Edibles and Infused Products: Botanical Drugs

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Roadmap

- ***Introduction***
- ***Part I*: Potential FDA regulation of edibles**
- ***Part II*: Development of edibles as botanical drugs**
- ***Part III*: Competitive landscape for cannabis-derived botanical drugs**

Introduction

Edibles: Medical Cannabis Users

- Users of medical cannabis are four-times more likely to consume edibles than users of recreational cannabis.
  - (i) edibles offer a more convenient and discreet way to dose and administer cannabis than smoking whole flower or concentrate;
  - (ii) medical users may prefer the subjective and therapeutic effects achieved by consuming edibles over those achieved by smoking cannabis; and
  - (iii) edibles avoid the harmful toxins and health risks associated with smoking cannabis

Edibles: Challenges

- Uncertainty over the future legal status of these products and how they will be regulated creates business risk.
  - Legal status
    - Scheduled, descheduled, or rescheduled?
  - Regulation
    - State regulation?
    - Federal regulation by FDA?
    - Cooperative approach?

Part I: Potential FDA regulation of edibles

Federal Regulation of Edibles

- ***Congress' power under the Commerce Clause***
  - *Gonzales v. Raich*, 545 U.S. 1 (2005) (upheld the constitutionality of federal laws prohibiting the possession of home-grown cannabis intended for personal use)

- ***FDA's authority under the FDCA***
  - Jurisdiction over intrastate activities likely limited where the operative provision recites a specific nexus to interstate commerce.

FDA Jurisdiction

- Under existing authorities, FDA could potentially take enforcement action against edibles in the following situations:

  1) An edible meets the definition of a drug/new drug.

  2) An edible is a food to which a drug has been added.

  3) An edible is an adulterated food.

FDA Jurisdiction

- ***Types of FDA enforcement actions***
  - Warning Letters
  - Seizure and forfeiture of the product
  - Injunction (to prevent further violations of the FDCA)
  - Criminal prosecution (fines and/or imprisonment)

(1) FDA Regulation of Edibles: Drug/New Drug

Drug/New Drug

- ***Key elements:*** 21 U.S.C. §§ 331(d), 355(a)

  1) Disease claim

  2) Interstate commerce

Drug/New Drug

1) ***Disease claim***
   - A product's intended use (to treat a disease) is determined objectively by:
     - The claims made in the product's labeling, advertising, or other promotions.
     - Other circumstances surrounding distribution of the product.
   - Warning Letter to Natural Alchemist (Oct. 31, 2017)
     - Claims on website provide evidence that the cannabidiol (CBD)-containing product is intended for use as a drug.

Drug/New Drug

2) Interstate commerce

– "No person shall introduce or deliver for introduction into interstate commerce any new drug . . ."

(2) FDA Regulation of Edibles: Food With An Added Drug

Food With An Added Drug

- ***Key elements:*** 21 U.S.C. § 331(ll)

  1) Added drug

  2) Interstate commerce

Food With An Added Drug

1) ***Added drug***
   - FDA-approved active ingredient; OR an active ingredient for which substantial clinical investigations have been instituted and made public.
     - Ex: THC (MARINOL) and CBD (EPIDIOLEX).
   - Warning Letter to Greenroads Health (Oct. 31, 2017)
     - FDA concluded that § 331(ll) prohibits the introduction into interstate commerce of any food to which cannabidiol (CBD) has been added.

Food With An Added Drug

2) *Interstate commerce*

- "The introduction or delivery for introduction into interstate commerce of any food to which has been added a drug . . ."
- *United States v. Sanders*, 196 F.2d 895 (10th Cir. 1952)
  - "delivery for introduction into interstate commerce" includes making intrastate sales to out-of-state customers with knowledge that the product will be transported across state lines.

Food With An Added Drug

2) Interstate commerce (continued)

– 21 U.S.C. § 379a (amended by FDAMA in 1997)

- In FDA enforcement actions against a food or drug, the connection with interstate commerce required for jurisdiction is presumed to exist.
- Thus, the burden of proof for challenging FDA's jurisdiction falls on the regulated entity who must establish that the product (edible) was not introduced into interstate commerce.

(3) FDA Regulation of Edibles: Adulterated Food

Adulterated Food

- ***Key elements:*** 21 U.S.C. § 331(k)

  1) Adulterated food

  2) Held for sale **after** shipment in interstate commerce

Adulterated Food

1) ***Adulterated food (21 U.S.C. § 342(a))***
   - An edible may be deemed adulterated if it bears or contains:
     - a “poisonous or deleterious substance which may render it injurious to health”;
     - a pesticide residue; or
     - an unapproved food additive.

Adulterated Food

2) Held for sale <u>after</u> shipment in interstate commerce

- 21 U.S.C. § 321(f)(3).
  - The term “food” also means ingredients used as components of food.
- “Component jurisdiction”
  - The interstate commerce prerequisite under § 331(k) is established when one or more components used in the manufacture of the food have crossed State lines.

