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# Inclusion of Hemp-derived CBD Extracts as Food Additives and Dietary Ingredients

# Deficiencies of Scientific Research

- Clinical trials for substantiation of structure/function benefit claims – huge need for studies (mood/stress, joint health, muscle tension, intensity of addiction withdrawal, healthy sleep, neuroprotection, skin health), provide the endpoints that would define a maximal acceptable daily intake from all products … FDA's Question No. 4)
- While conventional foods are not permitted to make structure function claims (only allowed for dietary supplements), there is Agency enforcement discretion to apply the Jan 6, 2000 Structure Function Final Rule to conventional foods making claims
- Clear need for additional mechanism of action studies to support competent and reliable scientific evidence for FTC's Substantiation Standard
- Need to demonstrate identity and safety of ingredients to FDA when used in foods (dietary supplement or conventional food)
- A company's NDI Notification would provide **margin of exposure** for each product introduced into the market
- No NDIs submitted, no NOAELs to review, no margin of exposure to evaluate
- Margin of exposure
- Need to develop an No Observed Adverse Effect Level for ingestion of gummies, capsules, tablets, liquids, etc.
- Cosmetics vs. ingestibles – need for safety studies involving topical use in minipigs

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# How to Ensure Quality and Safety of CBD in Food

## Systems in Place to Ensure Quality and Safety (Identity and Safety) of CBD in Foods

- Dietary Supplements are subject to part 111 (Dietary Supplement cGMP final rule)
- Conventional Foods are subject to part 110

## Established Monitoring

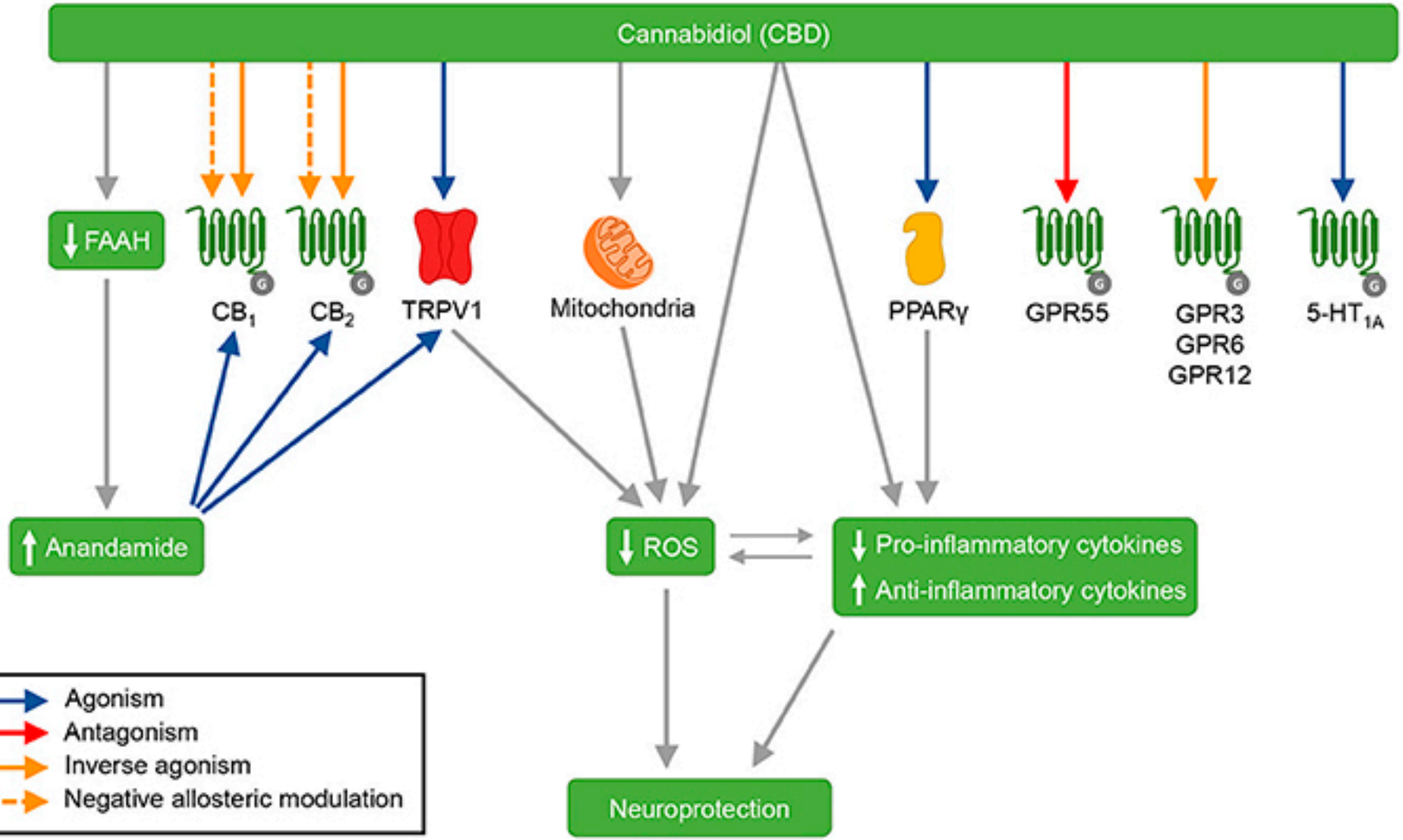
- CAERS Database - CFSAN Adverse Event Reporting System
- Dietary Supplements are the ONLY commodity of food for which there is mandatory reporting for SERIOUS adverse events

