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Ephedrine Alkaloid-Containing Dietary Supplements

Statement of

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before

the Subcommittees on Commerce, Trade, and Consumer Protection and Oversight and Investigations
House Committee on Energy and Commerce

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INTRODUCTION

Thank you, Mr. Chairman for this opportunity testify before your Subcommittees at this joint hearing on ephedrine alkaloid containing dietary supplements.

BACKGROUND ON REGULATION OF DIETARY SUPPLEMENTS

More than half of the population of the United States uses "dietary supplements." The Dietary Supplement Health and Education Act of 1994 (DSHEA) (P.L. 103-417) set up a unique regulatory framework in an attempt to strike the right balance between providing consumers access to dietary supplements that they may choose to use to help maintain and improve their health, and giving FDA the necessary regulatory authority to take action against supplements or supplement ingredients that present safety problems, have false or misleading claims, or are otherwise adulterated or misbranded. Although dietary supplements are generally regulated as foods, there are special statutory provisions and implementing regulations for dietary supplements that differ in some respects from those covering "conventional" foods. Moreover, the regulatory requirements for dietary supplements also differ from those that apply to drug products (prescription and over-the-counter).

Congress defined the term "dietary supplement" as a product that, among other things, is ingested, is intended to supplement the diet, is labeled as a dietary supplement, is not represented as a conventional food or as a sole item of a meal or the diet, and contains a "dietary ingredient." The "dietary ingredients" in these products may include vitamins, minerals, herbs or other botanicals, amino acids, and dietary substances such as enzymes. Dietary ingredients also can be metabolites, constituents, extracts, concentrates, or combinations of the preceding types of ingredients. Dietary supplements may be found in many forms, such as tablets, capsules, liquids, or bars. DSHEA placed dietary supplements in a special sub-category under the general umbrella of "foods," but products that meet the drug definition are subject to regulation as drugs.

LABELING OF DIETARY SUPPLEMENTS

Under the Federal Food, Drug, and Cosmetic (FD&C) Act and FDA's implementing regulations, the label of a dietary supplement must bear a statement of identity (product name) that identifies the product as a dietary supplement; nutrition information in the form of a Supplement Facts panel; a list of any ingredients not listed in the Supplement Facts panel; the name and address of the manufacturer, packer, or distributor; and the net quantity of contents. In addition, if the labeling includes a claim to affect the structure or function of the body, a claim of general well-being, or a claim of a benefit related to a classical nutrient deficiency disease, the product must also bear a disclaimer stating that FDA has not evaluated the claim and that the product is not intended to diagnose, treat, cure, mitigate, or prevent any disease.

Products containing ephedrine alkaloids have unusual features and present complex regulatory issues. If the product is a botanical, it may meet the definition of a dietary supplement regulated under DSHEA. On the other hand, if it contains synthetic ephedrine, that ingredient and other synthetic ephedrine alkaloids (including pseudoephedrine) are regulated as drugs, which are only marketed for indications where safety and effectiveness have been demonstrated. Synthetic ephedrine and pseudoephedrine are available as components of various over-the-counter and some prescription drug products for treating allergies, asthma, nasal congestion, and related upper respiratory symptoms. None of these drug products include other ephedrine alkaloids, caffeine, or other stimulants that may interact with their effects. Synthetic ephedrine drug products are subject to stringent manufacturing, labeling, and dosing requirements. There are no synthetic ephedrine drug products approved for long-term use. Some dietary supplements have been found to contain synthetic ephedrine and FDA has taken enforcement action against their use. Nevertheless, synthetic ephedrine poses serious law enforcement and public health challenges, which are beyond the scope of this testimony.

ADVERSE EVENT REPORTING

DSHEA's regulatory framework is primarily a postmarket program like the bulk of food regulation. Thus, as with most foods, there is no requirement for manufacturers to provide evidence of product safety to FDA prior to marketing ephedrine-containing dietary supplements. In contrast, drug regulation involves an extensive premarket evaluation of safety and effectiveness with explicit standards of evidence. This evidence provides a basis to guide not only approval decisions but also conditions of use to manage benefits and risks. In addition, there are post-market reporting requirements for drugs to

support product safety monitoring. These requirements do not exist for dietary supplements.

