Keep the cap tightly closed
 - Discard unused portion 12 weeks after first opening
- Include a space for the bar code on the bottle label
- Ensure the NDC number is correct on the container label
- Include the lot number and expiration date on the container label

Overall Assessment and Recommendation: Adequate

Primary Labeling Reviewer Name and Date: Andrei Ponta, Ph.D.

Secondary Reviewer Name and Date: Wendy Wilson



Andrei
Ponta

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Wilson- Lee

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MICROBIOLOGY

Product Background:

NDA: 210365

Drug Product Name / Strength: (b) (4) 100 mg/ml

Route of Administration: Oral solution

Applicant Name: GW Research Ltd.

Manufacturing Site: (b) (4)

Method of Sterilization: Not applicable (non-sterile)

Review Summary: Recommended for Approval

List Submissions being reviewed: 10/27/2017, 1/16/2018 & 2/27/2018

Highlight Key Outstanding Issues from Last Cycle: None

Concise Description Outstanding Issues Remaining: None

Supporting/Related Documents: None

Remarks Section: This is an eCTD submission. The submission is for a non-sterile, non-preserved, non-aqueous oral solution. Some of the tables and figures in this review are adapted from the original submission.

P.1 Description of the Composition of the Drug Product

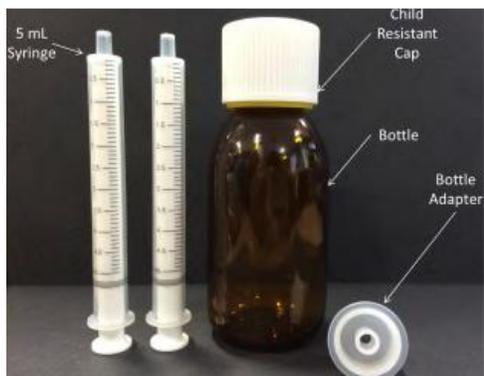
Drug product is a multi-dose oral non-aqueous solution of 100 mg/ml cannabidiol (CBD). The drug product composition is described below.

Drug product composition:

Ingredient	Content per 1 ml
Cannabidiol (CBD)	100 mg
(b) (4)	(b) (4)
Sucralose, USP	
Strawberry flavor, (b) (4)	
(b) (4) Sesame oil, USP	

Description of the container closure system:

The drug product is presented in a (b) (4) 105 ml amber glass bottle with a tamper-evident child resistant screw cap. Each bottle will be supplied with two 5 ml oral syringes and a bottle adapter (see diagram below).



Adequate

Reviewer's Assessment: The firm provided an adequate description of the drug product composition and the container closure system.

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

(P.2 Microbiological Attributes; P.4.1 Specifications)

As part of the microbiological attribute studies, the firm performed (b) (4), microbial enumeration and antimicrobial effectiveness testing studies to show that the drug product does not promote microbial growth. The studies were performed with batches manufactured in the same facility as proposed for commercial production. These studies are described below.

(b) (4)

Microbial enumeration:

The firm indicated that microbial testing “has routinely been carried out on every drug product batch manufactured for clinical use” following the recommendations of USP <1111>. The firm indicated that “all batches were manufactured at GW Pharma Ltd and there have been no significant changes to the manufacturing process since early clinical development other than scale.” A total of 129 batches have been manufactured for the drug product and all were tested for microbial levels. These batches were manufactured from October 2013 to September 2017. A table was provided to show “the typical results of batches tested” for microbial enumeration (see below).

Table 3.2.P.2.5-4 Microbial Testing on drug product batches

Microbial	Ph.Eur criteria	Results for all batches
Total Aerobic Microbial Count (TAMC)	NMT 10 ⁵ cfu/g	< 10
Total Combined Yeasts/Molds Count (TYMC)	NMT 10 ² cfu/g	< 10
<i>Escherichia coli</i>	Absent in 1 g	Not Detected
<i>Bulkholderia cepacia complex</i> (BCC)	Absent in 1 g	Not Detected

Antimicrobial Effectiveness Testing

The drug product is a non-sterile multi-dose non-aqueous solution formulated without a preservative, and thus is not required to be tested per USP <51>. However, the firm provided antimicrobial effectiveness studies performed as per USP<51>. The results are shown below.