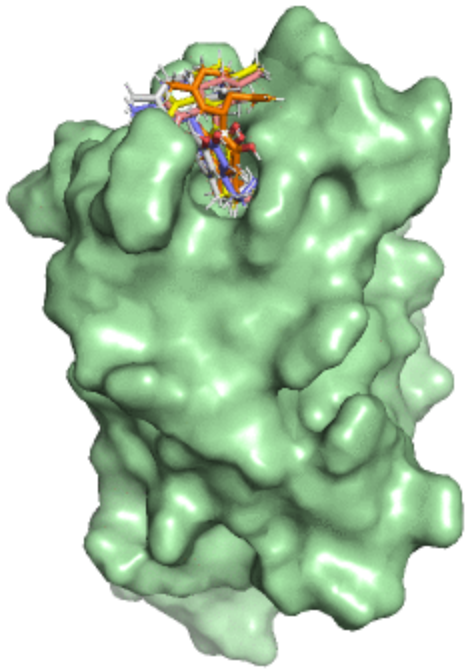
## New Dietary Ingredients

- All CBD dietary supplements marketed in the U.S. are/should be required by law to submit a New Dietary Ingredient notification
- New Dietary Ingredient Notification = ensures identity and safety to consumers, allows FDA to monitor each company
- No way for a company to ride on another NDI because they have no idea how someone else manufactures it
- Identity: limits on contaminants, specifications (no or very low THC in product), concerns over dimer formation, unsafe solvents used in extraction (hexanes, methanol, toluene
- Safety: demonstration of Max Tolerated Dose and subchronic, 90-day, repeat dose study in rodents using the product of commerce (meaning: **everyone has to submit**)
- NDI enforcement: use of import alerts (detention on the basis of failing to file an NDIN)
- If NDI enforcement, there will be a product movement from supplement category to exclusively conventional foods
- FDA must prepare for that (e.g. shift in energy drinks moving from supplements to conventional foods with Rockstar Warning Letter)
- FDA must deal with companies riding/piggybacking on another company's GRAS Conclusion through FDA Notification (no IP protection)

# Ligand Targets for CBD in Humans

- Multiple targets for CBD in the human body
- Clear need for additional mechanism of action studies and clinical trials for efficacy to support a structure/function benefit



