U.S. FOOD & DRUG ADMINISTRATION

Cannabis and Cannabis-Derived Products, Including Cannabidiol (CBD) at Retail

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2021 FDA Retail Food Protection Seminar
(Wed Sept 15, 12:10 – 1:00 ET)

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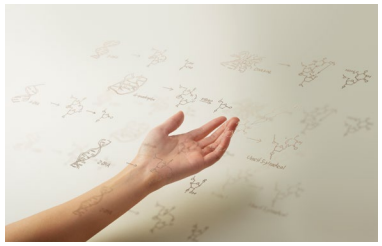


Presentation Outline

- Introduction to FDA Food Additives and Ingredient Safety Program
- Safety Assessment Approaches for Food Substances
- Food Additives vs GRAS Distinction
- The Farm bill and Cannabis
- FDA authorities and CBD
- Concerns for CBD in Food
- Looking forward

The Food "Ingredient" Universe

Direct Food Ingredients:
Sweeteners; preservatives; nutrients; fat substitutes; texturizers (e.g., thickeners, emulsifiers); flavors

Color Additives: In food, animal feed, drugs, cosmetics, and medical devices (e.g., sutures, contact lenses)

Food Irradiation Equipment:
To process food or to inspect food

GRAS Substances: Certain enzymes, fibers, proteins, lipids, sugars, antimicrobials, phytosterols/stanols, flavors, and infant formula ingredients

Secondary Direct Additives:
Antimicrobials (meat and poultry processing); defoamers; ion exchange resins

Food Contact Substances:
Coatings (paper, metal, etc.); new/recycled plastics including polymers and monomers; paper; adhesives; colorants, antimicrobials, and antioxidants in packaging; packaging materials used during food irradiation; packaging "formulations"

Foods/Ingredients Produced Via Biotechnology/Cell Culture Technology: GE Plants w/ herbicide and insect resistance, delayed ripening, improved nutrition, etc.; cultured animal cells from livestock, poultry, fish, seafood, etc.

