

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>.

FOR FURTHER INFORMATION CONTACT: Anthony Curry, Center for Food Safety and Applied Nutrition (HFS-306), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740, 301-436-2071.

SUPPLEMENTARY INFORMATION:

I. Reopening of Comment Period

In the **Federal Register** of June 4, 1997 (62 FR 30678) (the June 1997 proposal), FDA (“we” or “the agency”) proposed to amend our regulations to require the label of dietary supplements containing ephedrine alkaloids to bear a warning statement. The proposed warning statement contained several elements, including cautions that consumers not use the product if they have certain diseases or health conditions or are using certain drugs, and that they stop using the product if they develop certain signs or symptoms. FDA also proposed restrictions on the potency and composition of dietary supplements containing ephedrine alkaloids, including a prohibition on the use of ephedrine alkaloids in dietary supplements with ingredients, or with ingredients that contain substances that have a known stimulant effect, such as caffeine. In addition, the agency proposed several requirements and

restrictions relating to labeling claims and directions for use.

We proposed these actions in response to reports of serious illnesses and injuries, including a number of deaths, associated with the use of dietary supplements containing ephedrine alkaloids and the agency’s investigations and assessment of these illnesses and injuries.

The comment period for the proposed rule closed on August 18, 1997. On September 18, 1997, FDA reopened the comment period for 75 days until December 2, 1997 (62 FR 48968).

In the **Federal Register** of April 3, 2000 (65 FR 17474), we withdrew the proposed requirements and restrictions concerning potency, labeling claims, and directions for use, but not the proposed warning statement or the proposed prohibition on dietary supplements that combine ephedrine alkaloids with other stimulant ingredients. In the same issue of the **Federal Register** (65 FR 17510), we also announced the availability of adverse event reports and related information that had become available since the June 1997 proposal; we reopened the comment period until May 18, 2000, to receive comments on this new information (Docket No. 00N-1200).

Recently, more scientific evidence has come to light concerning the risks posed by ephedrine alkaloids, including approximately 17,000 adverse event reports received overall by FDA. For example, one study compared the risks of adverse events attributable to ephedra and other herbal products through a

comparative case series investigation based upon poison control center reporting (Ref. 1). Another study, a case-controlled investigation, examined the association between the use of ephedra and the risk for hemorrhagic stroke (Ref. 2). One study evaluated the adverse cardiovascular events from the FDA database that were temporally associated with the use of ephedra (Ref. 3). Another study evaluated the pharmacology of ephedrine alkaloids and caffeine after a single dose in humans (Ref. 4). Two studies were double-blind controlled clinical trials that evaluated the efficacy of ephedra in combination with caffeine for weight loss, with treatment durations of 6 weeks (Ref. 5) or 6 months (Ref. 6). Further, the RAND Corporation, under contract with the U.S. Department of Health and Human Services, has conducted an evidence based review of all available sources of information on ephedrine alkaloid containing dietary supplements (Ref. 7).

Comments to the June 1997 proposal stressed the importance of ensuring that consumers were aware of the risks of consuming dietary supplements containing ephedrine alkaloids. Therefore, in light of the new scientific evidence as well as the comments received in response to the June 1997 proposal, FDA is considering the following warning statement for dietary supplements containing ephedrine alkaloids. This statement is consistent with the recent scientific reports referenced in this document.