As a result, voluntary adverse event reports (AERs) are the primary means FDA has for identifying potential safety problems with dietary supplements. Under DSHEA, FDA must rely on AERs as a major component of its post-market regulatory surveillance efforts under DSHEA. Also, unlike drug regulation, FDA cannot compel reporting of adverse events by dietary supplement manufacturers.

FDA's Center for Food Safety and Applied Nutrition (CFSAN) has recently put in place the CFSAN Adverse Event Reporting System (CAERS) to monitor adverse event reports on food, cosmetics and dietary supplement products. CAERS includes a comprehensive single computerized system that captures and analyzes all reports of consumer complaints and adverse events related to CFSAN-regulated products. This state-of-the-art system started collecting reports after June 15, 2003, and combines all existing CFSAN adverse event-reporting systems and logs reports into one portal within CFSAN.

DIETARY SUPPLEMENTS CONTAINING EPHEDRINE ALKALOIDS

A number of plant genera, including ephedra, are known to contain ephedrine alkaloids. Ma huang is a common name given to Chinese Ephedra, which is used in traditional Chinese medicine. Ephedra has been shown to contain various chemical stimulants, including the alkaloids ephedrine, pseudoephedrine and norpseudoephedrine, as well as various tannins and related chemicals. The concentrations of these alkaloids depend upon many factors, such as the species, parts of the plant used, time of harvest, growing location, and production methods. Ephedrine and pseudoephedrine are used in some over-the-counter and prescription drugs, where they have been demonstrated to be safe and effective for the labeled use. Many of these stimulants have known, and potentially serious, side effects. While ephedra has been used in herbal medicine preparations for thousands of years, in recent years ephedra has been sold primarily in dietary supplement products for weight control, as well as in products promoted to boost energy levels or to enhance athletic performance. Some ephedra-containing products have been marketed as alternatives to illicit street drugs. Ephedra-containing products often contain other stimulants, such as caffeine, that may have synergistic effects and increase the potential for adverse effects.

A number of adverse effects associated with ephedrine alkaloid-containing dietary supplements have been reported to FDA. These include elevated blood pressure, rapid heartbeat, nerve damage, muscle injury, and psychosis and memory loss. More serious effects have also been reported, including heart attack, stroke, seizure and death.

As the tragic deaths of the Baltimore Orioles' pitching prospect Steve Bechler and of Sean Riggins, the sixteen year old from Illinois have reminded us, use of ephedra, particularly in sports, raises serious concerns about safety and has long posed difficult issues for health care professionals, regulators, and for consumers. These concerns stem from both the mechanism of action of ephedrine alkaloids on the sympathetic nervous system, and accumulating evidence of potentially serious adverse events after use of ephedra-containing products.

While there has been considerable debate about the safety and effectiveness of dietary supplements like ephedra, as well as the most effective approach to regulating them, one thing is clear: Although dietary supplements are regulated as foods and not drugs, the consumer should not assume they are always safe to use. "Natural" does not necessarily mean safe. In particular, botanical and herbal products may have active ingredients with pharmacologic properties similar to, or in the case of ephedra identical to, drug products.

USE OF EPHEDRA BY ATHLETES

I want to take this opportunity to applaud the National Football League, National Collegiate Athletic Association, and the International Olympic Committee for banning the use of ephedra by their players. Although FDA is reviewing ephedrine alkaloids under DSHEA to assess the safety concerns, FDA has particular concerns about the use of ephedra by persons engaged in strenuous exercise. A recent study by RAND, discussed in more detail below, concluded that ephedra has minimal if any proven benefit for enhancing sports performance. Yet ephedra acts like an adrenaline boost, stressing the heart, raising blood pressure, and increasing metabolism. Moreover, the stimulating effects of ephedra may mask the signs of fatigue, causing even the most well conditioned athletes to push beyond their physical limits. Thus, ephedra's risks are potentially much more serious for competitive athletes than for the general population. As FDA has said before, ephedra should not be used by people who engage in strenuous activity.

