



1660 Lincoln Street  
Suite 1900  
Denver, CO 80264  
303-830-1776  
Facsimile 303-894-9239  
www.pattonboggs.com

1013 10 21:37

April 7, 2003

Susan D. Brienza  
(303) 894-6146  
sbrienza@pattonboggs.com

Attn: Mr. Anthony Curry  
Dockets Management Branch (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

Re: Comment on Proposed Rule on Ephedra, Docket No. 95N--0304, on behalf of Wellness International Network, Ltd.

Dear Mr. Curry:

We represent Wellness International Network, Ltd. ("WIN") with respect to regulatory compliance matters, and are filing on its behalf this Comment concerning the Proposed Rule on Dietary Supplements Containing Ephedrine Alkaloids, noticed on February 28, 2003. 68 Fed. Reg. 10417 (hereafter "Proposed Rule" and "ephedra or ephedrine supplements"). WIN is a manufacturer and marketer of dietary supplements, with its principal place of business at 5800 Democracy Drive, Plano, Texas. WIN opposes the Proposed Rule, in large part because available science, in particular the RAND Report<sup>1</sup>, does not indicate a "significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling," and does not support a warning of the length and severity as proposed by the Food and Drug Administration ("FDA"). Instead, WIN suggests that if a warning is to be required by the FDA, it be the warning for ephedrine-containing products currently required by the Texas Department of Health.

The Agency has indicated that its Proposed Rule is largely based on a Report issued by the RAND Corporation, also issued on February 28, 2003. However, in at least five places in the RAND Report, the authors state that a causal relationship between ephedra supplements and serious adverse events has not been shown. The RAND Report ends, not by recommending a safety warning, but by strongly recommending a well-controlled scientific study "to assess the possible association" between ephedra and serious AERs (p. 221). In other words, RAND has answered the safety question with a question, not with a finding of causality. In our view, as a whole, the data and the science concerning the safety of ephedra-containing products, from 1995 to the present, does not warrant the Warning presented in the Proposed Rule, or any other FDA

95N-0304

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<sup>1</sup> Shekelle, P., S. Morton, M. Maglione, et al., "Ephedra and Ephedrine for Weight Loss and Athletic Performance Enhancement: Clinical Efficacy and Side Effects," Evidence Report/Technology Assessment No. 76 (Prepared by Southern California Evidence-based Practice Center, RAND, under Contract No. 290-97-0001, Task Order No. 9), Agency for Healthcare Research and Quality, February 2003, Publication No. 03-E022, Rockville, MD.

FDA, Dockets Management Branch  
April 7, 2003  
Page 2

action. Neither the FDA's 1,000 AERs, nor the RAND Report, nor recent athlete deaths due to heat stroke may be the basis for an extensive required warning, for a significant restriction on the quantity of ephedrine alkaloids per day or, in the extreme, for a total ban on ephedra-containing supplements. Indeed, the thrust of the RAND Report, the most comprehensive and complete synthesis to date on this issue, is that any Proposed Rule is premature in light of the fact that the RAND Report recommends that the hypothesis of causality be further tested.

**Profile of the Company:**

Founded in 1992, Wellness International Network, Ltd. offers a premium line of products for targeted health and wellness needs, including weight management, sports and fitness, mental fitness, stress management, nutrition, immune system strength, and health and beauty. Its products—formulated in the context of the best available science and nutrition information—are offered through a network of distributors all over the world, including the United States, Holland, the United Kingdom, France, Belgium, Canada, India, and South Africa. WIN has always supported regulatory action based on science, and has included warnings much stronger than FDA's standards for years on many of its products, including BioLean®, which contains ephedra.

**Description of BioLean® and Its Safety Record:**

BioLean® is a weight loss product containing 37.5 mg ephedra alkaloids per day (25mg in an AM serving and 12.5 in a PM serving) and no more than 12 mg of caffeine per serving, which is much less than the amount in a cup of tea. WIN's description of its ingredient is: given that Ephedra alkaloids have 6 isomers, one of which is ephedrine, in the 37.5 mg above, the majority is ephedrine alkaloids, while the rest consists of pseudo-ephedrine and methyl-ephedrine; these are collectively referred to as "ephedra alkaloids." BioLean®'s daily recommended ephedra alkaloid amount of 37.5 mg is well below the industry standard of 100 mg, which is also the daily limit enacted in Ohio, Texas, and other states. WIN has never used synthetic ephedrine or any salts of ephedrine; instead, its ephedra is derived from the herb Ma Huang and of the finest quality. In its 11 years on the market, over 35 million servings of BioLean® have been sold with no serious adverse events reported. (As stated below, by "serious" WIN means an event requiring or resulting in a trip to the emergency room.) The warning on each BioLean® label is identical to the ephedra warning required in the state of Texas for ephedrine-containing products.

