Abuse Potential Assessment: FDA Perspective

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

Food Drug &Cosmetics Act (FD&CA 1938)

- FDA -Public Health Mission
- Ensure Americans have access to safe and effective drug products
- Regulates Drug Products (also foods, cosmetics)

Pre-Market Product Review

New Drug Review

- **Investigational New Drug (IND)**
  - Process by which a sponsor advances to the next stage of drug development known as clinical trials
    - Animal Pharmacology and Toxicology Studies
    - Manufacturing Information
    - Clinical Protocols and Investigator Information
- **New Drug Application (NDA)**
  - Formal application to the FDA for approval of a new drug
- **Biological License Application (BLA)**
  - Transfer of applications from CBER in FY 2002 for medicines such as:
    - Monoclonal antibodies, cytokines, growth factors, enzymes, other therapeutic immunotherapies

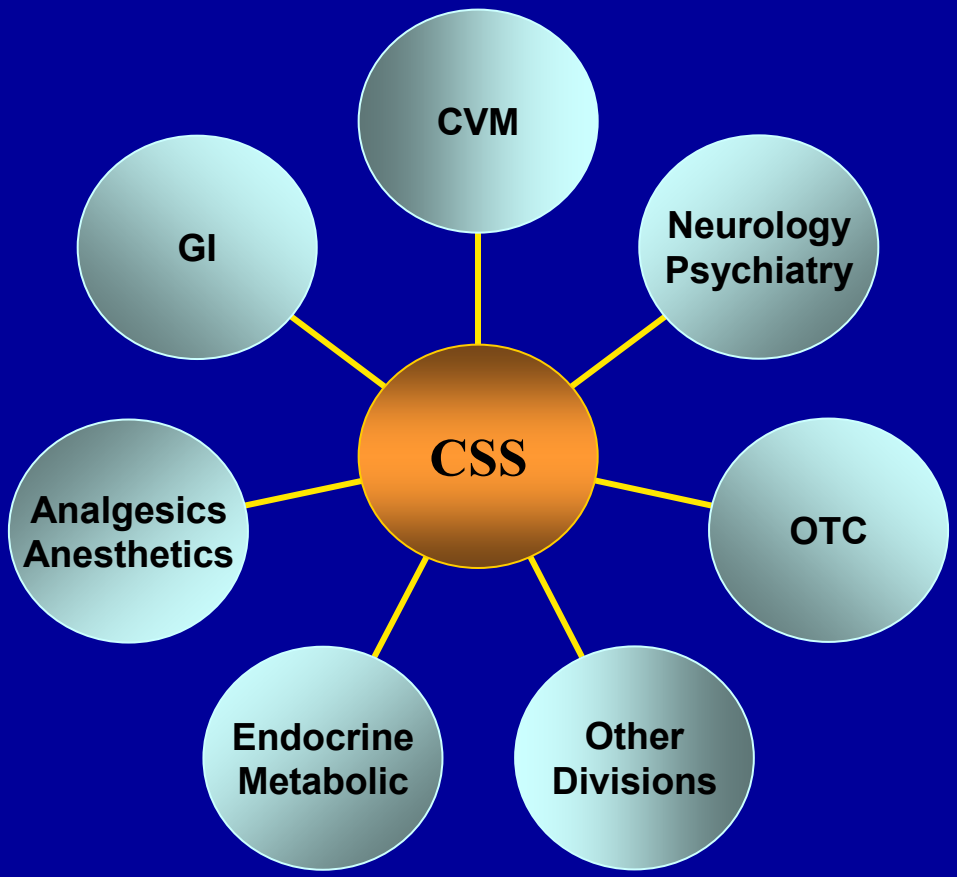
U.S. Law Controlled Substances Act (CSA) 1970

- Purpose
  - to comply with international treaties
  - to combat drug diversion
  - to assure drug availability for legitimate medical use
- Establishes legal procedures
- Defines roles of DEA and DHHS

