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May 27, 2003

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Commissioner of Food and Drugs
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Dockets Management Branch (HFA-305)
Food and Drug Administration
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Rockville, MD 20852

Re: Docket 95N-0304
Dietary Supplements Containing Ephedrine Alkaloids

Dear Commissioner McClellan:

I am writing on behalf of the Ephedra Education Council (EEC) to respond to an exchange of e-mails between you and Dr. Paul Shekelle on April 4 and April 7, 2003. Attachment A. The EEC has serious concerns about this exchange, and is particularly concerned because Dr. Shekelle's response to your e-mail represents a dramatic departure from the objective, peer-reviewed findings of the RAND Report, "Ephedra and Ephedrine for Weight Loss and Athletic Performance Enhancement: Clinical Efficacy and Side Effects." Dr. Shekelle's response also makes a statement concerning the relationship between ephedra consumption and hemorrhagic stroke that is seriously in error but that has

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the potential for significantly influencing the ongoing Food and Drug Administration (FDA) rulemaking.

Because of the serious concerns that Dr. Shekelle's recent e-mail and other written statements raise, the EEC has submitted these supplemental comments and is requesting that, if FDA intends to rely on Dr. Shekelle's e-mail or any of this other post-RAND Report writings as a basis for making regulatory decisions, FDA arrange a meeting to permit a full discussion of the scientific issues that are raised in these comments. A meeting would be the best mechanism for resolving any remaining doubt that FDA might have concerning the questions raised given that FDA has indicated its intent to make a decision in the very near future regarding the regulation of ephedra products.

I. SUMMARY OF CONCERNS

The EEC has reviewed the April 4, 2003 e-mail from FDA Commissioner Dr. Mark McClellan to the author and director of the RAND Report on ephedra, Dr. Shekelle, and Dr. Shekelle's April 7 reply, and has the following serious concerns:

- Dr. Shekelle's brief and informal e-mail response concludes that there is "much more likely than not" a causal connection between ephedra and serious adverse events, and that the likelihood of causality "certainly exceeds by a substantial margin a '50% confidence' threshold." This statement is not consistent with the peer-reviewed RAND Report, which was careful to repeatedly emphasize that even the classification of an event as a "sentinel event" "does not imply a proven cause and effect relationship," and that a case control study would be necessary to even "assess the possible association."

- Dr. Shekelle's e-mail lists four bases for his new assessment that ephedra use is "much more likely than not" a cause of death and other serious adverse events. The first three bases are brief characterizations of information that was available to and reviewed by RAND, and that was part of the peer-review process. These first three bases were never represented in the RAND Report as supporting a conclusion that ephedra is "much more likely than not" causally connected to serious adverse events, the position that Dr. Shekelle now advocates in his e-mail. The fourth basis cited in Dr. Shekelle's e-mail is a new study published in the journal Neurology[1] that was not considered by

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[1] Morgenstern LB, Viscoli CM, Kernan WN, et al. Use of *Ephedra*-containing products and risk for hemorrhagic stroke. Neurology 2003; 60: 132-135.

RAND, and therefore is apparently the most important if not the only real basis for Dr. Shekelle's personal assessment of causality.

- Dr. Shekelle's analysis of the Neurology paper is simply wrong. According to Dr. Stephen Kimmel[2], Attachment B, there are several reasons why Dr. Shekelle's analysis of the Neurology paper is incorrect – specifically, neither the data nor the authors' conclusions from the Neurology paper supports Dr. Shekelle's conclusion that "this report alone would indicate that there was a relationship between ephedra consumption and the risk of hemorrhagic stroke with 90% confidence."

- Because Dr. Shekelle was an author of the RAND Report and his e-mail refers throughout to "we" rather than "I," his e-mail creates a serious concern that FDA and others will interpret Dr. Shekelle's e-mail as an extension or interpretation of the RAND Report, which was peer-reviewed by over 30 reviewers, when in fact the e-mail is at best very brief and poorly-drafted, and includes an erroneous interpretation of a published paper that has little relevance to ephedra safety other than to confirm what we already know – even though not a single serious adverse event has occurred in any clinical trial to date, further study ought to be conducted to determine whether there is any possible connection between ephedra consumption and increased risk of serious adverse events.

