

Medical Products Containing Marijuana: An FDA Perspective

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Food and Drug Administration (FDA)

Smart Approaches to Marijuana (SAM)

Atlanta, GA

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Disclosure Statement

I have no financial relationships with proprietary entities that produce health care goods and services

The opinions and information in this presentation are my own and do not necessarily reflect the views and policies of the FDA

“It was impossible to get a conversation going, everybody was talking too much.”

Yogi Berra





“If you don't know where you're going, any road will get you there.”
Lewis Carroll



“If you don't know where you're going, you'll wind up somewhere else.”

Yogi Berra



FDA approves
pharmaceuticals based on
validated demonstration of:

- Safety
- Effectiveness
- Quality

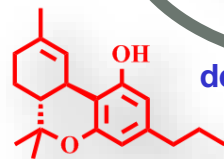
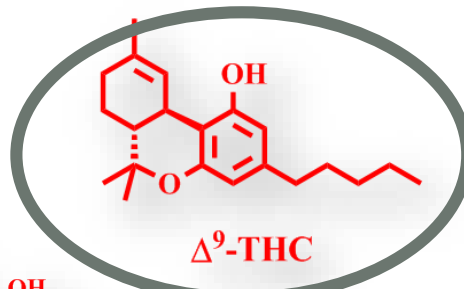
CURRENT STATUS OF MARIJUANA

State and Federal

Marijuana as defined in the Controlled Substances Act (CSA)

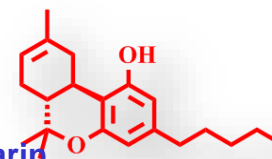
- All parts of the plant *Cannabis sativa* L., whether growing or not; the seeds thereof; the resin extracted from any part of such plant; and every compound, manufacture, salt, derivative, mixture, or preparation of such plant, its seeds or resin.
- Such term does not include the mature stalks of such plant, fiber produced from such stalks, oil or cake made from the seeds of such plant, any other compound, manufacture, salt, derivative, mixture, or preparation of such mature stalks (except the resin extracted therefrom), fiber, oil, or cake, or the sterilized seed of such plant which is incapable of germination (21 U.S.C. 802(16)).

Constituents of MJ



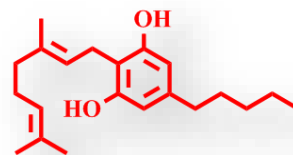
Δ^9 -THCV

delta-9-tetrahydrocannabinol



Δ^8 -THC

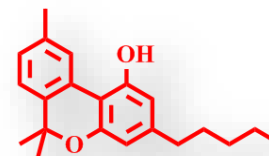
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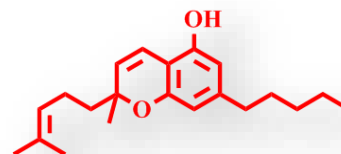
CBG