Controlled Substance Staff (CSS) Mission

- To promote the public health through the medical science-based assessment and management of drug abuse risks.
- To assess new drugs for their abuse potential, makes recommendations (with NIDA) on scheduling and risk management interventions of controlled substances
- To Interact with multiple outside groups on drug abuse issues, both domestic and international
  - » NIDA
  - » DEA
  - » HHS
  - » SAMHSA
  - » CDC

CSS Interaction with Drug Review Teams



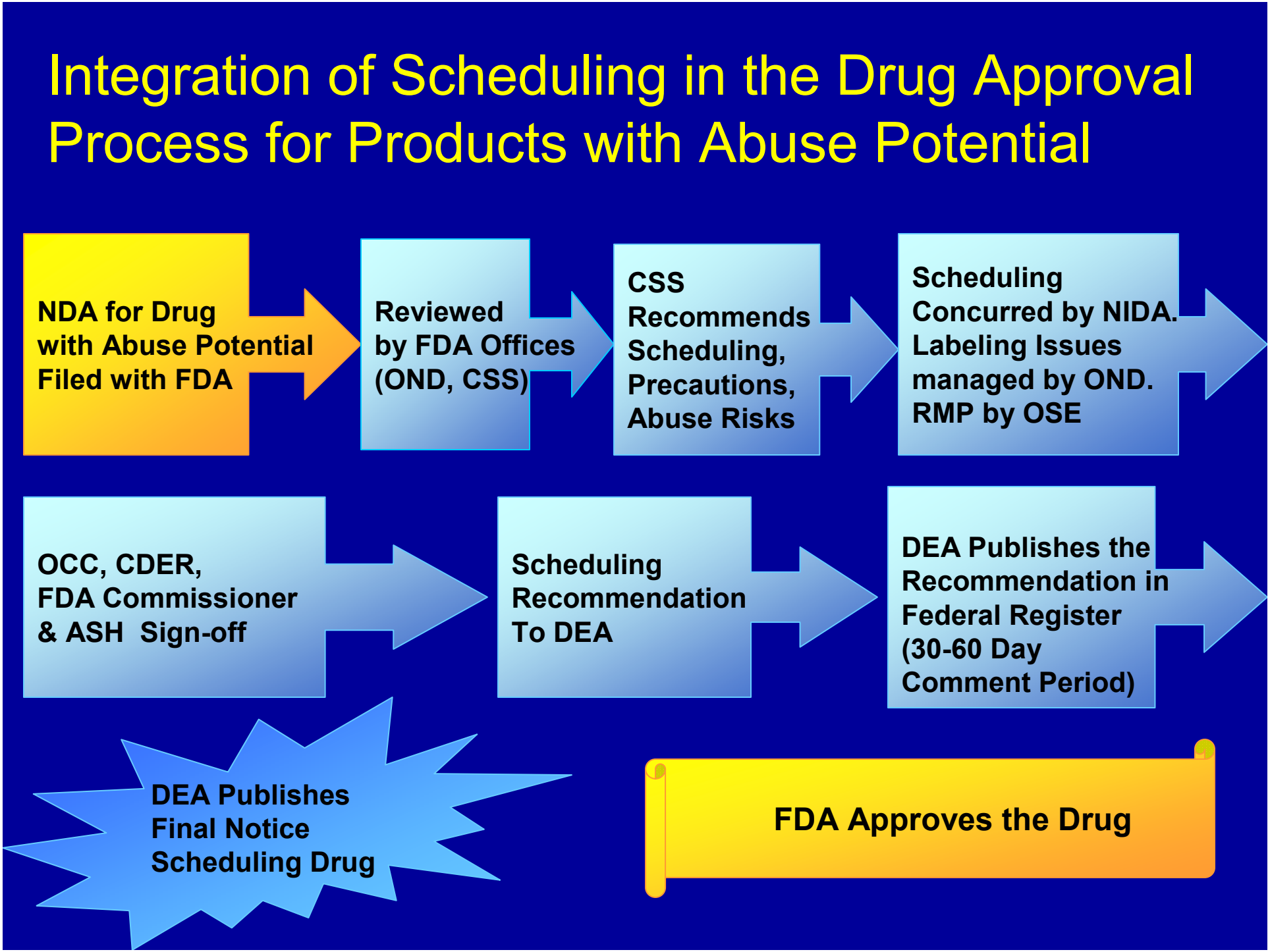
Drug Classes Subject to Regulation Under the CSA

