# FDA Work on Medical Products Containing Marijuana

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March, 2015

# 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

# Outline

- State of Marijuana 2015
- FDA Scientific Activities
  - Drug Scheduling
  - Marijuana 8-FactorDevelopment of Drugs from Marijuana
- FDA Enforcement Actions
  - Warning Letters
- Other Activities:
  - State interactions, Post-marketing Safety Assessment

# Central Messages

- FDA has clear role in supporting scientific and rigorous assessment of marijuana, including product development
  - The promise of safety, efficacy and reliability is not good enough

<u>However</u>

- FDA needs to do all it can to support the needed scientific research with marijuana to characterize its therapeutic promise

# FDA Work on Marijuana (MJ)

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**T**oxicological
**R**esearch

**C**enter for
**T**obacco

# CDER Highlights

- CDER mission: to ensure that safe and effective drugs are available to the American people
- CDER Center Director
  - Janet Woodcock, M.D.
- Personnel
  - More than 4300 scientists and staff:
    - MDs, Toxicologists, Epidemiologists, Statisticians, Chemists, Microbiologists…

# State of Marijuana 2015

- Access
  - 23 States with medical marijuana statutes
  - 4 states (AK, CO, OR; WA)and DC have approved recreational marijuana
- Legal Status
  - Marijuana is a Schedule I substance
  - High risk of abuse and lacking any accepted medical use

# Selected FDA Roles in Regulating MJ

- Providing scientific input ('8-factor analysis') on appropriate controls ('schedule') for MJ to DEA
- Supporting drug development from MJ
- Enforcement actions

- **Providing Scientific Input ('8-factor analysis') on Appropriate Controls ('Schedule') for MJ**
  - Supporting Drug Development
    - Enforcement Actions

# Drug Scheduling 101

- Scheduling is the classification of drugs based on their abuse potential, medical use, and physical or psychological dependence (8 factors)
- Five Schedules for control (CI- CV). (In decreasing abuse potential order) based Each schedule is associated with different manufacturing, distribution and prescribing controls necessary to ensure medical availability while reducing abuse and diversion
- In addition to the regulations, different penalties are also associated with the various Schedules

# Basis for Scheduling Recommendation

Section 201(c) of the CSA requires HHS to considered Eight Factors :

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

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

CRITERIA

| Abuse Potential | | | | |
|---|---|---|---|---|
| High | High | Low relative to CII | Low relative to CIII | Low relative to CIV |
| No Medical Use | Medical Use | | | |
| 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 |

SCHEDULES

| SCHEDULE I | SCHEDULE II | SCHEDULE III | SCHEDULE IV | SCHEDULE V |
|---|---|---|---|---|
| Heroin<br>Hallucinogens<br>Marijuana<br>Others | Opioids<br>Barbiturates<br>Cocaine<br>Amphetamine<br>Methylphenidate<br>Methamphetamine<br>PCP | Opioids (Codeine combinations, Buprenorphine)<br>Barbiturates (combinations and products)<br>Ketamine<br>GHB<br>Marinol<br>Anabolic Steroids | Benzodiazepines and other depressants (Zaleplon, Zolpidem, Eszoplicone)<br>Fenfluramine<br>Modafinil<br>Butorphanol<br>Tramadol | Opioids in limited quantities and in combinations (Codeine, Dihydrocodeine, Difenoxin)<br>Pregabalin<br>Lacosamide |

