DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

AUG 18 2003

Robert Ullman, Esquire
Bass & Ullman, P.C.
Counsellors at Law
747 Third Avenue
New York, New York 10017

Re: Docket No. 94P-0215
Comment No. PSA1

Dear Mr. Ullman:

This letter concerns your July 27, 1994 citizen petition on behalf of American Vitamin Products, Inc. (AVPI) to request that the Food and Drug Administration (FDA) refrain from taking any action relating to a June 23, 1994 Warning Letter (94-NWK-54) issued to AVPI, or that FDA refrain from engaging in any other form of administrative action directed to AVPI's product, "Nite-Nite" during the pendency of FDA's determination of two citizen petitions to amend the monograph for over-the-counter (OTC) nighttime sleep-aid drug products to add valerian as an active ingredient. One citizen petition was from your firm; the other was filed on behalf of the European-American Phytomedicines Coalition (EAPC). Your firm's petition requesting stay of action described above was filed in the Dockets Management Branch under Docket No. 94P-0215 and was logged as Comment No. PSA1 as stated in our letter dated July 28, 1994.

Your firm's petition to amend the OTC nighttime sleep-aid monograph to add valerian as an active ingredient did not include safety or effectiveness data. We sent your firm a letter dated April 19, 2002, filed in the Dockets Management Branch under the docket number above and coded LET5, which stated that we do not intend to take action on your firm's citizen petition. We never received any response to that letter.

In your citizen petition, you referred to the petition submitted by EAPC on June 8, 1994. FDA responded to that petition on April 7, 2003 (copy enclosed) and stated that we cannot generally recognize valerian as safe and effective for OTC use as a nighttime sleep-aid at this time. We suggested that if EAPC wants to pursue inclusion of valerian in the OTC drug monograph system, it should submit a Time and Extent Application (TEA). Accordingly, both petitions have been addressed, and your request for a stay of action is now considered moot. However, the agency reserves the right to take regulatory action as it deems necessary.

Any comment you wish to make on the above information should be submitted in three copies, identified with the docket and comment numbers shown at the beginning of this letter, to the Dockets Management Branch (HFA-305), Food and Drug Administration, Room 1061, 5630 Fishers Lane, Rockville, MD 20852.

94P-0215

ANS 1

We hope this information will be helpful.

Sincerely yours,

John M. Taylor, III
Associate Commissioner
for Regulatory Affairs

Enclosure

DEPARTMENT OF HEALTH & HUMAN SERVICES

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APR 7 2003

Robert G. Pinco, Esquire
Counsel to European-American
Phytomedicines Coalition
Akin, Gump, Strauss, Hauer & Feld, L.L.P.
1333 New Hampshire Avenue, N.W.
Suite 400
Washington, DC 20036

Re: Docket No. 94P-0215
Comments No. CP1, SUP1, LET2

Dear Mr. Pinco:

This letter concerns your June 8, 1994 citizen petition and March 17, 1995 supplement submitted on behalf of the European-American Phytomedicines Coalition (EAPC) to amend the final monograph for OTC nighttime sleep-aid drug products to include valerian as an active ingredient. The petition and supplement were filed in the Dockets Management Branch under Docket No. 94P-0215 and are logged as Comments No. CP1 and SUP1, respectively.

The petition contains published and unpublished reports of clinical trials as well as discussions of chemistry, toxicology, and pharmacology in support of the safety and effectiveness of valerian as an OTC nighttime sleep-aid. The petition mentions that valerian has been marketed in many European countries as a nonprescription sleep-aid for decades and that Eli Lilly and Company distributed a tincture of valerian in the United States until 1985. The supplement contains information on valerian compositions and sources used in six studies and was submitted by Mark M. Yacura, Esquire, of your firm in response to a telephone request from Michael Kennedy of the Division of OTC Drug Evaluation.

We obtained from Eli Lilly and Company a copy of labeling of its formerly marketed product, Tincture Valerian, and a copy of a 1962 Physician's Desk Reference page (Ref. 1). The product was labeled for use as a sedative in minor nervous disorders with a dosing of one teaspoon three times a day. Nothing in the product's labeling indicates use as a nighttime sleep-aid. Therefore, we conclude that Lilly's Tincture Valerian was marketed in the United States as a daytime sedative, but not as a nighttime sleep-aid. We are unaware of the marketing of any valerian drug products as an OTC nighttime sleep-aid in the United States.

