DEPARTMENT OF HEALTH & HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Public Health Service

Memorandum

Date . OCT - 1 1999

From Senior Regulatory Scientist, Regulatory Branch, Division of Programs & Enforcement Policy (DPEP), Office of Special Nutritionals, HFS-456

Subject 75-day Premarket Notification for New Dietary Ingredient

TO Dockets Management Branch, HFA-305

New Dietary Ingredients:	Huperzine A
Firm:	Solgar Vitamin and Herb
Date Received by FDA:	September 30, 1999
90-day Date:	December 28, 1999

In accordance with the requirements of section 413(a)(2) 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-03 16 after December 28, 1999.

Robert J. Moore, Ph.D.

95S-0316

RPT 55

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC 20204

OCT - 1 1999

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

Dear Ms. LaSasso:

This is to notify you that your submission pursuant to section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act) dated September 28, 1999, concerning the marketing of a substance that you assert is a new dietary ingredient (i.e., Huperzine A) was received by the Food and Drug Administration (FDA) on September 30, 1999. Your submission will be kept confidential for 90 days from the date of receipt, and after December 28, 1999, your submission will be placed on public display at Dockets Management Branch (Docket No. 953-03 16). Commercial and confidential information in the notification will not be made available to the public.

Please contact us if you have questions concerning this matter.

Sincerely,

Robert J. Moore, Ph.D.
Senior Regulatory Scientist
Division of Programs and Enforcement Policy
Office of Special Nutritionals

SOLGAR VITAMIN AND HERB
WORLD HEADQUARTERS

500 WILLOW TREE ROAD, LEONIA, NJ 07605 USA
PHONE 201-944.2311 FAX 201-944.7351

6 7419

September 28, 1999

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, Huperzine A. Accordingly, enclosed please find two (2) copies of this Notification.

Please be advised as follows:

I. 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:

Hupenine A

3. A description of the dietary supplement:

Dietary supplement Huperzine A is the alkaloid compound extracted from the herb *Huperzia serrata* present in tablet form.

(a) the level of the new dietary ingredient is:

50 mcg per tablet

(b) the conditions of use suggested on the label are:

Suggested Use: As a dietary supplement for adults, one (1) to four (4) tablets daily, preferably at mealtimes, or as directed by a healthcare provider.

SOLGAR
Since 1947

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, Huperzine A, when used under the conditions suggested on the label, will reasonably be expected to be safe. This documentation includes a Certificate of Analysis, toxicity information, review articles and efficacy studies. Additionally, in support of this Notification, Solgar includes by reference correspondence dated August 25, 1997 from John P. Troup, Ph.D., Vice President Scientific Affairs of GENERAL NUTRITION CENTER (GNC) and the supporting documentation annexed thereto. In addition, reference is made to correspondence from James Tanner, Ph.D. of the Office of Special Nutritionals responding to said letter.

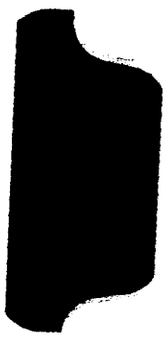
Thank you for your time and attention to this matter. If you have any questions or comments, please do not hesitate to contact the undersigned.

Very truly yours,
SOLGAR VITAMIN AND HERB

Karla LaSasso
International Registration Coordinator

Enclosure

Certified Mail - Return Receipt Requested (P035906605)



CERTIFICATE OF ANALYSIS

Marco Hi-Tech JV Ltd.

369 Bayview Avenue
Amityville, New York 11701

Phone 516-789 8228
Fax 516-789 1240

Certificate of Analysis

Sample Name	Huperzine A	**Quantity**	10 grams
Packing	Plastic bottle	**Batch Size**	350 g
Deliverer	Plant-extra. workshop	**Manufacturer**	
Batch No.	980601	**Receiving Date**	98-06-01
Criteria	WS-127(X)-94	**Reporting Date**	98-06-10

Result

1. **Characteristics:** A white needle-like crystalline powder; odorless; hydroscopic.

2. **Melting Point:** 228.5 - 229.5 °C (should be 227 - 231 °C)

3. **Identification:** (1) μ_{max} 231 nm, 313 nm
(2), (3) positive

4. **Loss on Drying:** 2.8% (not more than 5.0%)

5. **Related Substances:**

alkaloid impurities I	in accord
alkaloid impurities II	in accord
other impurities I	in accord

6. **Assay:** 99.7% (should be 98.0 - 102.0%)

Conclusion:

This batch of product is in conformity with the above criterion.

