Cannabidiol (CBD)-Related Adverse Events Reports from the FDA CFSAN Adverse Event Reporting System (CAERS), 2020

Oliver Ou[1], Annette Atoigue[1], Jonathan Midura[1], Ella Smith[1], Stephanie Kenez[1], Michelle Trachy[1], Esther Ocuin[2], David Goldman[3], Nichole Nolan[1], and Katherine Vierk[1]

[1]Office of Analytics and Outreach, Center for Food Safety and Applied Nutrition, Food and Drug Administration, College Park, MD, 20740, USA
[2]Office of Dietary Supplement Programs, Center for Food Safety and Applied Nutrition, Food and Drug Administration, College Park, MD, 20740, USA
[3]Chief Medical Officer, Office of Food Policy and Response, Food and Drug Administration, College Park, MD, 20740, USA

Introduction

A 2019 Gallup poll found that 14% of U.S. adults say they use CBD-based products. These products, which may be sold as food, dietary supplements, and cosmetics, are widely available in U.S. retail spaces and online. Despite its soaring popularity, very limited human safety data are currently available. Thus, more data is urgently needed to help understand the safety profile of CBD products.

The Center for Food Safety and Applied Nutrition (CFSAN) is one of six product-oriented centers within FDA. CFSAN is responsible for regulating food, dietary supplements, and cosmetics.

Under the Food, Drug, and Cosmetic (FD&C) Act, it is illegal to market CBD by adding it to a food or labeling it as a dietary supplement.

Additionally, under the FD&C Act, cosmetic products and ingredients are not subject to premarket approval by FDA, except for most color additives. Adding CBD to cosmetic products is not prohibited by regulation. FDA can take actions if it has information that a cosmetic product is adulterated or unsafe to consumers.

To monitor the safety of foods, dietary supplements, and cosmetic products, one post-market surveillance tool that the FDA uses is the **CFSAN Adverse Event Reporting System (CAERS)**. Consumers and health care providers can submit adverse event reports related to food, dietary supplements, and cosmetics voluntarily, and dietary supplement manufacturers have a legal obligation to report serious adverse events to CAERS.

In this analysis we focus on reviewing the severity and causality information within adverse event reports in order to understand the quality of data received by FDA for evaluating potential health effects associated with CBD products marketed for ingestion or topical use by humans.

Materials and Methods

CAERS receives adverse event reports from the fifty states and US territories via MedWatch, Safety Reporting Portal (SRP), Field Accomplishments and Compliance Tracking System (FACTS), Drug Induced Liver Injury Network (DILIN), Consumer Product Safety Commission (CPSC), Emails, and telephone calls. Adverse events are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. One CAERS adverse event report can have multiple outcomes.

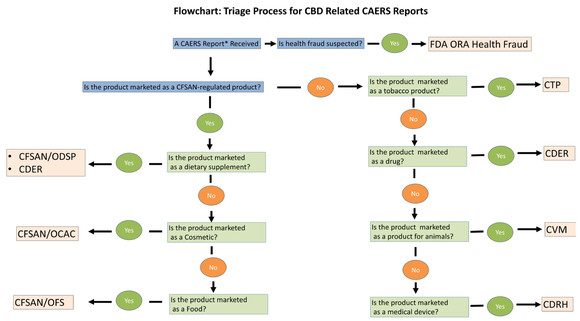
We **queried the CAERS database for reports that contain "CBD" and/or "cannabidiol"** in product name(s), ingredient(s), or narratives. We extracted the CAERS ID, age, sex, outcomes, symptoms, CFSAN product type, and System Organ Classes (SOCs).

A **causality assessment** was performed by a CFSAN Medical Officer using the World Health Organization Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (WHO-UMC) and the causality terms include certain, probably, possible, unlikely, insufficient information, and unrelated.

A CFSAN Medical Officer also performed a **severity assessment** according to the 21CFR312.32(a) which defines that an adverse event is considered "serious" if the event resulted in death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

Results and Discussion

- A comprehensive triage process has been developed by CFSAN to ensure CBD related reports are disseminated to appropriate program offices.
- CFSAN's Signals Management Branch (SMB) manages the receipt of incoming reports and coordinates the review of reports by the appropriate CFSAN program offices and/or refers the report to the appropriate FDA Center.
- SMB also manages the capture of report information into CAERS, provides responses to adverse event data inquiries, and works with epidemiologists, biostatisticians, medical officers, and program office subject matter experts to monitors trends related to CFSAN adverse event data.



