



Memorandum

NOV 20 2003

Date: _____
From: Interdisciplinary Scientist/Pharmacist, Division of Dietary Supplement Programs
, Office of Nutritional Products, Labeling and Dietary Supplements, HFS-810
Subject: 75-Day Premarket Notification of New Dietary Ingredients
To: Dockets Management Branch, HFA-305

Subject of the Notification: Cumaris (Powdered Exts of Rhizoma Chuanxiong,
Radix Angelicae Dahuricae and Imperatorin)
Firm: Hi Tech Pharma Inc.
2010 Twelve Oaks Drive
Palm Bay, Florida 32909

Date Received by FDA: February 24, 2003
90-Day Date: 5/25/03

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and
Cosmetic Act, the attached 75-day premarket notification and related correspondence for the
aforementioned substance should be placed on public display in docket number 95S-0316 as
soon possible since it is past the 90-day date. Thank you for your assistance.

Gloria Chavez

P drive/ NDI/ NDI File Closeout/DDSP SOP closeout process...

95S-0316

RPT177



MAY - 5 2003

Terry M. Walcott
Regulatory Affairs
Hi-Tech Pharma Inc.
2010 Twelve Oaks Drive
Palm Bay, Florida 32909

Dear Mr. Walcott:

This is in response to your new dietary ingredient premarket notification dated January 2, 2003, you submitted pursuant to 21 U.S.C. 350b(a)(2) and Title 21 of the Code of Federal Regulations (21 CFR) Part 190.6 and received by the Food and Drug Administration (FDA) on February 21, 2003. Subsequently, we requested a third copy of the notification in accordance with 21 CFR 190.6(a). The copy was received on February 24, 2003, which is the filing date. Your notification concerns the substances you describe as the powdered herbal extracts of *Rhizoma Chuanxiong*, and *Radix Angelicae Dahuriace*, and Imperatorin, a coumarin compound, which you assert are new dietary ingredients. You state that you plan to market the formulation under the product name, Cumaris. You indicate that Cumaris will contain 17 milligrams (mg) of *Rhizoma Chuanxiong* and 9.3 mg of *Radix Angelicae Dahuriace* and 0.7 mg of imperatorin (a coumarin compound) per capsule. The suggested conditions of use are as a dietary supplement for adults, two capsules twice daily, preferably in the morning or evening, or as provided by a healthcare provider.

Under 21 U.S.C. 350b(a), the manufacturer or distributor of a dietary supplement that contains a new dietary ingredient that has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered must submit to FDA, at least 75 days before a new 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 the 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 or injury.

FDA has carefully considered the information in your submission, and the agency has significant concerns about the evidence on which you rely to support your conclusion that a dietary supplement containing powdered herbal extracts of *Rhizoma Chuanxiong*, and

Radix Angelicae Dahuriace, and imperatorin, a coumarin compound, will be reasonably expected to be safe. There is no information included in the notification that indicates that the dietary supplement identified as Cumaris has a history of use in China or in any other country. The source herbs *Radix Angelicae Dahuricae* and *Rhizoma Chuanxiong* are included in your referenced publication titled Chinese Materia Medica. The history of use of imperatorin, a coumarin compound, appears to be only that associated with consumption of the source herb *Radix Angelicae Dahuricae*.

The general information provided includes reports using a number of different preparations of the herbs. No information is provided that related the composition or effects of such preparations to the composition of the specific preparation named Cumaris that is the subject of the notification. Taken together, the information submitted in the notification does not support the safe use of Cumaris by the general population.

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that Cumaris, 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 ingredient does not present a significant or unreasonable risk of illness or injury. Introduction of this product into interstate commerce is prohibited under 21 U.S.C.331(a) and (v).

Your notification will be kept confidential for 90 days after the filing date of February 24, 2003. After May 25, 2003, the notification will be placed on public display at FDA's Docket Management Branch in docket number 95S-0316. Prior to May 25, 2003, you may wish to identify in writing specifically what information you believe is proprietary (a trade secret or otherwise confidential) for FDA's consideration.

If you have any questions concerning this matter, please contact Victoria Lutwak at (301) 436-1775.

Sincerely yours,



Susan J. Walker, M.D.
Acting Division Director
Division of Dietary Supplement Programs
Office of Nutritional Products, Labeling and
Dietary Supplements
Center for Food Safety and Applied Nutrition

Hi-Tech Pharma Inc.

6483 NW 38th Way, Boca Raton, FL 33496, 561-999-9734 Tel, 561-995-9734 Fax
Delivering Your Future Health Now

January 2, 2003

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

RE: Premarket Notification For Cumaris, a New Dietary Ingredient

Dear Sir/Madam:

In compliance with section 413(a)(2) of the Dietary Health and Education Act of 1994, Hi-Tech Pharma, Inc., a Florida corporation, makes its official Premarket Notification for *Cumaris*, a new dietary supplement. We take this action with the understanding that we cannot market this product for a period of at least 75 days after the FDA's receipt of this notification.

