



J. Detmold & Co. N.Y.

Mrs. Winslow's Soothing Syrup (c. 1887)

Drug Scheduling

John J. Coleman, M.A., M.S.

President

Prescription Drug Research Center LLC

George Mason University Enterprise Center

4031 University Drive, Suite 200

Fairfax, VA 22030

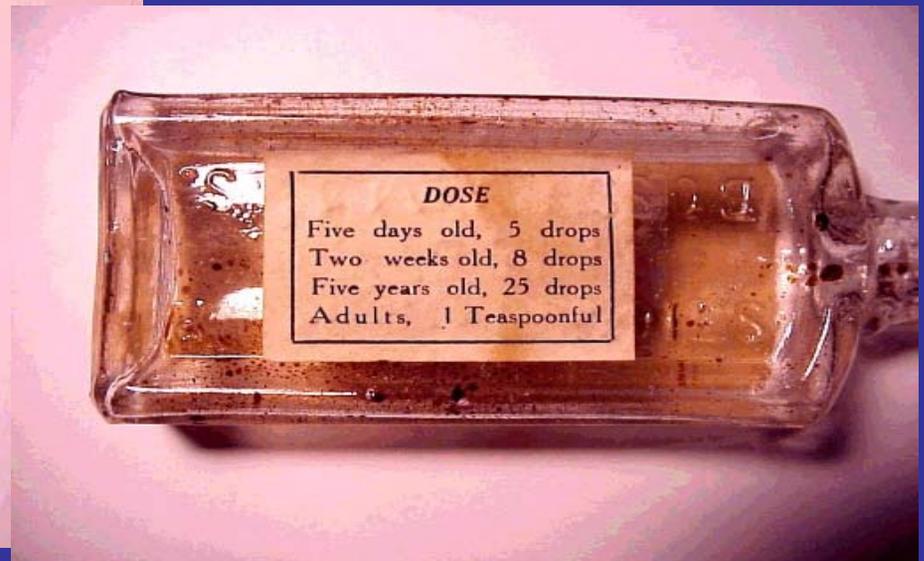
jcoleman@PDRCLLC.com

History of U.S. Drug Control

- **1887: Congress passed legislation outlawing the importation of Chinese smoking opium.**
- **1906: Pure Food and Drugs Act was enacted and, among other things, required drug makers to list ingredients on product labels.**
- **1900: American Medical Association (AMA) took strong stand against "patent medicine" industry and established a laboratory division to investigate and expose false claims.**
- **1912: Foster Bill to regulate opium, coca, and other drugs is defeated.**
- **1914: With AMA support, Congress passed Harrison Narcotic Tax Act, establishing registration requirements for prescribers of opium and coca, their derivatives, salts, and optical isomers. Law required annual tax, recordkeeping, written prescriptions, and prohibited prescribing or dispensing these drugs except by an authorized person acting "in the course of his (sic) professional practice only."**
- **1937: Congress passes Marihuana Tax Act to regulate cannabis.**



46% alcohol = 92 proof!
1.8 grains opium = 117 mg opium!
(~ 11.7 mg morphine/fl oz.)



DOSE
Five days old, 5 drops
Two weeks old, 8 drops
Five years old, 25 drops
Adults, 1 Teaspoonful

PAREGORIC (c. 1906)

Origin of Drug Scheduling

- **1925 League of Nations Opium Convention establishes international regulations for producing and exporting opium**
- **1931 League of Nations Convention on Manufacturing**
 - **Established international schema for controlling potentially addicting, but medicinally useful, substances such as codeine and morphine**
 - **Germany, producer of most of the world's codeine at the time, opposed regulations**
 - **German delegation to the Convention proposed a "two-schedule" (i.e., Group I and Group II) system**
 - **Heroin, cocaine, and opium would be in Group I and regulated, while codeine would occupy Group II, a category exempted from international reporting requirements that had been agreed upon by League members in 1925**



The United States Delegation to the 1925 League of Nations Opium Convention

Changing Times

- **What is an *addictive* drug?**
 - **International treaties negotiated in 1912, 1925, 1931, 1936, 1948, 1953, and the omnibus 1961 Single Convention, all defined an addicting drug as a substance that generated effects similar to those produced by opiates or coca.**
 - **By the 1960s, the emergence of new abusable drugs of illicit origin, such as peyote and LSD, or licit origin, such as CNS stimulants, depressants, and tranquilizers, required changes in domestic laws and international agreements.**
 - **The United Nations recommended amending the 1961 Single Convention to include "psychotropic" substances but this was opposed by pharmaceutical-producing nations, including Great Britain, West Germany, the United States, Japan, and Switzerland, insofar as it might regulate barbiturates and amphetamines.**