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

Products Reviewed By CSS Before Marketing Include:

- **Treatment of Addiction & Dependence**
- **Muscle Relaxants**
- **Analgesics**
- **Anticonvulsants**
- **Antiemetics**
- **Antidepressants**
- **Narcolepsy**
- **Anorectics**
- **Antianxiety**
- **Treatment of Alzheimer's Disease**
- **Anesthetics**
- **Analgesics**
- **Neuropathic Pain**
- **Treatment of Insomnia**
- **Management of Cough & Cold**
- **Antiepileptics**
- **Smoking Cessation**

Integration of Scheduling in the Drug Approval Process for Products with Abuse Potential



Part II

Science of Abuse Potential Assessment and Drug Scheduling

Abuse Potential Assessment

Mandated by two distinct laws

- Federal Food, Drug and Cosmetic Act (FD&C Act, 1938)
  - Determination of Abuse Potential
  - Labeling - Drug Abuse and Dependence Section
  - Risk Management
- 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)

Abuse Potential

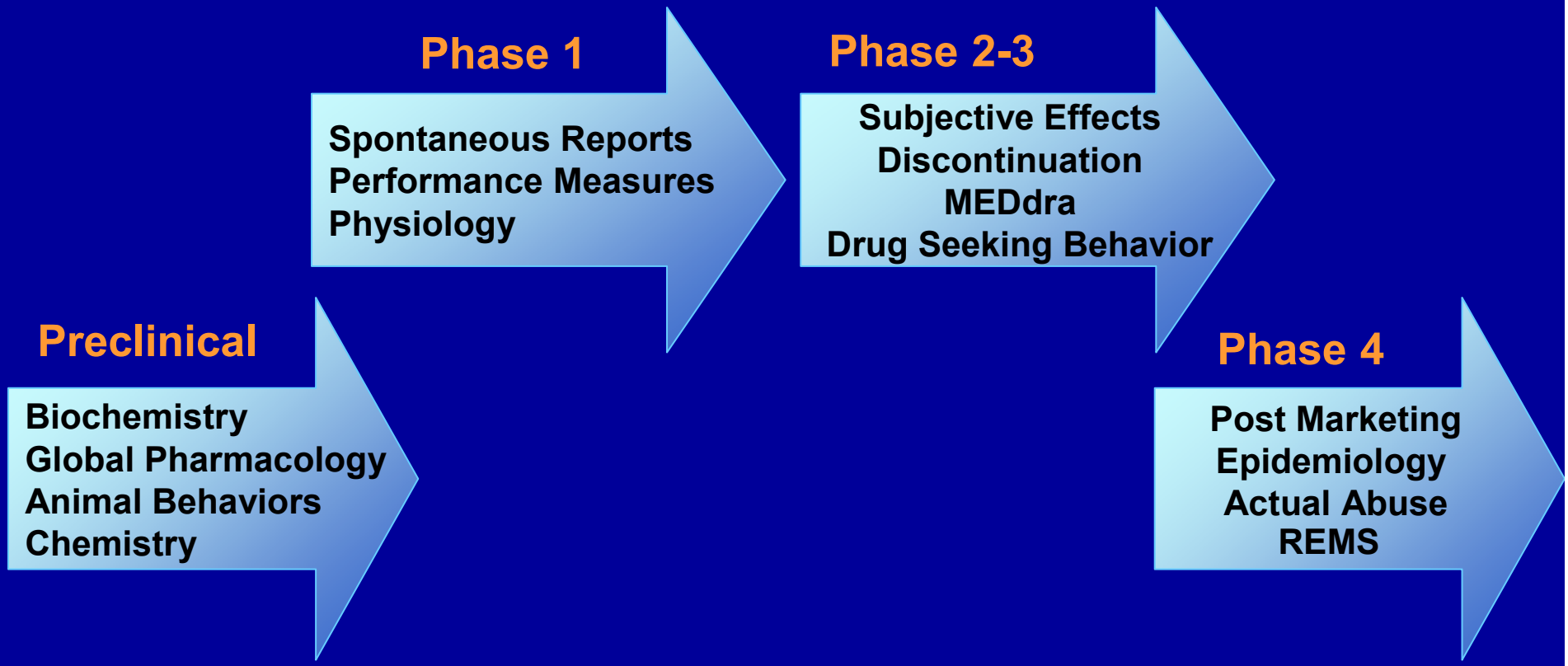
- Ability of a CNS-active drug to produce a positive or reinforcing psychic effect
- Correlated with / predictive of the risk of addiction