- Finally, Dr. Shekelle and his colleagues have recently published an article titled "Preponderance of the Evidence," the cover article for the Spring 2003 RAND Review, that implicitly calls for FDA to ban ephedra and includes emotional pictures of the grieving relatives of Steve Bechler and Sean Riggins, with misleading captions that make it clear that the authors have determined to use emotion and the press to make their case, regardless of the facts to the contrary. We are submitting new information from an expert cardiac pathologist from The Johns Hopkins University, Dr. Grover Hutchins, on the tragic death of Sean Riggins that shows that this widely publicized case, in the expert opinion of Dr. Hutchins, most likely had nothing to do with ephedra. Regardless, neither the use of emotive pictures and misleading captions in this article, nor the conclusions of the article, can be reconciled with the stated goal of "objectivity" or the conclusions of the RAND Report.

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[2] Letter from Stephen E. Kimmel to A. Wes Siegner, Hyman, Phelps & McNamara (May 2, 2003).

II. THE OBJECTIVE FINDINGS OF THE RAND REPORT SUPPPORT CONTINUED MARKETING OF EPHEDRA, WHILE THE SUBJECTIVE CASE REPORTS RAISE "POTENTIAL" SAFETY ISSUES THAT DESERVE FURTHER STUDY

The RAND Report carefully and appropriately separates the conclusions that are based on the analysis of objective, "hypothesis-testing" clinical data, from the conclusions that are based on the analysis of subjective, "hypothesis-generating" information contained in case reports. The former conclusions are a valid basis for regulatory decisionmaking, while the latter are not.

The conclusions of the RAND Report that are based on objective clinical data are as follows:

- short-term use of ephedra leads to short-term weight loss, RAND Report pages vi, xii, 73-77, and 201-02 (this conclusion, and the likelihood of long-term benefits, is bolstered by a more recent 1-year study that RAND did not consider – see Comments of Dr. Greenway[3], previously submitted by the EEC on April 7, 2003, Attachment C – "In conclusion . . . ephedra/caffeine appear to be at least as efficacious for weight loss as the presently available prescription drugs approved for that purpose.");

- the use of ephedra is associated with an increased risk of mild to moderate side effects, RAND Report pages vii, xvi-xvii, 79 and 202; and

- "[n]o serious adverse events (e.g., death, myocardial infarction, stroke, etc.) were reported in the 52 clinical trials that reported sample sizes." RAND Report page 79.

According to the experts in weight loss such as Dr. Greenway who are best situated because of their training to assess the relative risks and benefits of ephedra products, the appropriate conclusion from the "objective" data is that properly formulated ephedra supplements have significant health benefits that far outweigh the relatively minor risks. See Comments of Dr. Greenway.

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[3] Frank Greenway, Response to RAND Report on ephedra for weight loss 3 (Mar. 21, 2003).

In contrast to the objective findings based on clinical data, RAND stressed the subjective nature of analyzing case reports and that causality cannot be "assumed or proven" based on such reports.

In its assessment of case reports of adverse events, RAND was careful to stress the subjective nature of such reviews, the significant disagreement between reviewers of the same reports, and the inability to use such reports as "proof" of causality. RAND stated that the "peer review comments demonstrate that case report reviews involve considerably more subjective interpretation than do reviews of randomized trials. **Because our goal in this evidence report is to report the evidence as objectively as possible, we ceased to assign assessments of causality to the case reports.**" RAND Report page 30 (emphasis added). Instead, RAND defined certain events as "sentinel" events, but cautioned that "[c]lassification as a sentinel event does not imply a proven cause and effect relationship." Id. page xvii.

RAND itself had difficulty following its own criteria for the designation of reports of adverse events associated with ephedra as "sentinel events," a problem that provides strong support for RAND's cautions about drawing any conclusions from analyses of such case reports. RAND identified two deaths that occurred in conjunction with ephedra consumption as "sentinel events." RAND Report pages 81-82. However, these events were apparently not reviewed by an expert cardiac pathologist. Dr. Grover Hutchins, a Professor of Pathology at The Johns Hopkins University, is such an expert. He has already submitted comments to FDA revealing that in one of the two deaths described as a "sentinel event," RAND failed to include information that the heart from the decedent was studied by the Armed Forces Institute of Pathology and showed "active myocarditis," a condition "well known to cause sudden death" that is not consistent with ephedra or ephedrine consumption. Comments of Dr. Grover Hutchins[4], Attachment D.