cannabigerol

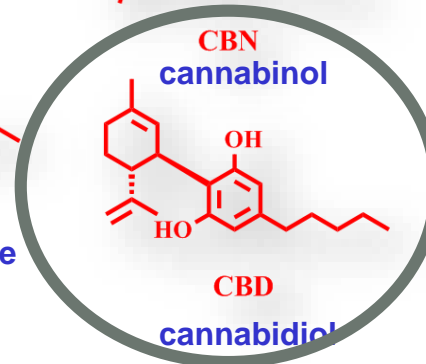
delta-8-tetrahydrocannabinol



CBN
cannabinol



CBC
cannabichromene



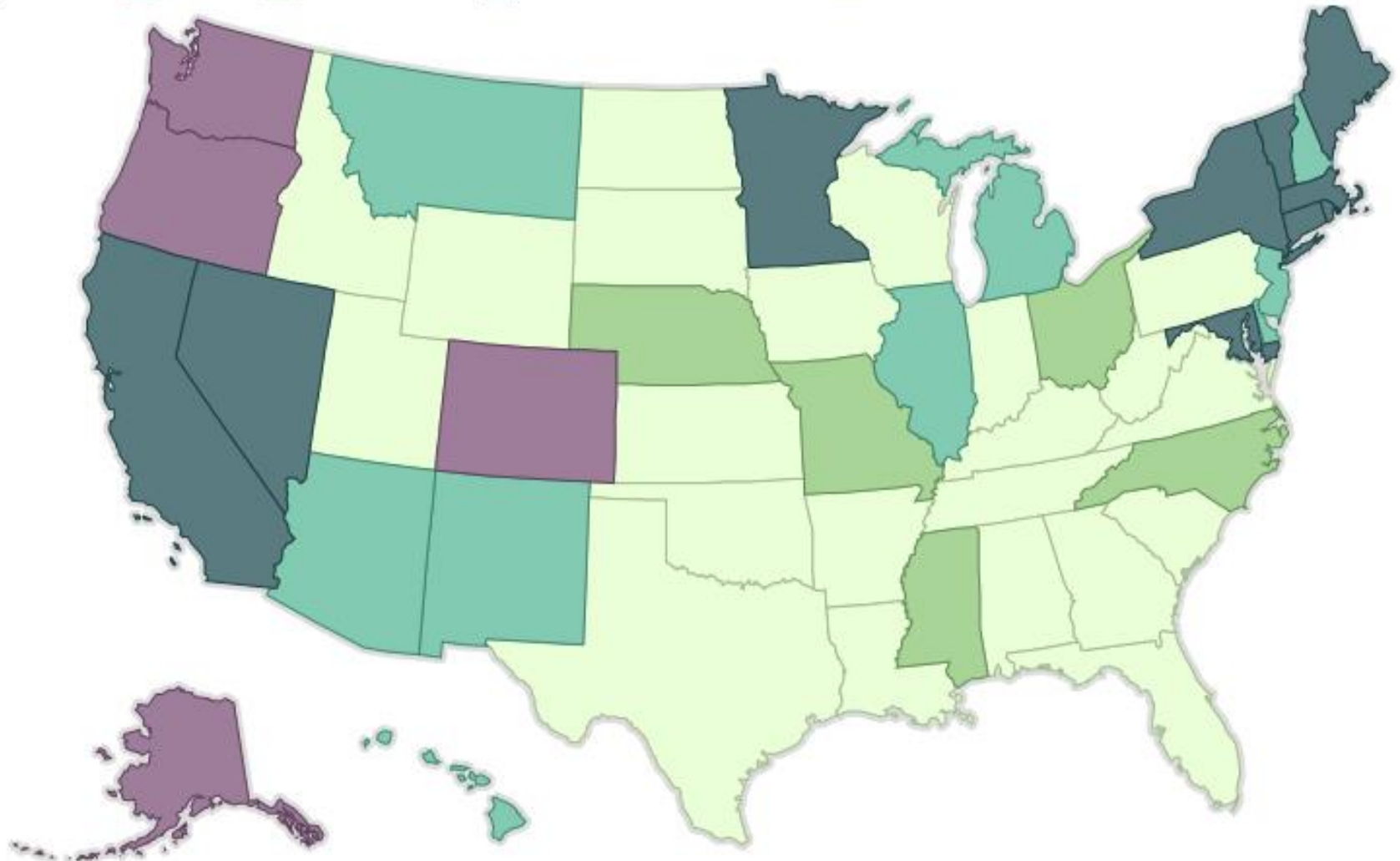
CBD
cannabidiol

Status of Marijuana in the States

- As of March 2016
 - 23 States have statutes recognizing “medical marijuana”
 - 4 states (AK, CO, OR, WA) and DC have approved recreational marijuana
 - 13 states have statutes recognizing cannabidiol (CBD) for medical use

Status of Marijuana Laws in the US

Legend: Legalized (Purple), Medical (Teal), Decriminalized (Light Green), Medical and decriminalized (Dark Teal), Fully illegal (Yellow-Green)