Abuse Potential Assessment – When?

- Pre-IND
- IND
- NDA
- Post-Marketing

CNS-Active Drugs

Data on the drug's abuse potential can be obtained at critical times in the drug development process



Abuse Potential Assessment – What?

- No single test or characteristic alone predictive
- Composite of multiple sources of data
- Evaluation of:
  - -Chemistry
  - -Pharmacology (animal and human)
  - -Pharmacokinetics & pharmacodynamics
  - -Adverse events reported in clinical trials
- Compare to a pharmacologically similar substance

Preclinical Pharmacology - Evidence of Abuse Potential

- Neuropharmacological characterization
- Receptor binding
- Animal behavioral studies
  - Reinforcing effects (self-administration)
  - Discriminative effects (drug discrimination)
  - Physical dependence (withdrawal)
  - Tolerance

Intrinsic Properties of the Drug

- Intrinsic efficacy at target
- Selectivity vs. other targets
- Pharmacodynamic potencies
- Uncertainty surrounding novel targets

Human Pharmacology

- Subjective effects – “drug liking”
- Toxicity and performance impairment
- Tolerance
- Physical dependence

Human Pharmacology - Evidence of Abuse Potential

- From clinical trials evaluation of AE profiles
  - Systematic categorization, tabulation, analysis of AEs for stimulant, mood elevation, sedation and psychotomimetic events (MedDRA)
  - Prospective evaluation of withdrawal AEs after abrupt discontinuation of treatment – “drug liking”
- From human abuse studies
  - Subjective & mood effects
  - Cognitive & performance impairment

Objectives of the Human Abuse Study

- To provide information on the relative abuse potential of new drugs in humans
- Predictive of the likelihood of abuse by recreational drug abusers
- Predictive of the extent of drug diversion and illicit street sales when the new drug becomes available to the drug abuse community

Study Considerations

- Evaluates measures following repeated single dose administrations over a period of time, depending on the time-course of the drug's effects
- Doses range from minimally effective to supratherapeutic
- Double-blind placebo controlled, within-subject or crossover design
- Conducted in recreational drug abusers, preferably in a closed residential unit
  - **Other abuse-related data in patient and normal populations exposed to the drug may be reported in other parts of the NDA**

Outcome Measures

- Ratings of “drug liking”
- Disposition to take the drug again
- Drug identification
- Subject-rated side effects
- Profile of Mood States (POMS)
- Addiction Research Center Inventory (ARCI)
- Behavioral & cognitive performance
- Physiological effects

Review Questions

- Is the study being conducted appropriately?
- Is the appropriate population studied?
- Is an appropriate positive control selected?
- Are the right doses being studied?
  - For safety?
  - For assessment of abuse potential?
- Are the appropriate outcome measures selected?
- Does the study have adequate statistical power?

