MINUTES

of the
FDA FOOD ADVISORY COMMITTEE[1]
meeting on

Dietary Supplements Containing Ephedrine Alkaloids

August 27-28, 1996

Marriott MetroCenter
Washington, DC

Members present: E. Wayne Askew, Ph.D., Acting Chair; Rhona S. Applebaum, Ph.D.; Stephen E. Benedict, Ph.D; Henry W. Blackburn, M.D.; Denise E. Bruner[2], M.D.; Bruce M. Chassy, Ph.D.; Fergus M. Clydesdale, Ph.D.; Edward N. Croom[2], Ph.D.; Steven J. Dentali[2], Ph.D.; Harry H.S. Fong[2], Ph.D.; Naomi K. Fukagawa, M.D.; John W. Georgitis[2], M.D.; John J. Guzewich, M.P.H.; Susan K. Harlander, Ph.D.; Dennis P.H.-T. Hsieh, Sc.D.; Ka Kit Paul Hui[2], M.D., F.A.C.P.; Mario A. Inchioso[2], Ph.D.; Donald R. Jasinski[2], M.D.; Robert W. Katz, M.D.; Lauren B. Marangel[2], M.D.; Morris E. Potter, D.V.M.; Donna R. Richardson, J.D., R.N.; George A. Ricaurte[2], M.D., Ph.D.; Mary Y. Wang, Ph.D.; Raymond L. Woosley[2], M.D., Ph.D.; and Irwin Ziment[2], M.B., F.R.C.P.

Members absent: Edward N. Brandt, Jr., M.D., Ph.D.; Katherine L. Clancy, Ph.D.; Owen R. Fennema, Ph.D.; and Patricia M. Rodier, Ph.D.;

Special Industry Liaisons: Mr. Michael Ford, Executive Director, National Nutritional Foods Association; and Mr. Loren D. Israelsen, Executive Director, Utah Natural Products Alliance.

Food and Drug Administration (FDA) representatives: **(Center for Food Safety and Applied Nutrition - CFSAN)** Lynn A. Larsen, Ph.D., Executive Secretary of the Food Advisory Committee; Fred R. Shank, Ph.D., Center Director;

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[1] Note: The entire meeting was open to the public. Copies of written information provided to the Committee for consideration are available from the Committee Staff. This includes written materials received from public participants. A transcript of this meeting is available from the FDA Dockets Management Branch (HFA-305), 12420 Parklawn Drive, Rockville, MD 20857.

[2] Consultant and ad hoc member of the committee.

Ms. Catherine M. DeRoever, Ms. Indya P. Gordon, Linda H. Hayden, and Ms. Sylvia M. Washington, Committee Staff; Margaret C. Binzer, J.D., Constance J. Hardy, R.D., M.S., Lori A. Love, M.D., Ph.D., and Elizabeth A. Yetley, Ph.D., Office of Special Nutritionals; William R. Obermeyer, Jr., Ph.D., Office of Plant and Dairy Foods and Beverages. **(Office of the Commissioner)** David A. Kessler, M.D., J.D., Commissioner of Food and Drugs; and William B. Schultz, J.D., Deputy Commissioner for Policy. **(Office of the General Counsel)** Louisa T. Nickerson, J.D. **(Center for Drug Evaluation and Research - CDER)** Michael Weintraub, M.D.; Debra L. Bowen, M.D.

Guest Speakers: Cynthia T. Culmo, R.Ph., Director, Drugs and Medical Devices Division, Bureau of Food and Drug Safety, Texas Department of Health (accompanied by Gary Coody, R.Ph., Senior Pharmacist); Frank W. Wickham, M.S.Pharmacol., Executive Director, Ohio Board of Pharmacy; and Ms. Micheline Ho, Chief, Product Regulation Division, Bureau of Pharmaceutical Assessment, Health Protection Branch, Health Canada.

Public Speakers: **Session 1:** Mr. Michael McGuffin, President, American Herbal Products Association, Bethesda, MD; and Michael Davidson, M.D., F.A.C.C., Medical Director, Chicago Center for Clinical Research, Chicago, IL. **Session 2:** Ms. Mary Miller, Alternatives to Violence Project, Dover, DE; Mr. Anthony Young (Piper & Marbury, Washington, DC) on behalf of the National Nutritional Foods Association; Dennis Jones, Ph.D., President, Fytoresearch Inc., Lachine, Quebec; and Annette Dickinson, Ph.D., Director of Scientific and Regulatory Affairs, Council for Responsible Nutrition, Washington, DC. **Session 3:** Mr. James R. Prochnow, attorney, Patton and Boggs, Denver; Ms. Betsy Woodward, (Department of Agriculture, FL) as President, Association of Food and Drug Officials; Mr. Michael Betz (Banowsky, Betz and Levine, Dallas, TX), for Omnitrition International Inc.; Mr. Adam Gissen, Vitamin Research Products; Mr. Stephen Shapiro, attorney, Bass & Ullman, New York, NY; Mr. Gordon Pedersen, Eola Products Inc. St. George, UT; Calvin McCauseland, Ph.D., Enrich International, Orem, UT; Mr. William Appler (Regulatory Strategies Consultants, Washington, DC), as Executive Director, Ad Hoc Committee on the Safety of Ma Huang; and Mr. Blaine Wilson (Program Director, Cardiopulmonary Rehabilitation Institute, University Medical Center, Lubbock, TX), as husband of consumer. Letters were submitted for the record from: Ms. Pamela Richardson, Plain City, OH, mother of consumer; Texas Medical Association, Austin, TX; Mr. Ervin A. Gonzalez and Mr. Raymond W. Valori, attorneys, Robles & Gonzales P.A., Miami, FL; and Mr. Charles E. Nanney, Miami, FL, consumer.

Summary Conclusions

The purpose of the meeting was to review the recommendations of the Committee's Special Working Group on Food Products Containing Ephedrine Alkaloids (hereinafter, the WG)[3], which met on October 11-12, 1995, and to consider new information that FDA had acquired in the intervening time. The charge to the Committee was to review the scientific data and other information related to adverse events associated with the use of dietary supplements containing ephedrine alkaloids, and to provide expert advice on specific ways to address the public health concerns associated with the use of ephedrine alkaloid-containing dietary supplement products.[4]

The Committee was not asked to reach a consensus. Each member provided an opinion on, and a rationale for, specific ways to address public health concerns associated with the use of ephedrine alkaloid-containing dietary supplements, including whether safe levels of ephedrine alkaloids can be established.

Over half of the members concluded that no safe level for ephedrine alkaloids could be identified and they recommended that dietary supplements containing ephedrine alkaloids be removed from the market. Most of the other members felt that a fairly low level would be "reasonably safe" (views varied in the range of <1 mg to 8 mg/serving, or 2-24 mg/day).

It was noted that to impart some benefit (i.e., to provide a reason for its consumption), a product must be taken at a dose that could potentially harm some consumers. No member could identify a documented benefit for ephedrine alkaloids other than the traditional medical use.