See Addendum A attached

ADDENDUM A

1. Product Specifications:

Chemical Classification	Organic, Nutritive
Physical Classification	Powder
Identification:	
IR	Conforms to standard supplied by Seller
UV	Conforms to standard supplied by Seller
Color	White needle-like crystalline powder
Odor	Odorless
Solubility	To be determined
pH (1% Solution)	To be determined
Moisture (%)	No more than 5
Melting Point (°C)	227 - 231
Identification:	
UV max	231 nm, 313 nm
Active Ingredients:	
Huperzine A (%)	98 - 102
Heavy Metals:	
Pb (ppm)	Less than 2
As (ppm)	Less than 2
Hg (ppm)	Less than 1
Cd (ppm)	Less than 1
Infestation	None
Foreign Material	None
Microbiological Assays:	
Total Plate Count (CFU/gm)	Less than 1000
Yeast & Mold (CFU/gm)	Less than 100
E. coli (CFU/gm)	None
Salmonella (CFU/gm)	None
Hygroscopic	Positve

2. Representations and Warrandes:

a) Common or Usual Name – Huperzine A

b) Product Description - Product consists of a standardized extract of Huperzine A, a natural alkaloid from the club moss *Huperzia serrata*. Product may also consist of synthetically derived Huperzine A, but only upon prior written approval from Buyer and at mutually agreed upon prices.

c) Product Application - Product is a nutritional ingredient for use in food, beverage and dietary supplement products.

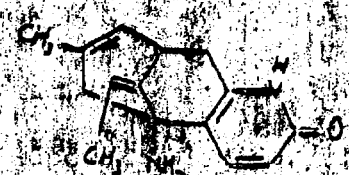
d) Product Dosage - Recommended dosage is 100 micrograms per day.

Huperzine A (Fordine)

Raw Material

Quality Specification Protocol

HUPERZINE A



$(C_{15}H_{18}N_2O$ = 242.32)

$C_{15}H_{18}N_2O$

Huperzine A contains not less than 98.0 percent and not more than 102.0% of Biological Alkaloid $C_{15}H_{18}N_2O$, calculated on the dried basis.

Description: White or off white, odorless, hygroscopic, needle shape crystals, very slightly soluble in water, slightly soluble in ether, freely soluble in anhydrous ethanol and chloroform.

Melting Point: (CP 1990 edition, Part 2 appendix page 15) between 227 and 231°C (but the melting range between beginning and end of melting does not exceed 2°C). It decomposes upon melting.

Identification:

(1) The U.V. absorption spectrum determination (CP 1990 edition, part 2 , appendix Page 24) of a solution obtained under assay preparation exhibits maxima at wavelengths 231±1 nm and 313± nm

(2) Spot a filter paper with a drop of sample preparation solution obtained under related substances and allow to dry. Repeat the procedure once more. Place 1 mg of p-dimethyl-amino-benzaldehyde and 1 drop of benzene on the spot and allow to dry. Place the filter paper over hot acetic acid vapor for 1 -2 min. a yellow spot appears.

(3) Add 3 drops of water and one drop of Bromine TS to 0.1 ml of a test preparation solution obtained under related substances and shake. Yellow color disappears and a white precipitate is produced.

Testing :

Loss on Drying: (CP 1990 edition, part 2 appendix page 55) Dry about 0.5 gm sample at 80°C to constant weight: it loses not more than 5% of its weight.

Related Substances: (1) Biological Alkaloid Impurity I (simply named isomer)

A. Test preparation -- Dissolve a suitable quantity of the product in anhydrous ethanol to obtain a solution having a concentration of 20mg/ml.

B. Standard preparation -- Dissolve a suitable quantity of isomer reference standard in anhydrous ethanol to obtain a solution having a concentration 0.2 mg/ml.

Procedure: - Apply separate 4 µl portions of standard preparation, and test preparation on a 5 X 10 cm Chromatographic Plate coated with GF254 silica gel and CMC (method of making plate see below). Dry with hair dryer. Develop the chromatogram in a solvent system consisting of a mixture of dichloromethane, acetone, methanol, 95% ethanol, and water (3.5 : 1.5 : 1.0 : 0.20 : 0.25). Develop the chromatogram vertically twice. (After the first development when the solvent front has reached the pre-determined end of the plate, allow it to dry for 10 minutes. Discard the used solvent and replace with fresh solvent for subsequent development of the chromatogram the second time.) Allow the solvent to evaporate. Examine the plate under UV lamp (254 nm). Mark the major spots. Spray the plate with 0.1% $KMnO_4$ solution. Examine the plate after 2 minutes. Compare the intensities and sizes of spots observed in the chromatograms of the Test Preparation to those spots in the chromatograms of the Standard Preparation. No isomer spots observed from the chromatograms of the Test Preparation is larger or more intense than those spots obtained from Standard Preparation (<1%).

(2) Biological Alkaloid Impurity II.

A. Test Preparation: same as (1)A above.

B. Standard Preparation: Dissolve a suitable quantity of Huperzine A reference standard in anhydrous ethanol to obtain a solution having a concentration of 20 mg/ml.

