Consumers Union
Publisher of Consumer Reports

Dockets Management Branch
(HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, Maryland 20852
e-Comments to http://www.fda.gov/dockets/ecomments

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

Introduction

These comments are submitted by Consumers Union (CU)[1] regarding the Proposed Rule in the above docket (Proposed Rule). In an initial proposed rule published in the Federal Register on June 4, 1997, the U.S. Food and Drug Administration (FDA or Agency) proposed to amend its regulations to require a warning label on dietary supplements containing ephedrine alkaloids and mau huang (collectively referred to as "ephedra" in these comments). On April 3, 2000, the Agency withdrew the proposed requirements and restrictions. The Agency now has reopened the comment period, and has requested comments on: (1) A proposed warning label for ephedra-containing products; (2) Whether, in light of more recent evidence, FDA should determine that dietary supplement products present a significant or unreasonable risk of

[1]Consumers Union is a nonprofit membership organization chartered in 1936 under the laws of the State of New York to provide consumers with information, education and counsel about good, services, health, and personal finance; and to initiate and cooperate with individual and group efforts to maintain and enhance the quality of life for consumers. Consumers Union's income is solely derived from the sale of *Consumer Reports*, its other publications and from noncommercial contributions, grants and fees. In addition to reports on Consumers Union's own product testing, *Consumer Reports* with approximately 4.5 million paid circulation, regularly, carries articles on health, product safety, marketplace economics and legislative, judicial and regulatory actions which affect consumer welfare. Consumers Union's publications carry no advertising and receive no commercial support.

illness or injury; and (3) What additional legislative authorities, if any, would be necessary or appropriate to enable FDA to address this issue more effectively?

Summary of Consumers Union Position

Ephedra's known risks include hypertension, heart attack, irregular heartbeat, stroke, and seizures. In an article published in *Consumer Reports* in 1995, Consumers Union was among the first to warn the public about the risks associated with the use of ephedra. In addition, Consumers Union and ConsumerReports.org repeatedly have called on the Department of Health and Human Services (DHHS) and the FDA to ban the use of ephedra in dietary supplements. We believe that the FDA's proposed warning label is an inadequate response to this serious public health hazard and fails to protect consumers from those risks. We believe that based upon information available to Consumers Union, and to the Agency, it is clear that dietary supplements containing ephedra do indeed pose "an unreasonable risk of illness or injury" and that the Secretary of DHHS Secretary Tommy Thompson should commence with the process to ban ephedra immediately under the powers he currently holds under the Dietary Supplement Health and Education Act of 1994[2]

Secretary Thompson Should Immediately Ban Ephedra

Since 1993, the FDA "has received 117 reports of deaths among ephedra users, as well as 16,000 reports of other problems such as strokes, seizures, heatstroke, heart disorders, and psychotic episodes."[3] As stated in a letter from Consumers Union's President James Guest to Secretary Thompson, dated November 15, 2002, we urge

[2] Dietary Supplement Health and Education Act, Pub. L. No. 103-417.
[3] "Bottom Line in Mind, Doctors Sell Ephedra," The New York Times, March 21, 2003.

Secretary Thompson to declare dietary supplements containing ephedrine alkaloids and mau huang adulterated under Section 402 of the Federal Food Drug and Cosmetic Act ("The Act"), 21 U.S.C. §§ 342(f)(1)(A)(i) because they "[present] a significant or unreasonable risk of illness or injury and 342(f)(1)(C under…conditions of use recommended or suggested in labeling…." In addition, we urged the Secretary to initiate proceedings to ban the production and sale of dietary supplements containing ephedra under Section 402 of the Act, 21 U.S.C. 342(f)(1)(C), because they "pose an imminent hazard to public health or safety."

In the time interval since Consumers Union sent the above letter, the Agency has failed to act, and more consumers have suffered and possibly have died from use of ephedra-containing products. The February 17, 2003 death of Baltimore Orioles pitcher Steve Bechler focused additional attention on ephedra. As is well known, Bechler, 23, died of heatstroke after a spring-training practice session. Several news reports after his death revealed that ephedra supplements were found in his locker. On March 13, 2002, the Associated Press reported that Broward County, Florida, medical examiner Dr. Joshua Perper stated that toxicology tests disclosed significant amounts of ephedra in his body tissues. The presence of that substance probably contributed to the victim's heatstroke and eventual demise.