Along with level restrictions, other mechanisms for addressing the public health concerns were also recommended by Committee members (e.g., require warning labels and establish good manufacturing practices).

Agenda

The Food Advisory Committee Chair, Dr. Ed Brandt, could not attend the meeting. Dr. Wayne Askew kindly consented to serve as Acting Chair. Dr. Askew convened the meeting at 8:17 a.m., Tuesday, August 27, 1996. Dr. Larsen announced that conflict of interest reviews had revealed potential financial conflicts for Drs. Askew and Dentali, and that

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[3] See Background section of the attached Charge and Questions Posed to the Food Advisory Committee and Special Working Group for a summary of WG recommendations.

[4] See the attachment for the complete focus, charge and questions posed to the Committee.

FDA had approved waivers to permit both members to participate in the meeting. Following introductions and announcements, Dr. Yetley explained to the Committee the issues about dietary supplements containing ephedrine alkaloids. Dr. Larsen briefly commented on the assembling of the WG, following which Ms. Binzer summarized the information that was presented for WG consideration. In the absence of Dr. Brandt, who chaired the WG, Dr. Larsen summarized the responses of the WG to the questions posed by FDA and the WG recommendations.

The Open Public Hearing, originally scheduled for Tuesday afternoon, was instead divided into three sessions (Tuesday morning, Tuesday afternoon, and Wednesday morning) for the convenience of the speakers and of FDA. Following the Tuesday morning session, Ms. Culmo, speaking on behalf of David R. Smith, M.D., Texas Commissioner of Health, provided the Committee with an update on the Texas experience with the products in question. Mr. Wickham next detailed the actions by the State of Ohio to control these products. Ms. Ho likewise spoke about Canadian regulation of products containing ephedrine alkaloids.

FDA then began its presentation of new data, beginning with Dr. Yetley who delivered the focus, charge and questions to the Committee. Ms. Hardy summarized the data acquired in the second market review. Dr. Love summarized the additional adverse event reports received by FDA and she provided details of FDA's evaluation of the products. At the conclusion of the afternoon Open Public Hearing session, Dr. Askew recessed the meeting at 5:17 p.m.

The Committee reconvened at 8:17 a.m., Wednesday, August 28, 1996. The first order of business was the third Open Public Hearing session. Dr. Yetley then recapped the focus, charge and questions, and the Committee began its deliberations. In mid-afternoon Dr. Askew had to depart, and Dr. Chassy kindly consented to Chair the remainder of the meeting. The meeting was adjourned at 4:57 p.m.

Presentations - FDA

Dr. Yetley announced that FDA had received over 600 reports of illness or injury associated with use of dietary supplements containing ephedrine alkaloids, about double the number received at the time of the WG meeting in October 1995. The reports include a broad spectrum of the population, but most adverse events occurred in young to middle-aged women using the products for energy or weight loss purposes. The adverse events primarily involved the cardiovascular system or the central nervous system. With this introduction to the issue, Dr. Yetley went on to outline the agenda for the meeting and the nature of the information to be presented by each speaker. She described the types of additional expertise that the ad hoc members brought to the Committee, and she provided an overview of the Dietary Supplement Health and Education Act (DSHEA) under which FDA regulates the dietary supplements in

question. She advised that the meeting was not about whether these products should be regulated as drugs, nor about whether the products are effective; it was to be a discussion of the scientific basis for dealing with the safety concerns.

After Ms. Binzer's presentation, Dr. Yetley reinforced her statements about the purpose of the meeting and what issues were not on the table for Committee discussion. She noted that samples of products in the marketplace obtained by FDA were on display in the back of the meeting room. Dr. Yetley then gave the Committee its charge.

Dr. Yetley reiterated the charge following presentations by Ms. Hardy and Dr. Love, and just prior to Committee discussion. She reminded the Committee that FDA would make the legal and regulatory decisions, including evaluation of label claims and all that they implied, on the basis of a scientific evaluation.

Ms. Binzer provided an overview of FDA's presentations to the WG in October 1995[5]. She displayed the chemical structures of the various ephedrine alkaloids, which are natural stimulants and occur in several botanical species (including those known as ma huang) at concentrations ranging from about 0.018 to 3.4 percent in the raw plant. She noted the long history of use of ma huang tea in traditional Chinese medicine for treatment of colds and respiratory symptoms. Ms. Binzer outlined FDA's 1995 marketplace review, performed to obtain an approximate picture of what products were available, the nature of the labeling, and quantitative data on the ephedrine alkaloid content. Because of concerns about synergistic actions, the xanthine alkaloid (e.g., caffeine) content was also determined. Ms. Binzer reviewed the number and nature of the adverse event reports accumulated up to the time of the October 1995 WG meeting. She stated that the nature and patterns of the adverse events were found (by FDA) to be consistent with the known physiological effects of sympathomimetic agents, with adverse events reported in clinical trials of such agents, and with case reports of adverse events associated with the use of drugs containing these agents.

Dr. Larsen had introduced Ms. Binzer's presentation by providing FDA's rationale for assembling the WG and summarizing the questions posed to that group. Following Ms. Binzer's presentation, and on behalf of Dr. Brandt who was the WG Chair, he summarized the WG's conclusions, as contained in the WG minutes (Tab D of the briefing books for this (August 1996) meeting).

Ms. Hardy began her presentation with a brief overview of the purpose and results of FDA's 1995 market review. The death of a college student, who had used an ephedrine alkaloid-containing botanical promoted as a street drug alternative, focussed FDA's attention on these types of products. This and the increase in number of adverse event reports led FDA to conduct a second market review, beginning in April 1996. The emphasis in the second

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[5] See the minutes and transcript of the October 1995 meeting for the detailed information that was presented.

review was on the products offered as street drug alternatives. Ms. Hardy presented the combined information from the two reviews, which covered about 125 different products.[6] She noted that in addition to *Ephedra* species, *Sida cordifolia* is a botanical source of ephedrine alkaloids. Total ephedrine alkaloid content of the products ranged from not detectable (below 1 mg per serving) to about 110 mg per serving, with a median of about 17 mg per serving. She indicated that matrix effects in protein products appear to interfere with analysis of ephedrine alkaloids and that FDA's analyses likely under-reported the content for such products. Ms. Hardy drew the Committee's attention to the numerous other substances often contained in the products, some of which may increase risk of adverse events when combined with ephedrine alkaloids. She briefly reviewed the types of labeling seen on these products. She noted that the types of ingredients and range of ephedrine alkaloid content for products purveyed as street drug alternatives were similar to those for products promoted for other uses. Ms. Hardy closed by advising that the issue of concern, regardless of label claims or representations, was the presence of ephedrine alkaloids.

Dr. Love summarized safety data on products containing ephedrine alkaloids (provided in more detail in Tab F of the briefing book and in handout materials). She noted that CFSAN had compiled and integrated information from a variety of sources, including adverse event reports and the scientific literature. She proceeded to describe some of the characteristics of the products associated with the over 600 adverse event reports CFSAN had evaluated (out of about 800 reported to that time). Ninety-two percent of the adverse events were associated with products represented for weight loss or energy purposes, and 72% of the events involved consumers in the 20- to 49-year-old age range (74% of whom were women). About one-third of the events occurred within one week, and nearly 60% within one month, of initiating use. The majority of adverse events involved the cardiovascular system or nervous system. Dr. Love detailed some of the signs and symptoms reported, e.g., seizures, strokes, anxiety, "palpitations," and chest pains. She highlighted five particular cases as examples.

