DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: May 8, 2001

3752 '01 MAY 10 P3:12

From: Director, Division of Standards and Labeling Regulations, Office of Nutritional Products, Labeling and Dietary Supplements, HFS-820

Subject: 75-Day Premarket Notification for New Dietary Ingredients

To: Dockets Management Branch, HFA-305

New Dietary Ingredient:	SAM-e
Firm:	Pharmavite Corporation
Date Received by FDA:	February 8, 2001
90-Day Date:	May 9, 2001

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification for the aforementioned new dietary ingredient should be placed on pubic display in docket number 95S-0316 **after** May 9, 2001.

Felicia B. Satchell

Felicia B. Satchell

95S-0316

RPT92

APR 2 2001

3753 '01 MAY 10 P3:13

David Kropp
Acting Director
Regulatory and Consumer Affairs
Pharmavite Corporation
Post Office Box 9606
Mission Hills, California 91346-9606

Dear Mr. Kropp:

This is to inform you that the notification dated February 6, 2001, you submitted pursuant to 21 U.S.C. 350b(a)(2) was received and filed by the Food and Drug Administration (FDA) on February 8, 2001. Your notification concerns the substance "S-adenosylmethionine (SAM-e)" that you assert is a new dietary ingredient.

In accordance with 21 C.F.R. § 190.6(c), FDA must acknowledge its receipt of a notification for a new dietary ingredient. For 75 days after the filing date (i.e., after April 24, 2001), you must not introduce or deliver for introduction into interstate commerce any dietary supplement that contains "SAM-e."

Please note that the acceptance of this notification for filing is a procedural matter and thus, does not constitute a finding by FDA that the new dietary ingredient or the dietary supplement that contains the new dietary ingredient is safe or is not adulterated under 21 U.S.C. 342. As another procedural matter, your notification will be kept confidential for 90 days after the filing date. After May 9, 2001, your notification will be placed on public display at FDA's Docket Management Branch in docket number 95S-0316. However, any information that is trade secret or otherwise commercial confidential information in the notification will not be disclosed to the public.

Please contact us at (202) 205-4168, if you have any questions concerning this matter.

Sincerely yours,

Rhonda R. Kane

Rhonda R. Kane, M.S., R.D.
Consumer Safety Officer
Dietary Supplements Team
Division of Standards
and Labeling Regulations
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety
and Applied Nutrition

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service

Food and Drug Administration
Washington, DC

3754 '01 MAY 10 P3:13

APR 24 2001

VIA FAX AND MAIL

Mr. David Kropp
Acting Director
Regulatory and Consumer Affairs
Pharmavite Corporation
Post Office Box 9696
Mission Hills, California 91346-9606

Dear Mr. Kropp:

This is in response to your letter to the Food and Drug Administration (FDA) dated February 6, 2001, making a submission of a new dietary ingredient pursuant to 21 U.S.C. 350b(a)(2) (section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)). Your letter notified FDA of your intent to market a dietary supplement product containing the new dietary ingredient called S-adenosylmethionine (SAM-e).

21 U.S.C. 350b(a)(2) requires that a manufacturer or distributor of a dietary supplement that contains a new dietary ingredient submit certain information to FDA at least 75 days before the dietary ingredient is introduced or delivered for introduction into commerce. This information must include the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under section 350b(a)(2), there must be a history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the dietary supplement is deemed to be adulterated under 21 U.S.C. 342(f)(1)(B) because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness and injury.

We have carefully considered the information in your notification concerning whether a dietary supplement containing SAM-e will reasonably be expected to be safe under the conditions of use recommended or suggested in its labeling. The agency has significant concerns about the potential for consumers who have certain diseases or conditions to experience serious adverse effects with the use of SAM-e. For example, the scientific

literature[1] -- that you provided in your notification -- suggests that persons who have a bipolar major affective disorder (manic-depressive disease) may experience mood switching from depression to hypomania when supplemented with SAM-e. You fail to explain in your notification how you were able to conclude that a dietary supplement containing SAM-e would be reasonably expected to be safe to persons who have this disorder in light of the information concerning the potential for an increased risk of serious adverse effects. The scientific literature also suggests that SAM-e displays neuropsychiatric properties. However, your notification does not address the potential serious risks that might exist for persons already taking drugs or other products with similar pharmacological effects, if any, that would result from the use of a dietary supplement containing SAM-e at your recommended intake of up to 1600 milligrams per day. Additional journal articles[2,3,4] in your notification stated that taking supplements of SAM-e at daily levels ranging from 400 to 1200 mg (which are lower than the daily level suggested for your SAM-e supplement) may cause unwanted side effects (e.g., heartburn, nausea, and other gastrointestinal symptoms).

Under 21 U.S.C. 321(n) and 343(a) (sections 201(n) and 403(a) of the Act), an article is misbranded if its labeling fails to reveal material facts about the consequences of using the product under its labeled conditions of use. FDA has interpreted these sections to require warning label statements where an ingredient has presented special health risks to consumers under certain conditions of use. Therefore, failure to reveal on the labeling information concerning serious adverse effects attendant to the use of a dietary supplement under conditions of use (e.g., for those who have particular medical condition or are taking certain medications) when the scientific evidence indicates that there are potential health risks may render the dietary supplement misbranded under 21 U.S.C. 321(n) and 343(a) (sections 201(n) and 403(a) of the Act).