Recent Evidence from Studies on Ephedra

Alarming evidence about the harmful effects of ephedra have been mounting for years. We believe there is ample evidence that ephedra poses an unacceptable risk to consumers and provides minimal benefits. Below is a summary of recent reports and studies illustrating the grave, life-threatening, and sometimes fatal, dangers posed by dietary supplements containing ephedra.

1 Annals of Internal Medicine

A report in the February 2003 Annals of Internal Medicine revealed additional evidence of ephedra-related harms. The study showed that products containing ephedra accounted for 64% of all adverse reactions to herbal products reported to the American Association of Poison Control Centers in 2001. The researchers calculated that the relative risk for an adverse reaction to ephedra compared with other herbs in the database was 100-fold or more.[4]

2. Journal of the American Medical Association - RAND Report

An article based upon an evaluation of scientific reports conducted by the authors and the Southern California Evidence-Based Practice Center -- RAND, and commissioned by DHHS and NIH, appeared in the March 26, 2003 issue of The Journal of the American Medical Association. This report links the use of ephedra with risks of heart, psychiatric, and gastrointestinal problems, while finding insufficient evidence to support its use to enhance athletic performance, or to promote long-term weight loss.[5] The researchers stated: "We found sufficient evidence to conclude that ephedrine and ephedra are associated with 2 to 3 times the risk of psychiatric symptoms, autonomic symptoms, upper gastroenterological symptoms and heart palpitations."[6]

3. The American Association of Poison Control Centers

The American Association of Poison Control Centers (AAPCC) has reported a steadily increasing number of serious adverse events related to supplements containing ephedra over the last five years. Data released in 2002 by the AAPCC indicates that in the year 2001 alone there were 812 reported events relating to the use of dietary

[4] Bent, Stephen et al. "The Relative Safety of Ephedra Compared with Other Herbal Products," 18 March 2003, Annals of Internal Medicine, Vol. 138, No. 6 pp. 1-4.

supplements containing ephedra as a sole ingredient, including 3 deaths, 103 adverse reactions, 10 "major effects" (defined as exhibiting signs or symptoms that were life-threatening or resulted in significant residual disability) and 139 "moderate effects" (defined as exhibiting symptoms or signs that were more pronounced, more prolonged or more systemic in nature than minor symptoms -- and where usually some form of treatment is indicated). Of the 812 exposures, 440 persons (54%) were treated in a health care facility. Forty-eight percent (48%) of reported exposures occurred in individuals over 19 years of age.

In addition to the above reports there were 7,115 reported events linked to the use of multi-botanical supplements containing ephedra as an ingredient, including three deaths, 1,075 adverse reactions, 87 "major effects" and 1,325 "moderate effects." Of the 7,115 exposures, 3,849 persons (54%) were treated in a health care facility. Forty-three percent (43%) of reported exposures occurred in individuals over 19 years of age.[7]

4. Other Studies

Two recent independent studies reported in peer-reviewed journals, scrutinized adverse events reports filed with the FDA between 1995 and 1999. In the reports, researchers found dozens of cases of abnormal heartbeats, strokes and heart attacks that were likely related to ephedra use.

Samenuk and others at the New England Medical Center in Boston analyzed almost 1,000 cases of possible ephedra toxicity submitted to the FDA. The researchers

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[5] Shekelle, et. al., "Efficacy and Safety Data of Ephedra and Ephedrine for Weight Loss and Athletic Performance," Journal of the American Medical Association, March 26, 2003, Vol. 289, No. 12, pp. 1537-1545.
[6] Id. at 1544.
[7] American Association of Poison Control Centers, 2001 Annual Report of AAPCC Toxic Exposure Surveillance System, also reported in American Journal of Emergency Medicine, Vol. 20, No. 5,

reported in the January 2002 issue of Mayo Clinic Proceedings that adverse events were clearly related to immediate prior use of the ephedra-containing products in 37 people, and that 36 of these 37 victims had taken the dietary supplement products according to the manufacturer's directions. Sixteen suffered a stroke; 10 had a heart attack; and 11 died. The study concluded that "ma Huang use is temporally related to stroke, myocardial infarction, and sudden death; (2) underlying heart or vascular disease is not a prerequisite for ma Huang–related adverse events; and (3) the cardio-vascular toxic effects associated with ma Huang were not limited to massive doses."[8]