Table 3.2.P.2.5-2 Microbial Testing on CBD 100 mg/mL oral solution

Micro-organism	Log ₁₀ (cfu/mL) recovered	Log ₁₀ Reduction in viability	
	0 hours	After 14 days	After 28 days
<i>P.aeruginosa</i>	< 1.0	> 4.0	> 4.0
<i>S.aureus</i>	< 1.0	> 4.2	> 4.2
<i>E.coli</i>	< 1.0	> 4.2	> 4.2
<i>A.brasiliensis</i>	3.3	> 4.7	> 4.7
<i>C.albicans</i>	2.0	> 4.4	> 4.4

The results for AET met the acceptance criteria.

Adequate

Reviewer’s Assessment: The firm provided the results for studies in support of the microbial quality of the drug product, which included (b) (4) microbial enumeration, absence of BCC, and AET. The microbial limits used are consistent with USP<1111> for non-aqueous oral solutions. The results provided for all the microbial testing studies showed that the drug product does not sustain or promote microbial proliferation. The firm did not state that the drug product has antimicrobial activity; however, the AET results showed that the drug product might have inherent antimicrobial activity because viability of all organisms tested was reduced by >4 log after 14 days. Since the firm is requesting a waiver for microbial testing at release, additional data is requested for AET test performed (i.e., suitability testing); this information is requested in section P.5. The results provided for the overall microbial attributes studies of the drug product are deemed adequate.

P.3 Manufacture

P.3.1 Manufacturers

(b) (4)

Adequate

Reviewer's assessment: The information provided for the overall manufacturing of the drug product is deemed adequate.

P.5 Control of Drug Product

P.5.1 Specification

P.7 Container Closure System - See P.1.

P.8 Stability

P.8.1 Stability Summary and Conclusion

The firm indicated that the proposed expiry is 24 months.

The firm indicated that three primary stability batches (exhibit batches) have been placed on the stability program on long term storage conditions (25°C/60% RH), and microbial enumeration testing (see description of tests in P.8.3 below), following the recommendations of USP<1111>, will be conducted. Stability studies that include microbial enumeration testing were also conducted on 3 supportive batches placed on long term storage conditions, and testing has been completed through expiry. The primary and supportive batch sizes were (b) (4) and (b) (4) respectively.

P.8.2 Post-Approval Stability Protocol and Stability Commitment

The firm commits to place the first 3 commercial batches of the subject drug product into their stability program. Thereafter, on an annual basis, one production lot will be added to the stability program. Microbiological quality testing will not be performed annually. However, microbiological quality testing will be performed at expiry (24 months); see the table below, for which “z” represents the time point for the performance of the microbiological quality testing.

Annual stability protocol:

Storage Conditions	Time Point (months)		
	Initial	12	24
Long-term 25°C/60% RH	X	XY	XYZ

P.8.3 Stability Data

The firm provided long term (25°C/60% RH) stability results for three primary batches (exhibit batches) K17439, K17440 and K17447 at 0 and 3 months, and the results for the supportive batches K14218, K14219 & K14223 at 0, 6, 12, 18 and 24 months (expiry). The primary batches were placed on the stability program on April 2017 and the supportive batches on December 2014. The results are presented in the tables below.

Primary stability batches (K17439, K17440 & K17447):

Test	Specification	Time-Point (Months)	
		0	3
Appearance of Solution	A clear, colorless to yellow solution	Complies	Complies
Microbiological Quality:			
Total Aerobic Microbial Count (TAMC)	NMT 10 ³ CFU/1 g	<10	
Total Yeasts/Moulds Count (TYMC)	NMT 10 ² CFU/1 g	<10	NT
<i>Escherichia coli</i>	Absent in 1 g	Absent	
<i>Burkholderia cepacia</i> complex	Absent in 1 g	Absent	

Supportive stability batches (K14218, K14219 & K14223):

Test	Specification	Time (months)						
		0	3	6	9	12	18	24
Microbiological Quality:								
Total Aerobic Microbial Count (TAMC)	NMT 10 ³ CFU/1 g	<10		<10		<10	<10	<10
Total Yeasts/Moulds Count (TYMC)	NMT 10 ² CFU/1 g	<10	NT	<10	NT	<10	<10	<10
<i>Escherichia coli</i>	Absent in 1 g	Absent		Absent		Absent	Absent	Absent
<i>Burkholderia cepacia</i> complex ²	Absent in 1 g	NT		Absent		Absent	Absent	Absent

Adequate

Reviewer’s Assessment: The stability information and data provided to support the shelf-life of the subject drug product, from a product quality microbiology perspective, is deemed adequate.