The Food and Drug Administration ("FDA") is hereby notified of the following:

1a. The name and address of the manufacturer is:

Beijing Tong Yuan Pharmaceutical Co.
14/FA, Block D, Cahua Mansion
Ghaoyaugmen, North Avenue No. 8F,
Zhongcheng District, Beijing, CHINA 100027

1b. The name and address of the United States Distributor is:

Hi-Tech Pharma, Inc.
6483 NW 38th Way
Boca Raton, FL 33496

2. The name of the new Dietary Ingredient is:

Cumaris

3. A description of the dietary supplement:

Dietary supplement *Cumaris* is a combination of powdered herbal extracts of *Radix Angelicae Dahuricae*, *Rhizoma Chuanxiong*, and *Imperatorin*, a coumarin compound.

a. The level of the new Dietary Ingredient is:

17 mg *Rhizoma Chuanxiong* per capsule, and 9.3 mg *Radix Angelicae Dahuricae* per capsule, and 0.7 mg imperatorin per capsule.

b. The conditions of use suggested on the label are:

Suggested Use: As a dietary supplement for adults, two capsules twice daily, preferably in morning and evening, or as provided by a healthcare provider.

Enclosed herewith please find two copies of this Notification, which includes documentation establishing that this new dietary ingredient, *Cumaris*, when used under the conditions suggested on the label, will reasonably be expected to be safe. This documentation includes two certificates of analysis, a list of ingredients, and photocopies of three herbal references for *Rhizoma Chuanxiong* and three herbal references for *Radix Angelicae Dahuricae* that support the safety/non-toxicity of each herb and imperatorin.

Imperatorin is a coumarin, a class of widely occurring phenolic compounds that is especially abundant in citrus fruit. Coumarins (including imperatorin) are ubiquitous in higher plants and are particularly prevalent in citrus oils and certain vegetables such as celery. Imperatorin is regularly ingested by humans.

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

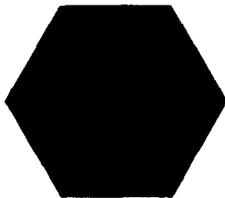
HI-TECH PHARMA, INC.



Terry M. Walcott
Regulatory Affairs
561-756-0149 Voice

Enclosure

Sent Via FedEx 1/2/03



Tianjing Zhongxin Pharmaceutical Group Co., Ltd.

Lerentang Pharmaceutical Factory

Laboratory Centre

Certificate of Analysis--Determination of Imperatorin in Cumaris® by RP-HPLC

Summary: A RP-HPLC method was used to determine the presence and amounts of the coumarin Imperatorin[C₁₆H₁₄O₄] in Cumaris® capsules. The sample was dissolved in ethanol and extracted by refluxing in a water bath, then chromatographed on LUNA-C₁₈ column with mobile phase of methanol-0.5% phosphoric acid (69:31). The flow rate was set at 0.8mL/min and the detection wavelength was of 300nm. The resolution between imperatorin and its neighboring peak was 2.0; the number of theoretical plates was 15367 according to the peak of imperatorin. The linear range was 19.50/58.50µg/mL, r was 0.9999, and the average recovery was 99.8%. This HPLC method is rapid and accurate.

TEST: RP-HPLC, Cumaris® Capsule, Imperatorin

Cumaris Capsule is made of *Radix Angelicae Dahuricae* and *Rhizoma Chuanxiong*, which are recorded in the eighth volume (1993) of Medicine Standards published by the Ministry of Health of the People's Republic of China. The function of *Radix Angelicae Dahuricae* is to regulate the flow of vital energy and remove obstruction to it, to invigorate the circulation of blood and to relieve pain. It can be used to treat stomach pain caused by stagnation of the circulation of vital energy and blood stasis, to treat rib pain, headache and menses pain and so on.

Imperatorin is the main active component of *Radix Angelicae Dahuricae*. The quality of Cumaris® Capsule is identified by the characteristics and general rule of capsule examination in Medicine Standards (1993).

1. INSTRUMENT AND REAGENTS

The HPLC system consists of LC-6A liquid pump of Shimadzu Corp. of Japan, SIL-6B automatic sample injector, SPD-6AV ultraviolet-visible spectrophotometer detector and Chromatopac C-R 6A data processor. Cumaris® Capsules were supplied by the manufacturer, Beijing Tong Yuan Pharmaceutical Company, Ltd., of Beijing, China, and was identified by us. The standard sample of imperatorin was purchased from the National Institute for the Control of Pharmaceutical and Biological Products of China. Methanol was of HPLC grade and ethanol was analytical reagent. The stock solution of imperatorin standard sample was ethanol solution of 97.50m g/mL.