Takeaways

- Avoid making express or implied disease claims about edibles.
- Some caution may be warranted with sales to out-of-state customers.
- Implement practices to prevent products from being deemed adulterated under the FDCA (even if state requirements are satisfied).

Part II: Development of edibles as botanical drugs

Botanical Drugs v. Edibles

- ***Potential benefits***
  - Ability to make medical claims about approved indications
  - Access to the national market
  - More predictable legal/regulatory risks
  - Possible transition (eventually) to OTC status
  - Other benefits from legal status: different tax treatment, etc.

Botanical Drugs: Overview

- ***Description:*** a drug product derived from plant materials, algae, macroscopic fungi, and combinations thereof.
  - ***Excludes:*** highly purified botanical substances.
    - Ex: EPIDIOLEX (a highly purified, cannabis-derived extract of CBD) was primarily reviewed as a traditional NDA—not as a botanical NDA.

Manufacturing Process

Cultivated Plants

“Botanical Raw Material”

“Botanical Drug Substance”

“Botanical Drug Product”

Botanical drug vs. non-botanical drug

Botanical	Non-botanical
Naturally derived	Chemically Synthesized
Complex heterogeneous mixture	Single molecule
Variation in raw materials	Stable raw material
Unknown active component	Known identity
Variable strength or potency	quantifiable strength or potency
Unclear mechanism	Known mechanism

FDA's Modified Approach

- Incentives to encourage early-phase clinical trials of botanical drugs
  - Nonclinical Pharmacology/Toxicology
  - Chemistry, Manufacturing, and Controls (CMC)
- Modified CMC approach for late-phase development and NDA submission
  - "totality-of-evidence" approach.

Nonclinical Pharmacology/Toxicology

- ***Early-phase studies***: prior human experience may substitute for preclinical animal toxicology studies
  - Previous studies on the botanical.
  - Marketing history of the botanical as a dietary supplement (US), herbal medicine (Europe), or traditional medicine (China).
  - (Possibly) marketing history of medical & recreational cannabis.

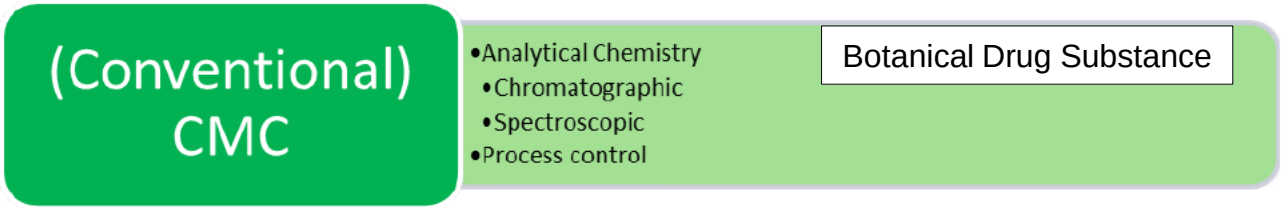
Chemistry, Manufacturing, and Controls

- ***Late-phase development***: One of the critical issues for botanical drugs is batch-to-batch therapeutic consistency due to the complex nature of these products.
  - The conventional CMC approach for assessing the identity of small-molecule drugs—which mainly consists of analytical testing—is generally insufficient for quality control of botanical drugs.

“Totality-of-Evidence” Approach

Therapeutic Consistency for Botanicals

An Integrated Assessment



Takeaways

- FDA's "totality-of-evidence" approach makes cannabis-based botanical drugs **possible**, whereas before, approval may have been difficult as a traditional NDA.
- ***BUT:*** drug development costs make this approach a non-starter for most cannabis firms.
  - *Estimated time and cost:* 6-8 years; 10s to a few 100 M$.
- Development of cannabis-based botanical drugs could still be an option for established pharmaceutical firms.

Part III: Competitive landscape for cannabis-derived botanicals

Efforts to Recoup Costs

- ***Factors influencing market exclusivity***

  1) Generic drug (ANDA) approval requirements

  2) Regulatory exclusivity periods

  3) Patent term extension

ANDA Requirements

- ***Generic drug must be therapeutically equivalent to RLD***

PE + BE = TE

  - Pharmaceutically equivalent (PE)
    - (i) same active ingredient;
    - (ii) same dosage form & route of administration; and
    - (iii) same strength.
  - Bioequivalent (BE)

Complex Cannabis APIs

- ***Question 1:*** How to define the active ingredient of a cannabis-derived botanical drug?
  - Cannabis extracts may contain multiple active constituents (cannabinoids, terpenoids, flavonoids).
  - Mechanism(s) of action may be complex (“entourage effect”).
- ***Answer:*** In the near-term, the entire cannabis extract will likely be considered the active ingredient.
  - Consistent with FDA’s current approach to approving botanical drugs & other complex, naturally derived mixtures (e.g., LOVAZA).