Office of Food Additive Safety

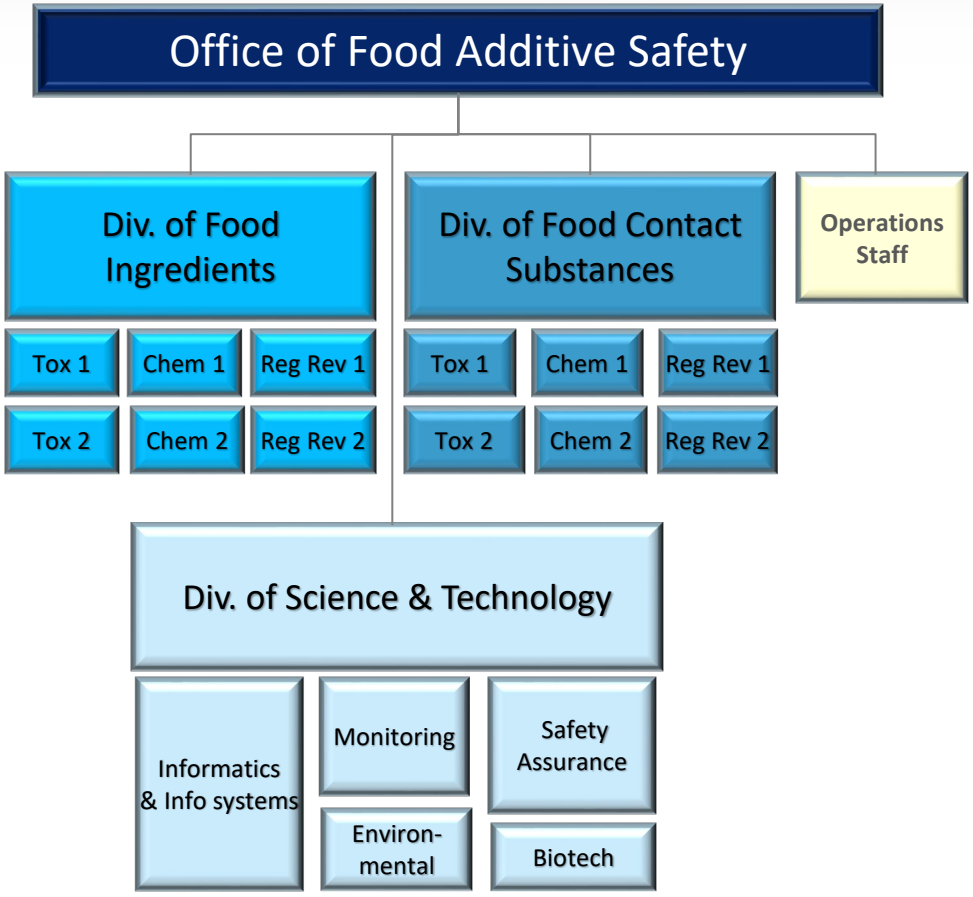
MISSION STATEMENT

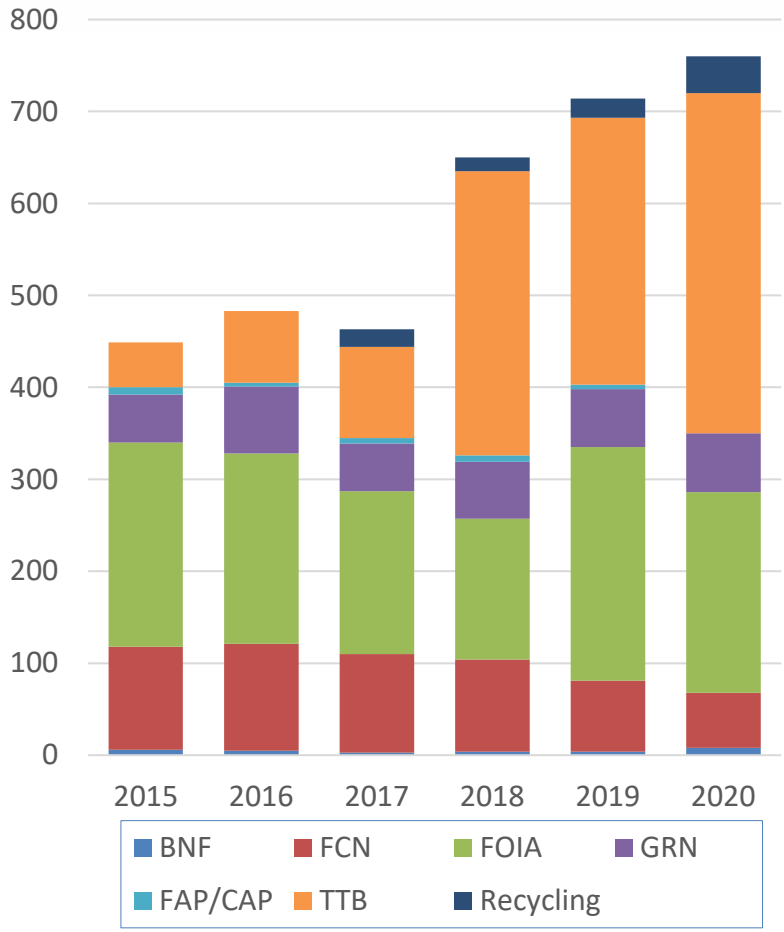
To protect and enhance consumer health by ensuring the safety of substances added to food and food contact materials.

VISION STATEMENT

OFAS is the world leader in applying sound science to food safety decisions and supporting and developing an exceptional workforce to serve the public.

Office of Food Additive Safety





FDA Food Additive Authority

Federal Food Drug and Cosmetic Act. Sec. 201(s) Food Additives

201(s) The term **"food additive"** means any substance the intended use of which results or may reasonably be expected to result, **directly or indirectly**, in its becoming a component or otherwise affecting the characteristics of any food (including any substance intended for **use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food**; and **including any source of radiation intended for any such use**), if such substance is **not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use**; except that such term does not include—

(1) a pesticide chemical residue in or on a raw agricultural commodity or processed food; or

(2) a pesticide chemical; or

(3) a color additive; or

(4) any substance used in accordance with a sanction or approval granted prior to September 6, 1958, pursuant to this chapter, the Poultry Products Inspection Act [21 U.S.C. 451 et seq.] or the Meat Inspection Act of March 4, 1907, as amended and extended [21 U.S.C. 601 et seq.];

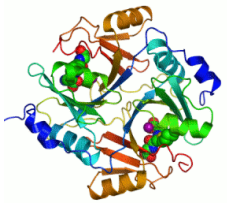
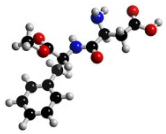
(5) a new animal drug; or

(6) an ingredient described in paragraph (ff) in, or intended for use in, a dietary supplement.

