

# **Abuse Liability and Drug Scheduling: The Role of the FDA**

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## **Abuse Potential Assessment**

### **Federal Food, Drug and Cosmetic Act (FD&C Act, 1938)**

- Determination of Abuse Potential
- Labeling - Drug Abuse and Dependence Section

### **Controlled Substances Act (CSA, 1970)**

- Scheduling
- Schedule I Protocols
- Estimates of U.S. Medical Needs for Schedule I and II Substances

## **NDA Requirements Under FD&C Act**

If potential for abuse exists, the following must be included:

- All data pertinent to abuse of the drug
- Proposal for scheduling under the Controlled Substances Act
- Data on overdose

21 CFR § 314.50 (5) (vii)

## **Controlled Substances Act (CSA) 1970**

- Provides a role for both DEA and DHHS
- Establishes legal procedures
- Scheduling based on scientifically verified and legally defensible data
- Legislatively scheduled Class I substances include heroin, LSD, marijuana
- Examples of Class II substances include cocaine, morphine, opium, oxycodone

## **Drug Classes Subject to Regulation (CSA)**

- Opioids
- CNS Depressants
- CNS Stimulants
- Hallucinogens
- Cannabinoids
- Anabolic Steroids

## **CSA Mandate for DHHS**

**“If, at the time a NDA is submitted to the Secretary for any drug having a stimulant, depressant, or hallucinogenic effect on the central nervous system, it appears that such drug has an abuse potential, such information shall be forwarded by the Secretary to the Attorney General”**

-21 USC 811 (f)

**Delegation to FDA by Secretary, DHHS**

-21 USC 5.10

## **Drug Scheduling Process**

- **FDA/DHHS performs scientific assessment and recommends initial schedule or change to DEA**
- **DEA schedules drugs through rule-making**
- **Schedule changes can be initiated by DEA, FDA, Congress, and by citizen or sponsor petitions**
- **Compliance with International Treaties**

## **Levels of Drug Control**

### **Five Classes or Schedules Under CSA**

- ***Schedule I:***
  - **Not approved in the U.S.**
  - **High abuse potential (most restrictive)**
  - **Special DEA license for research**
- ***Schedules II-V:***
  - **Approved medical use in the U.S.**
  - **High (C-II) to limited (C-IV/V) physical or psychological dependence liability**

## **Abuse Liability Assessment**

- **Pre-IND, IND, and NDA Phases**
- **Evaluation of All Data**
  - Chemistry
  - Pharmacology (Animal and Human)
  - Pharmacokinetics & Pharmacodynamics
  - Adverse events reported in clinical trials
- **Compare to a Pharmacologically Similar Substance**

## **Abuse Potential**

- **Chemical Structure**
- **Pharmaceutical Characteristics**
  - Ease of synthesis
  - Extractability
  - Solubility
- **CNS Pharmacology**
  - Receptor
  - Behavioral effects

## **Abuse Liability Assessment Package of the NDA Includes**

- **Preclinical Pharmacology**
- **Human Pharmacology**
- **Clinical Trial Data**
- **CSA Scheduling Proposal**
- **Data on Overdose**

## **Pharmacology - Preclinical**

- **Neuropharmacological Characterization**
- **Receptor Binding**
- **Animal Behavioral Studies**
  - **Reinforcing Effects (self-administration)**
  - **Discriminative Effects (drug discrimination)**
  - **Physical Dependence (withdrawal)**
  - **Tolerance**

## **Human Pharmacology**

- **Subjective Effects - Drug Liking**
- **Toxicity and Performance Impairment**
- **Tolerance**
- **Physical Dependence**

## **Eight Factor Analysis**

**(Required under CSA)**

- **Actual and potential for abuse**
- **Pharmacology**
- **Other current scientific knowledge**
- **History and current pattern of abuse**
- **Scope, duration and significance of abuse**
- **Public health risk**
- **Psychic or physiological dependence liability**
- **If an immediate precursor of a controlled substance**

**21 USC 811(c)**

## **Scheduling Criteria CII-CV Drugs**

- **Approved Medical Use**
- **Relative Potential for Abuse**
- **Dependence Liability**

21 USC 812 (b)

## **FDA and DEA Roles Under CSA**

- **FDA**
  - Abuse Potential = Risk Assessment
  - Labeling of abuse/dependence risks
  - No control at level of prescriber, dispenser, or patient
- **DEA**
  - Licenses CI-II manufacturers; sets quotas
  - Licenses prescribers
  - Law Enforcement

## **CONCLUSIONS**

- Abuse liability assessment is a composite - based upon review of the chemistry, pharmacology, clinical considerations, and the public health risks following introduction of the drug to the general population.
- Abuse or dependence potential is a risk that needs to be managed.
- Labeling and drug scheduling alone have limited impact.