Abuse Liability Assessment and Drug Dependence:

Scientific and Regulatory Considerations in Drug Development

DIA Workshop
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Abuse Liability Assessment and Drug Scheduling:

An Overview

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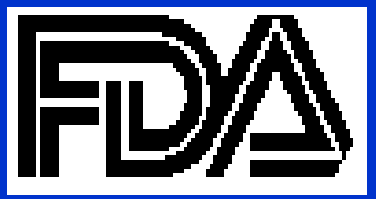

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Abuse Potential Assessment

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 under the 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 *(Single Convention on Narcotic Drugs, Psychotropic Convention)***

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**
  - **Regulates prescribers, dispensing pharmacies**
  - **Law enforcement**

Conclusions

- **Abuse liability assessment and drug scheduling are composites --based upon analysis of the chemistry, pharmacology, clinical considerations, and the public health risks following introduction of the drug to the general population**
- **Abuse or dependence potential can be best conceptualized as risks to be managed**
- **Responsibility shared by FDA and DEA**