Since your petition was submitted, the agency has informed you and other interested parties that it was developing a process by which drugs without any marketing experience in the United States could become eligible for consideration in the agency's OTC drug review. This process is described in a final rule entitled "Additional Criteria and Procedures for Classifying Over-the-Counter Drugs as Generally Recognized as Safe and Effective and Not Misbranded," which was published in the FEDERAL REGISTER of January 23, 2002 (67 FR 3060). We previously provided you a copy of this final rule.

The final rule requires the submission of a Time and Extent Application (TEA) (see § 330.14(c)) to request consideration under the OTC drug review. The required information and format for a TEA are set out in the final rule (see § 330.14(c)). Three copies of the TEA are to be submitted to the Central Document Room (see § 330.14(d)).

If your client wishes to pursue inclusion of valerian in the OTC drug monograph system, please submit a TEA in the required format. We believe that valerian should meet the eligibility criteria to allow the agency to proceed with a notice of eligibility (see § 330.14(e)).

The agency reviewed the EAPC data and, as discussed below, has determined that the submitted data at this time do not demonstrate valerian to be safe and effective as a nighttime sleep-aid. Should your client submit a TEA and the agency proceeds with a notice of eligibility, these are items that your client would want to address in the subsequent safety and effectiveness data submission (see § 330.14(e) and (f)).

Safety

Your petition states that the agency's approval of *Valeriana officinalis L.* as a direct food additive under 21 CFR 172.510 is indicative of valerian's safety. However, valerian's approval as a food additive is as a flavoring agent where it may appear in relatively minute amounts not exceeding 69 parts per million (Ref. 2). Those amounts are relatively insignificant compared to the amounts proposed for use as a nighttime sleep-aid. The agency notes that Houghton (Ref. 3) states that alkylation of the epoxide group of valepotriates and their cytotoxicity in valerian give cause for concern. Lindahl and Lindwall (Ref. 4) report that the valepotriate portion of valerian is cytotoxic, but not the sesquiterpene portion of valerian. The agency will need additional information addressing these safety factors for *Valeriana officinalis*.

Your client's petition states that valerian's mechanism of action appears to be the blocking of an enzyme that metabolizes gamma amino butyric acid (GABA) in the brain. If that mechanism of action is correct, the local level of GABA will increase, and the ultimate effect may resemble that of the benzodiazepine drugs. That class of drugs has been associated with addiction and withdrawal from known dependence. The agency needs additional data showing that such concerns from using valerian are not warranted to evaluate its safety as an OTC nighttime sleep-aid.

In addition, your petition acknowledges side effects from continual use of valerian, e.g., headache, excitability, uneasiness, insomnia, and disturbance of cardiac activity. An overdose can cause central paralysis, bradycardia, and decreased gastrointestinal motility. The agency has concerns about these factors with regard to safety. Adequate data addressing these concerns are necessary before this ingredient can be included in the monograph. We would need adverse event reporting information from the foreign countries where this ingredient is marketed as an OTC nighttime sleep-aid. We are also interested in seeing how valerian products marketed in foreign countries address these side effects in their labeling.

Further, valerian is a mixture of easily hydrolyzable esters and highly reactive epoxides, of which the active moiety is not identified. It contains volatile essential oils, iridoids (valepotriates), and alkaloids. The volatile essential oils and iridoids show the greatest quantitative and qualitative variability between species and genera and even within the same species. A straightforward test measuring some of the fingerprint chemicals, e.g., valepotriates, valerenic acid, valerenal, and selected essential oils, should be designed and an internal standard developed. The latter steps should be done in conjunction with the United States Pharmacopeial Convention to determine the chemical standards of valerian. These steps are not listed in the current National Formulary 21 monograph for valerian.

Because the water extract of *Valeriana officinalis* has been used in certain studies submitted in support of monograph status, the issues of whether valerian in the water extract changes chemically from that of its powdered form and the stability of the water extract need to be determined.

For reasons discussed above, the agency cannot generally recognize valerian as safe for OTC use at this time.

Effectiveness

Kamm-Kohl, et al. (Ref. 5) performed a double-blind study of Valdispert®, a tablet dosage form containing 45 mg dried valerian root extract compared to a placebo in 80 subjects between 59 and 79 years of age. Each subject received a one-time daily dose of 6 sugar-coated Valdispert® tablets (total of 270 mg valerian) or a placebo. The improvement ratings were reported as point differences in a 5-point scale of 0 (absent), 1, 2, 3, and 4 (very severe). Ratings were evaluated for difficulty in falling asleep (sleep latency) and problems in remaining asleep for a specific period of time as defined by the investigator (quality of sleep).