Procedure: Apply separate 5 µl portions of standard preparation and test preparation on a 5 X 20 cm Chromatographic Plate coated with GF254 silica gel and CMC (method of making plate see below). Continue the procedure as under Biological Alkaloid Impurity I, starting from "Dry with hair dryer". Examine the plate after 2 minutes. Major spots obtained from test preparation correspond in R_f value to that of standard preparation and no secondary spots are observed (<4.5%).

(3) Other Impurities.

Procedure: Apply separate 4µl of standard and test preparation prepared under Biological Alkaloid Impurity II on a 5 X 10 cm Chromatographic Plate coated with GF254 silica gel and CMC (method of making plate see below). Dry with hair drier. Develop the chromatography vertically in a solvent system consisting of a mixture of water saturated n-butanol (shake a quantity of n-butanol and water in a separatory funnel. Allow the layers to separate for two days. Separate and discard water layer before use) and glacial acetic acid (4 : 0.5). Allow to dry. Examine under UV light (265 nm). The number of impurity spots produced by the test preparation should be the same to that of standard preparation and no other spots are observed.

Assay: Accurately weigh about 10 mg of the raw material previously dried to constant weight. Dissolve in ethanol to obtain a a solution having a concentration of 10 µg per ml. Determine the absorbance (CP 1990 part 2 appendix page 24) of the the solution on 1 cm cell at a wavelength of maximum absorbance at 310±1 nm. Calculate the concentration based on the extinction coefficient of $C_{15}H_{18}N_2O$ ($E^{1\%}_{1cm}$)=331.

Indication and Uses: Truly reversible cholinesterase inhibitor, used for treatment of benign memory impairment, brain functional memory impairment, and dementia.

Dosage and administration: Omitted.

Precaution: Omitted

Storage: Tight sealed and protect from light.

Preparation of (5 X 10 cm) thin layer plate: Weigh 1.0 gm of silica gel GF 254 (10-40 µ). Add 2.3 ml of 0.5% CMC solution. Add sufficient water and mix to form a paste of batter consistency. (Along the two 10 cm edges apply 0.5 mm thick tape so the width of adsorbant will be about 4.3 cm.) Transfer and apply the adsorbant onto the plate. Level it with a spreader. Place the wet plate horizontally and allow to dry naturally. Activate the dried adsorbant the next day at 110°C for 30 minutes. Store in silica gel desiccator before use.

Preparation of (5 X 20 cm) thin layer plate: Weigh 2.5 gm of silica gel GF 254 (10-40 µ). Add 6 ml of 0.5% CMC solution. Add sufficient water and mix to form a paste of batter consistency. Follow the rest of the steps as in preparation of (5 X 10 cm) thin layer plate

TOXICITY INFORMATION

WILKE RESOURCES

Phone: (800) 779-5545 *15036 W. 106th Street, Lenexa, KS 66215* *FAX: (913) 438-5544*

Date: **Wednesday, July 29, 1998** **Pages: 1**

To: **Carl German0**
Solgar Vitamin & Herb Co. Inc.
Fax: 201-944-7351

From: **Jim France**
Wilke Resources, Inc.
Fax: 438-5554

Subject: Huperzine A Toxicity Information

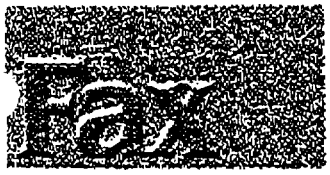
Our Chinese pharmaceutical manufacturer of the natural extract, Hupenine A, has provided us with the following results of **inhouse** animal toxicity testing for this product:

> Acute tests showed that Hup A will cause **ChE** inhibition poisoning if it is taken a at very high dosage by mouse, rat, rabbit and dog. In mice, the LD_{50} (ig) = 5.2 **mg/kg** , $LD_{50\ (iv)}$) = 0.63 **mg/kg, and** $LD_{50\ (ip)}$ = 1. **8 mg/kg while** in **rats the** $LD_{50\ (ig)}$ =25.9 **mg/kg,** LD_{50} (iv) = 2.55 **mg/kg,** and $LD_{50\ (ip)}$ = 5 **mg/kg.** The toxicity of **HupA,** however, is much lower than Physostigmine. In mice via **IP** testing, the treatment index (LD_{50}/ED_{50}) is 23.1 for Hup A , 8.6 for Neostigmine, and 3.8 **fo**r Physostigmine. In rats via IV testing, the treatment index is 72.9 for **HupA,** 34.0 for Neostigmine, and 7.2 for Physostigmine.
>
> In a subacute toxicity test, two dosages were used to treat dogs - 0.3 **mg/kg** and 0.6 **mg/kg.** After a period of 180 consecutive days of Hup A treatments, no clear side effects were found in any of the treated animals. The dosage used in this test was 45 times higher than the recommended clinical dosage. Other toxicity tests were **also** conducted, including mutagenic and teratogenical tests, with no effects found. Therefore, Huperzine A is a safe and very effective new herbal extract.