BioLean® has an excellent safety record, as documented through WIN's detailed AER reporting system, which begins with a "product reaction call":

- 1.) A call comes into the customer service area.
- 2.) If it is determined that it is a Product Reaction, it immediately gets referred to a supervisor or manager. Such personnel know to tell the caller that if he feels it is an emergency, to seek medical help immediately and tell doctors that BioLean® is in the PDR for nonprescription

FDA, Dockets Management Branch  
April 7, 2003  
Page 3

drugs and is a dietary supplement. WIN does get the Complainant's name and number for future use.

3.) In most cases, customer service gets calls a day or even a week after consumption, where a person is trying to find out why he or she had a reaction.

4.) The call at this point is turned over to the product coordinator or the Director of Regulatory Affairs. If both are not in the office, the call goes to another executive in the company.

5.) WIN has a form that is either sent to the caller, or personnel fill it in while talking to the caller. (See form attached at Tab 1.) If further issues need to be discussed, WIN has a medical consultant on call who will contact the person and discuss follow-up issues with him or her.<sup>2</sup>

Discussion with WIN's medical consultant has been required in less than 10 instances. The majority of customer-related inquiries involving BioLean® stem from customers wishing to return the product, not from reports of adverse reactions. While the most common response for a return has been "unsatisfied" or "had no effect," those who cited reactions typically listed "upset stomach" or "jitters," and rarely provided any further documentation. With "serious adverse events" defined as medical problems resulting in or requiring a visit to an emergency room, the number of serious adverse events associated with any WIN product is zero.

Probably the best evidence of the safe use of BioLean® comes from WIN's several distributors who are also M.D.s, who have been recommending the product for years, monitoring their patients, and seeing only positive results. These doctors have sent letters to Secretary of Health and Human Services Tommy Thompson in which they state: "I have examined the scientific literature on ephedra, which supports the weight loss benefits and safety when ephedra is used according to current standards for these products. . . . In addition to witnessing successful, long-term weight loss in my patients, I have seen their overall health improve as measured by healthier cholesterol levels and lower blood pressure." (Copies attached at Tab 2.) Although a recent article in the New York Times questioned the financial self-interest and ethics of these physicians who recommend BioLean®, the facts and the logic with respect to M.D.s' use of BioLean® speak for themselves. WIN reports that there have been no complaints against any of these doctors, either informal or formal, due to the consumption of BioLean®. If there were significant occurrences, or any occurrence, of serious illness associated with ephedrine supplements, would these doctors risk a product liability suit and a malpractice suit, as well as jeopardizing their licenses, and their medical reputations, all to continue recommending

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<sup>2</sup> WIN's formal complaint protocol, with use of the form, began in 1998. Before that year, such calls were forwarded to key personnel in the company and the same procedure as described above was followed, although without the form.

FDA, Dockets Management Branch  
April 7, 2003  
Page 4

BioLean®? Indeed, instead of complaints, these doctors receive letters of thanks from their patients, such as the one quoted in an article by Dr. John Adler (also at Tab 2).

There has never been a death, stroke, or other serious incident associated with consumption of BioLean®. A WIN employee scanned the FDA's AER database on March 20, 2000, and the result was "Sorry, there were no matches found for Wellness International Network, Ltd." As for the 6 AERs concerning BioLean® that reportedly were part of the original 864 AERs on which the FDA based its original proposed rule on ephedrine-containing supplements in 1997, these 6 reports, if they exist, would suffer from the same incomplete, poorly documented, and inconsistent information that marred the 864 AERs, as described in the Government Accounting Office ("GAO") report of July 1999.<sup>3</sup>

In general, the GAO Report found that the 864 AERs, as a whole, lacked data or had inconsistent information (e. g., any pre-existing conditions, the amount of product used, how often it was used, or how long it was used), which was relevant to the FDA's analysis and its decision to promulgate the original proposed rule of 1997. Sixty-two percent of the GAO's random sample of the 864 AERs did not contain medical records, which are important for determining potential underlying conditions that might have caused the adverse event.<sup>4</sup> In the same sample, cases existed in which the amount of product consumed or the duration for which it was consumed was listed differently in multiple locations in the same AER.<sup>5</sup>

As to the relationship between the data used and the specifics of the original proposed rule, the GAO Report found that the FDA did not establish a causal link between the ingestion of ephedrine alkaloids and the occurrence of adverse events<sup>6</sup> for either the FDA's proposed dosing level of 8 mg. per serving, or duration of use of 7 days.<sup>7</sup> The FDA's proposed restriction to an amount of 8 mg. per serving was based solely on information associated with only 13 AERs out of the 864 AERs that the agency had received on dietary supplements containing ephedrine alkaloids.<sup>8</sup> The number of AERs (that is, 13) used to support the dosing regimen was small; and the quality of these AERs was questionable, according to the GAO.