Dr. Love went on to discuss FDA's analyses of the products associated with some of the adverse events. The range of ephedrine alkaloid content "as the consumer used" the product was 0 to 50 mg per serving, with a median of about 20 mg; the range for ephedrine itself was the same, with a median of about 8 mg/serving. She also presented data on the variability, per serving, among samples of individual products. Dr. Love summarized the known physiological and pharmacological effects of ephedrine and related alkaloids, and results of clinical trials on these substances. She noted that while traditional Chinese medicine provided no formal mechanism for collection of adverse events, precautions were well established for this use of the herb, and that adverse events for botanical preparations have been reported in

[6] The information summarized by Ms. Hardy was contained in tables included in the Committee briefing book (Tab E), and in graphic materials provided in supplementary handouts.

the scientific literature. She concluded that the patterns of adverse events are consistent across the entire body of evidence, are consistent with known physiological and pharmacological effects of the substances, and are temporally associated with consumption of the products.

Guest Speaker Presentations

Ms. Culmo advised that the Texas Department of Health (TDH) had received over 1000 reports of adverse events associated with use or consumption of over-the-counter drugs and foods containing ephedrine. Roughly half of these were associated with food products. After three years of investigation, TDH has concluded that ma huang products pose a significant health concern unless used under medical supervision. Ms. Culmo noted that the products are promoted for uses other than the traditional Chinese medical use (respiratory disorders) and are self-prescribed in contrast with traditional use under the care of an experienced practitioner. She described reviews of the adverse event reports by an expert panel convened by TDH in 1995 and a panel convened by the Texas Medical Association in 1996. Based on these reviews, TDH proposed rules placing most ephedrine-containing products in a prescription status. Ms. Culmo stated that TDH supports prohibition of ephedrine alkaloids in foods and dietary supplements.

Mr. Wickham provided an overview of the responsibilities of the Ohio Board of Pharmacy, and State's actions regarding products containing ephedrine alkaloids. He stated that Ohio has not banned the products, but has placed their sale under the supervision of a pharmacist. After receiving numerous comments from vendors of such products, the Board identified over 205 products on the market. Mr. Wickham indicated that regulation of such products, under bills in the State legislature, would rely on FDA decisions about a safe content of ephedrine and duration of use. In the meantime, the Board under its existing authority has exempted from prescription sale one tea product that contains low levels of ephedrine and is promoted for breathing problems.

Ms. Ho noted that the Health Protection Branch is FDA's counterpart in Canada. She went on to describe the features of Canadian food and drug law and some aspects of its implementation. She detailed the circumstances under which herbal medicine products can legally be sold. Because most products containing ephedrine alkaloids provide a pharmacologic effect and are represented or intended for therapeutic or medicinal purposes, they are considered drugs under Canadian law. Furthermore, after assessment of reported adverse events, Canada no longer permits products containing ephedrine alkaloids to be sold as non-medicinal ingredients in herbal preparations or as food.

Public Hearing Presentations

Session 1. Dr. Larsen initiated the session by referring the Committee to the letters submitted by Mrs. Richardson, by Mr. Gonzalez and Mr. Valori on behalf of Mr. Nanney, and by Mr. Nanney himself. All the letters described adverse events (death in the case of Mrs. Richardson's son, and a stroke in the case of Mr. Nanney) that the writers attributed to the use of products containing ephedrine alkaloids.

Mr. McGuffin was the first speaker. He presented a position developed jointly by his organization (the American Herbal Products Association - AHPA), the Council for Responsible Nutrition (CRN), The National Nutritional Foods Association (NNFA), and the Utah Natural Products Alliance. The four groups support appropriate labeling, conservative safe levels of ephedrine alkaloids, and the absence of synthetic alkaloids, as reflected in various communications to their members since 1994. They believe the recommendations of the WG address the safety issues. They also believe that the products marketed as alternatives to illegal street drugs should not be considered legitimate dietary supplements.

Dr. Davidson, a cardiologist with experience in the conduct and evaluation of clinical trials, had been asked by NNFA to review the adverse event reports received by FDA. He categorized cases he reviewed as serious or non-serious, and assessed whether, in his opinion, the adverse event was related to ephedrine alkaloid exposure. He commented specifically on serious cases involving death, myocardial infarction, stroke and seizures. Dr. Davidson found cases with a possible or probable association in three of the four areas of serious events. Not being a neurologist, he felt unqualified to evaluate cases involving seizures. After comparing the total number of adverse event reports recorded by FDA to those which he could categorize as possibly or probably related to ephedrine alkaloid exposure, he concluded that there was only infrequent association of serious adverse events with the consumption of ephedrine alkaloids. He supported labeling and content levels as recommended by the WG, and improved manufacturing practices and quality assurance.

Session 2. The first speaker in this session was Ms. Miller. She read for the record a letter from an inmate in a Delaware prison, Mr. John Larson. He explained that, as a former methamphetamine addict, pain medications administered following two automobile accidents led to an addiction relapse. To aid his physical recovery without such medications, he sought assistance at a health food store. He asked for products to overcome fatigue and weakness, and forms of ephedrine were suggested. He soon was unable to control his ephedrine intake. He developed a number of symptoms, including the violent behavior which led to his arrest and incarceration. He continues to suffer physical symptoms which he attributes to the use of ephedrine products and the close chemical relationship between ephedrine and methamphetamine to which he was addicted. He asked the Committee to act on the products so that others predisposed to addiction are not also adversely affected.

Mr. Young spoke on behalf of NNFA. He explained that Association members manufacture and sell dietary supplements, some of which contain herbal ephedra or its extract. He advised that NNFA co-authored and supported the joint industry position presented by Mr. McGuffin [see Session 1], and the Association retained Dr. Davidson [see Session 1] to review the adverse event reports. He stated that appropriate labeling is an obvious priority for safe marketing and use of these products. Mr. Young indicated that the industry will promptly change labels and lower doses in response to Committee recommendations. He suggested that the trade associations also were prepared to develop an informative (and by implication, authoritative) brochure on ephedra.

Dr. Jones observed that he had trouble with what he felt were inconsistencies among the adverse event reports and other data, e.g., toxicology data on two of the consumers who died. He noted that there was very little concern about the botanical products in other countries, where few adverse events had been reported. He commented on the safe use in Denmark of an ephedrine/caffeine combination for weight loss. Dr. Jones advised that his firm's products are manufactured to strict specifications and under GMP (good manufacturing practice) conditions. He further stated that minor complaints obtained from his firm's market surveillance could generally be traced to a failure to follow label instructions. Dr. Jones argued that neither the historical nor scientific literature contain reports of adverse effects for herbal ephedra, even at levels much higher than those under discussion, and that the herbal product is better tolerated (than synthetic ephedrine) and possesses beneficial properties beyond those of the synthetic drug. He also suggested that the number of adverse event reports was small in comparison with the number of Americans he estimated had used the products and is inconsequential compared to other food and drug safety problems. He believed that the "perceived concerns" could be alleviated by labeling, compositional restrictions, adherence to GMP, and elimination of some marketing approaches.

