Appendix A

Summary of findings

Based on a review of the available published scientific literature and searches of relevant databases, cannabidiol (CBD) is a dietary ingredient under section 201(ff)(1)(F) of the Federal Food Drug and Cosmetic (FD&C) Act, and a new dietary ingredient under section 413(d) of the FD&C Act. In consultation with FDA's Center for Drug Evaluation and Research (CDER), the Office of Dietary Supplement Programs (ODSP) in FDA's Center for Food Safety and Applied Nutrition has concluded that cannabidiol products are excluded from the definition of "dietary supplement" under section 201(ff)(3)(B)(ii) of the FD&C Act.

As a result of the searches described below, the earliest evidence ODSP found of cannabidiol potentially being marketed as a conventional food or dietary supplement was a company press release announcing that cannabidiol products in tablet, capsule, and beverage form would be available to consumers in the United States as of August 1, 2011. ODSP also found records of Investigational New Drug applications (INDs) related to cannabidiol. ODSP therefore requested further evaluation by CDER.

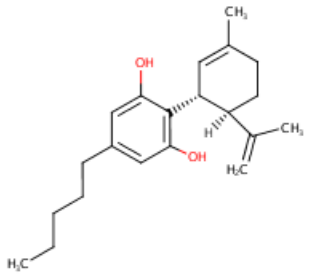
In response to this request, CDER provided details about several INDs involving the study of cannabidiol. Based on information about the INDs and studies conducted under them, CDER concluded that cannabidiol is an article authorized for investigation as a new drug for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public. CDER's analysis reflected multiple INDs that were authorized for investigation prior to August 1, 2011. (See Appendix B.)

Section 201(ff)(3)(B)(ii) of the FD&C Act states that the term "dietary supplement" does not include "an article 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, which was not before such . . . authorization marketed as a dietary supplement or as a food." In light of the results of ODSP's searches, and in light of CDER's conclusions, ODSP concludes that the term "dietary supplement" does not include cannabidiol products.

Resources used

1. Chemical Identity

Cannabidiol [(MW: 314.466 g/mol) CAS: 13956-29-1] is a compound isolated from *Cannabis sativa* L. [1]. As a constituent of a botanical, cannabidiol meets the definition of a dietary ingredient under section 201(ff)(1)(F) of the FD&C Act. This appendix provides our review of cannabidiol and the associated synonyms listed below.



cannabidiol

We identified the following synonyms for cannabidiol when we searched the relevant sources:

- CBD
- Epidiolex
- (-)-Cannabidiol
- (-)-CBD
- (-)-trans-Cannabidiol
- delta 1(2)-trans-Cannabidiol
- (-)-trans-2-p-Mentha-1,8-dien-3-yl-5-pentylresorcinol

In the remainder of this appendix, the ingredient name and synonyms above will be referred to as "cannabidiol and its synonyms" for brevity.

2. Patent information

The U.S. Patent & Trademark Office's patent database was searched for cannabidiol and its synonyms in March 2019 to identify any patents, patent applications, and published information pertaining to cannabidiol. The searches resulted in hits as indicated in Table 1. The search results indicated the use of cannabidiol as an anti-inflammatory agent, treatment of epilepsy, and as a component in pharmaceutical formulations.

There were no patents or patent applications found for the use of cannabidiol as or in a dietary supplement or other food. In addition, we found no published information pertaining to the marketing of cannabidiol as a dietary supplement or other food.

3. Search of available scientific literature

The relevant scientific literature databases were searched for cannabidiol and its synonyms in March 2019 to identify any published information about the ingredient relevant to its regulatory status under section 201(ff) of the FD&C Act. The searches resulted in some hits for the ingredient and synonyms, as shown in Table 1.

A review of these search results provided no evidence that cannabidiol has been marketed as a food or dietary supplement. Rather, the articles discussed its use as an antipsychotic drug[2, 3] and for treating epilepsy[4].

4. Search of Old Dietary Ingredient List

A search of the Old Dietary Ingredient List for cannabidiol and its synonyms was conducted in March 2019 to evaluate whether cannabidiol was marketed as a dietary ingredient prior to October 15, 1994. The search resulted in zero hits, indicating that cannabidiol was likely not marketed as a dietary ingredient prior to October 15th, 1994.

5. Search of New Dietary Ingredient Notification Internal Database

A search of FDA's New Dietary Ingredient internal database for cannabidiol and its synonyms was conducted in March 2019. The searches resulted in zero hits, indicating that cannabidiol has not been the subject of a New Dietary Ingredient notification.

6. Search of food databases[1]

The relevant food databases were searched for cannabidiol and its synonyms in March 2019 to identify any conventional food or dietary supplement usage of cannabidiol. The searches resulted in a total of 50 hits. The earliest date found in these hits was a March 25, 2015, entry

[1] As used in this appendix, "food databases" refers to databases with information about conventional foods, dietary supplements, or both. More specifically, to obtain additional information about past and current use of an ingredient in the food supply, we search numerous food databases using relevant search terms. While there is no database that provides a composite list of all substances present in the food supply, the databases below provide extensive information about ingredients available in the marketplace and represent the best available resources. If no information is found in the food databases, FDA may rely on internet search engines (e.g., Google) to find relevant information about the marketing of the ingredient in the food supply.