Source: NORML, Drug Policy Alliance, and the Marijuana Policy Project

Status of Marijuana at the Federal Level

- Controlled Substances Act of 1970:
 - Marijuana regulated under **Schedule I**, defined as having:
 - High potential for abuse
 - No currently accepted medical use
 - Lack of accepted safety for use under medical supervision

FEDERAL ROLES RELATED TO MARIJUANA

NIDA, DEA, and FDA

NIDA/NIH

- **National Institute on Drug Abuse (NIDA):**
 - Conducts and supports scientific research with marijuana and compounds found in marijuana
 - Oversees the cultivation of marijuana at the University of Mississippi (through a contract)
 - Designated by DEA as the **single** source of marijuana for medical research
 - NIDA assesses the varieties and quantities needed to meet anticipated US research needs
 - DEA establishes yearly quota of the amount grown
 - NIDA provides marijuana to researchers when:
 - Demonstrated scientific validity and ethical soundness of study
 - Submitted/approved IND to the FDA
 - Have a DEA Schedule 1 controlled substance license

DEA

- **Oversees investigator registration and site licensure to conduct studies using marijuana**
 - As a Schedule I controlled substance marijuana use in a clinical trial DEA requires special registration for the investigator and the site where the study will be conducted ([CFR §1301.18 DEA, Research Protocols](#))

FDA

- **Regulatory role:**

- Regulatory oversight for products containing marijuana or its compounds

- **Scientific role:**

- Scientific assessment ('8-factor analysis') on appropriate controls ('schedule') for marijuana to HHS and DEA
 - In consultation with NIDA
- ***FDA supports rigorous scientific research on potential therapeutic uses of marijuana or compounds***

- **Enforcement role:**

- Take actions as necessary against products containing compounds found in marijuana, particularly those that present human health risks or that make illegal claims in labeling

FDA ROLES WITH MARIJUANA

Selected FDA Roles in Regulating Marijuana

- **Scientific:** providing scientific input ('8-factor analysis') on the appropriate controls for MJ ('scheduling')

Scheduling Basics

- Scheduling: Classification of drugs based on abuse potential; medical use; physical/psychological dependence ('8 factor analysis')
- Five Schedules for control (CI- CV) in decreasing abuse potential order
 - Each schedule has different manufacturing, distribution and prescribing controls necessary
 - Aim to ensure medical availability while reducing abuse and diversion
- Different penalties are also associated with the various Schedules

Criteria for Scheduling and Schedules under the Controlled Substance Act (CSA)

C R I T E R I A	Abuse Potential		Low relative	Low relative	Low relative
	High	High	to CII	to CIII	to CIV
	No Medical Use	Medical Use			
S C H E D U L E S	Lack of accepted safety under medical supervision	Psychological or Physiological Dependence			
		Severe Psych or Physical	High Psych or Moderate to low Physical	Ltd Psych or Physical relative to CIII	Ltd Psych or Physical relative to CIV
	SCHEDULE I	SCHEDULE II	SCHEDULE III	SCHEDULE IV	SCHEDULE V
	Heroin Hallucinogens Marijuana Others	Opioids Barbiturates Cocaine Amphetamine Methylphenidate Methamphetamine PCP	Opioids (Codeine combinations, Buprenorphine) Barbiturates (combinations and products) Ketamine GHB Marinol Anabolic Steroids	Benzodiazepines and other depressants (Zaleplon, Zolpidem, Eszopiclone) Fenfluramine Modafinil Butorphanol Tramadol	Opioids in limited quantities and in combinations (Codeine, Dihydrocodeine, Difenoxin) Pregabalin Lacosamide