Further, the FDA did not perform a causal analysis to determine whether the reported events in these 13 AERs were, in fact, caused by the ingestion of dietary supplements containing ephedrine alkaloids.<sup>9</sup> Numerous problems with the 13 AERs were found which raised questions

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<sup>3</sup> Dietary Supplements: Uncertainties in Analyses Underlying FDA's Proposed Rule on Ephedrine Alkaloids (GAO/GGD-99-90, July 2, 1999).

<sup>4</sup> GAO Report at 11.

<sup>5</sup> Id.

<sup>6</sup> An example of an adverse event is an increase in heart rate. A "serious" adverse event would be a stroke.

<sup>7</sup> Id., p. 3.

<sup>8</sup> Id. at 3, 11, 12, 70.

<sup>9</sup> Id. at 13.

FDA, Dockets Management Branch  
April 7, 2003  
Page 5

about the causal relationship between ingestion of the implicated product and the adverse events that occurred.<sup>10</sup> In 3 AERs, physician reports were included which stated that the cause of the adverse event was not related to a dietary supplement.<sup>11</sup> Significantly, three individuals reported having experienced similar problems prior to using the dietary supplement.<sup>12</sup>

In addition, uncertainties exist in the FDA's analysis of the relationship between duration of use of dietary supplements containing ephedrine alkaloids and the occurrence of adverse events. The FDA did not present scientific evidence which specifically pointed to an increase in adverse events after 7 days of normal use of dietary supplements containing ephedrine alkaloids.<sup>13</sup> Instead, the FDA relied on scientific information which outlined problems with extended use in terms of months and years.<sup>14</sup> Moreover, the use of these AERs to describe a pattern of consumer response over time was questionable because the FDA indicated 10 to 73 percent of the reported adverse events might not be related to the consumption of dietary supplements containing ephedrine alkaloids.<sup>15</sup>

Based on these findings, the GAO recommended that before proceeding to final rulemaking, the FDA needed to provide stronger evidence on the relationship between the intake of dietary supplements containing ephedrine alkaloids and the occurrence of adverse reactions, in order to support the serving size levels and duration of use limits in the FDA's proposed ephedra rule.<sup>16</sup> Largely based upon this GAO Report, the FDA withdrew 5 of the 7 sections of its original proposed rule on ephedrine supplements. The FDA concurred with the GAO's recommendation and began to accumulate additional information to determine the degree of support for the requirements in the proposed rule.<sup>17</sup> However, an additional 146 AERs beyond the original 864, which were analyzed by FDA-sponsored scientists, Christine Haller and Neil Benowitz, have been similarly questioned and criticized by other experts and by the industry trade associations.

Significantly, when one performs an Internet search to locate AERs at the present time, the following message appears:

*Data from the Special Nutritional Adverse Event Monitoring System website for dietary supplements has not been added to or updated since 1999, and the website has now been removed. The information previously available on dietary supplement adverse event reports on*

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<sup>10</sup> Id. at 13-14.

<sup>11</sup> Id. at 14.

<sup>12</sup> Id.

<sup>13</sup> Id.

<sup>14</sup> Id.

<sup>15</sup> Id. at 14-15.

<sup>16</sup> Id. at 24-25.

<sup>17</sup> Id. at 25, 68.

FDA, Dockets Management Branch  
April 7, 2003  
Page 6

*this website was very limited and was provided in a manner that made it difficult for users to appropriately interpret the adverse events.*

*The Center for Food Safety and Applied Nutrition (CFSAN) is currently evaluating how best to provide adverse event data in a manner that is useful, meaningful, and appropriate. By doing so, CFSAN hopes to be able to provide the best information about all adverse event reports on a user-friendly website.*

(Emphasis added.) This language seems to indicate that the previously reported and posted AERs were compromised at best, and at the very least too incomplete to be used to make scientific generalizations.

Our main point with all of these specifics is that just as the GAO Report concluded that the 864 AERs do not support the specifics of the FDA's original proposed rule, in exact parallel, the RAND Report, in essence shows that the 16,000 AERs do not support the current Proposed Rule. The RAND Report concludes that no causal relationship has been shown between ephedra consumption and death, strokes, heart attacks, etc. Thus, were the GAO to examine the FDA's new Proposed Rule as based on the RAND Report, the net result would be the same: the 16,000 AERs do not establish a causal link between ephedra supplement consumption and severe events such as death and stroke, and thus do not warrant proceeding to a Final Rule. In sum, the warning now proposed is not substantiated or warranted by the existing science.