- CB1 (CNS)
- CB2 (Periphery)

# What Levels of CBD Cause Safety Concerns

- A wide range of oral doses have been reported in the literature, with most ranging between 100 – 800 mg/day

  Fasinu P.S. et al. (2016). Current status and prospects for cannabidiol preparations as new therapeutic agents. Pharmacother 36: 781-796

- Low toxicity

*Machado Bergamaschi M., et al. (2011). Safety and side effects of cannabidiol, a Cannabis sativa constituent. Curr Drug Safety 6: 237-249.*
*Iffland K. and Grotenhermen F. (2017). An update on safety and side effects of cannabidiol: a review of clinical data and relevant animal studies. Cannabis and Cannabinoid Res 2: 139-154.*

- EPIDIOLEX is to be administered orally.
- The starting dosage is 2.5 mg/kg twice daily (5 mg/kg/day).
- After one week, the dosage can be increased to a maintenance dosage of 5 mg/kg twice daily (10 mg/kg/day).
- Patients who are tolerating EPIDIOLEX at 5 mg/kg twice daily and require further reduction of seizures may benefit from a dosage increase up to a maximum recommended maintenance dosage of 10 mg/kg twice daily (20 mg/kg/day), in weekly increments of 2.5 mg/kg twice daily (5 mg/kg/day), as tolerated. For patients in whom a more rapid titration from 10 mg/kg/day to 20 mg/kg/day is warranted, the dosage may be increased no more frequently than every other day. Administration of the 20 mg/kg/day dosage resulted in somewhat greater reductions in seizure rates than the recommended maintenance dosage of 10 mg/kg/day, but with an increase in adverse reactions.

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# Highlights of Animal Studies

- Low toxicity

No Effect on embryonic development
No effect on a wide range of physiological and biochemical parameters
No significant effects on animal behavior UNLESS extremely high doses administered (excess of 15 mg/kg IV as acute dose or excess of 30 mg/kg oral with repeat dosing for 90 days in non-human primates)
Possible effects on immune system … data remains unclear

- Mutagenicity/Carcinogenicity

CBD is negative for genotoxicity – for both *in vitro* (AMES assay) and *in vivo* (Comet and Micronucleus assays in rodents) assays
Adequate studies of carcinogenic potential have not been studied

- CNS/Addiction

Human physical dependence study, administration of CBD (1500 mg/day) to adults for 28 days did not produce signs or symptoms of withdrawal over a 6-week period following drug discontinuation (conclusion: no physical dependence)

- 600 mg CBD orally did not differ from placebo on Addiction Research Centre Inventory (ARCI) – WHO Study report
- Need more studies on repeat dose effects on place preference
- Sprague Dawley rats – 5 mg/kg does not change ICSS, but elevates the threshold at high doses (10 and 20 mg/kg) suggesting ability to diminish reward (opposite effect of cocaine, methamphetamine and opioids which lowers the threshold

# Potential for Food Ingredient-Drug Interactions

*There is only a potential for CBD to be associated with drug interactions through inhibition of some cytochrome P450 enzymes, but it is

not yet clear whether these effects occur at physiological concentrations

- **Substrate of CYP2C19 (minor), CYP3A4 (minor), UGT1A7, UGT1A9, UGT2B7**

Note: Assignment of Major/Minor substrate status based on clinically relevant drug interaction potential

- **Inhibits BSEP/ABCB11, CYP2C19 (moderate)**

*Example: Cilostazol - CYP2C19 Inhibitors may increase the serum concentration of Cilostazol.
*Example: Citalopram - CYP2C19 Inhibitors (Moderate) may increase the serum concentration of Citalopram
*Example: CloBAZam - Cannabidiol may increase serum concentrations of the active metabolite(s) of CloBAZam
*Example: Clopidogrel - CYP2C19 Inhibitors (Moderate) may decrease serum concentrations of the active metabolite(s) of Clopidogrel