Statutory Basis for Scheduling Recommendation

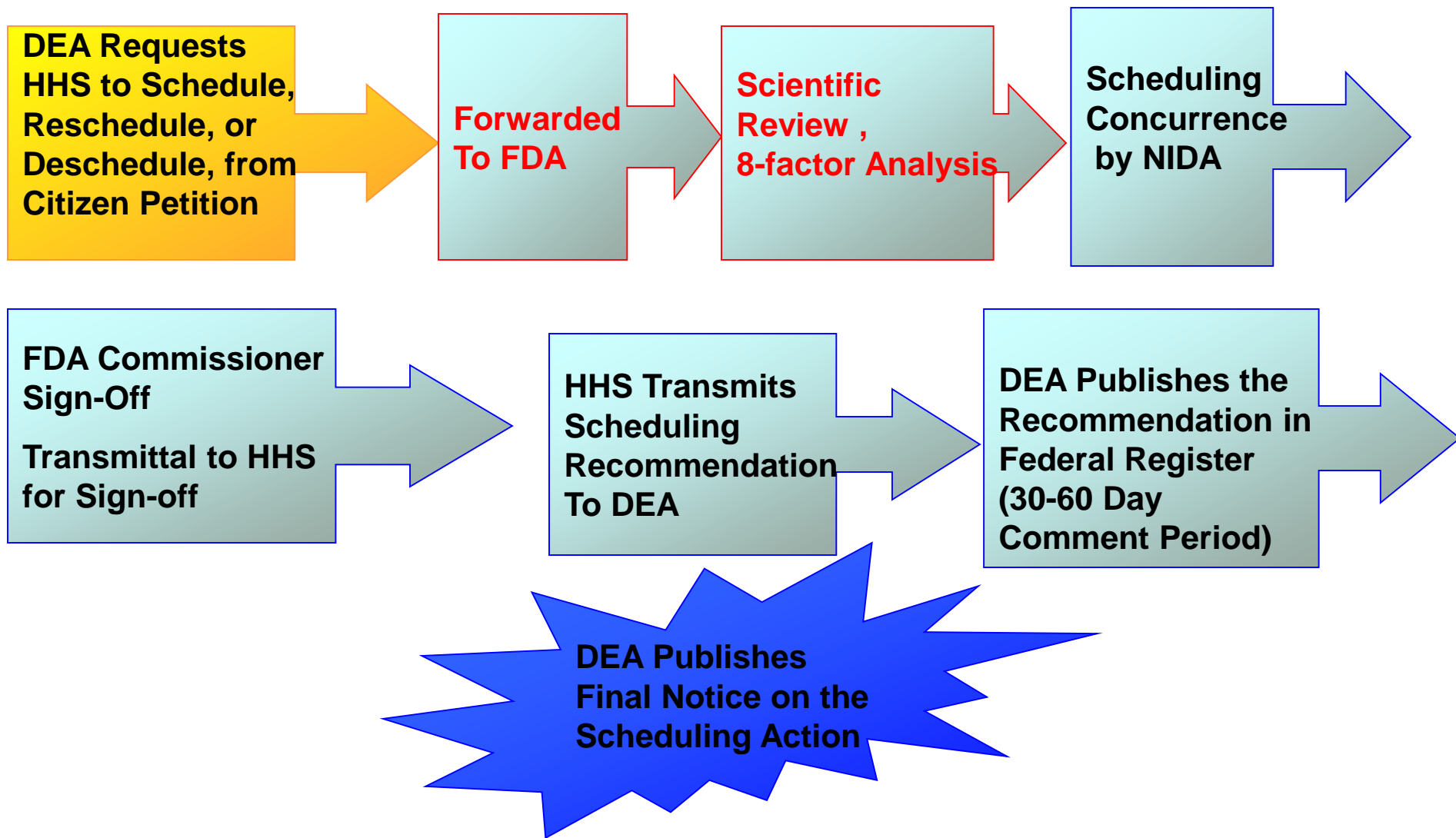
CSA requires HHS to consider 8 Factors :

1. Actual or relative potential for abuse
2. Scientific evidence of pharmacological effect
3. Current scientific knowledge regarding the substance
4. History and current pattern of abuse
5. Scope, duration, and significance of abuse
6. Risk to public health
7. Psychic or physiological dependence liability
8. Immediate precursor of a substance already controlled