Part III

Managing the Risk of Abuse

Drug Control Under CSA- Limitations of Drug Scheduling

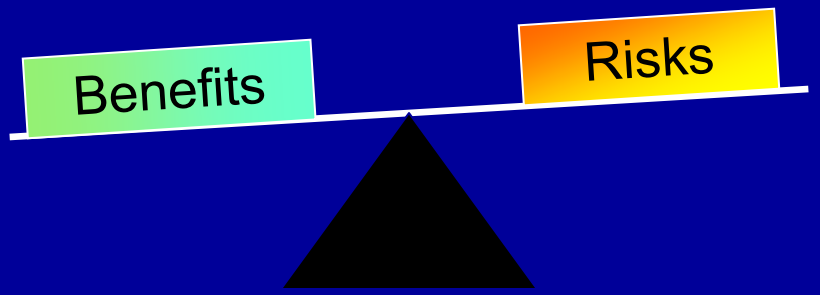
- Scheduling under the CSA does not manage all risks of misuse, abuse, and overdose of drugs
- Drug scheduling alone cannot address many challenges related to the modern health care system
  - Current patterns of medical practice
  - Ease of access to information and drugs

Importance to Stakeholder: CSA Regulations & Penalties Vary with CSA Schedules I - V

- Prescription & Product Labeling Requirements
- DEA Registration
- Records & Reports
- Security Requirements
- Import & Export Notifications & Declarations
- Quotas

Drug Approval

- Safe & Effective under Labeled Conditions of Use
- Risk Evaluation and Mitigation Strategies “REMS”
  - Food & Drug Administration Amendments Act (FDAAA) of 2007, Section 901
  - REMS is intended to ensure that benefits of the drug outweigh its risks
  - REMS is based on new legislation: Details of exactly how it will be implemented are not worked out