Because of the special risks of ephedra use in athletes, I believe that the sports leagues that have acted to restrict ephedra use are making a prudent decision. Even as the Agency evaluates the safety of ephedra use in the population more generally, including its use for weight loss, I have clearly and repeatedly indicated that ephedra poses special risks in the context of sports performance with little or no identified benefit for athletes.

FDA's RULEMAKING ON EPHEDRINE ALKALOIDS

Right now, the Agency's professional, scientific and legal staffs are working hard to address the extraordinary challenges presented by these products. The regulatory actions in process now have several major components. Earlier this year, the Agency published a *Federal Register* notice seeking comment on proposed warning label for ephedra-containing dietary supplements. These changes would make it clear to users, via a black-box warning on the front of the product, as well as additional information elsewhere in the product labeling, that serious adverse events and death have been reported after using ephedra, and that risks of adverse events are particularly high with strenuous exercise and/or use of stimulants including caffeine. In addition, the Agency reopened the comment period on its 1997 proposed rule on dietary supplements containing ephedrine alkaloids. There is now considerably more evidence available on ephedra's risks and benefits than when the proposed rule was published. In its recent *Federal Register* notice, FDA announced that it was seeking comments from health professionals, the supplement industry, and the general public on any additional data on ephedra's safety, so that we can acquire the most complete picture possible of the product's potential risks, as a basis for appropriate further regulatory action.

Our *Federal Register* announcement also sought comments on whether, in light of current information, FDA should

determine that dietary supplements containing ephedrine alkaloids present a significant or unreasonable risk of illness or injury under the conditions of use recommended or suggested in labeling or under ordinary conditions of use if the labeling is silent. In FDA's view, "unreasonable risk" implies a risk-benefit calculus. Such a calculus should examine the best available scientific evidence and take it into account in assessing whether the product's known or suspected risks outweigh its known or suspected benefits. The "sentinel" events identified by RAND, coupled with the adverse event information we have collected at the Agency and our knowledge of ephedra's pharmacology and mechanism of action, have all raised serious concerns about whether ephedra use poses an unreasonable risk.

By undertaking these regulatory actions and seeking public comments on these issues, our intent is to give DSHEA the meaning in practice that many of its supporters say it should have, by clarifying that public health authorities can use the standard in the law to determine whether a product poses unreasonable, albeit uncertain, safety risks and then take appropriate regulatory or enforcement action. We are establishing an up-to-date public record for further, legally sustainable actions based on the latest scientific evidence. We are currently in the process of analyzing the over 16,000 public comments we received earlier this summer. We are in the final stages of our deliberative review related to finalizing our rule, so I cannot discuss the specifics of that process or the anticipated outcome. However, I want to emphasize that we are committed to moving forward expeditiously to make a determination that is well grounded in all available scientific evidence and that is protective of the public health in accordance with DSHEA.

While we are undertaking these regulatory procedures, under my leadership, the Agency has dramatically increased its enforcement actions against ephedrine alkaloids and other dietary supplement products making false or misleading claims. These actions, many of which have been undertaken in collaboration with the Federal Trade Commission (FTC), are having an impact on the marketing of dietary supplements in general and ephedra in particular.

ENFORCEMENT ACTIONS

At the core of FDA's enforcement efforts is our commitment to enhance the legitimate manufacture, sale, and use of dietary supplements while enforcing the law aggressively against fraudulent product claims and other illegal practices. Achieving these goals relies on a number of strategies, including cooperation and coordination with other Federal, state, and international law enforcement agencies in protecting consumers against unapproved and potentially harmful products offered by Internet outlets, some of which are based abroad.

With a mutual goal of consumer protection, FDA and FTC formed a Dietary Supplement Enforcement Group to closely coordinate their enforcement efforts against health care fraud. In addition, FDA and FTC chair an interagency health fraud steering committee that meets regularly to coordinate activity on these issues. The workgroup currently includes Federal agencies in the U.S. and Canada. Mexico has been invited to join the group. As part of its effort to curb Internet health fraud, FDA has conducted several "surfs" to identify fraudulent marketing of health care products over the Internet. These actions were carried out in partnership with the FTC and other law enforcement and public health authorities in the United States and abroad.