Generally Recognized as Safe: Excluded from "Food Additive" Definition

…if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use

- **Safety by general consensus vs. FDA's safety decision**
- **Allows for:**
  - Effective resource allocation
  - Flexibility with evolving science

Review and Safety Standards for all Food Additives and Ingredients

- Considerations during review
  - Fair evaluation of all the data
  - Made in the absence of complete knowledge
  - Decisions are time-dependent (i.e., based on the data available at the time we make our decisions)
  - Must meet scientific, procedural, and legal requirements

- Definition of “safe”
  - Reasonable certainty of no harm
  - Safety-based analysis (not risk:benefit analysis)

**** Dietary supplement safety standards and programs are distinct and not covered in this presentation***

Safety Assessment Questions

What is it and how much is there in food?
- Chemistry data/information

What is the intended condition of use?
- Chemistry data establishing intended technical effect

Is it safe for its intended use?
- Toxicological and safety data/information

Responsibility of petitioner/notifier to establish safety

Data/Information considered to determine safety

CHEMISTRY

- Identity and composition, including impurities.
- Manufacturing method and stability.
- Physical/chemical specifications.
- Proposed use level and analysis methodology in food.
- Data establishing its intended technical effect.
- Estimated daily intake (EDI) or cumulative EDI.

TOXICOLOGY/ SAFETY

- Full reports of toxicology and safety studies (including primary data).
- No-observed adverse effect level (NOAEL), Acceptable daily intake (ADI), or other toxicology benchmark data used for establishing safety.

Toxicological and Safety Data

***In vivo* Toxicology (Non-Clinical) Data/Info from:**

- Genetic toxicity testing
- Metabolism and pharmacokinetic studies
- Short-term (e.g., less than a month), range-finding and sub-chronic (e.g., 90 day) feeding studies
- Chronic (1 year or longer) feeding studies
- Developmental and Reproductive Toxicology (DART) studies
- Carcinogenicity studies (e.g., 2 years, may also include an *in utero* exposure phase)
- Neurotoxicity and immunotoxicity studies, as needed

***In vitro* Toxicology Data/Info from:**

- Mechanistic studies
- Genetic toxicity testing
- Protein digestibility analysis for protein safety determination

Human (Clinical) Data/Info from:

- Specialized mechanistic or metabolism studies
- Randomized clinical or controlled feeding trials
- Epidemiology studies

Structure-Activity Relationship (Computational) Data/Info

- Analog read-across
- Bioinformatic analysis of protein sequence for protein safety determination

The type of toxicity studies recommended to support the safety of a food ingredient is determined on a case-by-case basis. Chemical identity, exposure from the intended uses, and toxicokinetic profiles (FAP,GRAS) are often taken into consideration

Safety Evaluation for Food Additives and GRAS substances

Reasonable Certainty of No Harm

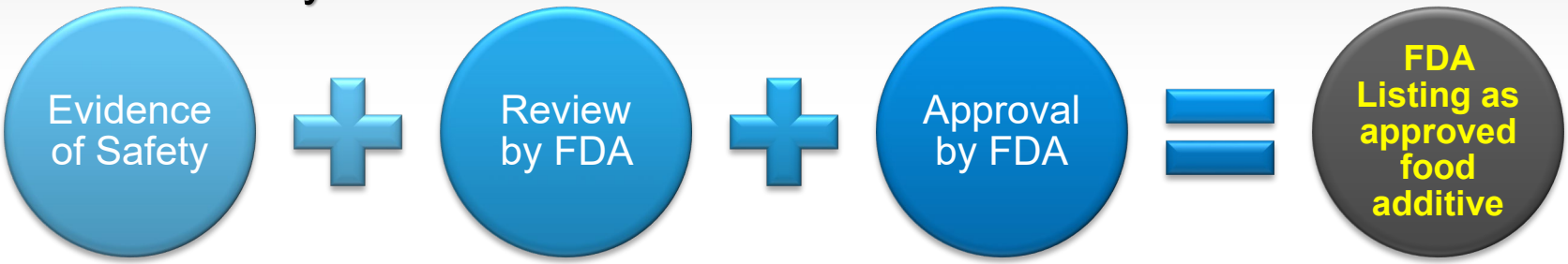
Comparing the ADI and the EDI in the context of all the data

ADI: Acceptable Daily Intake
Daily amount of a substance which may be consumed over a lifetime with reasonable certainty of no harm

