

THE U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Dietary Supplements Containing)
Ephedrine Alkaloids; Reopening)
of the Comment Period)
_____)

Docket No. 95N-0304

COMMENTS OF THE
CENTER FOR SCIENCE IN THE PUBLIC INTEREST

95N-0304

C 4001

Michael Jacobson, Ph.D.
Executive Director
1875 Connecticut Avenue, N.W.
Suite 300
Washington, D.C. 20009
(202) 332-9110

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

April 4, 2003

Re: Dietary Supplements Containing Ephedrine Alkaloids; Reopening of the Comment Period (Docket No. 95N-0304)

The Center for Science in the Public Interest (CSPI)¹ is filing these comments in response to the Food and Drug Administration's *Federal Register* notice regarding the Agency's regulation of dietary supplements containing ephedrine alkaloids. CSPI believes that such ingredients should no longer be permitted to be marketed as dietary supplements. Although we believe that the statute affords FDA adequate authority to ban the use of ephedrine alkaloids in dietary supplements, we believe that additional legislative authority would be useful to clarify that FDA does, indeed, have this authority. Otherwise, FDA's resources will be consumed in justifying Agency action rather than in actually taking action to protect the public.

I. FDA has the Authority to Require that Dietary Supplements Containing Ephedrine Alkaloids be Banned as a Dietary Supplement

Under the Federal Food, Drug, and Cosmetic Act as amended by the Dietary Supplement Health and Education Act, FDA has the authority to take enforcement action and issue regulations applicable to food that is adulterated.² A dietary supplement or dietary ingredient is adulterated if at least one of four conditions is met. The supplement or dietary ingredient: (1) presents a

¹ CSPI is a non-profit consumer organization supported by approximately 800,000 members and subscribers to its *Nutrition Action Healthletter*. CSPI has worked since 1971 to improve national health policies in the areas of food safety and nutrition.

² FDCA §§ 402, 701(a); 21 U.S.C. §§ 342, 371.

“significant or unreasonable risk of illness or injury”; (2) is a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury; (3) is declared to be an “imminent hazard to public health or safety”; or (4) is or contains a dietary ingredient that bears or contains “any poisonous or deleterious substance which may render it injurious to health.” In this case, dietary supplements containing ephedrine alkaloids are adulterated within the meaning of three of those provisions.

A. The Continued Marketing of Dietary Supplements Containing Ephedrine Alkaloids Presents an Imminent Hazard

The Food and Drug Administration defines the term “imminent hazard” as follows:

(a) Within the meaning of the Federal Food, Drug and Cosmetic Act, an imminent hazard is considered to exist when the evidence is sufficient to show that a product or practice, posing a significant threat of danger to health, creates a public health situation (1) that should be corrected immediately to prevent injury and (2) that should not be permitted to continue while a hearing or other formal proceeding is being held. . . .

(b) In exercising his judgment on whether an *imminent hazard exists*, the Commissioner will consider the number of injuries anticipated and the nature, severity, and duration of the anticipated injury.³

FDA has previously exercised its imminent hazard authority⁴ and withstood a legal challenge to the appropriateness of its action in an analogous situation relating to the drug phenformin hydrochloride (phenformin).⁵ Phenformin was a drug designed to control blood sugar levels in patients with adult onset diabetes. It permitted patients to control their condition with

³ 21 C.F.R. § 2.5.

⁴ *Forsham v. Califano*, 442 F. Supp. 203 (D.D.C. 1977).