In the second sentinel case, RAND omitted information contained in the report consistent with asthma as the cause of death. Comments of Dr. Grover Hutchins page 1. Therefore, both cases are inconsistent with RAND's own definition for sentinel events, which requires that "[a]lternative explanations where investigated and excluded with

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[4] Grover M. Hutchins, Comment on FDA Docket No. 95N-0304 "Dietary Supplements Containing Ephedrine Alkaloids: Reopening of Comment Period" 1 (Apr. 7, 2003).

reasonable certainty." RAND Report page 30. In Dr. Grover Hutchins' opinion, "[t]hese two cases do not appear to warrant any interpretation beyond the fact that the individuals had been exposed to ephedrine alkaloids, but died from conditions known to cause sudden death." Comments of Dr. Grover Hutchins page 1.

Consistent with the RAND Report's repeated cautions that "a causal relationship between ephedra or ephedrine use and these [reports of adverse] events cannot be assumed or proven," RAND Report page xvi, the Report concludes that "[s]cientific 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." RAND Report page 203 (emphasis added).

In summary, RAND found that the subjective analysis of the evidence from the case reports created a question, or generated a hypothesis, that a causal connection between ephedra and serious events might exist. RAND was appropriately very careful not to estimate the "probability," or "level of certainty" as asked by Commissioner McClellan, of a causal relationship, because objective data on which such an estimate could be based do not exist. In fact, to quote RAND's summary of its review of the only objective data that relate to the potential association of ephedra with serious adverse events, "[n]o serious adverse events (e.g., death, myocardial infarction, stroke, etc.) were reported in the 52 clinical trials that reported sample sizes." RAND Report page 79. RAND concluded that more scientific studies, not additional case reports, would be needed to confirm the findings of these already-existing studies. RAND Report page 203.

III. DR. SHEKELLE'S E-MAIL AND OTHER POST-RAND WRITINGS ARE NOT CONSISTENT WITH THE RAND REPORT, MISINTERPRET THE NEUROLOGY ARTICLE, AND ABANDON THE GOAL OF OBJECTIVITY IN THEIR USE OF EMOTIONAL PHOTOGRAPHS AND MISLEADING CAPTIONS

The RAND Report is a peer-reviewed and published report. The peer-review process included over 30 reviewers. Dr. Shekelle's e-mail is of course not peer reviewed or published, and is on its face hurriedly and poorly written, as is often typical with e-mail correspondence. For this reason alone, the e-mail does not warrant serious consideration.

More important, Dr. Shekelle has shown through his e-mail and other written statements subsequent to the publication of the RAND Report that he and his colleagues who wrote the Report have abandoned the stated goal of the RAND Report – that goal was

"to report the evidence as objectively as possible," and adherence to that goal led these same scientist to the decision, after peer review, to "cease[] to assign assessments of causality to the case reports." RAND Report page 30.

FDA should be careful to separate the objective findings of RAND from the speculative, erroneous and personal views that Dr. Shekelle has offered to FDA and the public through his April 7 e-mail and other written statements released after the RAND Report. Dr. Shekelle's personal speculation and erroneous assessment of the Neurology paper is not supported by or consistent with the objective scientific data and therefore is not a valid basis for issuing a regulation.

Dr. Shekelle's first departure from the RAND Report's stated goal of objectivity occurred on the same day that the Report was published, February 28, 2003. In a News Release issued by RAND, Dr. Shekelle was quoted as stating that, "[w]ith regard to catastrophic events, [the RAND Report] findings are a strong signal that there is a link between use of ephedra or ephedrine and the occurrence of death, heart attack, stroke, seizures and serious psychiatric symptoms," and that "[i]t is more likely than not that there is a relationship, although the available evidence falls short of the conventional level of scientific proof."[5] Attachment E.