Sports Uses of Ephedra

On February 28, 2003, based on the conclusions of the RAND study, FDA warned 26 firms to cease making unproven claims that ephedrine-containing dietary supplements enhance athletic performance. The actions were primarily a result of the Agency's surveillance of the firms' websites. Fourteen of the firms responded to the warning letters by discontinuing the product or the claim. The remaining twelve firms were inspected by FDA. Of those twelve inspected firms, all but one either discontinued the product or the objectionable claims. Investigation for consideration of regulatory action against the remaining firm is ongoing. Since performance enhancement was one of the two principal ways in which ephedra has been marketed, the impact of these warning letters has been substantial. As a result of FDA's enforcement actions, all but one of these products are no longer being marketed for sports enhancement.

Street Drug Alternatives

In September 2002, FDA became aware of the tragic death of Sean Riggins, the 16-year-old high school football player who had taken the product, Yellow Jackets. One source of the product was found to be a distributor in the Netherlands, which promoted the product on the Internet as an alternative to street drugs. The product was manufactured by NVE Pharmaceuticals in New Jersey.

Yellow Jackets capsules and Black Beauties capsules, another NVE product at the time, were both "street" terms for controlled substances, and are sold as herbal street drug alternatives. These products are labeled to contain ephedra extract and other herbal ingredients, including kola nut extract, a source of caffeine. Their sale as a substitute for controlled substances is illegal. FDA issued a Cyber Letter to Mr. Xoch Linnebank, Sjamaan Internet Department, The Netherlands, on October 4, 2002, regarding the sale of Yellow Jackets into the United States and placed the company's products on import alert on October 7, 2002.

On October 8, 2002, FDA attempted to inspect NVE Pharmaceuticals, the manufacturer of Yellow Jackets and Black Beauties. NVE refused to allow the inspection and on October 11, FDA and the U.S. Marshal's Service returned to NVE under a limited administrative inspection warrant. Although NVE refused to provide access to batch records and complaints during the October inspection, FDA obtained sufficient evidence to support an additional warrant. In January 2003, FDA and the U.S. Marshal's Service returned to NVE under a comprehensive inspection warrant and obtained both records and complaints. FDA witnessed the firm's voluntary destruction of both "street drug-alternative" products with a retail value of between \$4 and \$5 million.

After NVE stopped marketing Yellow Jackets and Black Beauties, they began marketing Yellow Swarm and Midnight Stallion as replacement products. These products appear to be almost identical in formulation and appearance, but they no longer bear street drug names or claims - yet safety issues associated with these types of products remain.

On March 31, 2003, FDA also took new enforcement action against firms marketing street drug alternative products, some of which contained ephedra or other sources of ephedrine. FDA sent warning letters to eight firms, again based primarily

on an investigation of the firms' websites. The investigation revealed that the firms sold products for "recreational" purposes with claims to produce such effects as euphoria, a "high" or hallucinations. As with Yellow Jackets and Black Beauties, these street drug alternatives are not dietary supplements under the legal definition, because they are not intended to supplement the diet. These eight letters went to manufacturers of products that contain the drugs ephedrine or norephedrine hydrochloride labeled as dietary supplements for use in weight loss, suppression of appetite and enhanced libido. The majority of the firms stopped selling these products or removed the street drug alternative claims for these products. We are currently working to assure that all of the firms are brought into full compliance.

DIETARY SUPPLEMENT GOOD MANUFACTURING PRACTICES

Another important arm of FDA's regulatory and surveillance activities to help ensure the safety of dietary supplement products is improving product quality and consistency. DSHEA gave FDA the authority to promulgate regulations for dietary supplement good manufacturing practices (GMPs).

Examples of product quality problems the GMPs will help prevent are: superpotent, subpotent, wrong ingredient, drug contaminant, other contaminant (e.g., bacteria, pesticide, glass, and lead), color variation, tablet size or size variation, under-filled containers, foreign material in a dietary supplement container, improper packaging, and mislabeling.

On March 7, 2003, FDA announced proposed rules to establish GMPs and labeling standards for dietary supplements. FDA's proposed rule, if adopted as proposed, would establish GMPs to help reduce risks associated with adulterated or misbranded dietary supplement products. FDA is soliciting comments from the public and industry on this proposal. Written comments will be received until August 11, 2003.

