

Officers

Hans A. de Haan, MD, PhD, FFPM
President and Chairman of the Board

John D. Irvin, MD, PhD
President-Elect

Vincent I. Ahonkhai, MD
Past President

Joan L. Drucker, MD
Treasurer

Gary A. Shangold, MD
Secretary

Board of Trustees

Vincent I. Ahonkhai, MD

Charles M. Alexander, MD

Patricia J. Byrns, MD

Hans A. de Haan, MD, PhD, FFPM

Anthony W. Fox, MD, PhD, FFPM

John D. Irvin, MD, PhD

Maria T. Koehler, MD, PhD

Thomas J. Newman, MD

Gary R. Noble, MD, MPH

Stephen M. Oppenheimer, MD, PhD

Richard G. Pellegrino, MD, PhD

Ihor W. Rak, MD

Peter H. Rheinstein, MD, JD, MS

Scott Segal, MD

Gary A. Shangold, MD

Vice Presidents

Charles M. Alexander, MD
Membership Development

Christopher P. Allen, MD, FFPM
International Relations

Joan L. Drucker, MD
Finance

Anthony W. Fox, MD, PhD, FFPM
Education & Professional Development

Joseph A. Franciosa, MD
Publications

Stanley B. Garbus, MD, MPH
Annual Meeting Planning

John D. Irvin, MD, PhD
Resource Development

Ira J. Isaacson, MD, MBA
Career/Professional Support

Gary R. Noble, MD, MPH
Ethics & Professional Conduct

Richard G. Pellegrino, MD, PhD
Patient Advocacy

Peter H. Rheinstein, MD, JD, MS
AMA Relations

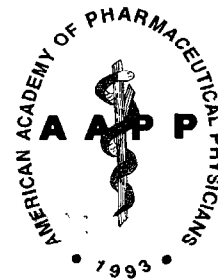
David A. Shapiro, MB, ChB
Public Affairs

Louis M. Sherwood, MD
Strategic Planning and Alliances

Hugh H. Tilson, MD, DrPH
Policy

Anne G. Arella
Executive Director

Dockets Management Branch (HFA-305),
Food and Drug Administration,
5630 Fishers Lane, Room 1061
Rockville, MD
20852



March 26, 2003

Dear Sir or Ma'am:

**Re: Docket no. 95N-0304 Dietary Supplements Containing Ephedrine alkaloids
Department of Health and Human Services
Federal Register Notice of proposed rule and reopening of comment
period March 5, 2003 (i.e., FR 68 (43): 10417-10420).**

On behalf of the American Academy of Pharmaceutical Physicians, this is to submit a response to the Agency's reopening of the comment period on this docket.

This Comment (see attachment) sets out the Academy's position on this subject. The position document is fairly brief, and its appendix is designed as a Background Document which lays out the principal evidence used to arrive at this position. In the interests of brevity, the background document cannot be an exhaustive review of the subject, but it is written in a way that is intended to be understood by people without specific pharmacological or regulatory training.

Please accept the Academy's congratulations to the Agency for its continued concern about this aspect of the public health.

Sincerely,

Hans de Haan, MD, PhD, FRCS, FFPM
President

95N-0304

C 3880

American Academy of Pharmaceutical Physicians

1031 Pemberton Hill Road • Suite 101 • Apex, NC 27502

Telephone: 919-355-1000 • Fax: 919-355-1010 • email: office@aapp.org • www.aapp.org

**American Academy of Pharmaceutical Physicians statement on
“Ephedra”-containing products.**

Ephedra-containing products (ma huang, ma huang-guarana) contain substantial quantities of phenylethylamine (ephedrine), a well-known partial alpha-adrenergic agonist. This is undisputed, and is, indeed, the basis of the manufacturers' claims for product efficacy in weight loss.