Two subjects (one in each group) dropped out during the study. All 39 subjects in each group exhibited problems falling asleep. After 14 days of treatment with Valdispert®, sleep latency improved by two points in 8 subjects, one point in 25 subjects, was unchanged in 5 subjects, and worsened by one point in 1 subject. In the placebo group, 10 subjects improved by one point, no change was observed in 28 subjects, and 1 subject worsened by one point.

Although the time to fall asleep was not measured, a time frame of 30 minutes or less, indicating efficacy, may be inferred from change in the 5-point scale (1.02 on Valdispert® and 0.22 on placebo). These figures demonstrate statistical significance ($p<0.001$, x^2-test) of improved versus no change or worse between the two groups.

All 39 subjects in each group reported poor sleep quality at baseline. After 14 days of treatment with Valdispert®, 24 subjects improved by one point, 5 subjects improved by two points, and 10 subjects were unchanged. In the placebo group, 12 subjects improved by one point, 1 subject improved by two points, and 26 subjects were unchanged. The difference between the two test groups is statistically significant ($p<0.001$, x^2-test).

The study demonstrates effectiveness of 270 mg valerian root extract derived from *Valeriana officinalis L.* as a nighttime sleep-aid by reducing sleep latency and by improving quality of sleep.

Many of the other studies submitted are supportive of valerian as a nighttime sleep-aid, but do not clearly demonstrate effectiveness for the following reasons:

(1) Crossover designs did not include appropriate washout periods (Refs. 6 and 7).

(2) No placebo control (Refs. 8 and 9).
(3) Trials were not adequately powered to evaluate the effect of valerian (Refs. 10 and 11).

(4) Results were equivocal (Ref. 12).

(5) Some studies include combinations of ingredients and do not allow the evaluation of valerian alone (Refs. 4, 11, and 13).

(6) The supplement to your client's petition points out that more detailed information on the composition of Valeriana Natt is not available to add to the study report (Ref. 4).

(7) The report does not indicate the doses of valerian root extract given to the subjects (Ref. 2).

Any comment you wish to make on the above information should be submitted in three copies, identified with the docket and comment numbers shown at the beginning of this letter, to the Dockets Management Branch (HFA-305), Food and Drug Administration, Room 1061, 5630 Fishers Lane, Rockville, MD 20852. We believe it would be more appropriate for any comments in response to our evaluation of the safety and effectiveness data to be included in a future TEA submission.

We hope this information will be helpful.

Sincerely yours,

John M. Taylor, III
Associate Commissioner
for Regulatory Affairs

Enclosure (list of references)

References

(1) Letter dated February 10, 1995 from A. E. Norris, Eli Lilly and Company, to M. D. Kennedy, FDA, coded LET1, Docket No. 94P-0215, Dockets Management Branch.

(2) Hall, R. L., and B. L. Oser, "Recent Progress in the Consideration of Flavoring Ingredients under the Food Additives Amendment, III. GRAS Substances," Food Technology, p. 196, February 1965.

(3) Houghton, P., "The Biological Activity of Valerian and Related Plants," Journal of Ethnopharmacology, 22:121-142, 1988.

(4) Lindahl, O., and L. Lindwall, "Double Blind Study of a Valerian Preparation," Pharmacology, Biochemistry & Behavior, 32:1065-1066, 1989.

(5) Kamm-Kohl, A. V., et al., "Modern Valerian Therapy of Nervous Disorders in Elderly Patients," Medwelt, 35:1450-1454, 1984.

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(8) Schmidt-Voigt, J., "Treatment of Nervous Sleep Disturbances and Inner Restlessness with a Purely Herbal Sedative," Therapiewoche, 36:663-667, 1986.

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(10) Leathwood, P. D., and F. Chauffard, "Aqueous Extract of Valerian Reduces Latency to Fall Asleep in Man," Planta Medica, (2):144-148, 1985.

(11) Muller-Limmroth, W., and W. Ehrenstein, "Investigations of the Effect of Seda-Kneipp® on Sleep in People with Sleeping Disturbances," Medizinische Klinik, 72(25): 1119-1125, 1977.

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(13) Drebing, M., et al., "Insomnia: Are Valerian/Balm Combinations of Equal Value to Benzodiazepine?," Therapiewoche, 42:726-736, 1992.