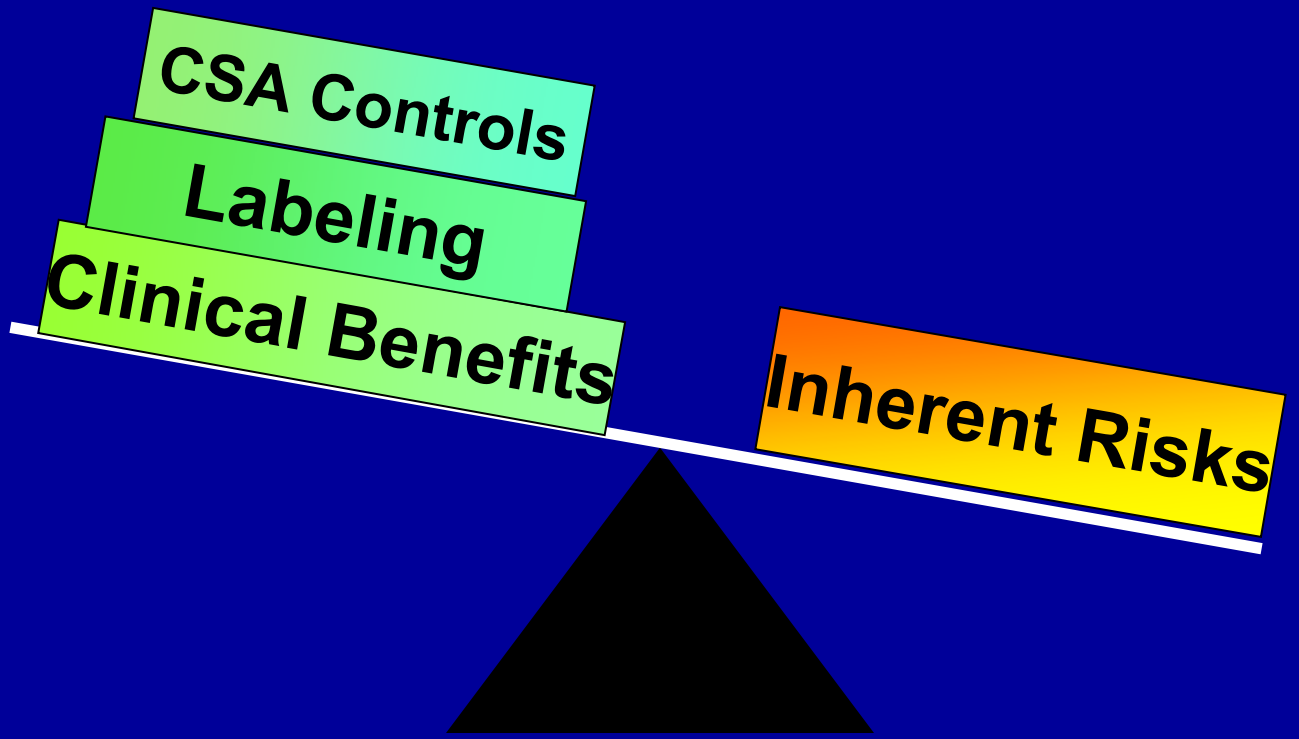


Abuse Potential is Related to Drug Safety

- Improved safety monitoring & evaluation
- Post-approval study clinical study can be required
  - To assess a known serious risk
  - A signal of a serious risk
  - Identify an unexpected serious risk when suggested by available data
- REMS
  - Assure safe use
  - Timetable for assessments
  - Communication plan, patient monitoring, training

When is a REMS considered for a Drug with Abuse Potential?

Whenever there is a need for risk minimization
To maintain a positive risk:benefit balance



REMS – Additional Considerations

- The Goals of the REMS for a Drug with Abuse Potential may include:
  - Prevention of Accidental Overdose or Unintended Exposure
  - Ensuring Proper Patient Selection
  - Prevention of Misuse and Abuse

Risk Management Issues Related to Indication & Patient Population

- Setting and context of use
- Risk of targeted patient population
- Drugs may pose greater risk in special populations
  - Different patient populations may present different profile of effects
  - Risks of extension into other populations
  - Current and former substance abusers
  - Psychiatric patients

Additionally, Companies Seeking to Market Drugs with Abuse Potential

- **Should Consider…**
  - How drug delivery affects safety and abuse liability of the drug
  - What specific risk management approaches may be appropriate for their drug

Formulation Influences on Abuse Potential

Marketing – Indication & Patient Issues:
Buprenorphine SL vs. IM & IV

C_{max} & AUC Variation:
Nicotine Products & Tobacco

Diversion Liability:
Methylphenidate IR vs. Extended Release

Modified Release:
Oxycodone IR & ER

Change in Route of Administration:
Fentanyl IV, TDS, SL
Butorphanol Injectable, IN

REMS Tools

- For Education, Outreach, Reminders:
  - Health Care Practitioner (HCP) Letters
  - Training Programs for HCP and Patients
  - Professional or Public Notifications
  - Continuing Education for HCP
  - Public Health Advisories
  - Patient-Oriented Labeling

Surveillance & Interventions

- Surveillance for overdose, misuse, unintended exposure, addiction, drug-related deaths
  - AEs monitoring for abuse, misuse, addiction and overdose
  - Surveys
  - Tracking national databases (DAWN, Toxic Exposure Surveillance System (TESS), Rocky Mountain Poison Control Centers, CDC, Medical Examiners
  - Monitoring prescription use and prescribing patterns
- Interventions
  - Patient Education
  - PPI's (Medication Guides)

Summary

- The evaluation of new drugs (NDAs) for abuse potential is based upon a comprehensive and coordinated interdisciplinary scientific review
- Abuse potential evaluation & drug scheduling are a shared responsibility by FDA/DHHS and DEA, with input from the health care community and pharmaceutical industry
- If a drug has a potential for abuse, appropriate abuse-related data must be included in the NDA for review
- FDA regulatory tools to prevent abuse include possible CSA Scheduling, changes to product labeling (Drug Abuse Section, Warning and Precaution Sections, Black Box Warnings), and possibly REMS