DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: November 28, 2000

1525 '00 DEC 21 A9:53

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

Subject: 75-Day Premarket Notification of New Dietary Ingredients

To: Dockets Management Branch, HFA-305

New Dietary Ingredient:	resveratrol
Firm:	Solgar Vitamin and Herb
Date Received by FDA:	September 13, 2000
90-Day Date:	December 12, 2000

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 public display in docket number 95S-0316 **after** December 12, 2000. Thank you for your assistance.

Felicia B. Satchell

Felicia B. Satchell

95S-0316

RPT 85

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC

NOV 27 2000

Karla LaSasso
Associate, International Registration
Solgar Vitamin and Herb
World Headquarters
500 Willow Tree Road
Leonia, New Jersey 07605

Dear Ms. LaSasso:

This is in response to your letter, dated September 8, 2000, to the Food and Drug Administration (FDA) 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 product containing a new dietary ingredient named resveratrol. FDA received your submission on September 13, 2000.

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) 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 information in your submission and the agency has concerns about the adequacy of the evidence on which you rely to support your conclusion that the new dietary ingredient "resveratrol" will be reasonably expected to be safe. The submission contains evidence of history of use and other information that you assert is an adequate basis to conclude the dietary supplement containing the new dietary ingredient will reasonably be expected to be safe. However, the information in the submission is inadequate to make such a determination (see 21 C.F.R. § 190.6(b)(4)).

The submission contains a certificate of analysis and a product specification sheet as part of your documentation that you assert establishes that "resveratrol," when used under the conditions suggested on the label, will reasonably be expected to be safe. However, these documents inconsistently describe the amount of the new dietary ingredient that is the subject

of the submission. The certificate of analysis states that trans-resveratrol accounts for 49.8 mg/g of the extract powder, while the specification sheet states that the product is 50% natural trans-resveratrol. Therefore, the amount of trans-resveratrol reported in the specification sheet is ten times greater than that reported in the certificate of analysis. In addition, your submission fails to contain an explanation of how "Protykin RSV-5000," as described in the specification sheet, relates to the new dietary ingredient "resveratrol." Without knowledge of the level of the new dietary ingredient that will be used in the dietary supplement, it is not possible to have a reasonable expectation of safety. The inconsistent statements in your submission concerning the level of the new dietary ingredient, make unclear the specific quantitative characteristics of the dietary ingredient that would enable a determination to be made that there is a reasonable expectation of safety.

With respect to history of use, the information on the traditional use of a decoction from the rhizome and root of *Polygonum cuspidatum* Sieb. et Zucc. in Chinese medicine fails to provide information on the conditions of use, including the level of exposure of resveratrol, the duration of use, whether the folk medicine was prescribed by a trained health practitioner based on the evaluation of a particular patient. Moreover, the traditional use was for specific health conditions (e.g., arthritic pain, jaundice, acute infections, and cough with excessive phlegm). Therefore, the history of use of a decoction from the rhizome and root of *Polygonum cuspidatum* Sieb. et Zucc. in Chinese medicine does not provide any assurance that a dietary supplement containing "resveratrol" would reasonably be expected to be safe under conditions of use recommended or suggested in the labeling or under ordinary conditions of use.

Your submission also contains review articles of resveratrol studied in vitro or with animal or human cell lines and studies concerning the beneficial effects of red wine. These studies were not specifically designed to provide data that are relevant to assessing the safety of "resveratrol" used chronically in a dietary supplement. Moreover, the dietary intakes of resveratrol in the study using grape juice enriched with resveratrol are not comparable to the amount of resveratrol recommended to be consumed in your dietary supplement and therefore it is inappropriate to extrapolate a safe level of supplementation from these studies. With respect to the studies using red wine, no information was provided on how these studies relate to the use of resveratrol as a dietary ingredient in a dietary supplement. Furthermore, no information was provided on how the level of resveratrol typically found in wine relates to the exposure of resveratrol that you intend to recommend to consumers. This information is necessary to evaluate whether it is appropriate to extrapolate a safe level of supplementation of resveratrol from dietary exposure to wine. Finally, the agency notes that the phytoestrogenic activity of resveratrol is a potential health concern. (See e.g., Gehm BC, Page McAndrews JM, Chien P-Y, and Jameson JL. Resveratrol, a polyphenolic compound found in grapes and wine, is an agonist for the estrogen receptor. *Proc Natl Acad Sci* **94:**14138-14143 (resveratrol stimulates the proliferation of human breast cancer cells (T47D)).

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that resveratrol, when used under the conditions recommended or suggested in the labeling of your product, 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 for which there is inadequate information to provide reasonable assurance that such ingredients do 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).

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

Sincerely yours,

Felicia B. Satchell

Felicia B. Satchell
Director
Division of Standards
and Labeling Regulations
Office of Nutritional Products, Labeling
and Dietary Supplements

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC

OCT 18 2000

Ms. Karla LaSasso
Associate, International Registration
Solgar Vitamin and Herb
World Headquarters
500 Willow Tree Road
Leonia, New Jersey 07605

Dear Ms. LaSasso:

This is to inform you that your notification, dated September 8, 2000, submitted pursuant to section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act was received and filed by the Food and Drug Administration (FDA) on September 13, 2000. Your notification concerns the substance called Resveratrol that you assert is a new dietary ingredient.