### **The RAND Report does not support the Proposed Rule.**

Given that the FDA's AER database was repeatedly called into question, and that the Agency sought an objective overview of the available science, in June of last year the Department of Health and Human Services (HHS), specifically the Agency for Healthcare Research & Quality, commissioned the RAND Corporation to conduct a comprehensive review of the existing science on ephedra dietary supplements. The Report consists of analysis of thousands of AERs and also meta-analysis, that is, analyses of the published literature on ephedra, published case reports, the reported human clinical trials on efficacy, and reports on file with FDA. The results of this objective, evidence-based review were released on February 28, 2003 and generally confirm what weight loss experts have stated all along—that well-designed clinical trials consistently show that ephedra supplements help healthy, overweight people lose more weight than diet and exercise alone.

More pertinent, as to the safety issue, RAND confirmed that no serious events have occurred in any clinical setting, and that the risk of experiencing any adverse reaction to ephedra is very low. Its review of over 16,000 adverse event reports revealed 21 sentinel events, which means cases involving ephedra that may indicate a safety problem but do not prove that ephedra caused the adverse event. The study also recognized and conceded that such case studies are a weak form of scientific evidence. (See p. 221.)

FDA, Dockets Management Branch  
April 7, 2003  
Page 7

In the safety analysis portions of the RAND Report, the authors first isolated the serious reports and then examined the cases in which causes other than ephedra had been excluded:

We reviewed all available reports of death, myocardial infarction (heart attack), cerebral vascular accident (stroke), seizure, and serious psychiatric illness reported to the FDA prior to September 30, 2001 and contained in their ephedra or ephedrine files, and all case reports identified in our literature search. (p. v)

In reviewing the individual adverse event reports, we searched for documentation that an adverse event had occurred, documentation that the subject had consumed ephedra within 24 hours prior to the adverse event, or a toxicological examination revealing ephedrine or one of its associated products in the blood or urine. We also sought evidence that an adequate investigation had assessed and excluded other potential causes. Cases that met all these criteria were labeled "sentinel events." Cases that met the first two criteria but had other possible causes of the event were labeled "possible sentinel events." Classification as a sentinel event does not imply a proven cause and effect relationship. . . . (pp. v-vi; emphasis added).

The authors of the RAND Report certainly recognize that prior consumption of ephedrine does not mean "caused by" consumption of ephedrine. The classic example of this post hoc fallacy is that the cock crowing in the pre-dawn light does not cause the sun to rise.

The majority of case reports are insufficiently documented to make an informed judgment about a relationship between the use of ephedrine or ephedra-containing dietary supplements and the adverse event in question. Prior ephedra consumption was associated with two deaths, four myocardial infarctions, nine cerebrovascular accidents, one seizure, and five psychiatric cases as sentinel events. Prior consumption of ephedrine was associated with three deaths, two myocardial infarctions, two cerebrovascular accidents, one seizure, and three psychiatric cases as sentinel events. We identified 43 additional cases as possible sentinel events with prior ephedra consumption and 7 additional cases as possible sentinel events with prior ephedrine consumption. About half the sentinel events occurred in persons aged 30 years or younger. (p. vi; emphasis added)

A reduction to absurdity argument, given these results, is that prior consumption of cotton candy in the 24 hours before a serious adverse event does not mean that eating cotton candy causes strokes or heart attacks. The main conclusion of the RAND Report is that more study is needed to reach a conclusion with respect to causality.

**Conclusions.** . . . Use of ephedra or ephedrine plus caffeine is associated with an increased risk of gastrointestinal, psychiatric, and autonomic symptoms. The adverse event reports contain a sufficient number of cases of death, myocardial

FDA, Dockets Management Branch  
April 7, 2003  
Page 8

infarction, cerebrovascular accident, seizure, or serious psychiatric illness in young adults to warrant a hypothesis-testing study, such as a case-control study, to support or refute the hypothesis that consumption of ephedra or ephedrine may be causally related to these serious adverse events. (p. vi-vii, emphasis added)

The Report concedes that several limitations in the data itself hampered and undercut its analysis and, therefore, limited its results. The authors also caution that any conclusions as to safety are not generalizable to the overall population.