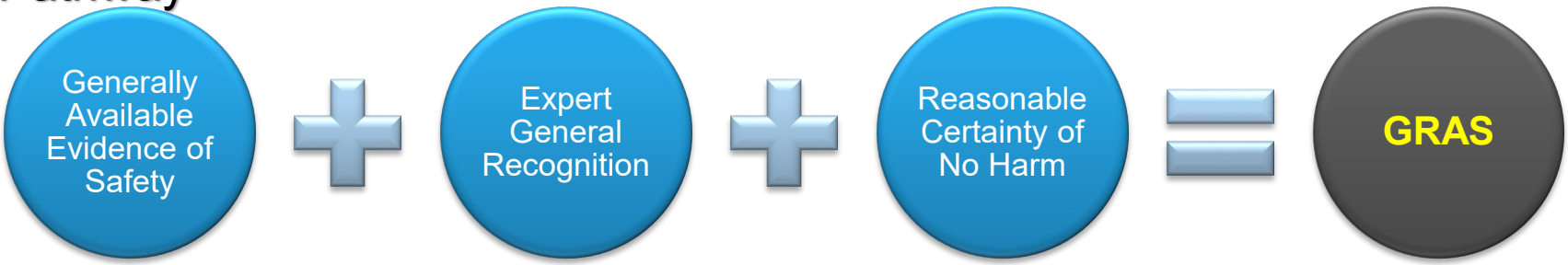
EDI: Estimated Daily Intake
Calculated based on exposure assessment data and maximum use levels

Food Additive vs. GRAS

Food Additive Pathway



GRAS Pathway



General recognition element distinguishes the GRAS standard from the food additive standard. GRAS status requires not just a demonstration of safety, but general recognition of the safety.

What about CBD?

So, is CBD GRAS?

NO

Has CBD been approved as a Food Additive?

NO

The Agriculture Improvement Act of 2018 (Farm Bill)

1. Removed hemp from the definition of marijuana in the Controlled Substances Act (CSA)

- 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 THC concentration of not more than 0.3 percent on a dry weight basis.
- CBD: One of the major cannabinoids extracted from hemp.

2. Directs US Department of Agriculture (USDA) to issue federal regulations and guidelines concerning hemp production.

- Individual States or Tribal Nations desiring primary regulatory authority over hemp production must submit a plan to USDA.

3. Marijuana is still regulated by DEA under Schedule 1 of the CSA

The Farm Bill preserved FDA's authorities

FDA's authorities under the Federal Food, Drug & Cosmetic Act (FD&C Act) and section 351 of the Public Health Service Act (PHS Act) were **specifically preserved by the Farm Bill**.

FDA's authorities include:

- Scientific and regulatory support for research on **potential therapeutic uses** of CBD products and **approval of CBD drug products** that are safe and effective.
- **Regulation of CBD products** (e.g., products marketed as foods or dietary supplements, drugs, cosmetics).
- **Enforcement actions as necessary** against violative CBD products.

Products *containing* ***CBD*** *are* ***subject to the same authorities and requirements*** *as FDA-regulated products* ***containing any other substance***.

Cannabis, Cannabis-derived, & Cannabis Related Compounds

CANNABIS

- *Cannabis sativa* L. is a plant that contains over 80 different naturally occurring compounds called "cannabinoids"
- Two well-known cannabinoids:
  - **Cannabidiol (CBD)**
  - **Tetrahydrocannabinol (THC)**
- Plants are grown to produce varying concentrations of cannabinoids – **THC** or **CBD**
- These plant variations are called cultivars

Cannabis-derived compounds

- Compounds occurring naturally in the plant – like **CBD** and **THC**
- These compounds are extracted directly from the plant
- Can be used to manufacture drug products
- Example: highly-purified CBD extracted from the plant
- FDA approved one cannabis-derived drug product: Epidiolex (cannabidiol)

Cannabis-related compounds

- These synthetic compounds are created in a laboratory
- Can be used to manufacture drug products
- Some synthetic compounds may also occur naturally in the plant and some may not
- Examples: Synthetically-derived dronabinol (also naturally occurring) and nabilone (not naturally occurring)
- FDA approved 3 synthetic cannabis-related drug products: Marinol & Syndros (dronabinol), Cesamet (nabilone)

FDA and Cannabis: Research and Drug Approval Process

FD&C Act: CBD in Foods and Supplements

If a substance has been **approved as a drug**, or **publicly studied as a drug**, it generally can't be put in human or animal foods, or dietary supplements.