Approximately one month later, Dr. Shekelle through his April 7, 2003 e-mail elevated his assessment of the causal link between ephedra, death and other serious events from "more likely than not" to "much more likely than not." Attachment A. The only apparent reason for this elevation was Dr. Shekelle's review and comment on the Neurology paper, which in his assessment "indicates that there is a relationship between ephedra consumption and the risk of hemorrhagic stroke with 90% confidence." This statement is alarming both for its inaccuracy and its inconsistency with the peer-reviewed findings of the authors.

Dr. Kimmel, a Professor at the University of Pennsylvania, is an expert in cardiology, epidemiology and the statistical interpretation of epidemiological studies like the study addressed in the Neurology paper. Attachment F (Dr. Kimmel's curriculum vitae). According to Dr. Kimmel, Dr. Shekelle's assessment of the data in the Neurology

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[5] Press Release, RAND Corp., RAND study raises safety concerns about Ephedra and Ephedrine (Feb. 28, 2003).

paper is incorrect. In Dr. Kimmel's view, "it is reasonable to interpret the paper in Neurology as a 'hypothesis-strengthening' study. However, the level of certainty that Ephedra could cause hemorrhagic stroke should rely on all considerations of the data, and certainly can not be quantified by the use of a p-value or confidence interval" as Dr. Shekelle has done in his e-mail. Letter from Dr. Kimmel to W. Siegner page 2.

The statements of the authors in the peer-reviewed Neurology paper that Dr. Shekelle seeks to interpret in his e-mail also fail to support Dr. Shekelle's finding that a relationship between ephedra and hemorrhagic stroke exists with "90% confidence." The peer-reviewed conclusion as stated in the abstract for this article is that "Ephedra is not associated with increased risk for hemorrhagic stroke, except possibly at higher doses." Morgenstern et al., 132. Consistent with Dr. Kimmel's assessment that these data do not lend themselves to quantifying the relationship between ephedra and stroke as Dr. Shekelle has done, the paper's authors make no attempt to so quantify the relationship between ephedra use and hemorrhagic stroke.

In sum, Dr. Shekelle's e-mail should be ignored for three reasons – (1) the e-mail is simply wrong on the science, (2) the attempt to quantify the level of confidence of any relationship between ephedra and serious events is admittedly speculative, and (3) the e-mail is inconsistent with the objective and even the subjective findings of the RAND Report.

RAND's recent publication of Dr. Shekelle's article "Preponderance of the Evidence" raises serious questions of personal bias against ephedra as well as the law that regulates dietary supplements.[6] Attachment G. In this case Dr. Shekelle and his colleagues have used the emotional impact of pictures of understandably grieving relatives to help make a case for the danger of ephedra without making appropriate inquiry as to the facts. Further, Dr. Shekelle and his colleagues incorrectly interpret the Dietary Supplement Health and Education Act (DSHEA) and vastly oversimplify this law, asserting that under

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6 Paul G. Shekelle et al., Preponderance of Evidence: Judging What To Do About Ephedra (2003).

DSHEA "manufacturers of dietary supplements need not show evidence of the efficacy or safety of the products prior to marketing them."[7]

The article's main message is that, while Dr. Shekelle and his colleagues could not prove that ephedra causes death and other serious adverse events, there is no question in these individuals minds that ephedra has and does cause such events, despite the RAND Report's emphasis on objectivity and the inability to draw conclusions of causality from the case reports. According to Dr. Shekelle, "we compiled enough evidence to reach fairly confident conclusions. Our efforts could serve as an example of how policymakers and researchers can help to keep the public safe despite the absence of incontrovertible scientific proof of danger." Shekelle et al., supra note 6, at 1.

To drive home the authors' real message behind the this statement, that ephedra should in their view be banned, the text quoted above is followed by emotion-laden pictures of Pat Bechler, the mother the recently deceased Baltimore Orioles pitcher, crying at a press conference, and of Kevin Riggins, described in the RAND article as "the father of Sean Riggins, a 16-year-old high school football player who died last fall after taking ephedra." The caption for this last picture also points out that Mr. Riggins is pictured speaking at the Illinois State Capitol building, and that "[o]n March 20, the Illinois state senate voted unanimously to ban the sale of ephedra products." Id. at 2.