Pathways to Scheduling

- Administrative process, initiated by DEA, HHS/FDA, or in response to citizen petitions or other petitioners
- Legislation by Congress to amend the CSA to add change, or remove a substance from a Schedule
 - GHB, synthetic cannabinoids present in “Spice”
- DEA can temporarily place an unscheduled substance in Schedule I to avoid an imminent hazard to public safety, and the substance is not being evaluated under IND or NDA
- DEA will schedule or reschedule a substance if required by international treaties

Inter-Agency Drug Scheduling Process



Recent Scheduling History of MJ

- Controlled Substances Act of 1970 – MJ in Schedule 1
- 2001, 2006, FDA/HHS recommends that marijuana remain in Schedule I
- 2009 – Bryan Krumm submits a petition to DEA requesting that marijuana be removed from Schedule I
- 2011 – Governors of Rhode Island and Washington petition DEA “for the reclassification of medical cannabis from Schedule I to Schedule II of the CSA.”

Status of Current 8-Factor Analysis and HHS Recommendation

- Scientific review of publically-available data on clinical uses of MJ by FDA and NIDA ongoing
 - Risk of abuse
 - Accepted medical use
- Results and recommendation follow process described earlier

Selected FDA Roles in Regulating Marijuana

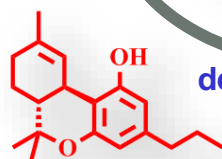
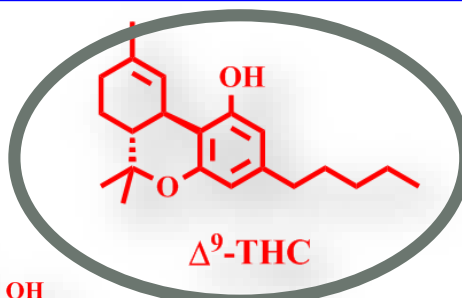
- **Scientific:** providing scientific input ('8-factor analysis') on appropriate controls on MJ
- **Regulatory:** supporting drug development from MJ

FDA & Marijuana Drug Development

- Two products approved:
 - Marinol (dronabinol) (1985): nausea from cancer chemotherapy
 - Cesamet (nabilone) (1985 (2006)): nausea & neuropathic pain

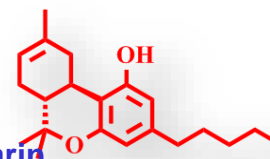


Constituents of MJ



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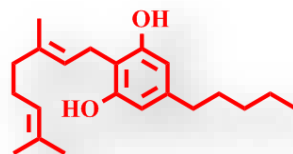
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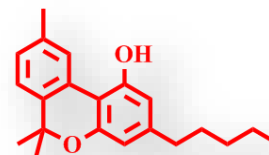
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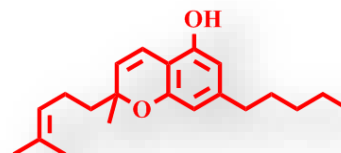
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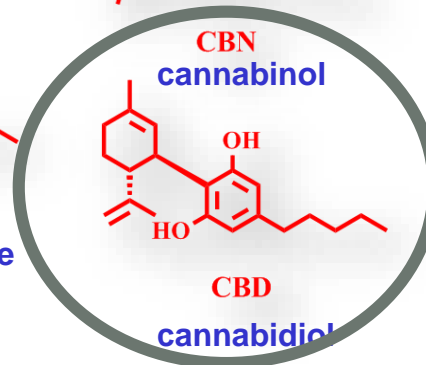
CBN

cannabinol



CBC

cannabichromene



cannabidiol

FDA & Marijuana Drug Development

- Current research focused on two compounds:
 - cannabidiol
 - tetrahydrocannabinol
- Drugs in clinical testing (IND):
 - Sativex (CBD & THC) for cancer pain & spasticity
 - Approved in Europe and Asia
 - Epidiolex (CBD) for childhood seizures
 - **March 14: GW Pharmaceuticals announced positive phase 3 pivotal study results in Dravet's Syndrome**
 - INSYS also investigating CBD for infantile spasms