Dr. Dickinson stated that CRN also worked on and supported the joint industry statement [see Mr. McGuffin, Session 1]. She said CRN supported Dr. Davidson's analysis [see Session 1] to obtain a better understanding of the potential causal relationship between consumption of products containing ephedrine alkaloids and the reported adverse effects. Dr. Dickinson advised that neither CRN or its three colleague associations support attempts by some industry members to minimize the importance of the adverse event reports. Rather, they wish to work to resolve the issues. Dr. Dickinson announced that CRN and others, at FDA's request, had developed a draft GMP document with quality standards for dietary supplements. She said FDA had advised her that the Agency will publish the document for public comment. Finally, she suggested that the history of this issue supports the need for improvements in the adverse event reporting system, both on the industry side and on the FDA side, and that there has to be improved communication between FDA and industry when either one learns about adverse events.

Session 3. Mr. Prochnow explained that, in his law practice, he specializes in representation of dietary supplement businesses. Most are small businesses run by persons who are familiar

with their customers and sensitive to complaints, and who have sold products containing ephedrine alkaloids for a decade with no report of serious adverse events. The firms Mr. Prochnow represents are members of AHPA and NNFA and support the position taken by those associations. Mr. Prochnow addressed various sections of DSHEA, and his understanding of how these must be applied in the regulation of the products under discussion. He stressed the DSHEA sections under which FDA must prove that a dietary supplement is adulterated (and therefore unsafe). Finally, he noted that Vanderbilt University had considered conducting acute and chronic clinical studies of products containing ephedrine alkaloids, but those studies were not funded. He recommended that these studies be funded by FDA, under authority of DSHEA.

Ms. Woodward advised that the Association of Food and Drug Officials (AFDO) had recommended in 1995 that ephedrine-containing products, both dietary supplements and drugs, be removed from over-the-counter sales status. Similarly, in 1996 AFDO supported a resolution opposing the marketing of herbal products as legal substitutes for illicit drugs. These actions stemmed from growing State concerns about adverse events and deaths associated with use and abuse of products containing ephedrine alkaloids. She emphasized the need for labeling that would appropriately inform consumers about these products.

Mr. Betz stated that both his client and he were concerned about the adverse event reports, but that they were also concerned about the accuracy of FDA's compilation. He particularly pointed out that some products manufactured by his client, but which contained no ephedrine alkaloids, appeared to be included in the compilation. He identified several adverse events by page and event number. Mr. Betz provided an approximate sales volume for his client, and from that estimated industry-wide sales of ephedra-based products to be about one billion servings in five years. He stated that his client is only aware of a few minor side effects for its products, and attributed this low rate to labeling that appropriately cautions consumers.

Mr. Gissen indicated that he was representing Omnitrition International, for whom he had developed several products containing ephedrine alkaloids. He expressed the view that side effects being reported do not fit the profile of those expected from ephedrine, and that ephedrine had been used as a drug for decades without the effects that are being reported for the dietary supplement use. He suggested that the presence of microbial and other contaminants should be investigated. He hypothesized that interactions of such contaminants, or of medications being taken by consumers, with ephedrine alkaloids could generate the adverse events. Mr. Gissen argued that safe use would occur if products were appropriately labeled, and if consumers began use at low dosages and gradually increased intake to recommended levels. He opined that advice to limit intake would make the product ineffective, and taking such products off the market would increase illegal use.

Mr. Shapiro spoke on behalf of several distributors and retailers. He agreed that caution is required when possible adverse events are connected with consumer products, but he also suggested that the reported injuries might be from misuse rather than correct use. His estimate

was that on any day, five million people consume a product containing ma huang. Mr. Shapiro advised that complaints received by his clients had been minimal and primarily were reports of insomnia. He supported the WG recommendations for dosage limitations and accurate label information and warnings.

Mr. Pedersen explained that, as a trained toxicologist, he had to convince himself of the safety of the products in question before he went to work in the industry. He outlined for the Committee the process by which he decided that ephedrine alkaloids could be safely used. He cited several standard pharmacology and toxicology texts and reference works, and reports from the medical literature on drug products. He then reported on an animal toxicology (LD_{50}) study he had commissioned at Utah State University. On the basis of this study and his literature search, Mr. Pedersen concluded that 25 mg per dose and 100 mg per day were safe intakes.

Dr. McCauseland suggested that dietary supplements have a value beyond that of ordinary foods, and that as a consequence DSHEA was enacted to protect their use. He further suggested that there was "reasonable doubt" that ephedrine alkaloid products were associated with some of the deaths included in the adverse event reports. Dr. McCauseland supported the 25 mg per dose and 100 mg per day use levels as safe. However, he argued that higher levels were also safe and that further reductions to ensure safety would cause loss of efficacy and loss of sales. He indicated that, under DSHEA, FDA had to prove the products were unsafe, and in his opinion the scientific evidence that the products were unsafe was lacking.

Mr. Appler advised that the Ad Hoc Committee on the Safety of Ma Huang had commissioned two independent literature reviews, had reviewed animal studies of ephedrine performed under the National Toxicology Program, and had commissioned its own toxicology study of a typical ephedra herbal product. The group also reviewed FDA's health hazard analysis, the Texas adverse event reports, and a retrospective study it commissioned of Canadian users of ephedra herbal weight loss products. The resultant three volume report was provided to the FAC. The report concludes that under its recommended doses and labeling, ephedra herbal products are safe for specified uses. He questioned why orally ingested ephedrine alkaloids should be the potential hazard FDA believes it to be when ephedrine is used as a bronchial dilator without thousands of injuries daily and without similar evidence from weight loss studies in the literature.

Mr. Appler also summarized a statement by Graham Patrick, Ph.D., who had reviewed the Texas adverse event reports for Mr. Appler's group. Mr. Appler's conclusion from Dr. Patrick's review was that relevance of most of the adverse event reports, as evidence of harm from ephedra herbal products, was suspect. He concluded by urging the FAC to adopt the WG's recommendations.

Mr. Wilson explained that he was a health care professional whose wife had suffered a severe adverse event attributed to use of a dietary supplement containing ephedrine alkaloids. He

revealed that his wife was patient number three cited in the Centers for Disease Control and Prevention's Morbidity and Mortality Weekly Report for August 16, 1996. Mr. Wilson stated that despite having no pre-disposing conditions for seizures, his wife suffered several after one day of use. He characterized the amount she ingested (two tablets per dose, and two doses) as conservative with respect to the label instructions. Mr. Wilson's wife has had no seizures since being discharged from the hospital, and has subsequently been able to discontinue her anti-seizure medication. Mr. Wilson concluded by reading a brief letter from Congressman Larry Combest of the 19th District of Texas, in which FDA was urged to control the use of such supplements if the data warrant such action.