- This applies to CBD.

Statutory Exceptions

- The substance was in foods or supplements first (e.g., caffeine). This **does not** apply to CBD.
- FDA issues a **regulation** (through notice and comment rulemaking) removing the prohibition/exclusion. FDA has never done this for any substance.

Safety Concerns for CBD and Cannabinoids in food

- FDA has not determined a level of CBD consumption that is safe outside of the prescription drug Epidiolex, which is approved for specific indications

- Toxicity and safety data available on CBD indicate safety concerns
  - Liver injury effects
  - Male Reproductive Toxicity
  - Potentially harmful drug-drug interactions
  - Gastrointestinal distress (e.g. Diarrhea)
  - Effects on Mood and alertness

Current FDA Warning Letters related to CBD products

- FDA issued **numerous WLs** from 2015 to present, including after passage of the Farm Bill:
  - Unapproved new drugs [§§201(p), 301(d), and 505(a)]
  - Misbranded drugs [§§301(a) and 502(f)(1)]
  - Illegally marketed food [§301(ll)]
  - Illegally marketed supplements [§201(ff)(3)(B)]
  - Unapproved new animal drugs [§§301(a) and 501(a)(5)]
  - Adulterated food [§§301(a) and 402(a)(2)(C)(i)]
    - ❖ *Several in 2020 related to unapproved COVID19 claims*
- FDA **posted lab results** for dozens of CBD products cited in the warning letters.
  - In many cases, the CBD content did not match the labeled claims and some products did not contain any CBD

Moving Forward

- Inter-agency collaboration opportunities
- FDA Voices Blog: Better Data for a Better Understanding of the Use and Safety Profile of Cannabidiol (CBD) Products
- Stakeholder Listening Sessions
  - Mechanism for stakeholders to share their perspectives with FDA staff
- Reopened public docket indefinitely (March 11, 2020)
  - Mechanism for submitting confidential data and information
- Encouraging, facilitating, and initiating research to fill the safety data gaps:
  - Grant to FDA's NCTR to conduct a study to better understand the effects of CBD exposure during pregnancy
  - Initiated study with U of Mississippi to evaluate the levels of CBD and THC in cosmetic products to assess sensitization of THC and CBD topically, and dermal penetration
- Continued monitoring of marketplace and enforcement
- Education Efforts
  - e.g., pregnant/breastfeeding women, alcohol consumption and drug interactions
- Encouraging drug development
  - Draft Guidance to Encourage Cannabis-Related Clinical Research (July 21, 2020)
  - Regulatory programs and expediting pathways (Priority Review of NDAs, Fast Track Designation, Breakthrough Therapy Designation)

Other Constituents in Hemp – Non-Cannabinoid Ingredients

Three GRAS notices have been evaluated by the FDA for specific products derived from hemp seeds

- Hemp seed oil – for use as a substitute for other edible oils, generally comprised of fats and fatty acids
- Hemp seed protein powder – for use as a source of protein, generally comprised of 30 – 65 % protein
- Dehulled hemp seed – for use as an ingredient, generally comprised of fat, protein and lesser amounts of fiber and carbohydrates

FDA has reviewed the available data and information for these ingredients and has no questions about the notifier's conclusion that they are GRAS for the intended use.

9/14/21 Consumer Update on delta-8 THC

Delta-8 tetrahydrocannabinol, also known as delta-8 THC, is a psychoactive substance found in the Cannabis sativaplant, of which marijuana and hemp are two varieties.

5 things you should know about delta-8 THC:

1. Delta-8 THC products have not been evaluated or approved by the FDA for safe use and may be marketed in ways that put the public health at risk.
2. The FDA has received adverse event reports involving delta-8 THC-containing products.
3. Delta-8 THC has psychoactive and intoxicating effects.
4. Delta-8 THC products often involve use of potentially harmful chemicals to create the concentrations of delta-8 THC claimed in the marketplace.
5. Delta-8 THC products should be kept out of the reach of children and pets.

