DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: September 6, 2001

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

88 40 '01 SEP 28 P2:22

New Dietary Ingredient:	L-Se-methylselenocysteine (SeMC)
Firm:	PharmaSe, Inc.
Date Received by FDA:	May 14, 2001
90-Day Date:	August 12, 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** August 12, 2001.

Felicia B. Satchell

Felicia B. Satchell

95S-0316

See Rpt 598 SUP 6
RPT 97

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC 20204

JUL 11 2001

Julian Spallholz, Ph.D.
President and CEO
PharmaSe, Inc.
3416 Knoxville Avenue
Lubbock, Texas 79413

Dear Dr. Spallholz:

This is to inform you that the notification dated May 10, 2001, you submitted pursuant to 21 U.S.C. 350b(a)(2) was received and filed by the Food and Drug Administration (FDA) on May 14, 2001. Your notification concerns the new dietary ingredient called "L-Se-methylselenocysteine (SeMC)."

In 1999, you initially notified FDA about your intent to market for adults only a dietary supplement containing 50 mcg of SeMC. Your earlier notification was filed at FDA's Dockets Management Branch in docket number 95S-0316 under the code numbers Rpt 59 and Sup 6. You reference your previous new dietary ingredient notification on SeMC in your current correspondence to FDA, stating that you wish to market for adults only a dietary supplement containing 100 mcg of SeMC. As a result, FDA will consider the supporting documentation in both your 1999 notification and 2001 correspondence for your May 14, 2001 submission.

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 July 28, 2001), you must not introduce or deliver for introduction into interstate commerce any dietary supplement that contains 100 mcg of SeMC.

Please note that 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 supplement that contains 100 mcg of SeMC 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. Therefore,

after August 12, 2001, the notification will be placed on public display at FDA's Dockets Management Branch in docket number 95S-0316. However, any trade secret or otherwise confidential commercial information that is 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, 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

JUL 27 2001

Julian Spallholz, Ph.D.
President and CEO
PharmaSe, Inc.
3416 Knoxville Avenue
Lubbock, Texas 79413

Dear Dr. Spallholz:

This is in response to your letter to the Food and Drug Administration (FDA) dated May 10, 2001, making a submission for a new dietary ingredient premarket notification 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 was received by us on May 14, 2001, and notified FDA of your intent to market for adults only the new dietary ingredient called "L-Se-methylselenocysteine (SeMC)" in a dietary supplement capsule providing 100 mcg of selenium (Se). Your notification suggests that up to 2 capsules of SeMC per day be consumed by adults 18 years of age or older.

In your current correspondence to FDA, you refer to your 1999 new dietary ingredient notification on SeMC. Your initial notification was filed at FDA's Dockets Management Branch in docket number 95S-0316 under the code numbers Rpt 59 and Sup 6. This earlier notification informed us that you intended to market for adults (18 years of age or older) only a SeMC dietary supplement capsule providing 50 mcg of Se to be consumed up to twice per day. FDA considered the supporting documentation provided in both your 1999 notification and 2001 correspondence for your May 14, 2001 submission.

21 U.S.C. 350b(a)(2) requires that a manufacturer or distributor of a dietary supplement that contains a new dietary ingredient submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, information that is 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 21 U.S.C 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) [section 402(f)(1)(B) of the Act] because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness or injury.

FDA has carefully considered the limited information in your notifications on SeMC, and has significant concerns about your conclusion that a dietary supplement of SeMC containing 100 mcg of Se taken twice a day by adults (18 years of age or older) will reasonably be expected to be safe. Your notification lacks the evidence to support this conclusion.

The normal level of intake of Se from the diet in the United States is sufficient to meet the Recommended Dietary Allowance (RDA) of 55 mcg for both male and female adults 19 or more years of age[1]. The Institute of Medicine (IOM) report on Se also estimates that 400 mcg is the daily Tolerable Upper Intake Level (UL) for Se for persons 19 or more years of age[1]. The IOM suggests that this is the highest level of daily intake that is likely not to pose a risk of adverse health effects in almost all individuals. Others have also estimated levels of concern for chronic oral exposure to Se. The United States Environmental Protection Agency and the Agency for Toxic Substances and Disease Registry have derived a chronic reference dose (RfD) and minimal risk level (MRL), respectively, for Se that is 350 mcg/day for a 70 kilogram adult[2].

Selenosis can result from excessive intakes of Se over long periods of time. Symptoms of this condition include brittle hair and nails, hair loss, gastrointestinal disturbances, skin rash, fatigue and nervous system abnormalities[1,2]. It is also important to note that Se has a very narrow margin of safety [3]. The difference in the margin of exposure between the RDA of 55 mcg and the MRL or RfD for Se is only about 6 fold.