In the December 21, 2000 issue of The New England Journal of Medicine, Haller and Benowitz from the University of California in San Francisco analyzed 140 cases of alleged ephedra toxicity that were reported to the FDA from 1997 to 1999. Abnormal heart rhythms, increases in blood pressure, stroke, sudden death, and heart attack led the list. Of those reactions, 62% were thought to be "definitely or probably" or "possibly" due to ephedra. Eight of the 10 deaths were attributed to ephedra, including that of a 15-year-old girl.[9]

Additional Legislative Authority

DSHEA allowed dietary supplements to receive reduced scrutiny under the Federal Food Drug and Cosmetic Act.[10] As the growing number of adverse event reports for ephedra alone illustrates, current law is inadequate to protect consumers from the risks of dietary supplements -- known and unknown. Although dietary

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September 2002, p. 439. Available at: http://www.aapcc.org/Annual%20Reports/01report/2001%20TESS%20tables%2022ab.pdf

[8] Samenuk, D. et al. "Adverse cardiovascular events temporally associated with Ma Huang, an herbal source of ephedrine." *Mayo Clin Proc* . January 2002;Vol. 77:pp. 12-16.

[9] Haller, C.A. and Benowitz, N.L. "Adverse Cardiovascular and Central Nervous System Events Associated with Dietary Supplements Containing Ephedra Alkaloids," NEJM, December 21, 2000, Vol. 343, No. 25, pp.1833-1838.

supplement manufacturers are prohibited from making specific disease-cure claims for products, the ability to make a truthful structure-function claim depends upon the biological effects any botanical may have. As such, all dietary supplements making health claims may have potential inherent risks, and therefore should be reviewed for safety prior to marketing. Efficacy is a separate problem and therefore has to be preceded by the establishment of adequate standards. Below is a summary of some of the most important legislative changes we believe are necessary protect consumers from harm relating to the use of dietary supplements:

(1) Adverse event reporting by manufacturers of dietary supplement products should be made mandatory. Under the current system, adverse event reporting is voluntary and creates a conflict of interest on the part of the manufacturer who might be inclined to overlook seemingly marginal risk reporting or simply fail to report adverse effects at all.[11] Since it is well known that only a small fraction of adverse events are ever reported to any authority, the ever-growing number of ephedra-related events take on even more significance.

(2) FDA must be granted meaningful authority to immediately halt sales of dietary supplement products posing any health risks to consumers. Since dietary supplement manufacturers are not required to prove efficacy, and claims of benefit are often exaggerated or dubious, any risk of harm to a user should make a given product unacceptable and result in its withdrawal from the market. The FDA should not have the burden of proving that a supplement is unsafe. Such proof is difficult to achieve since adverse event reporting is always anecdotal. In the case of ephedra that anecdotal evidence is overwhelming.

(3) Ephedra is a natural substance with recognized physiological effects. It belongs to a class of compounds known as pressor amines, all of which cause vasoconstriction and central nervous system stimulation in varying degrees. Tachycardia and euphoria are common effects. When millions of people are exposed to ephedra it should be expected that complications of those side effects (hypertensive episodes, arrhythmias, heart attacks, seizures, and strokes) will occur. In fact, they can be anticipated. It is

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[10] 21 U.S.C. 321, et. seq.

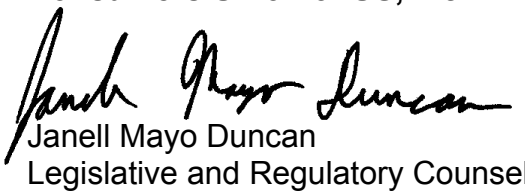
[11] In August of 2002, Metabolife, a leading manufacturer of an herbal ephedra stimulant, revealed that it had failed to disclose about 13,000 complaints it had received related to its product. Eighty incidents involved injury or death, and 100 to 200 involved hospitalization. In 1998, Michael Ellis, then President of the company had stated that Metabolife did not have any reports of serious health events. Many of the complaints preceded Mr. Ellis' statement.

therefore within the current power of the FDA to declare ephedra a drug and make it subject to all the regulations pertaining thereto.

Consumers Union requests that Secretary Thompson ban ephedra-containing dietary supplement products under the authority granted by DSHEA. In addition, we request that the FDA seek any and all additional legislative authority necessary to protect consumers from serious risks associated with dietary supplements, including FDA pre-market review, regulation of suspect dietary supplements as drugs, and mandatory adverse event reporting for all dietary supplements.

April 4, 2003

Respectfully Submitted,
Consumers Union of US, Inc.



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