- Of the 119 CBD related reports received in 2020, 54 (45%) were adverse events only, 43 (36%) were product complaints only, and 22 (18%) were for both adverse events and product complaints

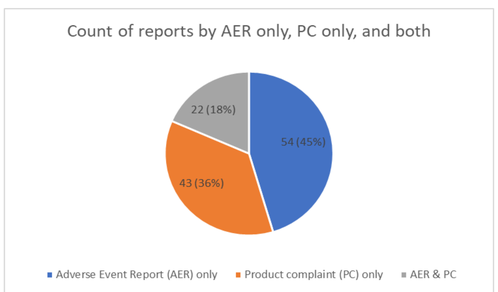


Figure 1. Count of CBD-related reports received by CAERS in 2020 by report type.

- 86 reports associated with products marketed for vaping, animals, and medical devices, as well as reports with incomplete information were excluded from the analysis.
- The remaining 33 adverse event reports associated with CBD products marketed for ingestion and topical use by humans to a CFSAN Medical Officer for in-depth review.
- The most frequent reported outcomes of the 33 reports include medically important event (21), hospitalization (12), and patient visited ER (12). There was also 1 death reported.
- The median, mean and range of ages for the complainants are 39, 43.6, and 8-85 years.
- Of the 23 complainants who provided gender information, 12 (52%) were female and 11 (48%) were male.

Table 1. Descriptive Characteristics of Adverse Event Reports with CBD products marketed for ingestion and topical use.

Age (years)	Median	39
(N=22)	Mean	43.6
	Range	[8-85]
Sex	Female	12
(N=23)	Male	11
Outcomes*	Medically important	23
(N=33)	Patient visited ER	12
	Hospitalization	12
	Other serious outcome	8
	Disability	4
	Life threatening	4
	Patient visited healthcare provider	3
	Death	1

*An adverse event report may include one or more outcomes

- Of the 33 CBD adverse event reports, 24 (73%) were deemed serious adverse events, and 9 (27%) non serious adverse events.
- Causality assessment resulted in "possible association" or "insufficient information" for most of these reports.

Table 2. Causality Assessment by Severity Assessment, CBD Adverse Event Reports (n=33).

Causality assessment	Serious AE	Non-Serious AE	Total AE
Certain	0	0	0
Probable	0	0	0
Possible	16	2	18
Unlikely	0	2	2
Insufficient information	8	5	13
Unrelated	0	0	0
Total AEs	**24**	**9**	**33**

- 28 adverse event reports indicated a wide range of organ systems with gastrointestinal disorders, psychiatric disorders, and nervous system disorders being the top 3.

Table 3. System Organ Class (SOC) for Adverse Events with CBD products marketed for ingestion and topical use (n=28).

SOCs	Counts
Gastrointestinal disorders	13
Psychiatric disorders	9
Nervous system disorders	7
General disorders and administration site conditions	6
Cardiac disorders	2
Respiratory	2
Thoracic and mediastinal disorders	2
Ear and labyrinth disorders	1
Endocrine disorders	1
Immune system disorders	1
Injury	1
Poisoning and procedural complications	1
Vascular disorders	1
* A report may include multiple adverse events that span multiple SOCs.	

- 16 of the 33 adverse event reports included at least one condition for using CBD products. A maximum of 24 conditions were reported.
- The top three self-reported conditions for using CBD products reported were for pain, anxiety, and insomnia.

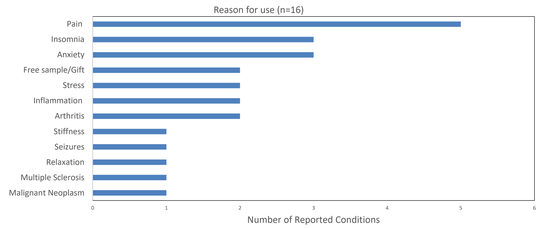


Figure 2. Number of conditions for which complainants reported using CBD products (n=16).

Conclusions

- In 2020, CAERS received 119 CBD related reports; 33 of these reports were associated with CBD products marketed for ingestion or topical use by humans and contained enough information for further review.
- Among these 33 reports:
  - Gastrointestinal disorders, psychiatric disorders, and nervous system disorders were the top three reported SOCs.
  - Pain, anxiety, and insomnia were self-reported as the top three reasons for using CBD products.
  - Causality can be difficult to fully evaluate if there is important information missing in the report, use of multiple products by the complainant, and/or too many ingredients in one product.
- While the reports submitted to CAERS vary in quality, review of adverse event reports may help provide needed real-world data.
- Continuing assessments of reports along with efforts to improve the quality of reporting information may help increase our understanding of potential health effects associated with CBD products.