In addition, selenocysteine is a biologically active organic form of Se that is very well absorbed. In comparison to exposure to inorganic forms of Se, seleno-amino acids such as selenomethionine and selenocysteine are potentially more toxic because less tends to be lost via urinary excretion and more tends to be incorporated into body tissue proteins.

Based on the Third National Health and Nutrition Examination Survey (NHANES III) data, the mean dietary intake of Se is 113.7 mcg for all individuals, including pregnant and lactating women[4]. Daily dietary exposure to Se in adults (19 or more years of age) at upper percentile levels of intake range from 108-211 mcg to 117-231 mcg to 138-280 mcg for the 90th, 95th and 99th percentiles, respectively[1].

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1 Food and Nutrition Board, Institute of Medicine, National Academy of Sciences: *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids*, National Academy Press, Washington, D.C., 2000, pp. 284-324 and 428-431.

2 Agency for Toxic Substances and Disease Registry: *Toxicological Profile for Selenium (Update)*, U.S. Department of Health and Human Services, Washington, D.C., 1996.

3 Spallholz, J.E.: Free radical generation by selenium compounds and their prooxidant toxicity, *Biomed. Environ. Sci.*, 10(2-3):260-270, Sept. 1997.

4 National Center for Health Statistics, U.S. Department of Health and Human Services: *The Third National Health and Nutrition Examination Survey (NHANES III), 1988-94*, U.S. Department of Health and Human Services, Washington, D.C., 1996.

Your proposed SeMC dietary supplement containing 100 mcg of Se taken twice a day could provide up to 200 mcg of additional Se above what is already consumed in the diet. If upper percentile consumers of dietary Se took your dietary supplement product, their total daily Se intake could range from 308 to 480 mcg, meaning that exposures in this range can exceed reference levels of concern for Se (i.e., UL, MRL, and RfD). This indicates that there is an insufficient margin of safety between the estimated exposure to Se and the level of Se at which chronic toxicity would reasonably be expected to appear for adults who are high percentile consumers of Se in the diet.

For the reasons discussed above, the information in your May 14, 2001 notification does not provide an adequate basis to conclude that a SeMC dietary supplement containing 100 mcg of selenium, when used under the conditions recommended or suggested in the labeling of your product (i.e., taken up to twice a day), will reasonably be expected to be safe. Therefore, your product may be adulterated under 21 U.S.C. 342(f)(1)(B) as a dietary supplement that contains a new dietary ingredient at a level for which there is inadequate information to provide reasonable assurance that it will not present a significant or unreasonable risk of illness or injury. Introduction of such products into interstate commerce is prohibited under 21 U.S.C. 331(a) and (v) [sections 301(a) and (v) of the Act].

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

Sincerely yours,

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

75909

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

May 10, 2001

MAY 14 2001

Dear Sir/Madam:

Last year your office allowed our proposal for L-Se-methylselenocysteine to be marketed as a new dietary supplement as described in the attached copy of our letter to your office of November 30, 1999.

We wish to request permission for L-Se-methylselenocysteine be marketed in capsules or tablet concentrations of 100 ug Se as the selenoamino acid. As before, the supplement will be made available only for adult usage. The label will be as follows:

Suggested Dose: As a dietary supplement for adults only (18 years or older), one (1) to two (2) capsules daily at mealtime or as directed by a healthcare practitioner.

Each capsule provides:
Selenium (L-Se-methylselenocysteine).....100 mcg

The human nutritional requirement for Selenium has been established and the Food and Nutrition Board, National Academy of Science have recommended a USRDA.

If this information is insufficient to complete our notification or if additional information is needed we will be pleased to respond.

Thank you,

Sincerely,

Julian Spallholz, PhD
President and CEO

PharmaSe, Inc
3416 Knoxville Ave
Lubbock, TX 79413 email: setech@door.net ph: 806-784-0104

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

November 30, 1999

Dear Dr. Larsen:

Thank you for your letter of November 12th in reply to our submission of documentation to distribute a new dietary supplement, L-Se-methylselenocysteine.

I spoke with Dr. Robert Moore to help clarify the additional needed information for complying with the requirements of 21 CRF 190.6.

Our target population for this supplement will be adults only. The label we propose to use is as follows:

Suggested Dose: As a dietary supplement for adults only (18 years or older), one(1) to two (2) capsules daily at mealtime or as directed by a healthcare practitioner.

Each capsule provides:
Selenium (L-Se-methylselenocysteine).....50 mcg

The human nutritional requirement for Selenium has been established and the Food and Nutrition Board, National Academy of Science have recommended a USRDA.

Packaging is planned for gelcaps with starch and calcium phosphate filler.

If this information is insufficient to complete our notification or if additional information is needed we will be pleased to respond.

Thank you,

Sincerely,

Julian Spallholz, PhD
President and CEO

PharmaSe, Inc
3416 Knoxville Ave
Lubbock, TX 79413 email: setech@door.net ph: 806-784-0104