Discussion

The Committee questioned many speakers at length, and used the question and answer periods also for extended discussion among members. In response to Committee questions, a number of brief impromptu presentations were made by FDA staff members and by the Commissioner. Some of these were responses to Committee requests for further clarification of the charge and questions. At the conclusion of discussion, members were asked to respond to the four questions posed by FDA, and to state whether the WG recommendations were accepted for transmittal to the Agency. Members also were afforded an opportunity to provide summary statements. (Points raised in those statements have been incorporated into the discussion topic summaries below.)

Major topic areas of discussion and issues raised or points made were the following:

WG recommendations. One industry liaison, early in the meeting, raised a question about FDA's delay in acting on the WG recommendations. Dr. Larsen explained that, under the Federal Advisory Committee Act, any advisory committee subgroup action must be considered by the parent committee. He detailed FDA's attempts to bring the issue to closure. He stated that the amount of elapsed time and the availability of additional information led to this August 1996 meeting of the Committee, augmented by members of the WG and additional subject matter experts.

Food or drug. The Committee struggled to separate in their minds the food (i.e., dietary supplement) issues from the drug issues throughout the meeting. Part of the difficulty arose from the fact that available physiological and pharmacological information was based on clinical trials of ephedrine as a drug. Drs. Weintraub and Bowen of FDA's Center for Drug Evaluation and Research sought to clarify for the Committee the current status of approved over-the-counter (OTC) drug use. Ephedrine is approved for use in OTC bronchodilators in an oral dosage of 12.5 mg to 25 mg. FDA for various reasons has published a proposal to remove these products from OTC status.

Regardless of the drug status, the Committee was repeatedly advised by the Commissioner and FDA staff that the task at hand was to consider the safe use of dietary supplement products containing ephedrine alkaloids. Dr. Kessler noted that the risk may never be reduced to zero, but FDA did need the Committee's best scientific advice on the science and on safety; FDA would deal with the regulatory and legal issues based on that science.

The Committee had concerns about what message it might be sending to consumers by its decisions. One point made by members was that there is never a completely safe level of a pharmacologic agent (a drug); safety is weighed against the expected benefits for some health problem. In that context, if there is a clinical benefit, a certain amount of risk may be acceptable. Some members specifically addressed, in their recommendations, whether such a consideration is appropriate for consumption of a dietary supplement where pharmacologic effects would not be expected. While recognizing their food-focussed charge, some members discussed the better-documented experience with ephedrine drug products as a foundation upon which to consider the questions relating to dietary supplement use. Other members were not comfortable extrapolating from data on pharmaceuticals to use of dietary supplements that contain different formulations and are used for unrelated purposes. (One member also opined that a typical food toxicological approach is also inappropriate because linear associations cannot be made, given the large size of the sensitive population.)

DSHEA. A number of members expressed the view that DSHEA contributed to the confusion about regulatory status by categorizing as dietary supplements those products that many viewed as drugs. One member went so far as to opine that under DSHEA the safety process had been reversed and the requisite clinical study was being done through marketing and collection of adverse event reports. Another suggested that the legislation had created a "safe harbor" for products the food and drug industries do not want to put through the approval processes. Members who expressed negative views about DSHEA recommended that Congress revisit the law and act to change the regulatory status of pharmacologically active botanical materials. One member even suggested that repeal should seriously be considered. An industry liaison suggested that while DSHEA may not be perfect, regulation of supplements prior to its enactment was imperfect as well. (It was noted that attempts to take herbal products through the OTC drug approval process had not been successful.)

Traditional use. One suggestion for revising the Act was to create a new regulatory category for traditional herbal medicines, to include appropriate safety evaluation mechanisms. This would place some of the safety burden back on industry. It would, some members felt, also address concerns of some members that safety concerns about, and consequent regulation of, pharmacologically active botanical products will not deprive the public of potentially useful herbal remedies. Such a change would, as one member put it, give botanicals "a home." It also was pointed out that regulation of botanicals under a traditional medicine category would harmonize U.S. law with current Canadian law.

The Committee commented on the differences between traditional use of ma huang in Chinese medicine and the uses for which the botanical products in question were being sold. One member cited a book (roughly equivalent to a Physician's Desk Reference) on traditional Chinese medicine - translated as "The Concise Summary of Chinese Pharmacognostics" - and precautions and instructions given therein. The members noted that traditionally ma huang was never intended as a dietary supplement; its medicinal use was for respiratory relief of certain conditions diagnosed by a traditional Chinese herbalist, it was administered for a prescribed period of time as a tea (with prescribed brewing instructions), and it always was used in conjunction with other materials (which, it was speculated, may have served to minimize potential side effects). Some members felt that industry was not being straight-forward when citing traditional Chinese medicine use as a basis for safety of the current, unrelated uses.

Members asked what the fate of ma huang as a medicinal herb (by implication, in Chinese pharmacies) would be if it was prohibited from dietary supplements. Mr. Schultz and Dr. Weintraub indicated that there were other statutory routes, under the drug provisions of the Act, by which FDA could continue to permit such uses. However, at least one member felt that the only viable regulatory category currently was as dietary supplements. Most members appeared to believe that modification of the Act that incorporate a traditional or herbal medicine category would be more satisfactory.

Chemistry. The Committee raised several questions about the analytical methods used to determine the ephedrine alkaloid content of the various products, both in the market survey and for products associated with adverse effects. Dr. Obermeyer advised that the recovery studies completed thus far, using known amounts - "spikes" - of added alkaloids and internal standards, indicate that the analytical method is able to quantitate about 80% of the ephedrine alkaloid content of the products, i.e. the levels found during analysis would be expected to be about 20% below the amount actually present. He also stated that the lower limit of quantitation, or assay sensitivity, was 0.25 mg ephedrine alkaloids per gram of product (about 5 mg alkaloids per capsule or tablet). Dr. Obermeyer indicated that the Agency intends to conduct interlaboratory validation of the method. He noted further that the protein products provided matrix effects that the analysts were still trying to resolve, and that analytical results to date on such products likely were significant underestimates.

Industry sales practices. The issue of sales volume of ephedrine alkaloid-containing dietary supplements was raised early in the meeting by the Committee. In addition to estimates by several speakers, one industry liaison estimated sales at one-and-a-half million doses per day at health food stores. He stated, however, that most of the products associated with adverse event reports were obtained from sources other than health food stores. On the separate issue of ingredient content and labeling, he indicated that his association's "true label program," which involves label registration and random testing, accepts products that contain from 90 to 110 percent of label claim.