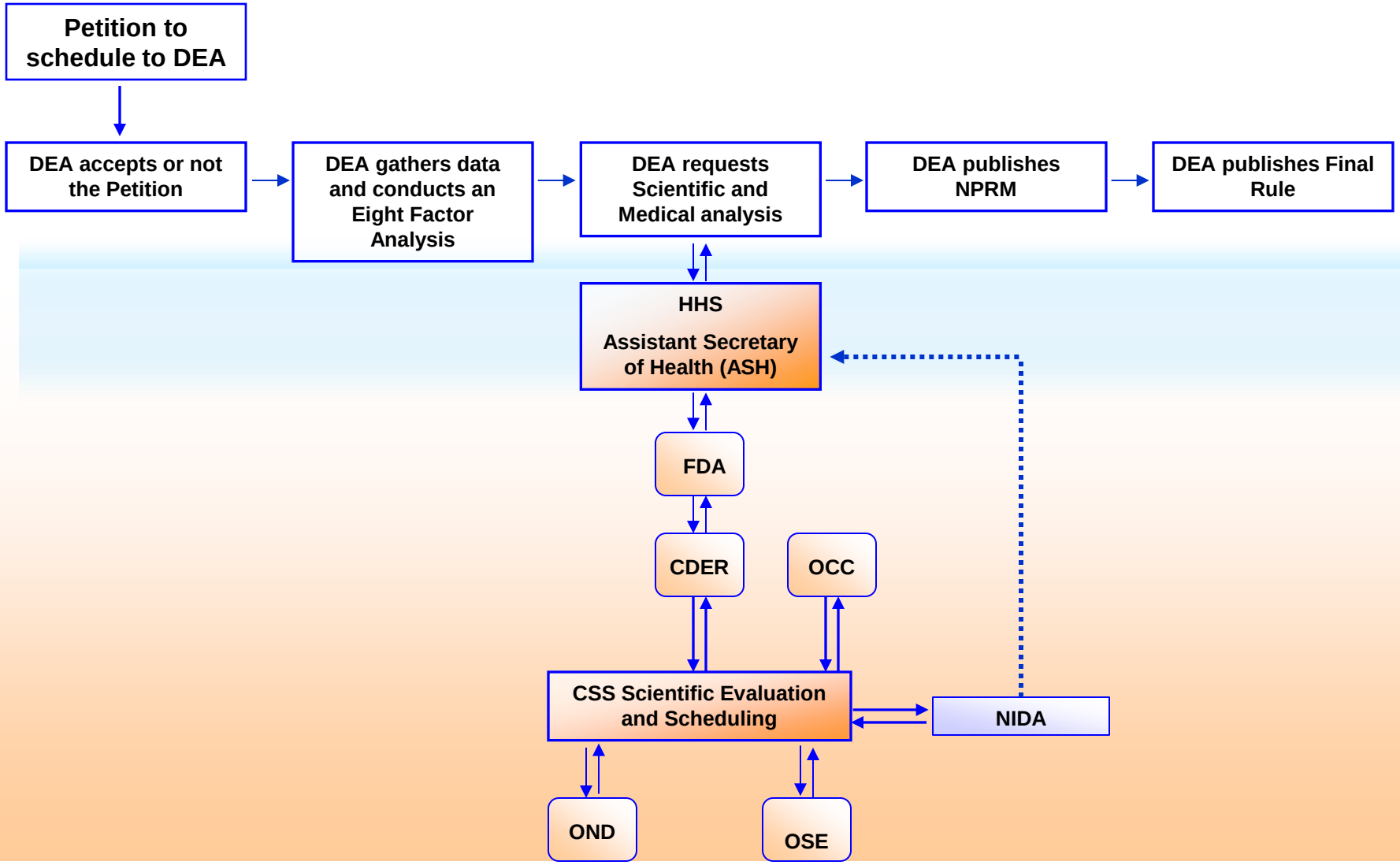
# Regulatory Requirements for Each Schedule

| | Schedule I | Schedule II | Schedule III | Schedule IV | Schedule V |
|---|---|---|---|---|---|
| Registration | Required | Required | Required | Required | Required |
| Recordkeeping | Separate | Separate | Readily Retrievable | Readily Retrievable | Readily Retrievable |
| Distribution Restrictions | Order Forms | Order Forms | Records Required | Records Required | Records Required |
| Dispensing Limits | Research use only | Rx: written No Refills | Rx: written or oral Refills with MD's authorization | Rx: written or oral Refills with MD's authorization | OTC (Rx drugs limited to MD's order |
| Manufacturing Security | Vault/Safe | Vault/Safe | Secure Storage | Secure Storage | Secure Storage |
| Manufacturing Quotas | Yes | Yes | No (Some drugs limited by Schedule II) | No (Some drugs limited by Schedule II) | No (Some drugs limited by Schedule II) |
| Import/Export Narcotic | Permit | Permit | Permit | Permit | Permit to import, declaration to export |
| Reports to DEA Mfr.& Distributor | Yes | Yes | Yes | Mfr. only | Mfr. Only |