The proposed rule would:

- Establish industry-wide standards necessary to ensure that dietary supplements are manufactured consistently as to identity, purity, quality, strength, and composition.
- Include requirements on the design and construction of physical plants that facilitate maintenance, cleaning, and proper manufacturing operations, for quality control procedures, for testing final product or incoming and in process materials, for handling consumer complaints, and for maintaining records.
- Apply to all firms that manufacture, package, or hold dietary ingredients or dietary supplements, including those involved with testing, quality control, packaging and labeling, and distributing them. The proposed regulations also would apply to both domestic firms and foreign firms that manufacture, package, or hold dietary ingredients and dietary supplements for distribution into the U.S.

FDA EFFORTS TO OBTAIN SCIENTIFIC DATA

In order to acquire the best available scientific data to support its regulatory decisions relating to ephedra, the Agency has undertaken numerous credible and appropriate steps to gain access to information, in the form of adverse event information, clinical studies, and other scientific reviews that could be helpful in evaluating the safety concerns identified by AERs associated with dietary supplements containing ephedrine alkaloids. These successful efforts have put the Agency in a better position to make meaningful science-based decisions about these products. In particular, FDA has sought unredacted complaints from Metabolife as well as the raw data from the six-month Boozer Daly study that was conducted at the request of the makers of dietary supplements containing ephedra.

On February 28, 2003, Secretary Tommy Thompson and I held a press conference and announced the conclusions from the RAND study, commissioned by the National Institutes of Health, which reviewed recent evidence on the risks and benefits of ephedra and ephedrine based on the adverse events reports provided by Metabolife. In evaluating potential benefits of ephedra, the RAND report found only limited evidence of an effect of ephedra on short-term weight loss, and minimal evidence of an effect on performance enhancement in certain physical activities. Also, the RAND study concluded that ephedra is associated with higher risks of mild to moderate side effects such as heart palpitations, psychiatric and upper gastrointestinal effects, and symptoms of autonomic hyperactivity such as tremor and insomnia, especially when it is taken with other stimulants. Moreover, its review of some 16,000 adverse event reports revealed two deaths, four heart attacks, nine strokes, one seizure, and five psychiatric cases involving ephedra in which the records appeared thorough and no other contributing factors were identified. RAND called such cases "sentinel events," because they may indicate a safety problem but do not prove that ephedra caused the adverse event. The study recognized that such case studies are a limited form of scientific evidence. The study also identified other adverse events potentially associated with ephedra, in which other factors may have contributed to the adverse events or in which records were inadequate.

The RAND review, along with the data provided to the Agency by Drs. Boozer and Daly from their controlled clinical study of ephedra use are being reviewed by the Agency and its outside experts, along with the adverse event information the Agency has received in its own CAERS. All three of FDA's outside reviewers of the Boozer Daly weight loss study have raised serious concerns about that study's ability to prove the safety of dietary supplements containing ephedra.

At this time, we have amassed a significant data set and conducted substantial analyses on ephedrine alkaloids. This data set includes AERs from FDA's Medwatch and from Metabolife as well as detailed assessments by Agency experts and outside experts at RAND that have identified ephedra as an ingredient of particular concern. But as the General Accounting Office and the Rand report have noted, AERs alone in this context are sentinel events indicative of a potential safety problem, but are not enough alone to make an empirical, scientific determination with a high degree of statistical confidence that ephedra causes serious adverse events. In addition, our careful review of the Boozer Daly study and underlying data have raised additional significant concerns about the empirical effects of ephedra. At this point, we are in the final stages of our deliberative review related to finalizing our rule, so while I cannot get into the specifics of that process or the anticipated outcome, I want to emphasize that we are moving forward as expeditiously as possible to make a determination that is well grounded in the scientific evidence we have and that is protective of the public health in accordance with DSHEA. Meanwhile, under my leadership the Agency will continue to use all available resources to target our limited enforcement resources on false and misleading dietary supplement claims among other top priorities.

Mr. Chairman, thank you for this opportunity to testify. I am happy to answer your questions.

Page Last Updated: 07/24/2009

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