Several members expressed concern over apparent lack of specifications, quality control and good manufacturing practices in general on the part of at least some manufacturers. Commentary was provoked, at least in part, by a statement during the open public hearing that contaminants introduced into source materials may be the cause of the adverse effects. The public hearing speaker argued that manufacturers are not required to test the materials, that such testing would be prohibitively expensive, and that the responsibility for testing lies with the regulatory agencies. The Committee's industry liaisons advised that the cooperating industry associations did not subscribe to this position; most companies in the industry do ensure the quality of the materials they are using. Member firms are expected to meet or exceed the GMP proposal submitted to FDA, and to be well aware of source materials before incorporation into products. The liaisons advised that industry had worked hard to come up with the GMP proposal presented to FDA so it will be acceptable and raise the quality of products in the industry. They pledged to continue working with FDA to establish reasonable policies on botanicals. Committee discussion gave implied support to this cooperative effort.

Adverse events. Members frequently called upon FDA staff to reiterate summary characteristics of adverse event data and details of particular cases (e.g., median levels - about 20 mg; distribution of events relative to non-zero ephedrine alkaloid content levels - about evenly distributed from low to high content; time to onset of events - about 1/3 of events occurred within first week of use; etc.). A question was raised, during the presentations and later during Committee discussion, about whether a full toxicology analysis had been performed as part of the autopsy for one of the reported deaths. Dr. Love stated that the initial report did not contain all this information because testing had not been completed when that information was placed in the public information file. Subsequently, the data did arrive and it was placed in the public file. The analyses demonstrated that no detectable levels of substances other than ephedrine alkaloids had been found. (The analytical screening covered long list of substances for which evidence of exposure is routinely sought in overdose cases.)

At least one member expressed dissatisfaction with the quality of the data provided to the Committee from the adverse event reporting system. The problems with such voluntary systems were discussed. It was also acknowledged that under-reporting is anticipated. The actual consumer impact therefore was expected to be larger.

Safe levels. The members extensively discussed the issue of safe intake levels. The levels debated were based, in part, on computations from traditional Chinese medicinal use, OTC drug use, the range of intake levels estimated from certain adverse event reports, and traditional toxicology safety margins. The discussion led to a range of conclusions, as detailed below in the summary of members' responses to questions FDA posed on safe intakes and safety margins. The discussion also sought to define what limitations, if any, should be placed on continuous use. (These suggestions are included with members' summary responses to questions on conditions under which use would pose no harm and conditions that might pose

harm.) One member suggested that products derived from the botanical sources, but with ephedrine alkaloids largely removed, might still be harmful due to the presence of other substances.

Labeling. A number of members expressed concern about what they characterized as exaggerated claims on current product labels, and about the amount of misinformation they believed was being distributed to the public. One member suggested that it was disingenuous of industry to defend the sale of products as dietary supplements labeled to provide energy, strength, ecstasy, etc. on the basis of traditional use as herbal medicines. This discussion, in part, led to a number of recommendations for cautions and other label information (see below).

Usefulness of products. Committee members discussed the many claimed uses for the products in an effort to identify those that might be safe for unsupervised consumption as dietary supplements. No member could identify a documented benefit for ephedrine alkaloids other than the traditional medical use. Several members questioned if there would be any usefulness if the ephedrine alkaloid content were reduced to levels suggested by others, and if most or all claims were removed. It was speculated that restrictions might eliminate any commercial viability, and might drive sales underground (or increase such sales, since some evidence suggest the underground market already exists). It was suggested that this could have an effect opposite to that intended, e.g., loss of any control on quality and increased adverse event problems. While raising this as a concern, the Committee offered no recommendations for addressing this potential problem. At least two members said this should not be a consideration because there are other means of controlling this type of problem.

Label warnings. One of the "restrictions" that was discussed was the content, extent and prominence of label statements about use of the products, especially statements that could lead to misuse. One member urged that warning statements be required to be as prominent as any claims. Exacerbation of psychiatric events and risk of myocardial necrosis were two of the more serious potential adverse events for which it was felt warnings were necessary. One member also stated more than once that consumers using the products for enhancement of exercise performance need to be advised that increased performance is only a perception and is not a real improvement, according to study data on similar central nervous system (CNS) stimulants. The study data indicate that consumers did not actually perform better when taking CNS stimulants; they only felt as if they did.

Clinical experiences. Some members provided technically detailed discourse on the pharmacologic effects of ephedrine and related alkaloids, and on the levels and conditions under which effects are manifested. A number of members related experiences with patients or coworkers and use or misuse of products containing ephedrine alkaloids. Products included both those marketed as OTC drugs and those marketed as dietary supplements. Experiences ranged from no observed serious adverse events to clearly adverse events for both categories of products. Medical supervision did not necessarily preclude occurrence of an adverse event.

One member, a bariatric physician, summarized four cases where a drug form of ephedrine was successfully being used in weight loss programs as anecdotal evidence that ephedrine can be useful for this purpose. All cases were under medical supervision and side effects were minor or absent.

Education. The Committee felt that education about dietary supplements that may contain substances also present in prescription (or herbal) medicines needs to be extended beyond consumers to include health professionals and athletic coaches. All three groups need to be aware of potential problems and to know what questions to ask about supplements or health foods. One member suggested that such an educational effort also is needed to combat the underground network of (mis)information and claims for these materials. The same member raised concerns about quality control (QC). He felt that QC is unregulated, and that consumers consequently need to know that use of the products is at their own risk. Somewhat in contrast with this view was that of another member who argued that consumers cannot know all they should about the available products; therefore, regulators have a responsibility to ensure that only safe products are available. It was recognized by members that it is difficult to change behavior, and education programs cannot be the sole answer. The discussion prompted one member to suggest that an FDA "800 number" be included on product labels so all comments would go directly to the Agency.

Conclusions/Recommendations

No votes were taken. Each member's views were individually recorded. Consequently, the responses below include those for members who are non-voting industry representatives and those for the industry liaisons.

Question #1. The first question asked the Committee to identify a safe level of total ephedrine alkaloids (TEA) and of ephedrine in dietary supplements, both on a per serving[7] and daily basis.

Fourteen members concluded that no safety level could be identified and they recommended that dietary supplements containing ephedrine alkaloids be removed from the market. The most frequently cited reason was the evidence of adverse events at low intake levels. Many of these members were uncomfortable with the unrestricted sale of the supplement products, as contrasted with sale and use of OTC, prescription or herbal medicines. They were concerned that conditions of use that may increase the risk of an adverse event might not be self-evident to consumers. Other concerns were: the potential for consumers to take more than the recommended amount, the occurrence of significant adverse effects with short term use,

[7] The meeting participants often mixed their use of the terms "serving" and "dose." The products about which FDA was seeking the Committee members' opinions are dietary supplements. Consequently, in these minutes, the term "serving" will be used in the summary of members' responses to the questions posed by the Agency.

positive results for those cases that were dechallenged and rechallenged, the potential need for a long label warning and levels so low as to provide no benefit, and product variability. One member suggested that attempts to identify safe lower intake levels is well intended but will not be effective for individuals predisposed to abuse of such products. Another observed that the public assumes supplements are safe, and assumes that FDA reviews their safety, although this is not the case. One member urged the industry to perform clinical studies. One member indicated that if a safe level must be set, the suggestion (see below) that arrived at 2 mg TEA/day should be used as guidance; one other member commented similarly about the 10 mg TEA/dose (40 mg TEA/day) suggestion.