The analysis of the adverse events from the randomized controlled trials have the following major potential limitations:

- In this analysis, we focused only on studies that addressed weight loss or athletic performance. Although we observed no serious adverse events in these trials, we might have identified adverse events in trials that tested the efficacy of ephedra for other conditions, had we included those conditions in our search. However, we did include all controlled trials of ephedra or ephedrine for weight loss or athletic performance; therefore, our estimates are relevant to the populations taking those supplements for these reasons, which certainly constitute the majority of users of ephedrine and ephedra products in the United States.
- As with efficacy, the results of the clinical trials with respect to safety are directly applicable only to the persons studied in those trials. In most cases, enrollment was highly selective to avoid certain comorbidities. Whether safety is equivalent in a more representative population is unknown.
- As with efficacy, the results for the ephedra studies with respect to safety cannot be generalized to all ephedra-containing dietary supplements, because these may vary in their constituents from those concoctions studied and reported on here. (pp. 216-217; emphasis added)

The Report also cautions that its analysis of the case reports of adverse events had six major potential limitations, the most important for this discussion being the following:

- We did not have access to all adverse event files.
- Many of the adverse event reports did not contain all the data that we needed to make assessments. Therefore, how the cases we classified as “insufficient evidence” might have influenced our findings had they contained appropriate documentation is unknown.

FDA, Dockets Management Branch

April 7, 2003

Page 9

- An important limitation is that we do not have an estimate of the number of people using ephedra or ephedrine; that is, we do not have a denominator with which to calculate an event rate. An additional complication, we believe, is that the use of ephedra and ephedrine is increasing over time, as is the probability that someone will report an adverse event due to publicity.
- The most important limitation is that the study design (that is, an assessment of case reports) is insufficient for us to reach conclusions regarding causality. (pp. 216-217, emphasis added)

Many FDA announcements and media reports on February 28, 2003, regarding the simultaneous issuance of the RAND Report and the Proposed Rule stated or implied that the Report had found causality between ephedrine supplement consumption and serious adverse events. In fact, just the opposite is the case, as the Report repeats and concludes with its inconclusiveness as to ephedrine supplements as the cause:

The data we reviewed on adverse consequences came from both clinical trials and case reports submitted to the FDA. The strongest evidence of causality should come from clinical trials; however, in most circumstances, such trials do not enroll sufficient numbers of patients to adequately assess the possibility of rare outcomes. Such was the case with our review of ephedrine and ephedra-containing dietary supplements. For rare outcomes, we reviewed case reports. However, we could not determine definite causality from case reports. (p. 220; emphasis added)

With these considerations in mind, the evidence we identified supports the following conclusions:

- . . . There were no reports of serious adverse events in the controlled trials of ephedrine or ephedra, but these studies are insufficient to assess adverse events that occurred at a rate of less than 1.0 per 1000. (emphasis added)
- A large number of adverse event reports regarding herbal ephedra-containing dietary supplements have been filed with FDA. The majority of FDA case reports are insufficiently documented to make an informed judgment about the relationship between the use of ephedra-containing dietary supplements and the adverse event in question. (emphasis added)
- A very large number of adverse events were reported to one manufacturer of ephedra-containing dietary supplements. Nearly all of the case reports were too poorly documented to permit us to make any judgments about

FDA, Dockets Management Branch  
April 7, 2003  
Page 10

the potential relationship between ephedra use and the event. . . . (pp. 220-221; emphasis added)

The Report's ultimate conclusion is that further scientific study is needed in order to make a determination as to causality.

. . . Scientific studies (not additional case reports) are necessary in order to assess the possible association between consumption of ephedra-containing dietary supplements and these serious adverse events. Given the rarity of such events, a properly designed case control study would be the appropriate next step. Such a study would need to control for caffeine consumption. (p. 221, emphasis added)

Clearly, the Proposed Rule is premised largely on the RAND report, and yet the conclusions of the RAND report do not support the Proposed Rule; indeed, the RAND report conclusions merely warrant further scientific study. Unfortunately, the actual conclusions of the RAND Report have been inaccurately summarized, in ways that do not capture the carefully-worded and precise language of the report itself. The RAND Report suggests not a Final Rule, but a final hypothesis on causality to be tested.

**Other evidence of the safety of Ephedra:**

A six-month, randomized, placebo-controlled clinical trial on ephedra, conducted by Columbia and Harvard universities (Boozer et al.) and published on April 25, 2002 in the peer-reviewed *International Journal of Obesity*, reaffirms the findings of a December 2000 comprehensive science-based risk assessment performed by Cantox Health Sciences International. The Cantox Report on Ephedra concluded that the dietary supplement ephedra is safe, under recommended conditions of use, at a total daily dosage of 90 mg, divided into smaller doses of up to 30 mg. According to John Cordaro, president and chief executive officer, The Council for Responsible Nutrition (CRN), "This newly-published study is an important aspect of the overall science base that we urge the Food and Drug Administration (FDA) to take into account as it considers establishing any regulatory action beyond those self-regulating steps already taken for ephedra by dietary supplement makers. Any regulatory policy established by FDA must be based on sound science, and our industry is committed to working with FDA to devise and implement those kinds of objective, scientifically appropriate actions."