A Appendices

A.2 Adventitious Agents Safety Evaluation



QUALITY ASSESSMENT



Reviewer's Assessment: Not applicable

Comparability Protocols

Reviewer's Assessment: No CP was included in the application.

Post-Approval Commitments:

Reviewer's Assessment: Not applicable

Lifecycle Management Considerations

Reviewer's Assessment: Possible manufacturing change that could affect the microbiological quality of the subject drug product is a change in the manufacturing site.

Microbiology Deficiencies: None

Primary Microbiology Reviewer Name and Date: Yeissa Chabrier-Roselló, Ph.D. (3/5/2018)

Secondary Reviewer Name and Date: Marla Stevens-Riley, Ph.D. **I concur** (3/6/2018)



Yeissa
Chabrier Rosello

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Marla
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Wendy
Wilson- Lee

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(b) (4)

(b) (4) Based on BRT's review of the information provided by the Applicant, the quality controls of the BRM, (b) (4) appear adequate.

Please see the timeline below for further details.

Consult Response

Timeline

- **10/30/2017:** BRT was informed NDA 210365 had been received by the Application Team Lead (ATL) and BRT was requested to join the review team to provide input on the quality control of the botanical raw material (BRM), (b) (4) BRT attended all associated meetings and worked with OPQ review team during review cycle.
- **11/27/2017:** BRT participated in the filing review.
- **12/20/2017:** Based on review of the application, BRT provided 18 questions (#6 – 23) in the Information Request (IR) received by Applicant on 12/20/2017, and Applicant provided IR responses in Module 1. BRT reviewed responses from the Applicant.
- **02/01/2018** (11am-12pm EST) and **02/22/2018** (9am-10am EST): BRT participated in OPQ-only teleconferences with the Applicant to ask additional questions pertaining to the quality control of the BRM.
- **02/14/2018:** BRT met with NDA 210365 ATL, Project Manager, and Director of Division of New Drug Products I (DNPI/ONDP) to discuss where BRT would place information in the IQA review, what additional IRs and/or commitments we could request from Applicant, as well as what content would be included in the BRT review. At conclusion of meeting, all parties agreed on BRT's review placement in the integrated quality assessment (IQA) and the content of the review, as well as what would be included.



- **02/20/2018:** BRT provided 6 additional questions in the IR received by Applicant on 02/20/2018, and the Applicant provided the IR responses in Module 1. BRT reviewed responses from the Applicant.
- **03/21/2018:** ONDP management determined the cannabidiol (CBD) is not a botanical drug substance and can be best described as a highly-purified drug substance. Per the IR sent to Applicant on 03/21/2018, in line with other highly purified drug substances sourced from plant material and reviewed by the Agency, the regulatory starting material should be designated as the [REDACTED] (b) (4) [REDACTED] instead of the [REDACTED] (b) (4)”, which was originally identified as the starting material. At this meeting, BRT was informed a chapter for quality control of the BRM was no longer required in the integrated quality assessment (IQA) for the NDA. BRT will now provide a consult memo to the drug substance reviewer that contains the discussion of the botanical raw material.

The consult below constitutes BRT’s review of the following:

- Information provided in Module 3 of the NDA application pertaining to BRM
- Applicant’s IR responses from 12/19/2017 and 02/20/2018 provided in Module 1
- Applicant’s verbal responses related to BRM from OPQ-only teleconferences on 02/01/2018 (11am-12pm EST) and 02/22/2018 (9am-10am EST)



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Product Background: Cannabidiol (CBD) Oral Solution

NDA: 210365

Drug Product Name / Strength: Cannabidiol, 100 mg/mL (b) (4) -conditional approval of proprietary name)

Route of Administration: Oral

Applicant Name: GW Research Ltd.