The other 12 members either suggested levels that they considered responsive to the question, or they agreed with their colleagues' suggestions. Many of these members qualified their recommendations with comments on interpretations of the term "safety." These comments indicated or implied that while the members felt their individual suggestions were "reasonably safe" for most consumers, an assurance of "complete" safety for all consumers of such products was not possible. Eight such suggestions were provided.

- Based upon the total body of data and historical use in the Orient, one member recommended a level of 10 mg TEA/serving, up to four times per day (40 mg TEA/day). In terms of ephedrine itself, the recommendation was 8 mg/serving, or 32 mg/day. Four other members supported this recommendation.

- Based on a pharmacology perspective, including comparison of ephedrine with caffeine and amphetamine, another member recommended a TEA content of 10-15 mg per serving, and as high as 60 mg per day. As noted, one other member supported this view.

- The recommendation by a third member was the result of two routes of computation. One route considered animal toxicology (LD_{50}) data and risk assessment extrapolation factors (four orders of magnitude) to arrive at a figure of about 2 mg TEA per day. The second route considered traditional Chinese medicine usage and two orders of magnitude for risk assessment extrapolation to also arrive at about 2 mg TEA per day.

- One member considered ephedrine content of herbal materials as identified in Chinese and Japanese pharmacopeia, and on German Commission E dosages. These considerations led to a recommendation of 7 mg TEA/serving, or 6 mg ephedrine/serving.

- Another member based his recommendation of 2 mg ephedrine per unit serving, three times a day (TID), on his experience and the body of data. He noted that some consumers may take two units at a time, giving a daily intake of up to 12 mg, which he felt would still be "reasonably safe."

- Canadian experience with traditional medicines led one member to suggest a level between zero and 3.1 mg per day. (A distinction between ephedrine and TEA was not provided.)

- The OTC drug level of ephedrine and risk factor considerations served as the starting point for a member who suggested 5 mg TEA per serving (15 mg TEA/day) and 2.5 mg ephedrine per serving (7.5 mg ephedrine/day).

- One member considered the "orthodox" drug dose and concluded that a lower "reasonably safe" level for dietary supplements would be 5 mg ephedrine/serving (15 mg ephedrine/day) and 6 mg TEA/serving (18 mg TEA/day). Alternatively, the member also suggested what he termed "holopathic doses" at less than 0.5 mg ephedrine per serving, up to seven times per day, but not more than 28-31 servings in seven days. Going even farther, the member suggested that a safe level would be a homeopathic dose of 10^{-30} g.

One industry liaison suggested, based on the Canadian experience with traditional medicine, 6-8 mg TEA per serving up to four times per day (24-32 mg TEA/day) with a maximum content of ephedrine itself at 80% of these levels. The other liaison supported the Committee member recommendation listed in the first bullet above.

Question #2. The second question asked the Committee what margin of safety should be used in determining a safe level.

Eight members did not address this question or declined to comment. Nine members felt that since they could identify no safe level, the question was moot or they simply could not identify a safety margin. One of these members suggested that because there are no documented benefits, no risk-benefit computation is possible. Nine members provided suggestions regarding a margin of safety. The suggestions reflect differing interpretations of the question. The recommendations were:

- A safety margin of 10 to 1 (as compared to a typical food additive margin of 100 to 1);

- A safety factor of 10-fold down from a drug use level;

- A 10^{-4} margin from the LD_{50} level, or a 10^{-2} margin from levels in Chinese medicine experience;

- A typical food additive margin of 100 to 1 from a no effect level (NOEL), but since an NOEL could not be identified this would end up at a homeopathic level;

- A margin at 10% of the lowest amount that gave an adverse effect (1 mg), decreased further by a 30-fold product variability factor, or a final figure of about 3 micrograms;

- An upper limit of intake of 20 mg/day (no distinction between ephedrine and TEA was provided);

- Assuming two unit servings per day, the maximum safe daily intake would be 12 mg (no distinction between ephedrine and TEA), but safety varies from person to person;

- A safe range of 10^{-4} mg up to 3.1 mg/day (no distinction between ephedrine and TEA); and

- A tolerable level of risk might be determined using traditional risk avoidance strategies if there were better data on low level effects.

The two industry liaisons did not comment specifically on this question.

Questions #3 and #4. Question #3 asked the Committee to identify conditions of use for ephedrine alkaloid-containing dietary supplements under which there is no risk of significant harm. Question #4 asked the converse: identify conditions of use that are associated with a risk of significant harm, including levels and frequency of use above which there is a risk of significant harm.

Most members considered these two questions together. Responses on safe use were often couched in terms of actions to avoid safety concerns. Some members, consistent with their response to Question #1, concluded that there were no conditions of safe use. These members went on to identify concerns under Question #4. Some members opined that nothing is without risk so the obvious answer to Question #3 had to be "no." Others qualified their "no" response as applicable to products sold as dietary supplements, and added that safe use could be identified if the products were regulated and sold as drugs, especially if under supervision of a health care professional. One member suggested there would be no risk at very low, no-effect levels, but the products would then be defrauding the public. Some safe conditions of use identified by members were:

- Use under supervision of a physician (or other health care professional) with knowledge about the materials and about chronic or side effects;
- Within the traditional therapeutic realm, e.g., as the natural raw herb under supervision of a health care professional;
- Good quality control (QC) and adherence to rigorous GMPs, including: identification of plant species, quantitative analysis of the final product, and certification of quality;
- Restriction on formulations and permit only single substance preparations, or at least exclusion of xanthine alkaloids, stimulant laxatives or other stimulant materials, and monoamine oxidase inhibitors from formulations;
- Prohibit promotion for many of the current advertised uses, e.g., weight loss, muscle building and euphoria;
- No labeling or nomenclature referring to physiologic effects;

- Label warnings for health conditions, drug interactions and populations at risk;
- Label advice against use for more than seven to ten days (i.e., short-term use only);
- Manufacture only in forms that do not resemble ordinary foods or beverages;
- Use at levels determined from toxicological principles for Question #1, if assumptions there are correct;
- Education to eliminate misinformation and disinformation; and
- Combined with Ipecac so excess use would cause vomiting (although this would require safety testing).

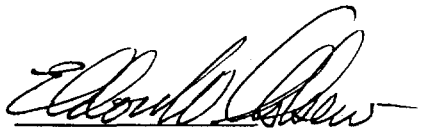
Several members suggested that FDA grant a temporary approval under the suggested restrictions, allowing time to see if the quality of science and industry performance would improve, and that the issue be reconsidered again at a later date.