Complex Cannabis APIs

- ***Question 2:*** How to determine whether the active ingredients of two cannabis-derived botanical drugs are the same?

- ***Potential answer:*** Adopt a “totality-of-evidence” approach based on the considerations set forth in the Botanical Drug Guidance
  - Ex: a product-specific version of this approach tailored to cannabis-derived products.

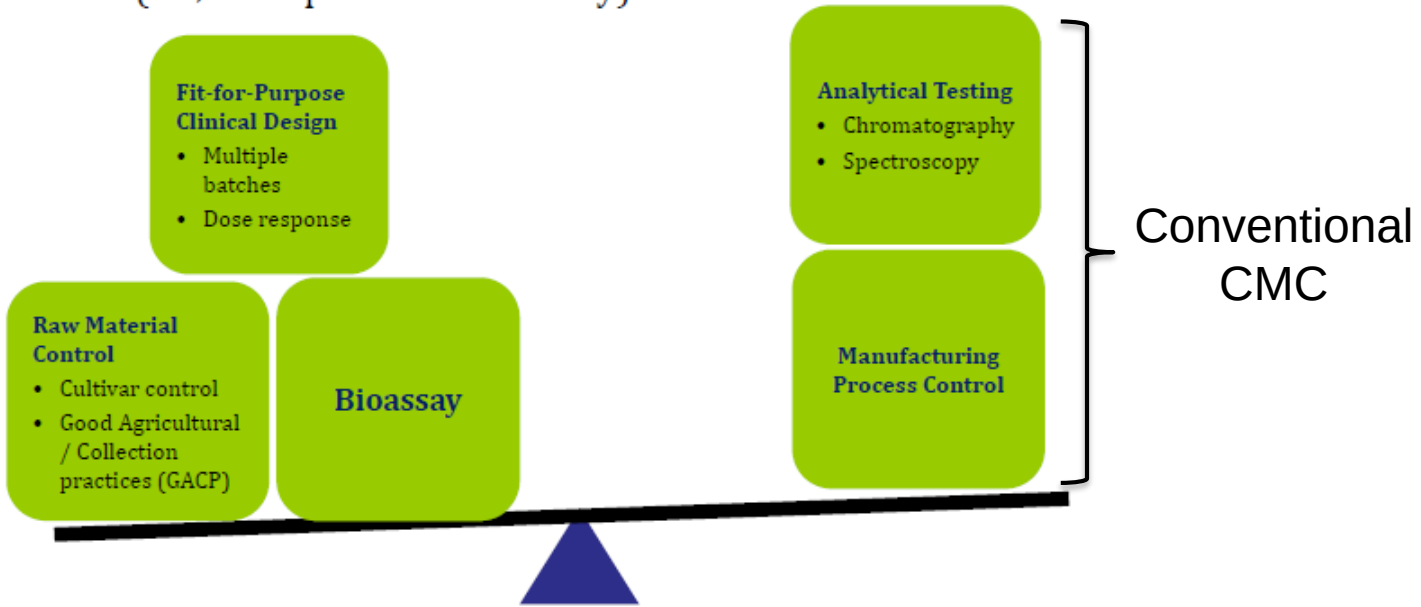
Takeaways

- In the near-term, it may be difficult for a generic manufacturer to demonstrate that its API (cannabis extract) is the “same” as the API of the brand-name botanical drug.
- If so, this may provide the brand-name botanical drug with an extended period of market exclusivity to recoup its drug development costs.
- ***BUT:*** Would the brand-name botanical drug still have to compete against unapproved medical & recreational cannabis products?

END

Modified Approach to CMC

- To ensure that marketed product batches deliver a therapeutic effect consistent with that observed for product batches tested in clinical studies (i.e., therapeutic consistency)



***Source*: FDA**

Conventional Food + Cannabis

- ***Prohibition against food containing a drug [§ 331(ll)]***
  - *UNLESS*: the Secretary, in the Secretary's discretion, has issued a regulation, after notice and comment, approving the use of such drug or such biological product in the food.

- ***Prohibition against food containing an unapproved food additive [§ 342(a)(2)(C)]***
  - *UNLESS:* (i) a food additive petition approved or (ii) a GRAS notification (GRN) or self-determination.

Conventional Food + Cannabis

- ***Products: conventional foods***
  - *Examples*: baked goods, beverages, etc.

