Hemp and Health: Phytocannabinoids that are not CBD

NYS Bar Association

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- Disclosure Statement:
  - No potentially conflicting affiliations.

Objectives

- Review FDA's regulatory authority in relation to 'drugs', 'unapproved' drugs, and dietary supplements
- Identify phytocannabinoids, other than THC and CBD, in the hemp 'entourage'
- Discuss evidence for clinical relevance of important substances
- Consider the specter of drug-drug interactions on existing prescription therapies

Note about DEA

- Schedule I: “no currently accepted medical use”
  - 21 USC §812(b)
- ‘Marihuana’ as a Schedule I controlled substance (21USC_§802(16))
  - the seeds thereof;
  - the resin extracted from any part of such plant; and
  - every **compound**, manufacture, salt, derivative, mixture, or **preparation** of such plant, its seeds or resin.
- The Farm Bill defined “hemp” as cannabis containing < 0.3% THC and removes it from Schedule I status
  - **(16) (B)** The term “marihuana” does not include—
    - **(i)** hemp, as defined in section 7 USC §1639*o*;

Phytocannabinoid-containing products

- Opens the door to grow and derive products without threat of DEA liability
  - Conditioned on adherence to federal and/or state regulations TBD

- What will be the role of FDA in connection with products that contain plant-based cannabinoids like CBD?
  - No easy answer given the regulatory background

Definition of Drug

(21 USC §321(g)(1))

- *(A) articles recognized in the official **USP**, HPUS, NF… and*
- ***(B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease**; and,*
- ***(C) articles (other than food) intended to affect the structure or any function of the body**… and*
- *(D) articles intended for use as a component of any article specified in clause (A), (B), or (C)*

Dietary Supplements

- Dietary Supplement Health Education Act 1994
  - "DSHEA"
- Removed thousands of products from FDA control
- Definition: 21 USC §321(ff).
  - *(ff) The term "dietary supplement" -*
  - *(1) Means a product […] intended to supplement the diet that bears or contains one or more of the following dietary ingredients:*
    - *A vitamin;*
    - *A mineral;*
    - *An **herb or other botanical**;*
    - *An amino acid;*
    - *A dietary substance for use by man to supplement the diet by increasing the total dietary intake; or*

FDA Compliance Policy Guide (2011)

https://www.fda.gov/media/71004/download (accessed Aug 22 2019)

- “Marketed Unapproved Drugs”

- Enforcement priorities

FDA regulation of labeling

- Drugs
  - Misbranding (21 USC §352(f))
    - "adequate directions for use" (OTC, by the consumer)
    - "adequate information for use" (21 CFR §201.100(c)(1))
      - Prescription
- Dietary supplements
    - More flexibility for structure/function claims,
      - "This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease."
    - Less for therapeutic ('treatment of disease') claims

Curaleaf "Warning Letter"

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/curaleaf-inc-579289-07222019

- Review of website and social media
- "Unapproved new drugs" and ∴ "adulterated" and "misbranded"
- Therapeutic claims included treatment of "chronic pain", "anxiety", "ADHD", "Parkinson's", "Alzheimer's", "depression", "opioid-related withdrawal", "PTSD" and more.

Curaleaf as dietary supplement

- CBD is excluded from dietary supplement definition b/c of active ingredient in a drug product.

Epidiolex® (cannabidiol)

- FDA-approved drug-product
- The approval ‘document’ (New Drug Application, or NDA) is based on ***substantial evidence*** that the product is ***safe and effective*** for the ***intended*** use
  - Seizures associated with Lennox-Gastaut and Dravet’s syndrome in patients 2 years and older
- Clinical trials have provided much information that the 70(plus)-year ban has deprived

Epidiolex ®
FDA-approved Package Insert

- "Prescribing information"
  - Dosing, benefits and risks of prescribing
    - Kinetics: time profile of drug action
    - Contraindications
    - Intrinsic adverse effects
      - Recall: Vioxx
      - E.g., liver injury

Clinical issues

What causes any effect?

- Endogenous cannabinoids
- Drug-drug interactions
  - Effect of other drugs on action of this one
  - Effect of this one on other drugs
- Drug-enzyme interactions
  - The root cause of many of the interactions listed above
  - Genomic variability

Selective breeding

- Necessary to grow hemp (< 0.3% THC)
    - tetrahydrocannabinol
- Can DNA also be modified for production of high levels of CBD?
    - cannabidiol
- Do we care about other phytocannabinoids?
  – We should!

Cannabigerol

- Analgesic properties
- Appetite stimulator
- Anti-emetic
- Inflammatory bowel disease
- Anti-bacterial
- Antitumor

Cannabichromene

- Anti- inflammatory
- Analgesic
- Anti-fungal

Cannabinol

- Oxidation of THC to this species; not initially produced by the plant

- Evidence of pharmacologic activity is weak, but may offer some sedative and antibacterial effects

Tetrahydrocannabivarin

- Not psychoactive
- May blunt effects of THC

Cannabidivarin

- Potential value as an anticonvulsant (like CBD)

Terpenes

- Pinenes
- Limonene
- β-myrcene
- β-caryophyllene
- Linalool
- Terpinolene
- Ocimene
- Some unproven/anecdotal information about therapeutic or adverse effects for all of these

Toxins of concern

Microbiological

- E coli
- Pseudomonas
- Salmonella
- Enterococci
- Clostridium
- Aspergillus
- Actinomycetes
- Aflatoxins
- Other gram negatives

Metals

- Antimony
- Arsenic
- Cadmium
- Chromium
- Copper
- Lead
- Nickel
- Zinc
- Mercury

FDA’s Press Release (12/23/2018)

- ‘Our role has not changed’

Since then

- It has become clear that an enormous number of products had already hit the retail market

- Producers
  - Curaleaf letter and concerns about therapeutic claims
  - NB: “CBD is excluded from dietary supplement definition”

The future of FDA regulation

- Hands off (unapproved drug)?
- Drug status?
- Dietary supplement status?
- Perhaps a hybrid application of CPG of 2011