Adverse Event Reporting

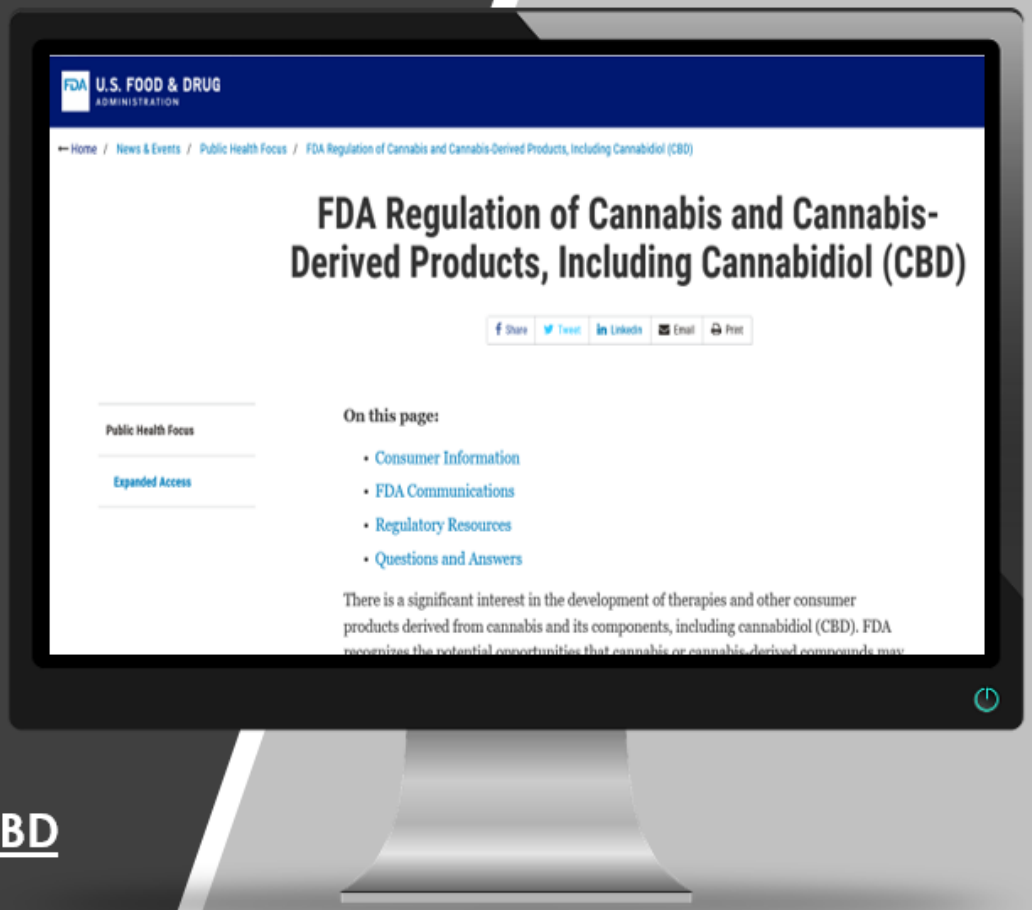
How to report complaints and cases of accidental exposure or adverse events

If you think you are having a serious side effect that is an immediate danger to your health, call 9-1-1 or go to your local emergency room. Health care professionals and patients are encouraged to report complaints and cases of accidental exposure and adverse events to the FDA's MedWatch Safety Information and Adverse Event Reporting Program:

- Call an FDA Consumer Complaint Coordinator if you wish to speak directly to a person about your problem.
- Complete an electronic Voluntary MedWatch form online or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the form, or submit by fax to 1-800-FDA-0178.
- Complete a paper Voluntary MedWatch form and mail it to the FDA.
- To report adverse events in animals to FDA's Center for Veterinary Medicine, please download and submit Form FDA 1932a found at: www.fda.gov/ReportAnimalAE.

FDA Information and Updates: Keep Informed and Educated

- *Consumer Information*
- *Communications*
- *Regulatory Resources*
- *Questions & Answers*



https://www.fda.gov/CBD

CPC@fda.hhs.gov

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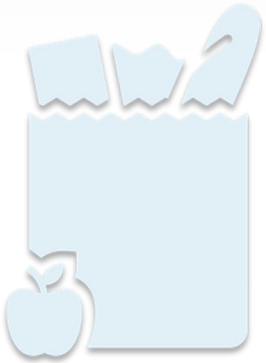
FDA Regulated Products

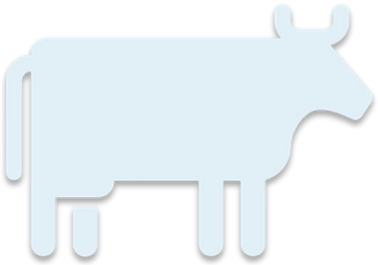
Human Food



Human Drugs/Biologics

Medical Devices

Veterinary Products



Cosmetics

Tobacco Products