The view of Dr. Shekelle and his colleagues is clear – ephedra is responsible for the deaths of Steve Bechler and Sean Riggins, regardless of the facts, and ephedra should be banned because of their subjective belief in a causal link, regardless of the objective findings of the RAND Report. But the facts, had Dr. Shekelle cared to evaluate them, point in a different direction. Dr. Shekelle does not mention any independent evaluation of the facts relating to the Riggins or Bechler cases, and it is clear that he did not conduct any such review. Had he contacted the EEC or other sources of information on ephedra, he would have learned significant facts that might have caused him to rethink his article, which plays to the emotional side of the ephedra debate rather than to objective science.

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[7] For a more thorough treatment of how DSHEA regulates dietary supplements and supplies the needed authority for FDA to assure the safety and benefits of these products, see Stephen H. McNamara & A. Wes Siegner, FDA has Substantial and Sufficient Authority to Regulate Dietary Supplements. 57 Food & Drug L.J. 15 (2002).

First, he would have learned that the only cardiac pathologist to review the Riggins case has determined, based on a review of the available information, including tissue slides, that "to a reasonable degree of medical certainty" Sean Riggins died as a result of a "severe inflammatory and necrotizing process in his heart that was ongoing over several days prior to his death," not from consuming ephedra.[8] Attachment H. The EEC wholeheartedly agrees with FDA's opinion that the product that Sean Riggins apparently consumed, Yellow Jackets, is not appropriate as a dietary supplement and that no ephedra products should be sold to minors. Nonetheless, Dr. Shekelle's attempt to use this death as support for his new position that ephedra should be banned is in direct conflict with the stated goals of the entire RAND review of ephedra.

Dr. Shekelle's use of the picture of an understandably grief-stricken Mrs. Bechler crying over the sudden and tragic death of her son is even more inappropriate. Although the coroner in the Bechler case was swayed to believe ephedra was implicated in Mr. Bechler's death, more knowledgeable experts have disagreed, and in this case the reasons for their disagreement were readily available on the internet.[9] Dr. Richard Krieder and his colleagues from Baylor University's Center for Exercise, Nutrition, & Preventive Health Research have publicly disagreed with the local coroner and provided detailed reasons for their conclusion that "[t]he supposed link that ephedra supplementation caused or contributed to heat stroke does not make sense from a physiological standpoint." Attachment I.

While the recent writings of Dr. Shekelle and his colleagues are hard to explain, there is no doubt that Dr. Shekelle and his colleagues are no longer engaged in objective scientific discourse. They have mischaracterized and misused case reports for emotional impact, they have assigned various levels of probability to the relationship between ephedra and serious adverse events in conflict with the stated goals of the RAND Report, and they have erroneously interpreted published data.

Their recent writings are based in part on admittedly subjective case reports and in part on incorrect analysis, and do not provide a scientific basis for rulemaking for ephedra

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8 Letter from Grover M. Hutchins to A. Wes Siegner, Hyman, Phelps & McNamara 2 (Jan. 11, 2003).

9 See http://www3.baylor.edu/HHPR/ESNL/EphedraStatement.htm.

dietary supplements. In contrast, the objective findings of the RAND Report do provide scientific support for the regulation and further scientific review of ephedra, including FDA's recent letters to companies marketing ephedra for performance enhancement, national warning labels, and further clinical study to assess the "possibility" of an association between ephedra and serious adverse events.

IV. CONCLUSION

Researchers and experts in weight loss agree that the findings of the RAND Report are consistent with what they have already determined through clinical research – that properly formulated ephedra products are safe when responsibly marketed and consumed and are one of the few very important options for those millions of Americans who need to lose weight. Banning ephedra based on what amounts to rumor and innuendo would be a serious public health mistake, even if these rumors are furthered by RAND scientists.

The recent e-mail and other written communications of Dr. Shekelle and his colleagues should be disregarded because they are a dramatic departure from RAND's stated goal of objectivity in the ephedra review. The conclusions of the e-mail should also be rejected because they present an incorrect scientific analysis of the Neurology paper.

The EEC is grateful for the opportunity to participate in this rulemaking and urges FDA to issue a final rule providing a national warning label for ephedra products and addressing the other action items identified by RAND in the very near future.

Sincerely,

A. Wes Siegner, Jr.

AWSjr/rh