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June 28, 2002

The Honorable Tommy Thompson
Secretary
U.S. Department of Health and Human Services
Hubert H. Humphrey Building
200 Independence Avenue, SW
Washington, DC 20201

Dear Secretary Thompson:

I am writing to express my disappointment that the Department of Health and Human Services has decided to delay taking effective action to protect consumers from the dangers of dietary supplements containing ephedra.

The Food and Drug Administration (FDA) first proposed regulations on ephedra in 1997, five years ago. Since then, FDA has compiled an extensive docket of information on ephedra. This docket includes: reviews of adverse event reports by experts; a petition from Dr. Ray Woosley and Dr. Sidney Wolfe calling for a ban on ephedra; requests from public health groups such as the Association of Food and Drug Officials that FDA take action on supplements containing ephedra; a request from the National Collegiate Athletic Association that FDA take action on ephedra; literature reviews on ephedra; and comments from industry and consumers. FDA has also received hundreds of additional adverse event reports as well as information from poison control centers about reports they have received regarding dietary supplements containing ephedra.

Instead of taking action, however, your Department announced on June 14 that you wanted to conduct still more study of this issue. Your announcement thus effectively postponed any decision on regulations of ephedra. The only regulatory step you took was the modest one of announcing aggressive enforcement against dietary supplements containing synthetic ephedrine. But since these products are only a small part of the ephedra market, this action will have little impact.

In the view of the experts I have consulted, your decision to delay action is unwarranted. Your commission of a literature review would add little to the current debate. There have already been numerous reviews of the literature, and HHS has heard expert testimony on all sides

of this debate. Proponents of ephedra have pointed to a recent study of ephedrine/caffeine combination products for weight loss.[1] This small study was not designed to assess, nor could it assess, the risk of serious side effects in large populations of people. It is therefore irrelevant to the question at hand. Indeed, the editor of the International Journal of Obesity, in an editorial that accompanied this article, wrote: "The lay public should use ephedra-caffeine supplements with great caution and, in the opinion of this Editor, only under the supervision of a physician."[2]

One of the justifications for further study is the assertion that FDA adverse event reports do not provide a scientific basis for assessing the safety of these products. This implies that FDA does not have information beyond the adverse event reports. This is not true. It is well known that ephedrine is a cardiovascular and central nervous system stimulant that has important physiological effects on those systems at doses in the range of exposure from dietary supplements containing ephedra. Moreover, it is also well known that many of the adverse events that have been reported are consistent with the known effects of sympathomimetic drugs, such as ephedrine, on the heart and central nervous system.[3] The large volume of reports of strokes, heart attacks, dizziness, seizures, increased blood pressure, and other cardiac effects from consumption of ephedra are thus consistent with the known effects of this class of compounds.

Moreover, it is simply wrong to say that adverse event reports cannot serve as the basis for regulatory action. FDA routinely moves against drugs on the basis of adverse events. For example, the FDA's action against the gastrointestinal drug cisapride (Propulsid) was based on reports of cardiac complications in the setting of the known effects of the drug on the heart.[4] The painkiller bromfenac sodium (Duract) was removed from the market on the basis of reports of liver damage.[5]

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[1]C.N. Boozer, *Herbal Ephedra/Caffeine For Weight Loss: A 6-Month Randomized Safety and Efficacy Trial*, International Journal of Obesity (2002).

[2]R.L. Atkinson, *The Herbal Ephedra and Caffeine Debate Continues*, International Journal of Obesity (2002).

[3]Bruce D. Lindsay, *Are Serious Adverse Cardiovascular Events an Unintended Consequence of the Dietary Supplement Health and Education Act of 1994?* (January 2002).

[4]FDA, *Janssen Pharmaceutica Stops Marketing Cisapride In the U.S.*, FDA Talk Paper (Mar. 23, 2000).

[5]M.A. Friedman et al, *The Safety of Newly Approved Medicines: Do Recent Market Removals Mean There Is a Problem?* JAMA 281:1728-1734, May 12, 1999.

In the case of ephedra, there are more adverse event reports than for either of these two other products. Your statement failed to mention that FDA has received over 1,400 adverse events. It also failed to mention that an independent review of 140 of those adverse events found that 31% of the reports analyzed were definitely or probably related to the use of ephedra-containing supplements, and 31% were possibly related to the use of those supplements. The adverse events that were determined to be definitely or probably related included severe cardiovascular and cerebrovascular events and death.[6]

Your decision to delay regulatory action on ephedra products also raises other issues. For this reason, I request that you provide answers to the following questions:

1. FDA has previously stated that it has received over 1,400 adverse event reports involving supplements containing ephedrine alkaloids. Please provide the exact number of adverse event reports FDA has received as of the date of this letter.

2. Please categorize these events into serious and non-serious for each organ-system group. I would also like a break-down of the serious and non-serious events by the age of the consumer.

3. Does FDA disagree with expert reviewers' conclusions that 31% of the reports were definitely or probably related to ephedra use? If not, on what basis does FDA disagree?

4. According to the press release, you characterize HHS's actions against companies selling synthetic ephedrine products as "another example of HHS' strong commitment to protecting the public from the dangers of unlawfully marketed drug products." What are the dangers of synthetic ephedrine? If the exact same chemical substance is found in natural ephedra products, why aren't these products dangerous as well?

5. Some experts believe that, given the risk associated with ephedrine products, it would be unethical to conduct a safety study of ephedra on humans. Is FDA's position that it would be ethical to give ephedra to human subjects during periods of intense exercise?

6. Is it FDA's position that if it receives a number of serious adverse event reports about a particular product that are consistent with what is known about that product's effect on the body at doses in the range of exposure from the product, that information is insufficient to take action against that product?

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[6]Christine A. Haller, *Adverse Cardiovascular and Central Nervous System Events Associated with Dietary Supplements Containing Ephedra Alkaloids*, New England Journal of Medicine (December 2001).

7. On the basis of what information was the recent warning about kava kava issued?

8. What information is necessary for FDA to issue a warning about a particular product?

9. Please describe in detail what kinds of information would be required to justify removing ephedra from the market.

Please provide this information by July 15, 2002. If you have any questions, please contact Sarah Despres at 225-5420.

Sincerely,

Henry A. Waxman
Ranking Minority Member

cc: The Honorable Dan Burton