One of the "B" list 2001 priorities for the Center for Food Safety and Applied Nutrition, FDA is to develop guidance or regulations on safety information and material fact labeling for dietary supplements. Work is underway to accomplish this goal. However, the absence of such guidance or regulations at this time does not dismiss manufacturers and distributors from their responsibility to ensure that the dietary supplements they market are safe and properly labeled.

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[1] Baldessarini, Ross J.: Neuropharmacology of S-Adenosyl-L—Methionine, *The American Journal of Medicine*, 83(suppl 5A):95-103, November 20, 1987.

[2] König, Benno: A Long-Term (Two Years) Clinical Trial with S-Adenosylmethionine for the Treatment of Osteoarthritis, *The American Journal of Medicine*, 83(suppl 54):89-94, November 20, 1987.

[3] Caruso, Innocenzo and Pietrogrande, Vincenzo: Italian Double-Blind Multicenter Study Comparing S-Adenosylmethionine, Naproxen, and Placebo in the Treatment of Degenerative Joint Disease, *The American Journal of Medicine*, 83(suppl 54):66-71, November 20, 1987.

[4] Berger, Rainer and Nowak, Horst: A New Medical Approach to the Treatment of Asteoarthritis: Report of an Open Phase IV Study with Ademethionine (Gumbaral), *The American Journal of Medicine*, 83(suppl 54):84-88, November 20, 1987.

If you have any questions concerning this matter, please contact me at (202) 205-4168.

Sincerely yours,

Ellen M. Anderson
for Felicia B. Satchell

Felicia B. Satchell
Director
Division of Standards
and Labeling Regulations
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety
and Applied Nutrition

PHARMAVITE

3755 '01 MAY 10 P3:13

May 8, 2001

Felicia B. Satchell, Director
Division of Standards and
Labeling Regulations
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C St. SW
Washington, DC 20204

Dear Ms. Satchell:

This replies to your letter of April 24, 2001 responding to our February 6, 2001 notification under Section 413(a)(2) as to the new dietary ingredient S-adenosylmethionine (SAM-e).

We understand your concern that the conditions of use set out in our notification did not specifically address potential risks of serious adverse effects to persons with bipolar (manic) depression and to persons taking antidepressant drugs which are suggested by the scientific literature including the Baldessarini article which we submitted in the notification.

Please be advised that products containing SAM-e distributed pursuant to this notice will contain clear label statements cautioning potential users that:

> "If you are taking prescription antidepressant medications, consult your physician before using this product. Individuals with bipolar (manic) depression should not use this product unless under medical supervision."

We note that these statements are consistent with the statement on product safety made by the submitter of the most recent notification for SAM-e accepted by the agency prior to this submission (See RPT 66).

We trust this information adequately addresses the agency's concerns.

Sincerely,

David Kropp
Acting Director, Regulatory and Consumer Affairs

DK:ak\legal\DM Satchell 1

Pharmavite Corporation • P.O. Box 9606 • Mission Hills, CA 91346-9606 • 818/221-6200 • 800/423-2405
Deliveries Only: 8510 Balboa Blvd., Northridge, CA 91325

PHARMAVITE

3756 '01 MAY 10 P3:13

April 23, 2001

Ms. Rhonda Kane
U.S. Food and Drug Administration
VIA FAX

Dear Ms. Kane,

To follow up on our phone conversation this morning, the s-adenosylmethionine (SAM-e) that was the subject of our February 6, 2001 New Dietary Ingredient Notification will be marketed in both the tosylate form and 1,4-butanedisulfonate form.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

David Kropp
Acting Director, Regulatory and Consumer Affairs

DK:ak\fda\RK SAM-e 1

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PHARMAVITE

3757 '01 MAY 10 P3:13

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February 6, 2001

Office of Special Nutritionals (HFS-450)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C St. SW
Washington, DC 20204

Re: Submission of a Premarket Notification for a New Dietary Ingredient

Dear Sir or Madam:

Pursuant to the Dietary Supplement Health and Education Act of 1994 and in accordance with 21 CFR 190.6, Pharmavite is hereby notifying the Food and Drug Administration of our intention to market dietary supplements containing a new dietary ingredient.

Distributor name and address
Pharmavite Corporation
PO Box 9606
Mission Hills, CA 91346-9606

Name of the New Dietary Ingredient
S-adenosylmethionine (SAM-e)

Description of the dietary supplement(s)

Level of the New Dietary Ingredient
200 mg to 400 mg per tablet

Conditions of use
Up to a maximum daily dose of 1,600 mg

Evidence of safety
See attached articles

Please do not hesitate to contact me if you have any questions.

Sincerely,

David Kropp
Acting Director, Regulatory and Consumer Affairs

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