While we **find** the above results to be indicative of Huperzine A's safety, we are asking the manufacturer to expand on the statement that "no clear side effects were found." Specifically, we are asking how this was determined and what tests if any were done on the liver, kidney, and heart to support this statement.

It is also important to note that the above refers to the natural herbal extract, **(-)Huperzine** A in its 98% plus purity form. **Lower** percent extracts will potentially contain additional plant chemicals that may or may not be toxic. In addition, this information does not relate to any synthetically prepared form of huperzine A which differs dramatically in reduced efficacy compared to the natural extract.

If you have any questions, please don't hesitate to call Jim France at (800) 779-5545.



WILKE RESOURCES

15036 W. 106th Street, Lenexa, KS 66215

Date: Monday, July 20, 1998 **Pages:** /

To:	Carl Germano Solgar Vitamin & Herb Co. Inc. Phone: 201-944-2311 Fax: 201-944-7351	**From:**	Jim France Wilke Resources, Inc. Phone: 913-438-5544 Fax: 438-5554

Subject: Huperzine-A (98%)

Wilke Resources has developed sourcing for a high purity (98%) Huperzine-A which is an alkaloid extracted from herb Huperzia serrata. Huperzine-A has demonstrated an excellent potential for memory enhancement as related to Benign Senescent Amnesia and, more importantly, Alzheimer's Disease.

Alzheimer's disease is believed to be attributed to aging and, as the population lives longer, it is becoming a common ailment among the elderly. Ten percent of the US population between the ages of 80 and 85 reportedly suffer from Alzheimer's with the percentage increasing to 25% for those over 85 years of age. Alzheimer's is a' chronic and progressively degenerative neurological disorder characterized by dementia and behavioral symptoms that severely reduces the quality of life of both the victim and the immediate family.

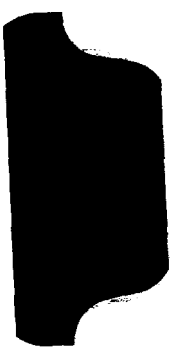
It has been shown that a severe deficiency of choline acetyl transferase and a decrease in the synthesis of acetylcholine represent the most prominent neurochemical changes that occur with Akheimer's. The concentration 'of acetylcholine, however, can be increased by inhibiting the roduction of the enzyme acetylcholinesterase (AChE), thus relieving certain symptoms such as cognition. A number of such inhibitors have been developed and two of which, tacriue (Cognex) nd donepezil (E2020; Aricept) are FDA approved for the symptomatic treatment of mild-to-moderate Alzheimer's diise in the US.

Research in China has revealed that Huperzine-A is a potent reversible inhibitor of AChE. Further studies at Weizmann Institute of Sciences in Rehovot, Israel and Gerogetown University in Washington suggest that Huperxiue-A is even more potent that either tacrine or donepezil. As reported in the Journal of the American Medical Association on March 12, 1997, Huperzine-A appears to be more selective and possibly less toxic that either of the FDA approved drugs. Compared to tacrine and donepezil, Huperzine-A has a longer half-life aud the AChE-HupA complex has a slower rate of dissociation, which may make it a more effective therapeutic agent.

Reports from China, where an estimated 100,000 people have been treated with Huperzine-A, further support the contention that the extract has low toxicity. In fact, since the herb is a traditional Chinese medication and used for generations, it may be reasonably believed to be safe without excessive application and marketed as a dietary supplement under DSHEA.

Huperzine-A is available via Wilke Resources from the original Chinese pharmaceutical manufacturer in powder form with a minimum purity of 98%. The literature reports that the effective daily dosage for the 98% pure product to be in the 100 to 200 microgram range. Based on a delivered selling price of US$750.00 per gram, the ingredient cost for a single individual's one month's supply would range from S2.25 to $4.50. This could easily translate into a retail price of $25 to $30 for one month's supply. The current prescription pricing for one month's supply of donepezil and tacrine is around $100 and $117-$234 respectively.

Huperzine-A (98%) is priced as follows: (1) l-9 grams = $750/gram; (2) 10 to 99 grams = $700/gram; and 100 grams or more = $650/gram (pricing includes air freight; all applicable duties aud taxes are the responsibility of the buyer). Payment must be ma& in advance of shipment with the understanding that the customer can return a given order within 10 days of receipt for a full refund. All shipments are by air aud are fully insured. Additional information is being sent via FEDEX. If you have any questions, please call Jim France at (800) 779-5545 for more information.



REVIEW ARTICLES