International Response

- **1971 Psychotropic Convention**
 - For the first time in the history of international drug control, the presence of industry representatives at the Convention meetings and the lobbying influence of large, multinational pharma companies exerted significant political pressure on delegates.
 - The 1971 Psychotropic Convention, according to historian McAllister, represented a diplomatic compromise between what was needed and what could be accomplished under the circumstances.
 - By the time agreement was reached, reporting requirements and the role of medical authorities in scheduling decisions were watered down substantially.
 - Proposals to regulate precursor chemicals failed, as did proposals to control any new derivatives of regulated substances.

Modern Era of U.S. Drug Control

- **1965: Congress passed Drug Abuse Control Amendments to 1938 Food, Drug, and Cosmetic Act (FDCA) that, among other things, established law enforcement agency (Bureau of Drug Abuse Control) under the jurisdiction of the Food and Drug Administration.**
- **1968: Federal Bureau of Narcotics and BDAC are merged to form Bureau of Narcotics and Dangerous Drugs, a component of the Department of Justice.**
- **1969: In *Leary v. United States*, U.S. Supreme Court overturned major provisions of 1937 Marihuana Tax Act.**
- **1969: Congress began work on comprehensive new drug Bill to address decision in *Leary v. United States*, and to align federal law with policy positions being negotiated in what later would become the 1971 Psychotropic Convention.**
- **1970: The result was the enactment of the Omnibus Drug Abuse and Control Act, also known as the Controlled Substances Act.**

1970 Controlled Substances Act

- Law was based on authority of Congress to regulate commerce
- Included five "schedules" (designated C-I to C-IV) for contraband drugs and lawfully manufactured drugs approved by FDA but deemed abusable
- Schedule I or C-I drugs are not approved by FDA for use in the United States
- While Bill was being drafted controversy arose over scheduling authority, with one side asking that it be vested in the Secretary of HEW (HSS today) and others asking that it be vested in the Attorney General.

1970 Controlled Substances Act

- A compromise was reached requiring collaboration between the Secretary of HEW (HSS) and the Attorney General in scheduling controlled substances.
- For the Secretary of HEW (HSS), authority has been delegated to the FDA; for the Attorney General, authority has been delegated to the DEA.
- The scheduling process begins with a decision by the FDA during the examination of an NDA or ANDA that the substance being proposed warrants control under the CSA.
- Under the FD&C Act, NDA applicants must furnish all data relevant to abuse of the drug, propose a scheduling under the CSA, and provide data regarding overdoses and abuse events that occur during clinical trials.

1970 Controlled Substances Act

- If warranted, the FDA will determine if and when a drug requires scheduling under the CSA. If deemed a controlled substance, the drug cannot be marketed until scheduled by DEA.
- The FDA, having conducted its examination, including an evaluation of abuse-related issues, will provide DEA with a scheduling recommendation.
- The CSA provides a statutory matrix of assessments that must be conducted before a drug is scheduled.
- This matrix is referred to as the "eight factors"
- Three of the factors are within DEA's jurisdiction and five are within the jurisdiction of the FDA.

1970 Controlled Substances Act

Eight Factors (Responsible agency)

1. **The drug's actual or potential for abuse. (DEA)**
2. **Scientific evidence of the drug's pharmacological effects. (FDA)**
3. **The state of current scientific knowledge regarding the substance. (FDA)**
4. **Its history and current patterns of abuse. (DEA)**
5. **The scope, duration, and significance of abuse. (DEA)**
6. **What, if any, risk there is to the public health. (FDA)**
7. **The drug's psychic or physiological dependence liability. (FDA)**
8. **Whether the substance is an immediate precursor of a substance already controlled. (FDA)**