⁵ The FDCA permits FDA to immediately suspend the approval of a new drug application if the Secretary finds that “there is an imminent hazard to the public health.” 21 U.S.C. § 505(e).

fewer dietary restrictions and to delay the time when insulin must be taken. In 1997, Health Research Group³³ petitioned FDA to suspend distribution of phenformin contending that it “constituted an imminent hazard.” HRG’s petition was based on reports that the product caused an “inordinately high incidence of lactic acidosis, an often-fatal metabolic disorder in which abnormal amounts of lactic acid accumulate in the blood.”⁶

FDA’s suspension of phenformin was based on a number of factors that are equally applicable to dietary supplements containing ephedrine alkaloids:

1. Marketing prohibitions by other governments

In the phenformin case, Norway and Canada had halted the marketing of the drug based on their experience with phenformin-related lactic acidosis.⁷ Similarly, with the exception of the Netherlands, ephedrine alkaloids cannot be used in dietary supplements or foods in the European Union (EU). Many EU members, including the United Kingdom, even prohibit the use of ephedrine in over-the-counter drugs. The EU has recently published draft legislation that will specifically prohibit the use of ephedrine alkaloids in any food product. This proposal is expected to be adopted. When it becomes effective, it will apply to the 15 states who are currently in the EU, as well as to the 10 states joining in May 2004.⁸ Canada has called for a voluntary recall of products containing ephedrine alkaloids that are marketed without government approval because of

⁶ *Id.* at 134.

⁷ *Id.* at 135.

⁸ Peter Berry Ottaway, Consultant, Berry Ottaway and Associates Ltd., Hereford, England.

the high incidence of adverse events.⁹

Moreover, a number of states and localities have taken action to either ban the sale of dietary supplements containing ephedrine alkaloids,¹⁰ declare ephedrine alkaloids a controlled substance,¹¹ prohibit the sale of products containing ephedrine alkaloids (other than over-the-counter drugs) to minors,¹² or make it available only by prescription unless it is labeled in accordance with FDA standards for over-the-counter drugs.¹³ In addition, the U.S. Military has

⁹ “Following two prior public advisories concerning health risks associated with unapproved products containing ephedra/ephedrine, Health Canada conducted a risk assessment and determined that, on the basis of at least 60 adverse event reports and one death in Canada (and similar international evidence), these products constituted a Class 1 health risk for some vulnerable population groups [persons with pre-existing conditions such as hypertension, diabetes, and heart disease]. A Class 1 health risk is a ‘situation where there is a reasonable probability that the use of, or exposure to, a product will cause serious adverse health consequences or death.’ Accordingly, Health Canada issued a voluntary recall of the offending products on Jan. 8, 2002... .Health Canada’s experience is that requests for recalls are almost universally respected making it virtually unnecessary to resort to more rigorous enforcement powers such as seizing products or obtaining injunctions against sale.” Testimony of Bill Jeffery, National Coordinator Centre for Science in the Public Interest (Canada) before the U.S. Senate Committee on Government Affairs, Subcommittee on Oversight of Government Management, Restructuring and the District of Columbia, Oct. 8, 2002.

¹⁰ Huntington, New York (Suffolk County) New York has banned the sale of ephedra in all forms. Rev. Ordinances ch, 28 § 28-1 (B).

¹¹ Ohio Rev. Code Ann. § 3719.44(2)(a). A product containing ephedrine is considered a controlled substance unless it contains less than 25 mg of ephedrine alkaloids or the maximum amount set by the FDA; prominent labeling disclosing mg of ephedrine in a serving or dosage; and a statement that maximum recommended is the lesser of 100 mg in a 24-hour period for not more than 12 weeks or maximum set by FDA. *Id.*

¹² Ohio Rev. Code Ann. § 3719.44(b)(i)
Mich. Stat. Ann. § 333.7339
Texas. Ann. Code § 431.022

¹³ Fla. Stat. Ch. 499.033 (1) and (2).

banned the sale of dietary supplements containing ephedrine alkaloids at its commissaries.¹⁴ As a matter of public policy, if the military determines that soldiers and their families should not use dietary supplements containing ephedrine alkaloids, FDA should provide the same level of protection to civilians.