The cluster of adverse event reports associated with the use of ephedra-containing products now numbers several hundred patients. Pharmacovigilance is an imprecise science, relying on a catch-all approach, and often without definite denominators, especially in cases where prescription censuses are unavailable. However, the types of adverse events that are being reported in association with ephedra-containing products are not randomly scattered across all the organ systems in the human body. Rather, they are, in large majority, serious cardiovascular and neurological adverse events. These particular adverse events are well-known as characterizing the effects of drugs with alpha-adrenergic properties.

On the spectrum of regulatory controls of pharmacological agents, ephedra-containing products are in the class that is least controlled. These products are freely available from diverse retail outlets, without any required warning labeling. Indeed, the manufacturers often affirmatively assert product safety in promotional materials.

By way of comparison, another member of this class of drugs was withdrawn from United States markets in 1999. It was called phenylpropanolamine (PPA), and it was contained in several different products; its adverse events were of the same types as those being reported for ephedra-containing products, although the PPA reports were fewer in number. Prior to its withdrawal, PPA was in over-the-counter products with FDA-compliant warning labeling, a relatively mild form of regulation that was, however, inadequate to prevent the adverse effects that led to product withdrawal.

It is therefore irrational that ephedra-containing products should be regulated to a degree that is less than that which preceded PPA withdrawal. Furthermore, the scale of the problem suggests that restrictions on ephedra-containing products should be greater than those hitherto applied to PPA. The current situation clearly fulfills the “unreasonable hazard” requirement that empowers FDA to take action under the Dietary Supplement Health & Education Act, 1994 (and may well fulfill other “trigger” criteria under both that Act and the Food, Drug & Cosmetics Act, as amended).

The American Academy of Pharmaceutical Physicians (AAPP) therefore recommends that ephedra-containing products should become available on a prescription-only basis. AAPP further recommends that under those conditions the situation should be monitored closely, and if the frequency of adverse events does not improve, then yet more restrictive action should be implemented, possibly including the complete withdrawal of ephedra-containing products from the marketplace.

AAPP further recommends that if it is suspected that there are particular patient sub-populations where ephedra-containing products have special benefit, thus outweighing the current hazard, then the manufacturers should be required to produce well-controlled evidence in support of that contention. This evidence, when available, should then be incorporated into product labeling.

AAPP further recommends that all promotional materials for ephedra-containing products should immediately cease making affirmative statements of product safety.

A background document is attached.

BACKGROUND INFORMATION

Regulatory and Statutory. The authority of the United States Food and Drug Administration (FDA) over dietary supplements / nutraceuticals / complementary therapies (among other nearly synonymous terms and products) was most recently enunciated in the Dietary Supplement Health and Education Act (DSHEA) of 1994. Although sometimes described as an amendment of the Food, Drugs and Cosmetics Act (FD&CA; as itself amended), in fact DSHEA is a *de novo* Act of Congress and may be seen as complementing legislation in this area. As is well-known, the FD&CA does not require FDA pre-approval of products in this category, although manufacturers are required to provide certain details about new products to FDA when they contain components that have not previously existed in the food supply.

The DSHEA authorizes FDA to take restrictive actions against dietary supplement[s] that "...pose[s] a significant and unreasonable risk". Restrictive actions can include labeling, product seizure and other remedies to protect the public health. The Act does not specify that someone actually must have been already harmed before this conclusion can be drawn. Nonetheless, there has to be some scientific justification for such a conclusion.

There are various other bases for regulatory actions under DSHEA. These are that materials are unfit as food, make an unjustified therapeutic claim, or are untruthfully labeled, among others. While a case could be made that the current marketing of ephedra-containing products violates some of these tenets, the central theme below is that the product presents an unreasonable risk to the public health.

