Congress of the United States
Washington, DC 20515

September 19, 2002

The Honorable Tommy G. Thompson
U.S. Department of Health and Human Services
200 Independence Avenue, SW
Washington, D.C. 20201

Dear Secretary Thompson:

Thank you for your response to Rep. Waxman's June 28, 2002, letter regarding ephedrine. We have followup questions in several areas.

1. Why is the Food and Drug Administration (FDA) only taking action on products containing synthetic ephedrine?

On June 16, 2002, you announced that you are banning products containing synthetic ephedrine. You characterized that action as "yet another example of HHS' strong commitment to protecting the public from the dangers of unlawfully marketed drug products."

Many experts say there is no pharmacological difference between synthetic and natural ephedrine. In fact, you made clear in your September 4, 2002, letter to Rep. Waxman that your position is that the difference between synthetic ephedrine and plant-derived ephedrine is not pharmacological. Instead, the distinction is a legal one. Your reading of the definition of "dietary supplement" in the Dietary Supplement Health and Education Act (DSHEA) apparently is that it does not include synthetic ingredients.

Under DSHEA, however, you have the authority to remove a natural product from the market if it presents an imminent hazard or an unreasonable risk of significant injury. Please explain why, given this authority, HHS has limited its enforcement action to synthetic ephedrine-group alkaloids alone.

2. What additional information does FDA require in order to take some action on naturally derived ephedrine products?

An extensive amount is currently known about ephedrine products. Ephedrine is a known 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.[1] Ephedrine has been associated with increased blood pressure, rapid heart rate, heart attack,

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[1] Dr. Christine Haller, *Pharmacology of Ephedra Alkaloids and Caffeine After Single-Dose Dietary Supplement Use,* Clinical Pharmacology and Therapeutics, 421 (June 2002) (finding that young healthy adults can have cardiovascular and central nervous system effects after a single dose of a dietary supplement labeled to contain 20 mg of ephedrine and 200 mg of caffeine).

stroke, and seizure.[2] FDA has received approximately 15,000 adverse event reports regarding ephedrine-containing supplements, including reports of heart attack, stroke, seizure, and death, all of which are consistent with the known effects of sympathomimetic drugs, of which ephedrine is one.[3] Furthermore, an independent analysis of a number of those events concluded that 31% of the reports analyzed were definitely or probably related to the use of ephedrine-containing supplements, and 31% were possibly related to the use of those supplements.[4] The adverse events that were determined to be definitely or probably related included several cardiovascular and cerebrovascular events and death.

Please explain with specificity what additional evidence would be needed for FDA to take the following actions, and why the following actions have so far not been taken:

a. Require a strong consumer warning on the label;

b. Issue a strong warning to consumers that these products have not been proven safe and that the side effects can include stroke, seizure, heart attack, and death;

c. Ban products that combine ephedrine with other stimulants such as caffeine or synephrine (citrus aurantium);

d Require that ephedrine products be available only by prescription; or

e. Ban the product completely.

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[2] Testimony of Dr. Ray Woosley, Professor and Chairman of the Department of Pharmacology, Georgetown University Medical Center, House Committee on Government Reform, *Hearing on How Accurate is the FDA's Monitoring of Supplements Like Ephedra?* 106th Cong. (May 27, 1999).

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

[4] Dr. Christine Haller, *Adverse Cardiovascular and Central Nervous System Events Associated With Dietary Supplements Containing Ephedra Alkaloids*, New England Journal of Medicine (2000); *see also* Dr. David Samenuk, *Adverse Cardiovascular Events Temporally Associated With Ma Huang, an Herbal Source of Ephedrine*, Mayo Clinic Proceedings (2002).

3. Does FDA have any scientific evidence that suggests that herbal ephedra is safer than phenylpropanolamine (PPA)?

On November 6, 2000, FDA announced its intention to ban any over-the-counter product containing the chemical phenylpropanolamine (PPA). This chemical is closely related to ephedrine, as well as to amphetamine. FDA based its decision on a study that indicated that women who took PPA as an appetite suppressant were as much as 16 times more likely than other women to suffer a hemorrhagic stroke.[5] FDA had also received 51 adverse event reports of hemorrhagic stroke for PPA users between 1991 and July 2000.

Although ephedrine is chemically similar to PPA, FDA has not taken similar action on natural ephedrine. Please explain whether FDA has any scientific evidence that ephedrine is safer than PPA.

4. What analysis has FDA or HHS performed of the recent study of ephedrine-containing supplements in the *International Journal of Obesity?*

We are also interested in information about the study by Dr. Carol Boozer on the efficacy of ephedra-containing supplements that was recently published in the *International Journal of Obesity*. We understand concerns have been raised that the study protocol may have been changed without appropriate notification to the Institutional Review Board that approved the study. Please send us any analyses of that study that have been performed by any agency within HHS, including analyses of the design, execution, and conclusions of the study.

5. Conclusion

We would appreciate a response to this letter by October 3, 2002. If you have any questions, you can call Sarah Despres of Rep. Waxman's staff at (202) 225-5420 or Anne Marie Murphy of Sen. Durbin's staff at (202) 224-8464.

Sincerely,

Henry A. Waxman
Ranking Minority Member
Committee on Government Reform
U.S. House of Representatives

Richard J. Durbin
Chairman
Subcommittee on Oversight of Government Management, Restructuring and the District of Columbia
U.S. Senate

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[5]Dr. Walter Kernan, *Phenylpropanolamine and the Risk of Hemorrhagic Stroke*, New England Journal of Medicine, V. 343, 1826-1832 (2000).