- ***Claims:***
  - no disease claims
  - no structure/function claims
  - (likely) no health claims

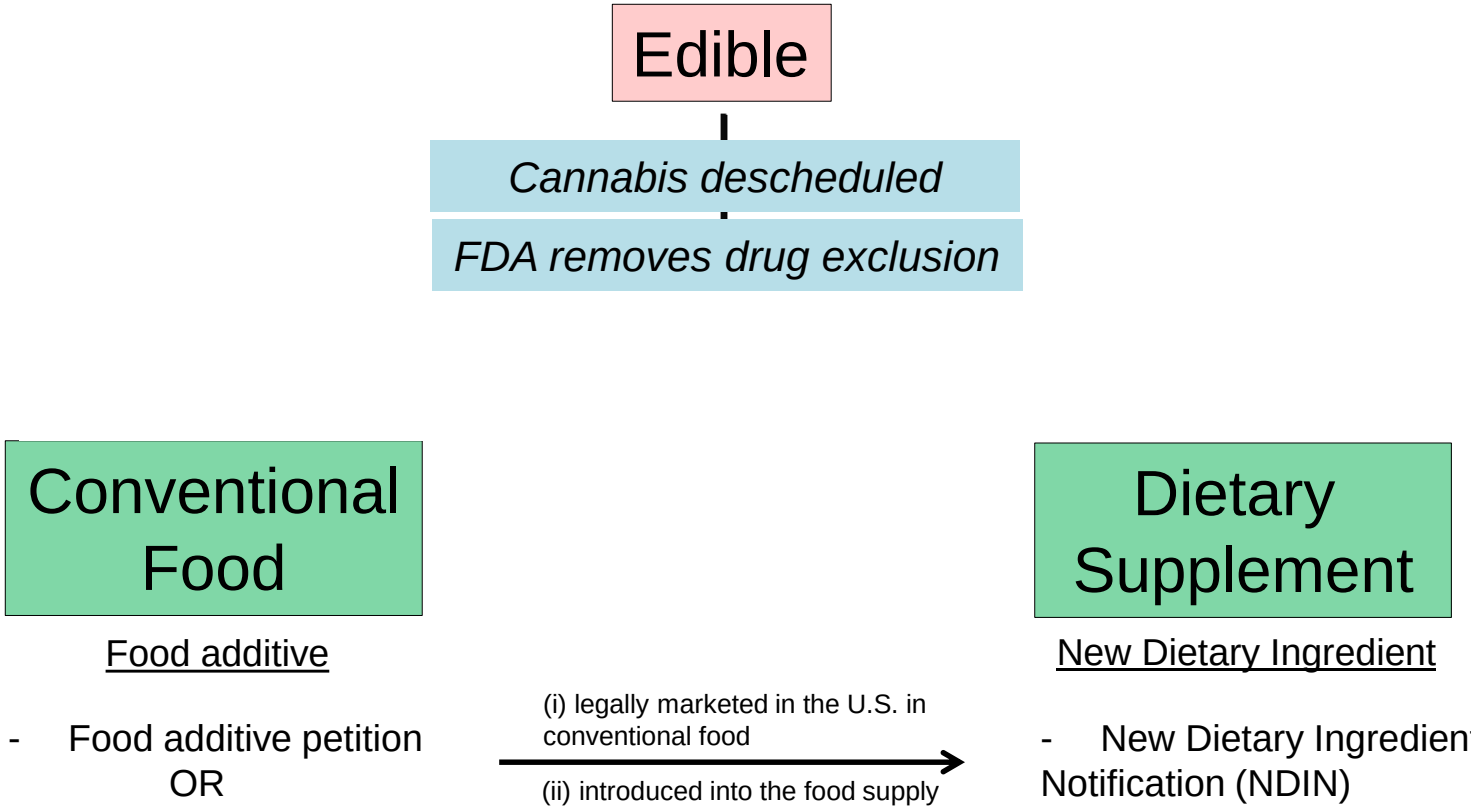
Dietary Supplement + Cannabis

- ***Prohibition against DS containing a drug [§ 321(ff)]***
  - *UNLESS*: the Secretary, in the Secretary's discretion, has issued a regulation, after notice and comment, finding that the article would be lawful under this chapter.

- ***Prohibition against DS containing a new dietary ingredient [§ 350b]***
  - *UNLESS:* manufacturer or distributor submits a premarket safety notification (NDIN) to FDA at least 75 days before introducing the product into interstate commerce.

Dietary Supplement + Cannabis

- ***Products: must be intended for "ingestion" + in a particular form***
  - *Permitted forms*: soft gel capsules, "gummies," etc.
  - *Excluded forms*: conventional foods, inhaled forms, sublingual forms/lozenges
- ***Claims:***
  - no disease claims
  - structure/function claims ("naturally acting aid to support sleep")


Edible
Cannabis descheduled
FDA removes drug exclusion
Conventional Food
Food additive
- Food additive petition
OR
- GRAS determination
(i) legally marketed in the U.S. in conventional food
(ii) introduced into the food supply
Dietary Supplement
New Dietary Ingredient
- New Dietary Ingredient Notification (NDIN)