"The publication of the Boozer et al. study in a peer-reviewed journal further confirms the validity and importance of the Cantox Report and the credible scientific evidence that shows that ephedra is a product that can be used safely and provide benefits for those for whom it is intended and when used according to label instructions," said John Hathcock, Ph.D., vice president, nutritional and regulatory science, CRN. Dr. Hathcock further pointed out that since the Cantox Report was issued, four additional studies have been reported, providing further evidence that ephedra can be safely and effectively used for weight loss under recommended conditions of use.

FDA, Dockets Management Branch  
April 7, 2003  
Page 11

The Tan Sheet of January 20, 2003 reported that a recent study did not find an association between ephedra products and stroke: "Association between the use of ephedra-containing products and increased risk for hemorrhagic stroke" was not demonstrated in Hemorrhagic Stroke Project, L.B. Morgenstern, MD, University of Texas at Houston, *et al.*, reported in the January issue of Neurology.

We also note the consistent position of a major trade association for the industry, the American Herbal Products Association ("AHPA"), an association that has been responsible and vigilant in monitoring the safety of herbs as witnessed by its publication of the Botanical Safety Handbook (1997), and its bringing safety issues as to kava kava to the attention of the FDA. We find it significant that AHPA's position, both in the Botanical Safety Handbook and in its current recommendations, revised September 2000, indicates safe use of ephedrine at the levels 25 mg per serving and 100 mg per day, which is the limitation it places on its members, when used in the context of cautionary language that it also recommends, that is similar to the warning below.

Based on the RAND Report itself, as shown above, the Proposed Rule should be withdrawn pending further scientific study, in particular a well-designed human clinical trial, as recommended by the Report. Alternatively, if the FDA does require a warning, in our view the cautionary language required by Texas Department of Health (and which currently appears on the BioLean® package) would be acceptable as a nationally-required warning for ephedra supplements:

**WARNING:** *Not for use by children under the age of 18. Do not use if you are pregnant or nursing, or if you have a family history of heart disease, thyroid disease, diabetes, high blood pressure, depression or other psychiatric condition, glaucoma, difficulty urinating, prostate enlargement, or seizure disorder, if you are using a monoamine oxidase inhibitor (MAOI) or any other prescription drug, over-the-counter drug or dietary supplement containing ephedrine, pseudoephedrine or phenylpropanolamine (ingredients found in certain allergy, asthma, cough/cold and weight control products). Exceeding recommended serving may cause serious adverse health effects including heart attack and stroke. Taking this product with other stimulants such as caffeine may cause serious adverse effects. Discontinue use and consult a physician or licensed qualified health care professional immediately if you experience rapid heartbeat, dizziness, severe headache, shortness of breath, or other similar symptoms. The maximum recommended daily dosage of ephedrine for a healthy, human adult is 100 mg, for not more than 12 weeks.*

Such a warning is arguably science-based, without being alarmist and unsubstantiated.

### **Recent athlete deaths after ephedra consumption do not support the Proposed Rule.**

It seems neither accident nor coincidence that the Proposed Rule was published in the Federal Register 11 days after the death of Oriole pitcher Steve Bechler on February 17, 2003.

FDA, Dockets Management Branch  
April 7, 2003  
Page 12

Unfortunately, in a rush to judgment, the media was too quick to point the finger of causality at ephedra supplements. However, three Ph.Ds and specialists in nutrition and training from Baylor University have provided a detailed analysis showing that several other factors were most probably the real culprits. "The Alleged Role of Ephedra in the Death of a Professional Baseball Player," by Richard B. Kreider, Ph.D., FACSM, EPC, FASEP, Mike Greenwood, Ph.D., CSCS\*D, and Lori Greenwood, Ph.D., ATC, LAT ( Exercise & Sport Nutrition Lab, Center for Exercise, Nutrition & Preventive Health Research, Baylor University), February 21, 2003. (Copy attached at Tab 3.)

In their analysis, the authors first examine the multiple facts surrounding the individual athlete and his death:

According to reports in the media, Mr. Bechler had the following risk factors for heat stroke:

a prior history of heat illness episodes while in high school—which heightens the probability of reoccurring incidents;

a family history of sudden death following exercise (his half-brother died of an aneurysm at the age of 20 after overheating from playing baseball);

a history of hypertension and liver problems;

he had not eaten solid food for a day or two, in an apparent attempt to lose weight;

he was apparently not adequately acclimatized to training in the heat and humidity of South Florida;

it appeared that he was wearing two or three layers of clothing during workouts, again, in an attempt to lose weight;

he was overweight and did not have a high enough fitness level to make it through conditioning drills; and,

he was allowed to exercise until he collapsed with a core temperature reportedly of 106° F before being removed from the field.

