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June 30, 2000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5603 Fishers Lane (Room 1061)
Rockville, MD 20852

Re: Docket No. 00N-1200, Dietary Supplements Containing Ephedrine Alkaloids

To whom it may concern:

These comments are submitted on behalf of the Ephedra Committee of the American Herbal Products Association (AHPA) in response to the new adverse event reports (AERs), and reviews of those reports, that the Food and Drug Administration (FDA) made public on April 3, 2000. The Ephedra Committee has undertaken a comprehensive review of the new information that FDA has released using a panel of independent scientists, researchers and physicians with expertise in toxicology, pharmacology, epidemiology, cardiology and neurology. This panel will (1) conduct a thorough review of the new AERs using accepted analytical techniques, (2) review the literature cited by FDA and other available literature relevant to dietary supplements, and (3) review the published literature on background rates for heart attacks, strokes and seizures as well as new consumption data to begin to put the AERs in their proper context.

Because of the enormity of this undertaking, the panel review is not yet complete. However, the initial review of FDA's new AERs and other information that FDA has provided shows that, once again, FDA has inappropriately attempted to base a public health assessment of these products on AERs alone.

FDA asked outside experts to review all or a portion of a set of AERs that FDA compiled, depending on their particular expertise, and, in the context of reviewing the

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AERs, asked these experts, "[t]aking into consideration the nature of the event, the usage level, and the available labeling, [to] address whether the use of ephedrine alkaloids in dietary supplement products is safe." The reviewers were not provided with any information on the extent of the consumption of these products, or with published information on the natural or background rate of occurrence of the events at issue in the population. Therefore, the reviewers were not able to tell whether the AERs they reviewed might simply be due to natural causes.

FDA itself recognizes that making judgments about product risk based on AERs is not scientifically valid. In the "Disclaimer" that accompanied the AERs that FDA released in 1997, FDA made this important point:

> Accumulated case reports cannot be used to calculate incidence or estimates of product risk. They must be carefully interpreted as reporting rates, and not as occurrence or incidence rates. The length of time that a product has been marketed, the market share, experience and sophistication of the population using the product or evaluation of the adverse event, publicity about an adverse reaction, and regulatory actions are all factors that influence the probability that an adverse event will be reported. Comparisons of product safety cannot be directly obtained from these data.

(Emphasis added.) And yet, FDA asked its outside reviewers to assess safety based on the AERs.

The lack of scientific validity of this approach is most dramatically demonstrated by the statements of FDA's own Center for Drug Evaluation and Research (CDER), which was also asked to review the AERs at issue. After presenting its written assessment of the AERs as requested, CDER stated in its conclusion that

> Additionally, it is possible that the reported serious adverse events are reflective of coincidental background spontaneous occurrences in the population and are not necessarily causally related to [dietary supplements containing ephedrine alkaloids]. The availability of additional information, including product market or usage data, would be useful to further characterize the potential risks associated with the use of these products.

(Emphasis added.) In other words, unlike FDA's outside experts, or FDA's Center for Food Safety and Applied Nutrition (CFSAN), FDA's own experts at CDER have concluded and informed CFSAN that no safety assessment could be made based on the AERs.

This is essentially the same message that the General Accounting Office attempted to deliver to FDA in its July 1999 report, "Dietary Supplements: Uncertainties in Analyses Underlying FDA's Proposed Rule on Ephedrine Alkaloids." The GAO determined that FDA had inappropriately relied primarily on AERs as the basis for the 1997 proposal, that FDA had relied on just 13 AERs that the agency never reviewed for causality as a basis for the proposed serving limits, that FDA had failed to provide a valid scientific basis for its proposed duration limits, and that FDA had not established a public health benefit to the proposed rule. (The GAO did not review or comment on FDA's proposed prohibition on combining ephedra with caffeine or other stimulants, or on FDA's proposed warnings. Nonetheless, the GAO's finding that FDA did not follow accepted procedures to evaluate the costs and benefits of the proposal also extend to these portions of the proposal.) As a direct result of the GAO report, FDA withdrew the proposed serving and duration limits on April 3, 2000. Now, according to FDA's own drug center (CDER), FDA's food center (CFSAN) has once again released and requested review of a group of AERs without producing the information needed to assess the public health implications of this information, or whether the events are just "coincidental background spontaneous occurrences."

Industry is working hard to provide the missing information that is necessary to conduct the type of analysis that FDA should have conducted long ago. But obtaining all of the needed information will take time, and will require the cooperation of FDA and other agencies, including the National Institutes of Health, which has been provided with funding to conduct studies on dietary supplements.

One study of significance to the safety questions FDA has posed, including the usefulness of ephedra products as an aid to weight loss, has already been completed by researchers from Harvard and Columbia Universities. This study will be published soon, we understand within a year. Other clinical data supporting the safety of ephedra and its importance as a tool for addressing the enormous public health problems associated with excess weight are also expected to be published this year. The usefulness of ephedra products for weight loss, and the public health benefits of such use, is an essential part of any review of the safety of these products.