In 1997, FDA marshaled a substantial quantity of data in support of restrictions on ephedra-containing products using the "unreasonable risk" justification. These data included more than 750 adverse event reports that FDA had received. The principal marketing orientation of these products at that time (still largely used today) was that ephedra was an effective agent in assisting weight loss (i.e., straying close to the definition of a drug claim). The proposed rule ran into intense industry lobbying, as well as opposition from the Small Business Administration which urged the rule's withdrawal in 2000. A General Accounting Office (GAO) investigation criticized FDA for failing to investigate the causal relationship (or otherwise) between these adverse event reports and the consumption of ephedra. In particular, FDA had relied on 13 of the best quality adverse event reports in proposing a maximum dose size that was much smaller, and a limit to the duration of therapy. The industry claimed that this would remove all efficacy for weight loss, and the GAO saw this as an inadequate amount of scientific evidence for an action by FDA that could have been excessive for its intended purpose.

The FDA then withdrew substantial parts of the rule, essentially allowing these products to remain on the market. An advisory committee meeting on the subject was then held (August 8 - 9, 2000). During this meeting, FDA and its invited experts recited the adverse event information that had been received as a justification for an unreasonable risk conclusion. The industry lobby and its invited experts recited the efficacy of the

product (not always based on well-controlled studies). The latter also cast doubt upon the reliability of the information provided by FDA, portraying it as a relatively small amount in comparison to the large volumes of consumption of the relevant products.

Scientific information.

1. The serious cardiovascular and neurological adverse events that concern FDA most have a background incidence. It is probably fair to say that there is currently no published comparison of the pharmacovigilance data associated with ephedra use with the background incidence of such effects. Naturally, assertions on both sides of the controversy have been made with regard to this comparison. The “Rand Report” on this subject, published by FDA, is probably the most authoritative source of data on the nature and volume of these reported adverse events.

2. Pharmacovigilance is almost always, quantitatively, an imprecise science. The reason is that one is trying to distil drug-attributable adverse event frequency from a background incidence of the same types of adverse events that occur spontaneously. Both require denominators and numerators. In the field of prescribed drugs, there are at least censuses of prescriptions that can be counted. For over-the-counter products, denominators basically rely upon the quantities of material reported as shipped by the manufacturers. The circumstances whereby ephedra-containing, over-the-counter products are used (dose, dose frequency, concomitant ingested materials, demography of consumers, etc.) are almost entirely unknown.

3. All pharmacological agents (whether accorded the name drug, dietary supplement, or whatever) have unwanted effects when ingested or administered at the wrong dose or dose frequency. The key to safe use by the general public, who can be expected neither to understand the nuances, nor even, necessarily, to be able to read, is for them to be well-informed. For prescribed drugs, labeling is supplemented by being advised by “learned intermediaries” (physicians, pharmacists, nurse practitioners, etc.), and monitored by these professionals, if necessary, for the early signs of adverse events.

Pharmacognosy. The *Ephedraceae* comprise several species of herb that contain a variety of pharmacologically active ingredients (or alkaloids). Most ephedra-containing products are purported to be components of *Ephedra sinica*, a species whose principal alkaloid is ephedrine (or phenylethylamine). The species is known by several vernacular names including ephedra grass, ma huang, and ma huang-guarana (the last sometimes being a mixture of two closely-related *Ephedra* species). The formulation is initially the dried leaves of the plant, although this is often powdered and reformulated into tablets or as infusions. Ingestion is almost always orally.

Chemistry. Ephedrine or phenylethylamine is closely related to a large class of drugs, of whose most familiar members are epinephrine (adrenaline) and amphetamine. Indeed,

ephedrine of herbal origin has been used as a starting material for the manufacture of these and other prescribed drugs.

Pharmacology. Among other actions, all phenylethylamine derivatives activate alpha-adrenergic receptors in most mammals (including man). Alpha-adrenergic receptors are found principally in peripheral arteries and in the brain, although other populations of this type of receptor are also found in the coronary arteries, the vas deferens, and along the gut.