Growing Sites: (b) (4)



Method of Growing: (b) (4)

List Submissions Being Reviewed:

- **Botanical Raw Material (BRM) Control information found in 3.2.S.2.3 Control of Materials**

Supporting Documents:

- **Response to FDA request 19-DEC-2017**
- **Response to FDA request 20-FEB-2018**
- **Applicant's verbal responses related to BRM from OPQ-only teleconferences on 02/01/2018 (11am-12pm EST) and 02/22/2018 (9am-10am EST)**



B. Botanical Raw Material and Quality Control

In NDA 210365, the drug substance is a highly purified extract (b) (4) produced from a plant source. The Botanical Raw Material (BRM) (b) (4)

Per the [Botanical Drug Development Guidance for Industry](#), “the term *botanicals* means products that include plant material, algae, macroscopic fungi, and combinations thereof. It does not include highly purified substances, either derived from a naturally occurring source or chemically modified.” Per this definition, the purified CBD extracted from cannabis plants and used in NDA 210365 is not a botanical, however the Botanical Review Team (BRT) was invited to provide a review on the quality control process of the BRM.

For clarity, in the Applicant’s original submission the *Cannabis sativa* L. plants (b) (4)

These acronyms are utilized in the consult below.

However, the Office of New Drug Products (ONDP) determined that cannabidiol (CBD) is not a botanical drug substance and can best be described as a highly-purified drug substance. The regulatory starting material should be designated as the (b) (4) instead of the (b) (4). The Applicant was sent an IR on 03-21-2018, and asked to update relevant sections of the NDA to capture that the (b) (4) has been designated as the regulatory start material (e.g., 3.2.S.2).

For additional information regarding the drug substance, refer to the Drug Substance Review by Dr. Rajan Pragani.

B.1 Botanical Origin

Originally, Carl Linnaeus described *Cannabis sativa* back in 1737 as a genus composed of a single species, *C. sativa*. At the time, Linnaeus was not aware of the drug-type cultivars prevalent in Asia and India and based his classification on his experiences with the fiber-type crops common in Europe.^{1, 2, 3} In 1785, Jean-Baptiste Lamarck classified the

¹ Hartsel, J.A.; Eades, J.; Hickory, B.; and Makriyannis, A. Chapter 53 – *Cannabis sativa* and Hemp, In *Nutraceuticals*; Gupta, R.C., Ed.; Academic Press, Boston, 2016, pp. 735 – 754. Accessed 03/19/2018: <https://www.sciencedirect.com/science/article/pii/B978012802147700053X>

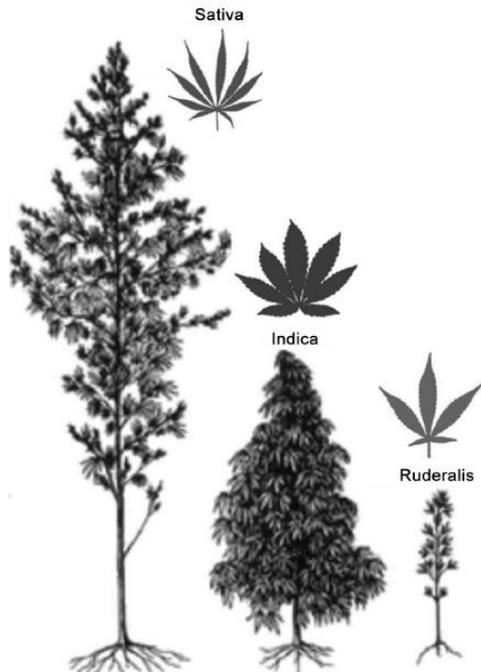
² Watts, G. Cannabis Confusions. *BMJ*, **2006**, 332 (7534), 175-176. Accessed 03/19/2018: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1336775/>

³ The Plant List. *Cannabis sativa* L. Accessed 03/19/2018: <http://www.theplantlist.org/tp1.1/record/kew-2696480>