FDA has been studying the ephedra issue for over seven years. In that time, despite exponential increases in sales, the number of reports of adverse events has declined. There is no basis for rushing to judgment on ephedra, and FDA should take the time necessary to assemble all of the data that is relevant to the safety of these products before taking further action.

In the seven-year period of FDA's review, responsible industry has established national standards for ephedra products. The attached AHPA Ephedra Trade Recommendation best illustrates the national standard, and laws reflecting these standards have been passed in several states, including Ohio, Hawaii, Michigan and Washington.

On May 6, 1999, industry met with FDA and requested that the agency adopt these standards either as final guidelines or as interim guidelines while further study is conducted to assess, as required by the Dietary Supplement Health and Education Act (DSHEA), whether the products are safe when consumed according to labeling required under the national standard. FDA has never responded to industry's request.

Because there is now an effective national standard for ephedra products, the initial inquiry for FDA, should FDA decide that further regulatory action is required, must be whether this standard is working to assure that the public is provided with safe and useful products, as industry is convinced is the case. This is another way of saying that FDA must address the concerns that the GAO raised in its report about the lack of a valid cost-benefit analysis, and FDA's failure to examine the effect of state regulation of ephedra products.

In conclusion, any safety assessment of ephedra must include all of the relevant data, and must include an assessment of the public health benefits of these products. Any review must begin with an assessment of safety based on products marketed under the current national standard.

FDA has failed to compile data, such as consumption data and background risk data, that are essential to this review. Other data that will help with the analysis are soon to be published.

If FDA is determined to conduct a public hearing in August, this will be just the beginning, rather than a conclusion, to the safety review process. As the experts from within FDA's own drug center, CDER, acknowledge, no conclusions can be reached based on what FDA has made available so far. The purpose of the August hearing, if it is held, should be to assess what additional information should be collected, and what, if any, additional studies should be conducted to do a valid review of these products. Additional hearings will be needed to reach a consensus once the necessary data is collected.

We appreciate the opportunity to provide comments on FDA's new materials, and understand that FDA will announce an extension of the final comment period on this material to September 30, 2000. We plan to submit comments by that date, with the understanding that additional hearings and comment periods will be established as necessary to assure an open, transparent and valid review of new data relevant to the ongoing review of these products.

Respectfully submitted,

A. Wes Siegner, Jr.
Cassandra A. Soltis

AWS/CAS/km
Attachment

Ephedra Trade Recommendation

of The American Herbal Products Association

January, 2000

The By-Laws of the American Herbal Products Association (AHPA), as revised in January, 1998, define "Obligations of Membership" to include "adherence to all policies and business practices as outlined in the Code of Ethics." The Code of Ethics, as amended in February, 1997, establishes a procedure whereby "The Board of Trustees may issue a trade recommendation which becomes an amendment to the Code." Any recommendation of the Board is thus automatically considered as a revision to the Code, requiring compliance from all members in good standing. The current recommendation for Ephedra is listed here.

EPHEDRA (adopted March, 1994; revised January, 2000)

AHPA recommends the following criteria for marketing of dietary supplement products containing ephedrine alkaloids:

Labeling

i. The label of the goods should bear an adequate cautionary statement, which shall at a minimum include the following language, or comparable language:

> *Not intended for use by anyone under the age of 18. Do not use this product if you are pregnant or nursing. Consult a health care professional before using this product if you have heart disease, thyroid disease, diabetes, high blood pressure, psychiatric condition, difficulty in urinating, prostate enlargement, or seizure disorder, if you are using a monoamine oxidase inhibitor (MAOI) or any other prescription drug, or you are using an over-the-counter drug containing ephedrine, pseudoephedrine or phenylpropanolamine (ingredients found in certain allergy, asthma, cough/cold and weight control products).*
>
> *Exceeding recommended serving will not improve results and may cause serious adverse health effects.*
>
> *Discontinue use and call a health care professional immediately if you experience rapid heartbeat, dizziness, severe headache, shortness of breath, or other similar symptoms.*

ii. The product label shall list the amount of ephedrine alkaloids per serving.

Serving Limits

Products are not to contain in excess of 25mg of total ephedrine alkaloids per serving; usage instructions should limit daily consumption to 100mg of total ephedrine alkaloids.

Herbs of Commerce Conformity

Label identification must be in conformity with the standard common name listed in *Herbs of Commerce.*

Synthetic Ingredients

Neither finished consumer goods nor raw materials used in their manufacture are to contain any synthetically derived ephedrine alkaloids or their salts (e.g., ephedrine sulfate; pseudoephedrine hydrochloride; phenylpropanolamine hydrochloride).

Marketing

No claims shall be made that the product may be useful to achieve an altered state of consciousness, euphoria, or as a "legal" alternative for an illicit drug.