2. Discontinued use by groups where product usage was high

FDA found it highly convincing that phenformin was an imminent hazard because of the fact that several clinics for diabetics had decided to discontinue its use. Similarly, a growing number of athletic organizations whose members frequently use supplements have banned the use of supplements containing ephedrine alkaloids: The International Olympic Committee, the National Collegiate Athletic Association, and the National Football League.¹⁵ Most recently, Minor League Baseball has prohibited players from using supplements containing ephedrine alkaloids. This action followed a coroner's determination that the supplement taken by Orioles pitcher Steve Bechler, which contained ephedrine alkaloids, was a contributing factor in his death. Toxicology reports revealed that when Bechler died, significant amounts of ephedrine alkaloids were found in his

¹⁴ The Marine Corps took all dietary supplements containing ephedrine alkaloids off the shelves of its exchanges and base nutritional outlets as of Feb. 1, 2002. The Army and Air Force banned the sale of supplements containing ephedra in September 2002 following the death of a Texas soldier in April 2002. The Navy has also banned sales. William Cole, *Army and Air Force Exchange Joins Ephedra Ban*, The Honolulu Advertiser, Sept. 4, 2002 at 1A. Sgt. Skip Osborn, *Study Prompts to Pull Performance Drug Shelves*, U.S. Marine Corps News on Drugs, Jan. 25, 2001 available at <http://www.dod.mil/specials/drugawareness/usmcnews09a.html>.

¹⁵ In addition, a jury has awarded \$13.3 million to an Alaskan woman who suffered a debilitating stroke after taking a weight-loss product containing ephedrine. Guy Gugliotta, *Woman Wins \$13.3 Million Against Dietary Company; Jurors Find Product Containing Ephedrine Caused Stroke*, Wash. Post, Feb. 8, 2001 at A-8. This award marked the first time that the safety of ephedrine alkaloids was argued in an open trial. The "award eclipsed any known out-of court settlement paid in an ephedra or ephedrine case." *Id.*

system.¹⁶

3. Recommendations of experts

One important factor leading to the declaration that phenformin constituted an imminent hazard was the unanimous recommendation by the FDA Endocrinology and Metabolism Advisory Committee that phenformin be removed from the market. Similarly, the American Medical Association¹⁷ and the American Heart Association¹⁸ have called for its ban. In addition, a study reported in the March 2003 issue of the *Annals of Internal Medicine* concluded that “the sale of ephedra as a dietary supplement should be restricted or banned to prevent serious adverse reactions in the general population.”¹⁹

4. High rate of adverse events when compared to products in a similar category

A significant factor in FDA’s decision to declare phenformin an imminent hazard was the fact that fatalities associated with the drug occurred at a rate 5 to 80 times higher than that of other

¹⁶ Douglas S. Kalman, *Ephedra is Risky, but So is Lack of Testing for Stressed Players*, N.Y. Times, Mar. 16, 2003 at Sec. 8 page 7.

¹⁷ Ron Davis, M.D., *AMA Applauds FDA Action to Protect Public from Dangers of Ephedra*, (Statement) Mar. 3, 2003 at <http://www.ama-assn.org/pub>. Davis said that “Dietary supplements containing ephedra have significant risks, which may be serious to fatal to people with pre-existing illnesses as well as those who were previously healthy. They should ultimately be removed from the market.” *Id.*

¹⁸ American Heart Association, *American Heart Association urges ban of popular dietary supplements* (Press release) Apr. 3, 2003 at <http://americanheart.org>. “Evidence continues to grow that the dangers posed by these dietary supplements far outweigh any potential benefit that they may have,” said American Heart Association President Robert O. Bonow, M.D. “Consumers who take these products may think they are doing something good for their health, but the truth is they may be putting themselves at serious risk.” *Id.*

¹⁹ Stephen Bent, M.D. et al, *The Relative Safety of Ephedra Compared with Other Herbal Products*, 138 *Annals of Internal Medicine* 468, 470 (Mar. 18, 2003).

widely used drugs known to cause fatalities even when properly used.²⁰ The study in the *Annals of Internal Medicine* revealed that:

the relative risk for an adverse reaction from ephedra was more than 100-fold higher compared with all other herbs. For example, persons using products containing ephedra were 720 times more likely to have an attributable adverse reaction to ephedra than persons using Ginkgo biloba.²¹

The authors also found that products containing ephedrine alkaloids accounted for 64% of all adverse reactions to herbs in the U.S., despite the fact that ephedra represented .82% of herbal product sales.²²