The many conditions of unsafe use identified by members in response to Question #4 ran parallel to conditions and restrictions identified for safe use, as already noted. Among the concerns and unsafe conditions identified were the following:

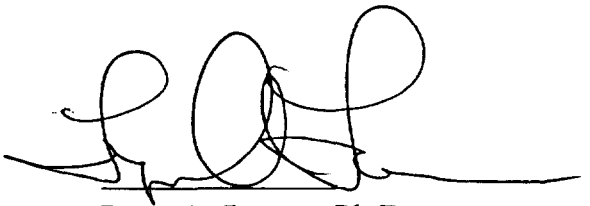
- Sale as a dietary supplement, i.e., use that is not under supervision of a physician or other health care professional;
- Any use other than traditional Chinese medicine use;
- Use by consumers under the misbelief that botanicals are safer than OTC or prescription drugs and will have no adverse effects;
- Promotion as alternatives to psychoactive drugs (because of potential for misuse) and use as a CNS stimulant;
- Use when certain medical conditions are present, e.g., hypertension, depression or psychiatric illness, conditions enhanced by an adrenergic state, glaucoma, pregnancy or lactation, physical stress, and heart disease (and those at risk for heart disease);
- Use by those with sensitivity to ephedrine;
- Use when consuming tyramine-containing foods (e.g., cheese, liver, and red wine);
- Use concomitantly with certain drugs;
- Use for weight loss;
- Sale to and use by consumers under 21 years of age;
- Sale in absence of warning labels;
- Poor QC and lack of GMPs;
- Presence of impurities;
- Multi-ingredient formulations; and
- Use above 20 mg TEA per day, high doses, or frequent doses.

Comments by the industry liaisons specifically in response to these questions supported the concept of GMPs and use of formulations that do not include other stimulant materials. They had also supported, in the earlier Committee discussion, labeling that would inform consumers about the products.

Working Group recommendations. Most members did not directly provide any recommendation regarding a Committee response to or position on the October 1995 Working Group recommendations. One member indicated that the WG did not go far enough, and therefore he disagreed with those recommendations. Four members generally accepted the WG recommendations, but either implicitly or explicitly qualified acceptance as being subject to labeling and intake considerations discussed at this Committee meeting.



E. Wayne Askew, Ph.D.
Acting Chair
Food Advisory Committee



Lynn A. Larsen, Ph.D.
Executive Secretary
Food Advisory Committee

ATTACHMENT

CHARGE & QUESTIONS POSED TO THE FOOD ADVISORY COMMITTEE AND SPECIAL WORKING GROUP

Background:

On October 11 and 12, 1995, a FDA Food Advisory Committee Special Working Group (Working Group) met to consider the public health problems associated with the use of dietary supplements containing ephedrine alkaloids. The Working Group reviewed the available data and information for the occurrence of adverse events associated with the use of dietary supplements containing ephedrine alkaloids in certain individuals. These data and information included the known pharmacology of ephedrine and its related alkaloids and numerous published findings from clinical studies involving the treatment of obese individuals with ephedrine. The data and information also included hundreds of reports, submitted by consumers and physicians, of adverse events associated with the consumption of dietary supplements known to contain, or suspected of containing, ephedrine alkaloids. Adverse events associated with the use of ephedrine-containing OTC drugs were also considered. The Working Group found that the available data were sufficient to demonstrate that the use of certain dietary supplements containing ephedrine alkaloids may cause consumers to experience serious adverse events, especially when the following factors are considered: 1) individual sensitivities to ephedrine alkaloids contained in dietary supplement products, 2) the amount of ephedrine-alkaloids consumed per serving, and 3) the duration of using the product.

The Working Group found that use of dietary supplements containing ephedrine alkaloids may cause serious adverse events and recommended that FDA establish appropriate conditions of use for these products. Based on the available information, the Working Group suggested that FDA 1) establish single serving limits and daily use limits for ephedrine and total ephedrine alkaloids - e.g., the total of ephedrine, pseudoephedrine, norpseudoephedrine, norephedrine, methylephedrine, and methylpseudoephedrine - contained in dietary supplements, 2) require instructions for use and warning or cautionary statements on the labels of these products, and 3) establish good manufacturing practice (GMP) requirements. Several members of the Working Group made suggestions concerning serving and daily use levels and specific warning label statements, although no agreement was reached by the group on what the levels or statements should be. Among the use and cautionary statements that members of the Working Group felt should be included in labeling were:

- a statement discouraging consumption of more than the recommended amount or more frequently than recommended, because of the potential for illness or injury at higher or chronic intake (e.g., cardiovascular, neurological or psychiatric reactions);

- use instructions, including safe duration of use and maximum safe intake ("dose") and

that taking more of the product does not increase the benefit or effectiveness;

- a statement noting that the product is not intended for use by persons under 18 years of age;
- a caution against consumption if a consumer is pregnant, is taking certain drugs, or has certain diseases or conditions (including psychiatric disorders);
- a statement that the product is intended to be used as a dietary supplement;
- a statement that identifies any other stimulants contained in the product, and their sources; and
- a statement that identifies the amount of ephedrine alkaloids contained in the product.

Focus

Since the October 1995 meeting, new information about adverse events has become available to the agency. For example, analytical evaluation of consumer samples of these products suggests that adverse events, often serious in nature, may occur with the use of products containing relatively low levels of ephedrine alkaloids. In addition, FDA has received over 300 additional adverse event reports, many serious in nature, associated with the use of dietary supplements containing ephedrine alkaloids. The agency believes that the sharp increase in adverse event reports and the association between dietary supplements containing relatively low levels of ephedrine alkaloids, raises additional concern with the use of these products and requires further evaluation by the Food Advisory Committee.

In making your evaluation, please consider the following points:

a. The potentially large population that is susceptible to experiencing adverse events with the use of ephedrine alkaloids.

b. The potential for additive effects of the different ephedrine alkaloids to increase the likelihood or severity of an adverse event.

c. Other ingredients in the product with potential physiological or pharmacological activity that may interact with ephedrine or other substances to increase the likelihood or severity of an adverse event.

d. Natural variation of the ephedrine alkaloids in the products.

e. The fact that in the data evaluated by FDA, the majority of adverse events appear to be related to short term use of the products (i.e., less than one month) and many of the events are reported to occur with the first use, or on the first day of use.

f. Evidence of serious adverse events resulting from long-term use of dietary supplements containing ephedrine alkaloids.

g. Other factors that may affect the likelihood or severity of adverse events or the nature and patterns of the illnesses and injuries associated with the use of these products.

Charge:

The task before the Food Advisory Committee at this meeting is to review the scientific data and other information related to adverse events associated with the use of dietary supplements containing ephedrine alkaloids, and to provide expert advice on specific ways to address the public health concerns associated with the use of ephedrine alkaloid-containing dietary supplement products.

Questions for the Food Advisory Committee:

Based on the information presented at this meeting and on your expertise and experience:

1. Can you identify a safe level in dietary supplements for:

   a. total ephedrine alkaloids?
      per serving?
      per day?

   b. ephedrine?
      per serving?
      per day?

2. What margin of safety should be used in determining a safe level?

3. Can you identify conditions of use for ephedrine alkaloid-containing dietary supplements under which there is no risk of significant harm? (For purposes of this question, significant harm means either a large number of adverse effects or a serious adverse effect in at least one individual).

4. Can you identify conditions of use that are associated with a risk of significant harm, including levels and frequency of use above which there is a risk of significant harm? (For the purposes of this question, significant harm is defined as in question 3).