# Pathways for Scheduling

- Administrative process, initiated by the DEA, HHS/FDA, or in response to citizen petitions or other petitioners
  - Marijuana, new drugs
- 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

# FDA Role in Scheduling



# MJ: Controlled Substances Act of 1970

- Marijuana regulated under **Schedule I**
  - High potential for abuse
  - No currently accepted medical use
  - Lack of accepted safety for use under medical supervision
- Petitions (to DEA) to reschedule marijuana

# FDA Scientific Recommendation to DEA about Scheduling of MJ

- 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 petitioned 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 public data ongoing
- Recommendation will follow process described above

- Providing Scientific Input ('8-factor analysis') on Appropriate Controls ('Schedule') for MJ
- **Supporting Drug Development from MJ**
- Enforcement Actions

# Drug Development from MJ

- Two products approved, one on the market (Marinol), and Nabilone (Cesamet)
- Research focus on two compounds: cannabidiol (CBD) and tetrahydrocannabinol (THC)
- Examples of drugs in clinical testing using CBD and THC
  - Sativex for cancer pain
  - Epidiolex for childhood seizures

# Three Agencies Involved in Research with MJ: NIDA

- **National Institute on Drug Abuse (NIDA) to obtain the marijuana for research**
  - Conducts and supports scientific research with marijuana
  - NIDA oversees the cultivation of MJ for medicinal research through contracts with the University of Mississippi to grow marijuana for research and approves release of MJ to researchers for studies

# Three Agencies Involved in Research with MJ: DEA

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

# Three Agencies Involved in Research with MJ: FDA

- **Drug developers submit investigational new drug (IND) application using MJ**
  - IND regulations, (and statutory timelines for FDA review) apply to clinical research with MJ
  - Guidance for Industry; Botanical Drugs Products
    - Provides sponsors with guidance on submitting investigational INDs for botanical drug products
    - Focus on measures to take to help assure quality manufacturing

# Drug Development from MJ

- FDA supports development of drugs from MJ:
  - Guidance on the use of botanicals (e.g., marijuana) as sources for drugs
  - Expediting drug development using available tools:
    - Orphan Disease designation, Priority Review, Fast Track Designation
  - Supporting access to experimental drug during development under IND by authorizing expanded access programs for Epidiolex
  - Interactions with other agencies, investigators, states, companies
  - FDA Marijuana WG to coordinate Agency work

http://www.fda.gov/newsevents/publichealthfocus/ucm421168.htm

- Providing Scientific Input (‘8-factor analysis’) on Appropriate Controls (‘Schedule’) for MJ
- Supporting Drug Development
- **Enforcement Actions**

# Warning Letters

- FDA has enforcement role to target nationally marketed products making egregious health claims
  - Includes products that allege to contain CBD
  - FDA recently issued several warning letters to firms that market unapproved drugs for the diagnosis, cure, mitigation, treatment, or prevention of diseases
  - Some of these firms claim that their products contain cannabidiol (CBD). FDA has tested those products and, in some of them, did not detect any CBD

--http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm421163.htm

# 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, Chrohn's [sic] disease…

http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm435591.htm

# Results of Analytic Testing

- 6/18 products making claims had no cannabinoids detected

# Other Marijuana Activities

- Work with outside groups on issues related to MJ:
  - CO, WA and legalization
    - CO providing grants to support clinical research
    - CO experience with safety
    - CO, WA on approaches to oversight
  - States interested in supporting research and in expanded access for patients
    - NY, Georgia
  - Press, legislators, advocacy groups, patients, researchers

# Other Marijuana Activities

- Safety Surveillance
  - Databases and data on MJ safety are challenged
    - FDA Adverse Event Reporting System (FAERS)
  - Need new data sources to help:
    - Describe relationship between levels of CBD or THC and adverse outcomes
    - Characterize at-risk populations (e.g., children)

# Summary

- FDA has multiple activities ongoing around marijuana
- Ongoing FDA work includes:
  - Providing scientific advice on the risks of marijuana and its constituents
  - Supporting appropriate 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 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