In upholding FDA's decision to exercise its imminent hazard authority, the court rejected the plaintiff's "crisis" interpretation of imminent hazard. The court was persuaded by cases interpreting the imminent hazard provisions of the Federal Insecticide, Fungicide, and Rodenticide Act (which is based on the imminent hazard provision in the FDCA).²³ Those courts held that "it is enough that there is substantial likelihood that serious harm will be experienced during. . . any realistic projection of the administrative process."²⁴

Based on FDA's interpretation of its imminent hazard authority, case law, and facts that parallel those used in a successful exercise of its imminent hazard authority with respect to phenformin, FDA has the authority to declare supplements containing ephedrine alkaloids an

²⁰ Forsham v. Califano at 207.

²¹ *Id.* "Relative risk is defined as the number of adverse reactions per unit sales of ephedra divided by the number of adverse reactions per unit sales of the comparison herb." *Id.* at 469.

²² *Id.*

²³ Nor-Am Agricultural Products, Inc. v. Hardin, 435 F.2d 1133, 1142 (7th Cir. 1970).

²⁴ Forsham v. Califano at 137 (quoting "imminent hazard" cases, citations omitted).

imminent hazard.

B. Dietary Supplements Containing Ephedrine Alkaloids Present a Significant or Unreasonable Risk of Illness or Injury

Under Section 402(f)(1)(A), a product presents a significant or unreasonable risk if the product risks outweigh the benefits. As FDA explained in its announcement that it was reopening the comment period on dietary supplements containing ephedrine alkaloids:

This legal standard of ‘significant or unreasonable risk’ implies a risk-benefit calculation based on the best available scientific evidence. It strongly suggests that the agency must determine if a product’s known or supposed risks outweigh any known or suspected benefits, based on the available scientific evidence, in light of the claims the product makes and in light of the product’s being directly sold to consumers without medical supervision.²⁵

This interpretation represents a reasonable and practical interpretation of the statute that offers some protection to the consumer. As FDA stated in its White Paper on Ephedra: “Such a reading helps give DSHEA the meaning in practice that many of its supporters say it should have, by clarifying that public health authorities can take actions to protect the public from unreasonable but uncertain safety risks associated with ephedra.”²⁶

Significantly, the RAND report concluded that there is no evidence that supplements containing ephedrine alkaloids are effective in weight loss over the long term or that such supplements substantially improve athletic performance.²⁷ Because these are the primary uses

²⁵ FDA, New Release, *HHS Acts to Reduce Potential Risks of Dietary Supplements Containing Ephedra*, Feb. 28, 2003.

²⁶ FDA, *Evidence on the Safety and Effectiveness of Ephedra: Implications for Regulation*, (FDA White Paper on Ephedra) (Feb. 28, 2003)

²⁷ *Ephedra and Ephedrine for Weight Loss and Athletic Performance Enhancement: Clinical Efficacy and Side Effects*, AHRQ Publication No. 03-E022 ((Rand Report), (Feb. 2003) at 201, 202.

associated with supplements containing ephedrine alkaloids, it is clear that the known risks far exceed any long-term benefits and that ephedrine alkaloids should be banned as supplements.

C. Ephedrine Alkaloids Are Poisonous and Deleterious Added Substances When Used in Dietary Supplements

In its proposed regulation, FDA correctly concluded that ephedrine alkaloids are poisonous or deleterious “added” substances within the meaning of Section 402(a), FDA’s general adulteration provision, when used in supplements.²⁸ In addition, the statute makes clear that section 401(a) is applicable to supplements.²⁹ The supplement provision states: “A food shall be adulterated if [it]...is or contains a dietary ingredient that renders it adulterated under paragraph (a)(1) under the conditions of use recommended or suggested in the labeling of such dietary supplement.”³⁰

Although ephedrine alkaloids may be present in some products as a single ingredient, the majority of supplements containing ephedrine alkaloids contain between 6 and 20 other ingredients.³¹ Thus, ephedrine alkaloids are “added substances” in most cases. Added substances are adulterated if they contain a substance which “may render it injurious to health.”³²

The ever-growing list of adverse events associated with supplements containing ephedrine alkaloids, including death and debilitating strokes, certainly satisfies the “may render injurious to health” standard. Therefore, dietary supplement products containing ephedrine alkaloids are

²⁸ 62 Fed. Reg. 30678, 30693 (June 4, 1997) (Proposed rule).