1970 Controlled Substances Act

- After considering the above eight factors, the DEA administrator must make specific findings that, in turn, determine the appropriate schedule for the drug.
- The medical and scientific findings provided by the FDA are binding on the administrator of DEA.
- DEA lacks authority to schedule a drug without a recommendation to do so from the FDA. An exception to this was included in a 1984 amendment to the CSA that allows the DEA administrator emergency authority to place a drug in Schedule I in instances posing an imminent hazard to public safety. [21 USC 811 (h)]

1970 Controlled Substances Act

- CSA provides five “classes” or “schedules”
- Schedule I drugs are not approved in the U.S., have a high abuse potential, and require DEA license for research
- Schedule II to V drugs are approved for medical use in the U.S., and vary from high (C-II) to limited (C-IV-C-V) psychological and/or physical dependence

1970 Controlled Substances Act

Major Concerns for FDA and DEA in making drug scheduling decisions:

- Is the benefit/risk ratio sufficient to approve drug for medical use?
- What is the drug's relative potential for abuse?
- What is the drug's dependence liability?

IMPACT OF DRUG SCHEDULING

Although the DEA and FDA are quick to say that, as drug regulatory agencies, they regulate products and devices but ***not*** the practice of medicine, it is difficult at times to regulate the one without having an effect on the other.

IMPACT OF DRUG SCHEDULING

Few have studied effect of drug scheduling on delivery of healthcare services and medications to the public.

Crosby and colleagues (1978) analyzed the influence of scheduling decisions on the prescribing of six controlled substances before and after their scheduling and/or rescheduling.

IMPACT OF DRUG SCHEDULING

For their study, Crosby & colleagues selected:

- Amphetamine (C-III to C-II in 1971)
- Diazepam (Unscheduled to C-IV in 1975)
- Flurazepam (Unscheduled to C-IV in 1975)
- Methaqualone (Unscheduled to C-II in 1973)
- Propoxyphene (Unscheduled to C-IV in 1976)
- Secobarbital (C-III to C-II in 1973)

IMPACT OF DRUG SCHEDULING

Using IMS Health National Prescription Audit data, Crosby and colleagues discovered that every one of the six study drugs showed a decrease in prescribing levels *after* the scheduling action.

- For methaqualone, amphetamine, and secobarbital, the decrease in volume of prescriptions was at least 50 percent in the first year following the scheduling action.

DRUG SCHEDULING

Scheduling decisions affect access to controlled substances directly and indirectly.

- Except for "emergency situations," C-II prescriptions "shall be written with ink or indelible pencil or typewriter and shall be manually signed by the practitioner."¹
- C-II prescriptions cannot be refilled.²
- C-III to C-IV prescriptions may be called in or faxed, and, when authorized, refilled up to five times within six months.

¹ 21 CFR 1306.05; 21 CFR 290.10

² 21 CFR 1306.12

DRUG SCHEDULING

- A drug that is “over-scheduled” may be needlessly difficult and expensive for pts to obtain.
- Some prescribers may be reluctant to prescribe C-II drugs, for example, even when properly indicated, because of a real or imagined fear of regulatory scrutiny.¹

¹ Hill CS, 1989; Joranson DE, et al., 2002

DRUG SCHEDULING

- A drug that is “under-scheduled,” on the other hand, may pose a threat to public health and safety by being too accessible and, therefore, more susceptible to diversion and abuse.
- Seeking the *Goldilocks* solution

DRUG SCHEDULING

- According to statements accompanying the passage of the 1970 CSA:

“The reported bill (CSA) strikes a balance between the extent to which control decisions should be based on medical and scientific determinations.”¹

¹Report of the U.S. House of Representatives, Committee on Interstate and Foreign Commerce, September 10, 1970

RECENT INITIATIVES

RISK MINIMIZATION ACTION PLANS

(RiskMAP)



“The Agency (FDA) assesses preclinical, clinical, and epidemiological data to determine whether a drug under review requires abuse liability studies, scheduling under the CSA, or a risk minimization action plan, (RiskMAP) designed to reduce abuse, overdose, or diversion. FDA’s job is not over after a drug scheduled as a controlled substance is approved. The goal of FDA’s post-marketing surveillance is to continue to monitor marketed drugs for safety. This is accomplished by reassessing drug risks based on new data obtained after the drug is marketed and recommending ways of trying to manage that risk most appropriately.”¹

¹Congressional testimony, 12/13/2005, by Robert J. Meyer, M.D., Director, Office of Drug Evaluation II, Center for Drug Evaluation and Research, FDA