In isolated pieces of smooth muscle (the type of muscle found in arteries, gut, and vas deferens), activation of alpha-adrenergic receptors causes contraction. In the intact animal and man, this causes abrupt elevations in blood pressure. In *ex vivo* brain slices, these receptors cause over-activity of neurons, and in the intact animal or man, this is observed as abnormal behaviors, psychosis (in man), and seizures. These drugs have these effects in a dose-related manner (i.e., these are typically graded responses, and, except for seizures, not all-or-nothing responses).

This class of drugs varies in its ability to cause these pharmacological effects. Firstly, the drugs have different potencies (e.g., a higher dose of, say, amphetamine might be needed to cause the same blood pressure increase as a smaller-sized dose of nor-adrenaline). Secondly, these drugs also differ in the largest-sized effect that they can produce. For example, no matter how much phenylpropanolamine one might add to an organ bath to make an artery contract, one can never make it contract quite as powerfully as when one uses nor-adrenaline). This latter effect is technically known as “efficacy”; nor-adrenaline in that artery is said to be fully efficacious (or that nor-adrenaline is a “full agonist”), while phenylpropanolamine is said to be partially efficacious (or a “partial agonist”).

Ephedrine is like phenylpropanolamine. They are both partial agonists.

A drug needs only to be a partial agonist in order to cause serious adverse effects in man. Phenylpropanolamine (PPA) was withdrawn from the market in the United States in 1999, after adverse events were reported. These adverse events are similar in type to those now being reported for ephedra-containing products. Before its withdrawal, PPA was being used as a nasal decongestant, and probably also for weight loss.

Risk-benefit analysis. Depending upon the circumstances, many of these types of drugs can be used without undue clinical hazard. Moreover, the use of even dangerous drugs may be justified when the potential benefit to the patient outweighs the risk.

Various tactics can be used to minimize such risks, even when they are known to occur. These tactics might include, for example, various types of clinical monitoring, or avoidance of foodstuffs or other drugs that might make adverse events more likely or more serious. Comparative approaches for risk-benefit assessment can also be valuable. For example, for a given treatment goal, in the presence of specified concomitant factors

(other drugs, etc), one from among a group of drugs can be chosen that presents the least simultaneous risk. Risk or hazard, however, can never be completely eliminated.

Risk-benefit assessment often requires the assimilation of large amounts of highly technical information. It is a process that cannot be expected of the general public.

Ephedrine risk-benefit. Ephedrine has a known pharmacology that is highly consistent with the adverse event types being reported. The volume of these adverse event reports is greater than that previously seen as justifying restrictions on phenylpropanolamine. The evidence that ephedrine causes weight loss any more easily than by dietary restriction alone is insecure in terms of well-controlled clinical trials. Thus, by comparison with PPA, there is both relatively more evidence of risk, and less evidence of benefit for ephedrine. The risk-benefit assessment for ephedrine is thus that it is more hazardous than PPA in the general population.

Note that this is a population-based statement. If we could be more precise about the population, then exceptions to this generalization may well exist. For example, hypothetically, if all the ephedra-associated adverse events occurred in people who also smoked tobacco, then we could develop two risk-benefit assessments for patients who do and do not smoke, respectively, and potentially recommend less restrictions on ephedra-containing products for non-smokers than for smokers. Equally, if there were some type of morbidly obese patients who responded only to ephedrine and to no other drug or treatment, and if we knew how to identify those particular patients, then the potential benefit in those patients might outweigh the risks of treatment. However, at the present time, no such precisely defined patient sub-populations are known for ephedrine.

Possible regulatory responses. These range from doing nothing, to complete abolition of ephedra-containing products from the market place. It should be noted that properly prescribed ephedrine has legitimate uses, including the treatment of asthma.

Currently, the product is in the least-restricted mode of use possible, being freely available in many types of retail outlets. By way of comparison, PPA, prior to its withdrawal, was a regulated, over-the-counter drug, with appropriate warnings in its label. This mild degree of restriction was insufficient to prevent PPA-associated adverse effects, and an eventual risk-benefit assessment that it should be withdrawn completely. It is, however, still possible to conduct clinical research, under controlled conditions, with PPA.