FDA & Drug Development from marijuana*

- FDA supportive of development of drugs from marijuana:
 - Guidance on the use of botanicals (e.g., marijuana) as sources for drugs – August 2015
 - Focus on measures to take to help assure quality manufacturing
 - Expediting drug development using available tools:
 - Orphan Disease designation, Priority Review, Fast Track Designation

* <http://www.fda.gov/newsevents/publichealthfocus/ucm421168.htm>

FDA & Drug Development from MJ

- FDA supports development of drugs from MJ:
 - Expanded Access (EA) programs allow access to experimental drugs during development under IND
 - Set up by developer and investigator
 - Requires safety data collection and human subjects protection
 - Example: EA program for Epidiolex
 - Over 400 children have received Epidiolex through EA
 - FDA and NIDA are reviewing the scientific data on CBD to identify gaps in the database on CBD abuse potential

Selected FDA Roles in Regulating Marijuana

- Scientific: providing scientific input ('8-factor analysis') on appropriate controls on MJ
- Regulatory: supporting drug development from MJ
- **Enforcement: taking enforcement actions against products containing MJ when necessary**

CBD Warning Letters

- FDA has enforcement role to target nationally marketed products making egregious health claims
 - Includes products that allege to contain CBD
- FDA has issued two sets (Feb 2015 & Feb 2016) of warning letters (14 total) to those marketing unapproved drugs for the diagnosis, cure, mitigation, treatment, or prevention of diseases
- Some of these firms claim that their products contain cannabidiol (CBD)

Examples of Claims

- “[S]tudies have found CBD to possess the following medical properties: ... Antipsychotic – combats psychosis disorders...combats neurodegenerative disorders ... Anti-tumoral – combats tumor and cancer cells ...combats...depression disorders”
- Treats rheumatoid arthritis
- CBD helps with cancer, multiple sclerosis ...diabetes, arthritis, dystonia, Crohn’s disease...

Results of Analytic Testing

- FDA has tested these products, and many were found to not contain the levels of CBD they claimed to contain. **Consumers should beware purchasing and using any such products.**
 - <http://www.fda.gov/newsevents/publichealthfocus/ucm484109.htm>

Other FDA Marijuana Activities

- Work with outside groups on issues related to marijuana:
 - States that have legalized use of MJ, either recreational or medical
 - Discuss state experiences and data related to safety
 - States interested in supporting research and in expanded access for patients
 - Press, state officials, legislators, advocacy groups, patients, researchers

Other FDA Marijuana Activities: Safety Surveillance on MJ

- Databases and data on MJ safety are limited
 - FDA Adverse Event Reporting System (FAERS) focused on collecting reports for drug products, MJ collected incompletely
- Need new data sources to help:
 - Describe relationship between levels of CBD or THC and adverse outcomes
 - Characterize at-risk populations (e.g., children)
- *FDA supporting CDC requested (Mar 2016) report from National Academies of Science, Engineering and Medicine to assess health risks and consequences of MJ use*

Summary

- FDA has multiple activities ongoing around marijuana
- Ongoing FDA work includes:
 - Providing scientific advice on the risks of marijuana and its constituents
 - Supporting rigorous scientific research into therapeutic value of marijuana and its constituents
 - Taking appropriate actions related to the marketing of products containing marijuana or its constituents

Conclusions

- FDA will continue to support development of specific new drugs that are safe, effective, and manufactured to a high quality
- Drug development, grounded in rigorous scientific research is essential to determining the appropriate uses of marijuana and its constituents in the treatment of human disease
- FDA is committed to making this process as efficient as possible and looking for ways to speed the availability of new drugs from marijuana for the American public

*“If you ask me anything I don’t know,
I’m not going to answer.”*

Yogi Berra