Indian cultivar as a separate species, *Cannabis indica* Lam. While in 1924, D.E. Janischewsky, classified a third Russian cultivar as a separate species called *Cannabis ruderalis* Janisch., and divided the genus into three distinct species: *Cannabis sativa* L., *Cannabis indica* Lam., and *Cannabis ruderalis* Janisch. The American Herbal Pharmacopeia has noted *C. sativa* L. has been historically bred as a tall plant and used mainly for fiber and seed (See Figure 1). In contrast, *C. indica* Lam. is a short, densely branched structure and has potent levels of the psychoactive component Δ^9 -tetrahydrocannabinol (Δ^9 -THC). *C. ruderalis* commonly has very low levels of THC and high levels of CBD, increasing its popularity among breeders.⁴ There are two competing schools of thought on cannabis taxonomy, either monotypic (single-species) or the polytypic (multi-species) perspective. Today, the debate continues about whether all cannabis cultivars are *C. sativa*. The monotypic perspective is popular and has strong evidence as *C. sativa* and *C. indica* are commonly crossbred to produce hybrid phenotypes with chosen characteristics. In the late 1970s and early 1980s, researchers suggested using the monotypic perspective to catalog all varieties as subspecies of *C. sativa*, such as *C. sativa sativa*, *C. sativa indica*, and *C. sativa ruderalis*. The monotypic subspecies naming is commonly used.

Figure 1: Subspecies of *Cannabis sativa* include *C. sativa sativa*, *C. sativa indica*, and *C. sativa ruderalis*.¹



⁴ What is Cannabis ruderalis? Last update May 7, 2017. Accessed 03/19/2018:

<https://www.leafscience.com/2017/05/07/what-is-cannabis-ruderalis/>

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When classifying cannabis, chemical phenotypes or chemotypes, can be very useful to distinguish the *C. sativa* as drug- or fiber-type varieties. The United Nations Office on Drugs and Crime⁵ categorizes *C. sativa* into three chemotypes based on the proportion of THC and cannabinol (CBN) relative to CBD, based on Equation 1 below. The three categories are Chemotype I, Chemotype II, and Chemotype III.

Equation 1: Calculation used to classify the three cannabis chemotypes.¹

$$X = \frac{[THC] + [CBN]}{[CBD]}$$

Chemotype I: drug-type cultivars with X value greater than 1; high THC, low CBD; found below the 30°N latitude

Chemotype II: intermediate cultivars with approximately equivalent levels of THC and CBD; found above the 30°N latitude

Chemotype III: fiber-type cultivars with X values less than 1, high CBD, low THC; found above the 30°N latitude

However, in 2004, Hillig and Mahlberg⁶ published their statistical approach to defining the chemotaxonomic trends in *C. sativa*. Their research found that most cultivars did not fall within the values proposed by the United Nation on Drugs and Crime, but instead most cultivars had values for the following chemotypes: Chemotype 1 ($X > 10$), Chemotype II ($0.2 < X < 10$), and Chemotype III ($X < 0.2$). Other researchers,^{7,8,9} demonstrated the cannabinoid levels in *C. sativa* stay constant from seedling stage through the plant lifecycle allowing for chemotype identification early in the plant's development before flowering.

B.2 Quality Control



(b) (4)

⁵ Drugs, U.N.O.O., 2009. Recommended Methods for the Identification and Analysis of Cannabis and Cannabis Products. United Nations Publications.

⁶ Hillig, K.W., Mahlberg, P.G., 2004. A chemotaxonomic analysis of cannabinoid variation in *Cannabis* (Cannabaceae). *Am. J. Bot.* 91 (6), 966–975.

⁷ Broséus, J., Anglada, F., Esseiva, P., 2010. The differentiation of fibre-and drug type Cannabis seedlings by gas chromatography/mass spectrometry and chemometric tools. *Forens. Sci. Intl.* 200 (1–3), 87–92.

⁸ Barni-Comparini, I., Ferri, S., Centini, F., 1984. Cannabinoid level in the leaves as a tool for the early discrimination of Cannabis chemiovariants. *Forens. Sci. Intl.* 24 (1), 37–42.