Many of these same factors can be applied to other high profile deaths of athletes during training or competition: "It has been extensively documented that untrained, overweight, and unacclimatized people who perform excessive exercise in heat/humidity are at great risk of heat illness and heat stroke—particularly if they have become dehydrated and are trying to lose weight quickly." *Id.* Then, examining the processes of training and heat stroke more generally, these

FDA, Dockets Management Branch  
April 7, 2003  
Page 13

experts concluded that it does not make scientific sense that ephedra was the cause of Mr. Bechler's death:

The supposed link that ephedra supplementation caused or contributed to heat stroke does not make sense from a physiological standpoint for the following reasons:

Some of Mr. Bechler's teammates claimed that he usually took three supplement capsules (1.5 servings) in the morning. According to that product's label, that would have provided 30 mg of herbal ephedra. This is one third of the dose shown in long-term clinical trials to be safe.

There is no scientific or medical evidence to indicate that ephedra/caffeine supplementation significantly increases thermal stress (increases core temperature 2-3 degrees above normal) during exercise, that it promotes dehydration, or increases the incidence of heat illness.

The thermogenic effects of ephedra and caffeine are relatively small, typically increasing resting caloric expenditure by 5-10 kcals per hour. One oral dose of ephedra/caffeine usually lasts less than 3 hours. Therefore, the total caloric (i.e., heat) load would be 15 – 30 calories in a 2-3 hour period following ingestion of one serving of an ephedra containing supplement. While this may be sufficient to promote a gradual weight loss (if one took 2-3 servings per day for 2-6 months), it would have minimal, if any, affects of [sic: effects on] core body temperature.

In contrast, athletes commonly expend 600-1,200 kcals per hour during intense exercise or 1,800 – 3,600 calories during an intense 3 hour practice. The thermal load of exercise generally increases core body temperature by 2-3 degrees when properly regulated.

The primary way heat from exercise is dissipated is through evaporation of sweat. Exercise in humid environments decreases the ability of sweat to evaporate making it more difficult to regulate body temperature. When the humidity is very high (i.e., > 70%), sweat may not fully evaporate which increases susceptibility to heat disorders. Humidity is higher in morning and evening hours. This is the primary rationale why intense exercise should be avoided during humid conditions and/or additional precautions should be employed to supervise athletes training or performing in hot/humid environments.

As with the media's unsupported "conviction" of ephedra in this case, in other athlete deaths and other serious AERs, the problem is that the conclusion that ephedra supplements must be the culprit 1) is based on incomplete data, or 2) "ignores known and obvious contributing factors."

FDA, Dockets Management Branch  
April 7, 2003  
Page 14

Id. This finding of other medical and personal factors in serious AERs associated with ephedrine supplements might well be the ultimate determination from the future scientific studies called for by the RAND Report as the logical next step.

**Long term safe use of OTC drugs argues against the Proposed Rule.**

In practical terms, evidence of the safety of ephedrine alkaloids in amounts of 25 mg per serving and 100 mg per day, and the safety of ephedrine alkaloid and caffeine combinations, can be found in the decades of safe use of bronchodilators and decongestants, sold over the counter, as OTC drugs, with much higher amounts of ephedrine alkaloids and caffeine. FDA's OTC monograph for nasal decongestant includes, as active ingredients, pseudoephedrine hydrochloride and pseudoephedrine sulfate, with an adult oral dosage of 60 mg every 4 to 6 hours not to exceed 240 mg per day. The OTC monograph for bronchodilator active ingredients has included ephedrine, ephedrine hydrochloride, and ephedrine sulfate, with an adult oral dosage of 12.5 to 25 mg every 4 hours not to exceed 150 mg per day. Actions undertaken by FDA in 1995 to remove ephedrine from the bronchodilator monograph were initiated not because of safety concerns or issues, but due to concerns related to abuse and to diversion of refined forms of the alkaloid for the manufacture of illicit drugs. 60 Fed. Reg. 39643-38647. Kreider et al. (above) also observe that "Many over-the-counter medications (e.g., cold medications) contain ephedrine alkaloids (e.g., pseudoephedrine, etc.) at higher concentrations than found in nutritional supplements containing ephedra."

The overall safe consumption of aspirin provides another significant OTC drug analogy. While more than 15,000 emergency room visits occur each year from aspirin's use, mostly through consumer misuse or abuse, no one proposes banning aspirin. There is no rational basis to deny its use to the millions who have used it for years, and have used it safely and responsibly. Similarly, especially in light of the RAND Report's mere 21 "sentinel events" out of over 16,000 AERs and only 3 serious sentinel events out of 16,000 AERs, there is no rational basis to require an extensive Warning for ephedra products. There is certainly no scientific basis for a total ban—as has been suggested by Secretary Thompson.