²⁹ FDCA § 402(f)(1)(D), 21 U.S.C. § 342(f)(1)(D).

³⁰ *Id.*

³¹ 62 Fed. Reg. 30678, 30679 (June 4, 1997).

³² FDCA § 402(a), 21 U.S.C. § 342(a).

adulterated and should be removed from the market.

D. FDA Has the Authority to Regulate Dietary Supplements Containing Ephedrine Alkaloids as Prescription Drugs

Under the FDCA, drugs that are not safe for use except under the supervision of a practitioner licensed by law to administer such drugs may be dispensed only by prescription. A drug may be required to be available on a prescription only basis because of its toxicity or other harmful effect, the method of its use, or the collateral measures necessary to its use.³³ It is noteworthy that FDA already regulates synthetic ephedrine alkaloids in products sold as both over-the-counter and prescription drugs and that fewer adverse events have been associated with those products.³⁴

A recent editorial in *The Journal of the American Medical Association* stated that supplements, such as those containing ephedrine alkaloids – which have biological action “as is evidenced by sympathomimetic pharmacological properties and adverse cardiovascular events” – should be regulated as active drugs.³⁵ Given the dangers of supplements containing ephedrine alkaloids and the growing number of adverse events associated with their sale, it would be appropriate to reclassify supplements containing those ingredients as prescription drugs so that they can only be used under a physician’s supervision.

³³ FDCA § 503(b)(1)(A) and (B), 21 U.S.C. § 353(b)(1)(A).

³⁴ FDA White Paper, *supra* note 25 at 3-4. Ephedra is approved for use in over-the-counter bronchodilators (21 C.F.R. § 341.16) and nasal decongestants (21 C.F.R. § 341.20).

³⁵ Phil B. Fontarosa, MD et al, *The Need for Regulation of Dietary Supplements – Lessons from Ephedra*, 289:1568-70 *Journal of the American Medical Association* (2003).

II. Congress Should Clarify That FDA Does Have the Authority to Ban Supplements Such as Those Containing Ephedrine Alkaloids

A. FDA has Been Reluctant to Exercise its Authority to Ban Unsafe Supplements

Because of its heavy burden of proof, the agency is, at this point, reluctant to conclude that it has proven that supplements containing ephedrine alkaloids pose a “significant or unreasonable risk” without getting public support for this position. The agency reopened a comment period that has already been reopened twice since the start of the rulemaking process in 1997.³⁶

As discussed above, we believe that FDA has the authority to ban supplements containing ephedrine alkaloids under existing authority. Given the controversy surrounding the regulation of those supplements, however, we understand FDA’s caution. We believe that FDA should seek legislation from Congress confirming this authority so that supplements containing ephedrine alkaloids can be banned.

B. FDA Lacks the Tools to Enable it to Act Promptly

Attempts to regulate supplements containing ephedrine alkaloids have illustrated the difficulty FDA has in mustering scientific evidence because of restrictions on its authority. At a minimum, the FDA should be given additional authority as follows.

1. Authority to require product “listing” and labeling

Although dietary supplements are now required to be registered with FDA, the agency does not have the authority to require that companies provide it with a list of the products they are making and ingredients that are used, as well as a copy of product labeling. Such authority is only

³⁶ 68 Fed. Reg. 10417 (Mar. 5, 2003).

provided to FDA for drugs.³⁷ This information is essential to FDA evaluations of reports of possible public health concerns. According to an Inspector General's (IG) Report appropriately called *Adverse Event Reporting: An Inadequate Safety Valve*:

FDA was unable to determine the ingredients for 32 percent (1,153 of 3,574) of the products mentioned in adverse event reports. FDA does not have the product labels for 77 percent (2,752 of 3,574) of the products mentioned in reports. FDA does not have product samples for 69 percent (130 of 188) of the products for which it requested them. Product samples are especially helpful because dietary supplement ingredients are not standardized.³⁸

2. Authority to require mandatory reporting of adverse events

Although FDA has a voluntary system for reporting adverse events associated with supplements, only 1% of adverse events ever get reported to FDA.³⁹ The IG report stated that:

FDA reports that it has received fewer than 10 adverse event reports directly from manufacturers. FDA was unable to determine the manufacturer of dietary supplement products for 32 percent (1,153 of 3,574) of the products involved in reports. FDA was unable to determine the city and State for 71 percent (644 of 904) of the manufacturers.⁴⁰

Accurate adverse event reports are crucial regulatory tools, particularly for supplements. Because FDA only regulates supplements *after* they are marketed, it relies heavily on its adverse event reporting system to identify safety problems.

As summed up in the IG Report, "FDA lacks vital information to adequately assess signals of possible public health concerns generated by the adverse event reporting system."⁴¹ It is

³⁷ FDCA § 510, 21 U.S.C. § 360.

³⁸ HHS Inspector General, *Adverse Event Reporting for Dietary Supplements: An Inadequate Safety Valve* (OEI-01-00-00180) (Apr. 2001) at ii.

³⁹ *Id.*

⁴⁰ *Id.*

⁴¹ *Id.*

essential that FDA seek legislative authority to require mandatory adverse event reporting.

3. New premarket approval authority for new stimulants and steroid substitutes

Currently, FDA has the authority to review notifications of intent to market new dietary ingredients 75 days in advance of marketing. However, the manufacturer may proceed with marketing whether or not it has heard from FDA. Since many of the most dangerous supplements appear to be stimulants and steroid substitutes, it is imperative that FDA be able to have premarket approval authority for these supplements.

4. Authority to receive judicial deference on adulteration violations

As currently drafted, the statute provides that if FDA brings an adulteration suit, it bears the burden of proving that a supplement is unsafe.⁴² Moreover, the statute requires that “a court shall decide any issue under this paragraph on a de novo basis.”⁴³ With respect to drugs and food additives, manufacturers have the burden of proving that a product is safe. But as the law is currently written, consumers are bearing the burden of being guinea pigs while FDA – with inadequate tools – tries to determine whether a safety problem exists.⁴⁴ FDA needs to ask Congress to put the burden back where it belongs.

⁴² FDCA § 402(f), 21 U.S.C. § 342.

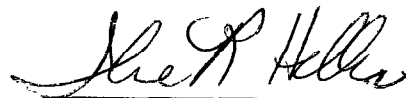
⁴³ *Id.*

⁴⁴ One tragic illustration of this problem involves a healthy high school athlete who died after using a product containing ephedrine alkaloids. Shortly before the tragedy, Sen Richard Durbin – who had concluded a hearing on ephedra – wrote a letter to Secretary Thompson, followed by a series of phone calls, calling upon the agency to take such products off the market. Transcript, U.S. Governmental Affairs Committee: Subcommittee on Oversight of Government Management, Restructuring and District of Columbia, Oct. 8, 2002. (Transcript provided by eMediaMillWorks, Inc.)

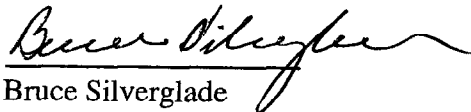
III. Conclusion

For the foregoing reasons we believe that FDA has the authority to ban supplements containing ephedrine alkaloids and should do so without further delay under its imminent hazard authority.

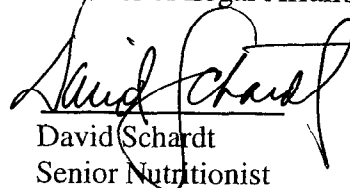
Respectfully submitted,



Ilene Ringel Heller
Senior Staff Attorney



Bruce Silverglade
Director of Legal Affairs



David Schardt
Senior Nutritionist