⁹ Vogelmann, A.F., Turner, J.C., Mahlberg, P.G., 1988. Cannabinoid composition in seedlings compared to adult plants of *Cannabis sativa*. *J. Nat. Prod.* 51 (6), 1075–1079.



B.2.6 Testing of Adventitious Agents

In regards to testing for aflatoxins and pesticides, the response to Question 1 of the IR response dated 19-DEC-2017, the Applicant provided a reasonable response from BRT's perspective. In regards of testing for heavy metals, the response to Question 10 of the IR response dated 19-DEC-2017, the Applicant provided a reasonable response from BRT's perspective. See [Section R.1.2](#) for more information.

B.2.8 Yields

During the Applicant and OPQ only teleconference held on 02/22/2018, the Applicant was asked approximately how much (b) (4)

[Redacted]
[Redacted]
[Redacted]

B.3 Previous Human Experience

Cannabis is a genus of flowering plant that includes three species, *Cannabis sativa*, *indica* and *ruderalis*, which are native to central Asia and India.^{10,11} *Cannabis sativa* grows in the wild throughout many tropical and humid regions in the world and the leaves are digitate with serrated leaves. Its fiber is often used for hemp rope, its seed have

¹⁰ *Cannabis sativa* L. U.S. National Plant Germplasm System. Accessed: 03/23/2018 <https://npgsweb.ars-grin.gov/gringlobal/taxonomydetail.aspx?8862>

¹¹ A. ElSohly, Mahmoud (2007). *Marijuana and the Cannabinoids*. Humana Press. p. 8. [ISBN 1-58829-456-0](#). Accessed 03/23/2018.



been used for animal feed and its oil has been used as a vehicle for paint.¹² It is a dioecious plant, meaning there are two separate female and male plants (See Figure 7) and occasionally hermaphrodite plants, containing both male and female characteristics. The male plants are taller and thinner and have flower like pods containing the fertilizing, pollen-generating anthers, while the female plant is darker and shorter and has short hair protruding at the of the bracteole pods. (b) (4)

. The glandular trichomes (Figure 8) found on the female plants' floral calyxes and bracts secrete chemical compounds mostly composed of cannabinoids (i.e. THC, CBD, CBN, CBG, THCA, etc.), which are reported to produce both mental and physical effects, as well as terpenoids.¹³

Figure 7: Male and Female Cannabis plants¹⁴



Figure 8: Trichomes on Cannabis plants¹⁵



¹² “Cannabis, Coca, & Poppy: Nature’s Addictive Plants”. DEA Museum. Accessed: 03/23/2018

<https://www.deamuseum.org/ccp/>

¹³ Mahlberg Paul G.; Soo Kim Eun (2001). *“THC (tetrahydrocannabinol) accumulation in glands of Cannabis (Cannabaceae)”*. *The Hemp Report*. 3 (17).

¹⁴ Royal Queen Seeds. Feminized Cannabis Seeds. Accessed: 08/16/2016:

<https://www.royalqueenseeds.com/img/cms/different%20between%20female%20and%20male%20cannabis%20plants.jpg>

¹⁵ Bubbleman and Jeremiah Vandermeer. “Inside the Trichome”. Cannabis Culture, June 12, 2009.

Accessed: 08/16/2016 <http://www.cannabisculture.com/content/2009/06/12/inside-trichome#prettyPhoto>



The oldest known written record of cannabis use is from the Chinese Emperor Shen Nung in 2727 BC.¹² Cannabis has reportedly been used by early ancestors around 440 BCE when the Greek historian Herodotus wrote about the central Eurasian Scythians taking cannabis steam baths.¹⁶ The ancient Greeks and Romans are reported to have used cannabis, and throughout the Middle East, usage spread in the Islamic empire to North Africa. Use spread to the western hemisphere in 1545 when the Spanish imported it to Chile for its use as a fiber. While in North America, cannabis was grown as hemp (a specific variety of *Cannabis sativa*) on many plantations to be used for rope, clothing and paper.¹²

Previous studies have utilized a wide range of oral doses of both CBD and THC for a variety of indications. According to Natural Medicines Comprehensive Database,¹⁷ 200-300mg CBD was used daily for up to 4.5 months to treat epilepsy,^{18,19} to treat symptoms of multiple sclerosis cannabis plant extracts containing 2.5-120mg of THC-CBD combination were taken daily for 2-15 weeks²⁰ and 40-1,280mg of CBD has been used daily for up to 4 weeks in patients with treatment-resistant schizophrenia.²¹ For

(b) (4)

¹⁶ Butrica, J. L. *The Medical Use of Cannabis Among the Greeks and Romans. Journal of Cannabis Therapeutics.* **2002**, 2 (2): 51–70.