**Comments to this Proposed Rule may not be used to authorize other Final Rules.**

As is well known, a regulation promulgated by an administrative agency, in order to be valid, is subject to notice and comment procedures under the Administrative Procedure Act ("APA"). Thus, it is a grave concern to read in the Proposed Rule that in addition to using the Comments now being solicited to develop a Final Rule on a Warning for ephedra products, the Agency intends to use these Comments as a basis for other "action" in an open-ended manner: "the agency will move quickly to publish a final rule requiring the appropriate warning statement and to take any other action we determine to be appropriate." 68 Fed. Reg. 10417, 10419. (emphasis added). If that "other action" is in the form of a different Final Rule (e.g., with a restriction on amount of ephedrine per serving), then by law a new notice and comment period is required. If

FDA, Dockets Management Branch  
April 7, 2003  
Page 15

that other action should take the form of a complete ban on the sale of ephedrine supplements, our position is that the “significant or unreasonable risk of illness” necessary for such action has not been shown. By the plain language of its own findings and conclusions, the RAND Report does not show that ephedrine supplements present a “significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in the labeling” under 21 U.S.C. 342(f)(1)(A). Instead, this Report, which is the main foundation for the Proposed Rule, concludes simply that further scientific study is needed as to causality.

If that “other action” should take the form of a complete ban on the sale of ephedrine supplements, our position is that the concern expressed by some commentators, scientists, and members of the public certainly do not rise to the level of the “imminent hazard to public health or safety” standard of Sec. 402(f)(1)(C) of the Federal Food Drug and Cosmetic Act, which was established by Section 4 of DSHEA. An imminent hazard case in the drug context is quite instructive. Forsham v. Califano, 442 F. Supp. 203 (D.D.C. 1977) was decided under 21 U.S.C. § 355(e), whose pertinent language states that “if the Secretary . . . finds that there is an imminent hazard to the public health he may suspend the approval of such [new drug] application immediately and give the applicant prompt notice of his action and afford the applicant the opportunity for an expedited hearing under this subsection.” Secretary Califano had issued a suspension order for phenformin hydrochloride, a prescription drug designed to control blood sugar levels in patients with adult-onset diabetes. In that case, the court accepted “the validity of the Bureau of Drug’s projection of between four and 60 phenformin related deaths each month” and considering this and other factors, had to determine “whether a rational connection exists between the facts on which [the Secretary] relied and his decision to suspend” (emphasis added). Citing “the magnitude of phenformin’s risk,” the court concluded that the Secretary’s decision was not arbitrary and capricious. By contrast, as to ephedrine-containing supplements, there is neither an imminent hazard nor any hazard or risk of this level of magnitude, nor is there a “rational connection” between the current science and a ban or an amount restriction.

### **Conclusion**

Our position, then, is that the RAND Report, finding no causal relationship between ephedra consumption and serious adverse events, based on the data reviewed, calls not for a Warning, but for further scientific study. For all of the reasons above, WIN opposes the Proposed Rule as not being warranted or justified by the AERs, the existing studies, and the RAND Corporation analysis of them. In particular, WIN strongly opposes the inclusion of the following language in any required warning for ephedra-containing dietary supplements: “Heart attack, stroke, seizure, and death have been reported after consumption of ephedrine alkaloids.” and “. . . which can have potentially dangerous effects on the heart and central nervous system.” Such warnings are not supported by the available science and not needed for the general public and consumers of these products.

FDA, Dockets Management Branch  
April 7, 2003  
Page 16

Recent coverage on ephedra, like the media scare and rush to judgment over the tragic death of Orioles pitcher Steve Bechler, has unnecessarily confused and alarmed consumers who have concluded that their ephedra supplements are safe and have significant health benefits when taken as directed. In short, misinformation in the media can have serious consequences for America's true health crisis: overweight. Unfounded speculation, such as we have seen in the case of Steven Bechler, is the worst reason to reach judgments, or to promulgate regulations, about any product.

Health policy should be based on sound science and on the presumption that educated consumers will act responsibly in matters involving their own health. They have the right to make their own choices, and to consume products that are proven safe by science, and to decide based on the science, and based on the reasonable warning already required by some States, what products they should be taking. FDA regulations should also be based on science and, thus, the Proposed Rule should not become a Final Rule based on either the 1,000 AERs that have been discredited or on the 16,000 AERs analyzed by RAND. The RAND Report conclusions did not recommend a ban on ephedra products or a warning on all product labels; it simply concluded that more studies were warranted as to causality. The "imminent hazard" provision of Section 4 of DSHEA should not be invoked by Secretary Thompson for these same reasons.

Sincerely,



Susan D. Brienza

SDB:dmh

Enclosures