

“FDA Ban on Dietary Supplements Containing Ephedrine Alkaloids”



U.S. Department of Health and Human Services

Food and Drug Administration

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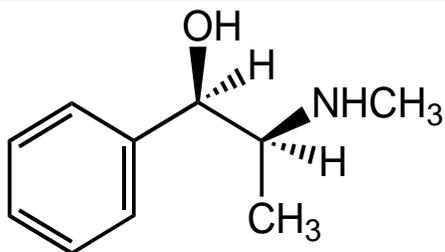
Outline of Presentation

- Ephedrine alkaloids:
 - Types and occurrence
 - Product regulation: drugs vs. dietary supplements
- History of FDA activities concerning dietary supplements containing ephedrine alkaloids
- Final Rule summary

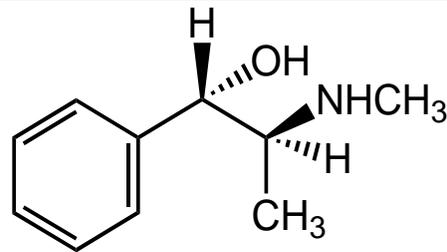
Ephedrine alkaloids:

- Ephedrine
- Pseudoephedrine
- Methylephedrine
- Norephedrine
- Norpseudoephedrine

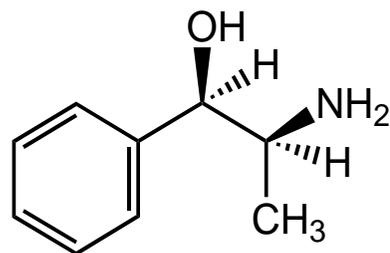
Ephedrine alkaloids



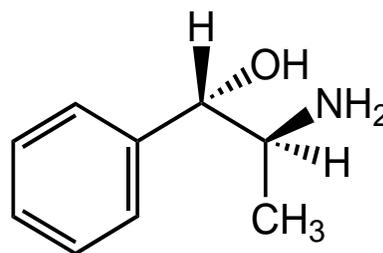
(1R,2S)-(-)-Ephedrine



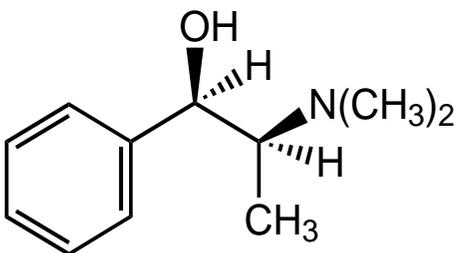
(1S,2S)-(+)-Pseudoephedrine



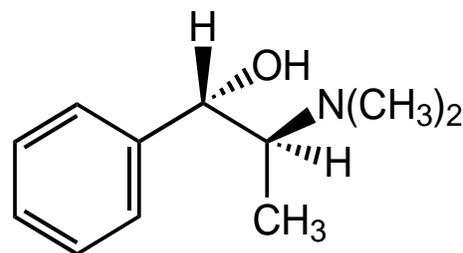
(1R,2S)-(-)-Norephedrine



(1S,2S)-(+)-Norpseudoephedrine



(1R,2S)-(-)-Methylephedrine



(1S,2S)-(+)-Methylpseudoephedrine

Sources of Ephedrine Alkaloids

- Raw botanicals:
 - *Ephedra spp* (*ma huang*)
 - *Sida cordifolia*
 - *Pinelliae ternata*
- Extracts from botanicals
- Synthetic chemicals



Ephedrine Alkaloids: What Are the Products We Are Talking About?

Ephedrine Alkaloid Containing Products

- Traditional medicines
 - Primarily for respiratory conditions
- Approved Drugs – both prescription and OTC
 - Approved uses:
 - Allergy, cough and cold preparations
 - Asthma products
- Street drug alternatives
- Dietary supplements

Regulatory classification of product matters because.....