**Drugs**:
CYP2C19 Inducers (Strong): May **decrease** the serum concentration of Cannabidiol.
CYP2C19 Inhibitors (Moderate or Strong): May **increase** the serum concentration of Cannabidiol.
CYP2C19 Inhibitors (Strong): May **increase** the serum concentration of Cannabidiol

CYP3A4 Inducers (Strong): May **decrease** the serum concentration of Cannabidiol.
CYP3A4 Inhibitors (Moderate): May **increase** the serum concentration of Cannabidiol.
CYP3A4 Inhibitors (Strong): May **increase** the serum concentration of Cannabidiol.
Flibanserin: CYP2C19 Inhibitors (Moderate) may **increase** the serum concentration of Flibanserin

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# Special/Unique Populations

**Pregnancy/Reproductive/Neonatal**

- Cannabidiol can be detected in the umbilical cord serum and meconium following maternal use of inhaled, non-medicinal cannabis during pregnancy (Kim 2018).
- Patients exposed to cannabidiol during pregnancy are encouraged to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry by calling 1-888-233-2334. Additional information is available at www.aedpregnancyregistry.org (http://www.aedpregnancyregistry.org/).
- Oral admin of CBD (0, 75, 150, or 250 mg/kg/day) to male & female rats prior to an throughout mating and continuing in females during early gestation, produced NO ADVERSE EFFECTS on fertility (highest dose tests was equivalent to 60 times the maximum dose recommended in humans (20 mg/kg/day)

**Breast Feeding Considerations**

- It is not known if cannabidiol is present in breast milk following oral use of cannabidiol.

**Geriatric Considerations**

- Lacking data at present in patients >55 years of age enrolled in clinical trials.
- Due to lack of clinical experience and the potential for Epidiolex to show CNS depression, recommendation is for older adults to use with caution.

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# Special/Unique Populations

**Table 1: Dose Adjustments in Patients with Hepatic Impairment**

| Hepatic Impairment | Starting Dosage | Maintenance Dosage | Maximum Recommended Dosage |
|---|---|---|---|
| **Mild** | 2.5 mg/kg twice daily (5 mg/kg/day) | 5 mg/kg twice daily (10 mg/kg/day) | 10 mg/kg twice daily (20 mg/kg/day) |
| **Moderate** | 1.25 mg/kg twice daily (2.5 mg/kg/day) | 2.5 mg/kg twice daily (5 mg/kg/day) | 5 mg/kg twice daily (10 mg/kg/day) |
| **Severe** | 0.5 mg/kg twice daily (1 mg/kg/day) | 1 mg/kg twice daily (2 mg/kg/day) | 2 mg/kg twice daily (4 mg/kg/day) |

**Hepatic Involvement**

CBD is metabolized by the liver. Epidiolex is to be used with caution in patients with hepatic impairment.
Epidiolex package insert suggests safe levels of use even in severe hepatic impairment.

<u>CBD Epidiolex vs. CBD Food</u>

- Epidiolex is exclusively pediatrics so dosing does not compare to adults
- CBD in foods is marketed to adults
- CBD in foods is not for a “disease” population but rather healthy consumers
- CBD in foods should not be marketed to those with hepatic impairment

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# Recommendations for Labeling & Claims for Dietary Supplements containing Hemp-Derived CBD Extracts

- Remove preclusion clause in 201(ff) for CBD products to permit eligibility as dietary ingredients.  Issue regulation approving as a food substance under section 301(ll)(2)
- Enforce regulations from the Dietary Supplement Health and Education Act of 1994 (DSHEA) and the 1990 Nutrition Labeling and Education Act (NLEA)
    - Will require a NDI notification within 75 days of marketing
    - Will require GRAS affirmation
- NDI status will allow lawful companies to make scientifically validated health claims regarding nutrient content, structure/function and qualified health claims
- Amend labelling regulations to include a separate identity statement and a standardized hemp-derived CBD symbol

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