THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

SEP 04 2002

The Honorable Henry A. Waxman
Ranking Minority Member
Committee on Government Reform
House of Representatives
Washington, D.C. 20515-6143

Dear Mr. Waxman:

Thank you for your letter of June 28 concerning the Department's recent action to defer making a final decision on Public Citizen's petition seeking a ban of all dietary supplements containing ephedrine alkaloids.

As you know, this is an issue the Department and the Food and Drug Administration (FDA) have been carefully considering. As conveyed in our June 14 public statement, we continue to be concerned about adverse events that have been reported to be associated with the use of these products. We believe the strength of this signal justifies a serious scientific evaluation. The Department has contracted with the RAND Corporation to conduct an evidence-based scientific review of existing data regarding ephedrine alkaloids. The RAND Ephedra: Clinical Efficacy and Side Effects Report is currently being reviewed by scientific experts and is expected to be published in Fall 2002.

Recently, the Department received approximately 13,000 adverse event reports dealing with health-related issues associated with the use of Metabolife 356 between 1997 and 2001. Metabolife's making these reports available coincided with the U.S. Department of Justice announcement that it has launched a criminal investigation into whether the firm made false statements to the FDA about adverse event reports concerning its ephedra supplements. The Metabolife adverse event reports are being reviewed expeditiously by the FDA.

It is our belief that conducting an evidence-based scientific review and evaluation of all available materials that address the safety of ephedrine alkaloids alone or in combination with other stimulants, such as caffeine, will help us decide on the appropriate next steps to address the use of products containing natural (botanical) ephedrine alkaloids. The FDA will continue to carefully monitor the reported adverse events and available scientific information and advise consumers as appropriate or take necessary action. I have enclosed the answers to the specific questions identified in your letter.

I appreciate your views on this important issue. Please call me if you have further thoughts or questions.

Sincerely,

Tommy G. Thompson

Enclosure

cc: The Honorable Dan Burton
Chairman, Committee on Government Reform
House of Representatives

Response to Representative Waxman's Questions

1. Question: 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 (6/28/02).

   Answer: As of June 28, 2002, the FDA has received approximately 1,780 dietary supplement adverse event reports associated with the use of ephedra claimed to be an ingredient in a given dietary supplement. While a signal has been generated by these reports, questions remain on the likelihood and strength of causation between ephedrine alkaloids and the adverse events reported. These reports provide a signal for further scientific review of the known clinical data, which is now being conducted by RAND. The RAND Ephedra: Clinical Efficacy and Side Effects Report is currently being reviewed by scientific experts and is expected to be published in Fall 2002. This approach is consistent with the findings and recommendation of the General Accounting Offices' July 1999 report.

2. Question: 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.

   Answer: Please refer to your previous correspondence of March 7, 2001 and FDA responses of July 11 and October 31, 2001 based upon 1,422 adverse events reported of ephedrine alkaloid containing-dietary supplements. Due to resource constraints, at this time FDA is not able to provide a detailed breakdown of the additional 300+ reports since its previous response.

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

   Answer: FDA and its experts evaluated the same patient dataset of approximately 140 selected adverse reports, but the experts chose their own methods and criteria for causality assessment. Because of this, these reviews are not directly comparable. Again, the reports provide a signal and a cause for further rigorous scientific review before determining the best course of further action.

4. Question: 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?

   Answer: FDA has initiated enforcement action against manufacturers and distributors of products marketed as dietary supplements that contain synthetic ephedrine alkaloids because these synthetic ingredients do not meet the definition of a dietary ingredient or supplement under DSHEA and NOT because of a determination of relative toxicity or pharmacologic

activity. There has been no convincing evidence made available yet that we are aware of that establishes relative potency between synthetic and natural sources of ephedrine alkaloids.

5. Question: 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?

   Answer: While one could not ethically justify asking research subjects to participate in a prospective clinical trial of an intervention with the single goal of determining whether the intervention is associated with severe adverse reactions, there are clinical and epidemiologic (e.g., case controlled) studies that can be done ethically and which would provide valuable data on the safety, as well as the efficacy, of the intervention. Specifically regarding the study of ephedra in people during periods of intense exercise, it may be possible to design a clinical trial that could be conducted in an ethical manner. In response to the RAND review, the NIH is convening an expert panel to advise on which research questions related to ephedra are of the greatest importance and which can be addressed ethically and credibly.

6. Question: 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.

   Answer: Not necessarily. FDA evaluates the sufficiency of evidence of risk on a case-by-case basis, considering the quantity, quality, and strength of available scientific information and the legal standard that applies to the product type in question.

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

   Answer: In March 2002, FDA issued a consumer alert about kava-containing dietary supplement products and the potential risk of serious liver injury. The basis for this alert was a review of adverse event reports involving kava kava from the United States and Europe by FDA health care professionals. In the United States, FDA had received a report of a previously healthy young female, who after using kava, required a liver transplant. In other countries, approximately 25 adverse events had been reported, four of which resulted in liver transplants. In addition, the Europeans had reported a documented case of hepatic toxicity in an individual who retook the kava-containing product even after experiencing an initial reaction. Taken together, this information warranted a consumer alert. FDA urged persons who have liver disease or liver problems, or persons who are taking drug products that can affect the liver, to consult a physician before using kava-containing supplements.

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

Answer: The type of information necessary for FDA to issue a warning about a particular product varies from case to case and depends on the regulatory status of the product (i.e., what is known about the product) and the specifics of the safety concern (i.e., nature and severity of the adverse event, population involved, pharmacology, toxicity, types of reports, literature, clinical studies, use, user population and other variables such as other medication use, health conditions, etc.)

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

Answer: FDA considers the same information as in #8 and evaluates, on a case-by-case basis, whether the scientific evidence is sufficient to show that the product is an imminent hazard to public health or safety or that the product poses a significant or unreasonable risk of illness or injury under conditions of use in its labeling or, if the labeling does not recommend conditions of use, under ordinary conditions of use. In addition, FDA often seeks advice from expert advisory committees or panels prior to removal of a product from the market.