- Different regulatory requirements
- Different substantiation
- Different safety considerations



Dietary
Supplement
Health and
Education
Act

Dietary Supplements: DSHEA

Definition

- Intended to supplement the diet
- Contains one or more of the following dietary ingredients:
 - Vitamin, mineral, amino acid
 - Herb or other botanical (not tobacco)
 - "dietary substance" for use by man to supplement the diet by increasing the total dietary intake
 - Concentrate, metabolite, constituent, extract, or combination of any of the above

Dietary Supplements under DSHEA

- A product that is:
 - Ingested in tablet, capsule, liquid, powder, gelcap, softgel
 - Not represented as conventional food
 - Not represented as sole item of meal
 - Not represented as a total diet
 - Labeled as a dietary supplement

Dietary Supplements under DSHEA

Exclusions: Does not include articles:

- that are approved new drugs, antibiotics, or biologics
 - that are authorized for investigation as a new drug or biologic if
 - substantial clinical investigations have been instituted; and
 - the existence of clinical investigations has been made public (e.g., in a company press release, newspaper, trade publication, or medical journal)
- UNLESS first marketed as a dietary supplement

Dietary Supplements Post- DSHEA



- No pre-market approval by FDA
 - Exception: new dietary ingredient – 75 d notification
- Exempt from food additive provisions
- GMP regulations pending
- FDA bears the burden of proving a dietary supplement is unsafe

Dietary Supplements Containing Ephedrine Alkaloids

- Widely sold in U.S.
- Most product contain multiple ingredients
- Uses:
 - Weight loss and energy
 - Fitness, body building
 - Other

Evolution of FDA Safety Concerns

- 1992 FDA first aware of safety issue
- 1993 FDA first indicated concerns about safety
- 1994 Health Hazard Evaluation
- 1995 Public meeting: FDA Working Group/FAC
- 1996 Public meeting: FDA FAC
- 1997 Proposed Rule
- 1999 GAO report
- 2000 HHS/OWH Public meeting
- 2003 FDA White Paper
- 2004 Final Regulation/Ban

Sources of Information About the Effects of Ephedrine Alkaloids

- Medical practice:
 - Traditional medicine > centuries of use
 - Allopathic medicine > 75 years of use
- Medical scientific research
- Post marketing surveillance

Ephedrine Alkaloids: Pharmacology and Mechanisms of Actions

- Cardiovascular system
 - Vasoconstriction
 - Cardiac stimulation (\uparrow contractility, HR, stroke volume)
- Central nervous system stimulation
- Other effects:
 - Bronchodilation
 - Skeletal and smooth muscles
 - Organs & glands

Ephedrine Alkaloids: Adverse Effects

- **Cardiovascular system:**
 - hypertension, angina, cardiac ischemia & infarction, cardiomyopathy, cerebrovascular events- hemorrhage & infraction
- **Nervous system:**
 - Central stimulant effects, mania & psychosis, seizures, drug abuse, dependence, addiction
- **Other:**
 - Myopathies, uropathies, GI & dermatological reactions

How does FDA generally evaluate Dietary Supplement Safety

- Considerations for safe use:
 - Population:
 - Special subpopulations
 - General population
 - Pattern of use
 - Used according to instructions
 - Real world use
 - Type of product and ingredients

Outside Scientific and Clinical Reviews

- Pharmacokinetic, pharmacodynamic properties and relative toxicity of botanical Ephedra versus ephedrine alkaloids
- Use of Ephedra in Traditional Medicine
- Assessment of likely reporting rates of adverse events on dietary supplements containing ephedrine alkaloids

Final Rule

- Published:

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 119

[Docket No. 1995N-0304]

RIN 0910-AA59

Final Rule Declaring Dietary Supplements Containing Ephedrine Alkaloids

Adulterated Because They Present an Unreasonable Risk

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

Display Date 2-6-04 2:00pm
Publication Date 2-11-04
Certifier A. Corbin

- Effective: April 12, 2004

What the Final Rule Does:

- Dietary supplements containing ephedrine alkaloids
 - Present an unreasonable risk of illness or injury under the conditions of use recommended or suggested in labeling, or if no conditions of use are suggested or recommended in labeling, under ordinary conditions of use.
 - pose a risk of serious adverse events, including heart attack, stroke, and death, and that these risks are unreasonable in light of any benefits that may result from the use of these products.
 - Are therefore adulterated under section 402(f)(1)(A) (21 U.S.C. 342(f)(1)(A) of the FD&C act

Scope of Final Regulation

- Included under FR: all marketed dietary supplements with ephedrine alkaloids
- Outside the scope of FR:
 - Traditional herbal remedies
 - Conventional foods
 - Ephedrine alkaloids are not GRAS for foods and not approved for use as a food additive

Since the Final Rule....

- FDA actions: surveillance, compliance & enforcement
- Legal challenges to the Final Rule