Your notification will be kept confidential for 90 days following the date of its receipt. After December 12, 2000, the notification will be placed on public display at FDA's Dockets Management Branch under Docket No. 95S-0316. However, any information that is trade secret or otherwise confidential commercial 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,

Felicia B. Satchell

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

SOLGAR VITAMIN AND HERB
WORLD HEADQUARTERS

500 WILLOW TREE ROAD, LEONIA, NJ 07605 USA
PHONE 201-944-2311 FAX 201-944-7351

1527 '00 DEC 21 A9:53

September 8, 2000

Office of Special Nutritionals (HFS-450)
Center for Food Safety and Applied Nutrition
FOOD AND DRUG ADMINISTRATION
200 C Street, S.W.
Washington, D.C. 20204

RE: Premarket Notification For A New Dietary Ingredient

Dear Sir/Madam:

In compliance with Dietary Supplement Health and Education Act of 1994, Solgar Vitamin and Herb hereby makes its official Premarket Notification for a new Dietary Ingredient, **Resveratrol**. Accordingly, enclosed please find two (2) copies of this Notification.

Please be advised as follows:

1. The name and address of the manufacturer is:
   Solgar Vitamin and Herb
   500 Willow Tree Road
   Leonia, New Jersey 07605 USA
2. The name of the new Dietary Ingredient is:
   Resveratrol
3. A description of the dietary supplement:
   Dietary supplement Resveratrol is a standardized extract of from the Chinese herb *Polygomun cuspidatum* (root) containing natural trans-resveratrol in tablet form for use as a dietary supplement.
   Resveratrol also occurs in the food supply in the following sources: peanuts, mulberries, grapes and red wine.
   (a) the level of the new dietary ingredient is:
   30 mg per tablet
   (b) the conditions of use suggested on the label are:
   Suggested Use: As a dietary supplement for adults, one (1) to two (2) tablets daily, preferably at mealtimes, or as directed by a healthcare provider.

SOLGAR VITAMIN AND HERB
WORLD HEADQUARTERS

500 WILLOW TREE ROAD, LEONIA, NJ 07605 USA
PHONE 201-944-2311 FAX 201-944-7351

Enclosed please find documentation that establishes this dietary ingredient, **Resveratrol**, when used under the conditions suggested on the label, will reasonably be expected to be safe. This documentation includes a Certificate of Analysis, Product Specification Sheet and several review articles.

Thank you for your time and attention to this matter. If you have any questions or comments, please do not hesitate to contact the undersigned.

Very truly yours,
SOLGAR VITAMIN AND HERB

Karla LaSasso
Associate, International Registration

Enclosure

Certified Mail - Return Receipt Requested (P035906595)

Table of Contents

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InterHealth Nutraceuticals Incorporated

Certificate of Analysis

102016

Product:	Protykin RSV-5000
Description:	Extract of *Polygonum cuspidatum*
Control Number:	006034
Analysis Performed By:	Green Laboratories
	Vendor Lab

Results of Analysis:

Identification:	Passes
Moisture (%):	1.6
Emodin (mg/gm):	1.3
Resveratrol (mg/gm):	49.9
trans-Resveratrol (mg/gm):	49.8
Heavy Metals as Pb (ppm):	<5
Particle Size:	
Wt % + 80 Mesh:	0
Wt % + 100 Mesh:	1
Wt % + 150 Mesh:	10
Microbiological Assays:	
Total Plate Count (CFU/gm)	<100
E coli:	Not Detected
Salmonella:	Not Detected

Confirmation that specification data from independent laboratory is accurately disclosed on this Certificate of Analysis.

InterHealth Nutraceuticals, Inc. By: Homer Bakanes

Date 6/27/00

Product Specification

PROTYKIN® RSV-5000 (Powder)

PRODUCT SPECIFICATIONS

DESCRIPTION

Protykin® RSV-5000 is a high-potency, standardized extract of *Polygonum cuspidatum* (root) containing 50% natural *trans*–resveratrol in powder form for use as a dietary supplement.

SPECIFICATIONS

Chemical Classification	Organic, Nutritive
Physical Classification	Powder, Non Fibrous
Color	Medium Brown
Odor	Characteristic Smokey–Herbal
Taste	Characteristic Bitter–Herbal
Plant Part Used	Root
Moisture	Less than 5%
Solubility (alcohol)	75%
Solubility (water)	None
Clarity (1g/100ml water)	Clear Light Reddish – Brown
pH (1g/100ml water)	5.0 – 7.0
trans–Resveratrol (%) by HPLC	50 ± 5
Emodin (%) by HPLC	Less than 2
Heavy Metals:	
Pb (ppm)	Less than 10
As (ppm)	Less than 10
Hg (ppm)	Less than 0.25
Cd (ppm)	Less than 0.25
Particle Size:	
Wt. % Through 150 Mesh	75
Microbiological Assays:	
Total Plate Count (CFU/g)	Less than 3000
Yeast and Mold (CFU/g)	Less than 10
E. Coli (CFU/g)	Negative
Salmonella (CFU/g)	Negative
Staph. aureus (CFU/g)	Negative
Shelf Life	2 years when stored in tightly closed containers free of excessive heat, moisture, light and air.

PACKAGING

Protykin RSV-5000 is available in 0.1 (minimum), 0.25, 0.5, 1, 2, 4 and 10 kilogram quantities packaged in moisture, air and light-resistant containers.

Product Code RSV–5000 Research Code IH727 Order Code FG14010

PK1-991116-000320

5451 Industrial Wy • Benicia, CA 94510 • (707) 751-2800 • FAX (707) 751-2801

Inter Health Nutraceuticals Incorporated