¹⁷ Cannabis. Natural Medicines Comprehensive Database. Accessed: 03/29/2018.

<https://naturalmedicines.therapeuticresearch.com/databases/food,-herbs-supplements/professional.aspx?productid=947>

¹⁸ Carlini EA, Cunha JM. Hypnotic and antiepileptic effects of cannabidiol. *J Clin Pharmacol* 1981;21(8-9 Suppl):417S-27S

¹⁹ Cunha, J. M., Carlini, E. A., Pereira, A. E., Ramos, O. L., Pimentel, C., Gagliardi, R., Sanvito, W. L., Lander, N., and Mechoulam, R. Chronic administration of cannabidiol to healthy volunteers and epileptic patients. *Pharmacology* 1980;21(3):175-185.

²⁰ Lakhan, S. E. and Rowland, M. Whole plant cannabis extracts in the treatment of spasticity in multiple sclerosis: a systematic review. *BMC.Neurol.* 2009;9:59

²¹ Zuardi, A. W., Hallak, J. E., Dursun, S. M., Morais, S. L., Sanches, R. F., Musty, R. E., and Crippa, J. A. Cannabidiol monotherapy for treatment-resistant schizophrenia. *J Psychopharmacol.* 2006;20(5):683-686.



[REDACTED]

Sesame seed oil is a widely consumed vegetable oil in the United States and is often used in a variety of cooking techniques across the Middle East, Africa, and many parts of Asia. The oil can be found in most U.S. grocery stores or specialty Asian market places for purchase. Sesame oil is composed mostly of fatty acids, such as linoleic, oleic, palmitic and stearic acids. Sesame was cultivated approximately 5000 years ago as a crop flourishing in areas commonly affected by droughts, and it was one of the first crops processed for oil. Sesame cultivation is thought to have originated in the Indus Valley of North India, and then spread throughout Asia.²² The Applicant plans to use USP/NF grade sesame seed oil that complies with the USP/NF Sesame Oil monograph specifications and the Certificate of Analysis provided for the batch tested also complies with EP specifications. Sesame seed oil's use [REDACTED] (b) (4) appears acceptable based on the extensive human use of the product as a food (i.e., oil) and its accessibility in the U.S. marketplace. There are no serious safety concerns regarding the use of sesame seed oil [REDACTED] (b) (4).

BRT Comments

BRT reviewed all the information the Applicant provided for the Botanical Raw Material (BRM). It is reasonable for the Applicant to have [REDACTED] (b) (4)

[REDACTED] (b) (4)

The Applicant controls the growing, harvesting, and primary processing of the BRM in accordance with the World Health Organization (WHO) guidelines on Good Agricultural and Collection Practices (GACP) and the GW Growing Protocol, which is acceptable and in line with the recommendations provided in the [Botanical Drug Development Guidance for Industry](#). Additionally, the specifications for [REDACTED] (b) (4) to maintain batch – to – batch consistency of the BRM in all the glasshouses used for growing was provided and appears acceptable. [REDACTED] (b) (4)

[REDACTED] (b) (4)

Based on BRT's review of the information provided by the Applicant, the quality controls of the BRM, [REDACTED] (b) (4) appear acceptable.

²² Raghav Ram; David Catlin; Juan Romero & Craig Cowley (1990). "[Sesame: New Approaches for Crop Improvement](#)". Purdue University.
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S. Drug Substance

S.2.3 Control of Materials





Cassandra
Taylor

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Comments: Approved



Charles
Wu

Digitally signed by Charles Wu

Date: 3/29/2018 04:00:26PM

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Comments: I concur with primary review.