A. FDA's Everything Added to Food in the U.S. (EAFUS) List: This inventory of ingredients provides information about ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as generally recognized as safe ("GRAS"). This inventory has not been updated since 2013.
B. FDA's GRAS Inventory: This inventory provides information about GRAS notices filed with FDA since 1998, when FDA received its first GRAS notice. This inventory is updated approximately monthly by FDA.
C. Code of Federal Regulations (CFR): We search Title 21 of the CFR for information regarding whether the substance is a direct food additive, a food contact substance, and other information pertaining to the substance at issue. If information about the ingredient at issue is found, we review the information in the CFR to determine whether it establishes that an ingredient is used in food or dietary supplements and whether it provides information about the date of marketing.
D. Label Insight by Food Essentials (food and ingredient database): Label Insight is a consumer packaged goods product database of 250,000 + labels including food, cosmetics, dietary supplements, and infant formulas. The database encompasses more than 17,000 brands, totaling 80 percent of U.S. retail food and beverage sales volume.
E. United States Department of Agriculture (USDA) Food Composition Databases: The USDA Agricultural Research Service's Food Composition Databases facilitates searches of the USDA Food Composition Databases, which include the USDA National Nutrient Database for Standard Reference (SR) and the USDA Branded Food Products database. Also included in the SR are data from the USDA Database for the Isoflavone Content of Selected Foods, the USDA Database for the Flavonoid Content of Selected Foods, and the USDA Database for the Proanthocyanidin Content of Selected Foods. The USDA Branded Food Products Database is the result of a Public-Private Partnership, whose goal is to enhance public health and the sharing of open data by complementing the SR with nutrient composition of branded foods and private label data provided by the food industry. The submission of data to the USDA Branded Food Products Database is voluntary.

into the NIH Dietary Supplement Label Database for a product called "CannaVest Plus +CBD Oil Capsules."

7. Internet search for marketing evidence

According to a July 11, 2011, press release, Medical Marijuana Inc. announced that its CBD products would be available to U.S. consumers nationwide as of August 1, 2011, in tablet, capsule, and beverage form.[2] This is the earliest evidence we have found about the potential marketing of cannabidiol as a dietary supplement or other food in the United States.

8. Search of drug databases

In March 2019, ODSP conducted a preliminary search for cannabidiol and its synonyms in the drug and clinical trial databases. The purpose of this search was to evaluate whether cannabidiol may be subject to the section 201(ff)(3)(B) exclusion from the dietary supplement definition. If ODSP discovers preliminary information suggesting that the section 201(ff)(3)(B) exclusion may apply, we refer the matter to CDER for further evaluation.

In light of the search results described above, ODSP tentatively concluded that cannabidiol may be excluded from the definition of "dietary supplement" under section 201(ff)(3)(B) of the FD&C Act. ODSP therefore requested further evaluation by CDER.

CDER has concluded that cannabidiol was authorized for investigation as a new drug no later than April 1975. CDER further concluded that substantial clinical investigations of cannabidiol have been instituted and the existence of such investigations has been made public. (See Appendix B.)

Results

Table 1: Search Results

Search Terms	Database/Date Searched	Search result numbers
Cannabidiol	USPTO/March 22, 2019	1832
	Google Scholar/March 22, 2019	32000
	PubMed/March 22, 2019	2322
	DARRTS/March 22 28, 2019	149
	ClinicalTrials.gov/March 22, 2019	181
	Drugs@FDA/March 22, 2019	1
CBD	USPTO/March 22, 2019	1832
	Google Scholar/March 22, 2019	449000 (CBD is an acronym for other substances)
	PubMed/March 22, 2019	6345
	LabelInsight/March 22, 2019	1
	NIH Dietary Supplement Label Database/March 22,2019	31

[2] https://investors.medicalmarijuanainc.com/medical-marijuana-inc-pinksheets-mjna-to-distribute-cbd-and-thc-free-product-lines-in-the-united-states/

	DARRTS/March 22, 2019	14
	ClinicalTrials.gov/March 22, 2019	541
Epidiolex	USPTO/March 22, 2019	1832
	Google Scholar/March 22, 2019	811
	PubMed/March 22, 2019	26
	DARRTS/March 22, 2019	75
	ClinicalTrials.gov/March 22, 2019	181
	Drugs@FDA/March 22, 2019	1
(-)-Cannabidiol	PubMed/March 22, 2019	2322
	Google Scholar/March 22, 2019	32100
	ClinicalTrials.gov/March 22, 2019	70
(-)-CBD	Google Scholar/March 22, 2019	449000
	PubMed/March 22, 2019	6345
	ClinicalTrials.gov/March 22, 2019	176
(-)-trans-Cannabidiol	PubMed/March 22, 2019	2322
	Google Scholar/March 22, 2019	35
delta 1(2)-trans-Cannabidiol	PubMed/March 22, 2019	314
(-)-trans-2-p-Mentha-1,8-dien-3-yl-5- pentylresorcinol	Google Scholar/March22, 2019	8
	PubMed/March 22, 2019	2322

Although the ingredient names and synonyms were searched in each indicated database, Table 1 lists only the search terms that yielded results in the indicated database on the indicated date.

Conclusion

The earliest evidence ODSP found about the potential marketing of cannabidiol as a dietary supplement or other food in the United States indicated that one firm planned to begin marketing beverages, tablets, and capsules containing cannabidiol on August 1, 2011. Appendix B demonstrates that cannabidiol has been authorized for investigation as a new drug for which substantial clinical investigations have been instituted and the existence of such investigations made public, and that multiple relevant INDs were authorized prior to August 1, 2011. ODSP therefore concludes, under section 201(ff)(3)(B)(ii) of the FD&C Act, that the term "dietary supplement" does not include cannabidiol products.

References

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