2. METHOD AND RESULTS

2.1 Chromatographic Conditions

LUNA C₁₈ column (4.6mm IDx250mm, particle diameter 5m m), ODS protective column (5mm IDx50mm, particle diameter 5mm) of Analytical Apparatus Factory of Beijing were used. The column temperature was at 35°C. The mobile phase was the mixture of methanol-0.5% phosphoric

acid (69:31) and the flow rate was set at 0.8mL/min. The detection wavelength was of 300nm, the injected volume was 10 μ L and the recorder paper rate was 1mm/min.

2.2 Experiment Operations

The standard sample of imperatorin was diluted to suitable concentration by ethanol, and then injected. The negative sample without imperatorin was prepared according to Beijing Tong Yuan capsule prescription. The sample of Cumaris® Capsule and the negative sample were taken and extracted according to the sample determination method, injected and the chromatograms were given in Figure 1. From the chromatograms, it was known that the other components of Cumaris® Capsule did not affected the determination of imperatorin. The retention time of imperatorin was about 16 min, the resolution between imperatorin and its neighboring peak was 2.0, the number of theoretical plates was 15367 according to the peak of imperatorin. Under the chromatographic conditions to be examined, imperatorin in Cumaris® Capsule can be determined quantitatively.

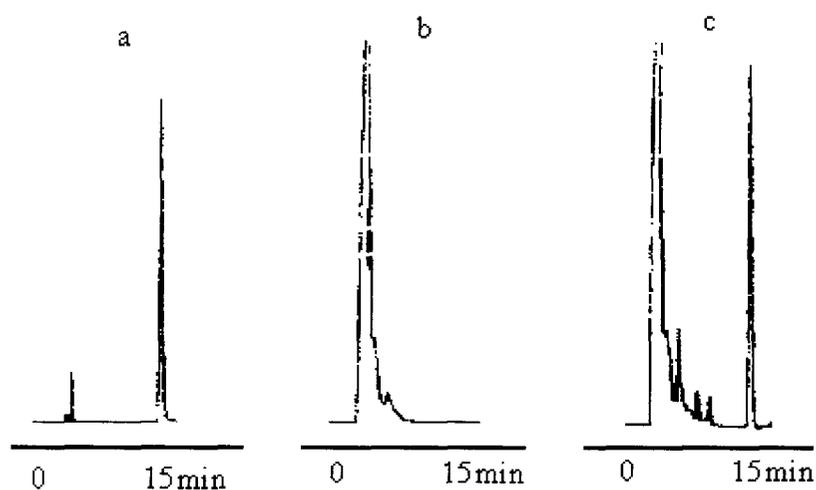


Fig.1 The chromatogram of (a) imperatorin (b) negative sample of Cumaris® capsule (c) Cumaris® Capsule, the peak of 1 in chromatogram (c) is imperatorin

2.3 Linear Relation and the Minimum Detection Limit

The standard sample was taken precisely and diluted to different concentration (19.50~58.50 μ g/mL) with ethanol, then injected 10 μ L respectively and the peak area was recorded. The linear regression was made between the mean peak area of imperatorin X and the injected concentration Y (μ g/mL). The regression equation: $Y=0.000070964X+3.1591$; $r=0.9999$.

The minimum detect limit was 0.1 μ g/mL according to the three times noise of baseline.

2.4 Extraction Method

The extraction rates of imperatorin by ethanol were examined by using different ultrasound time and different reflux time in water bath. Our results shown that the extraction rate was 96.3% by ultrasound for 60min, and that the extraction rate by reflux in water bath for 20min was 100%.

Therefore, the extraction method of refluxing in water bath was selected. If one takes the extraction rate as 100% by refluxing for 40min, then the extraction rate was 99.9%, 100% and 98.3% respectively by refluxing for 20, 60, 90min.

2.5 Apparatus Precision and Method Repeatability

A sample solution was taken into the automatic sample injector, and injections were made in 5h for n=5. (Interday) RSD% was 0.3170. The same sample was determined five times per day (n=5) for 3 consecutive days. (Intraday) RSD% was 3.864.

2.6 Standard Recovery

Six parts of the same batch of Cumaris® Capsules were weighed precisely. The imperatorin standard sample was added precisely into five parts, the other part was the blank. Every part was operated according to the sample determination method for determining the imperatorin concentration. The average recovery was 99.8%. RSD% was 0.63 (n=5).

2.7 Sample Determination

Fifteen Cumaris® capsules were taken and ground into powder. A certain amount of the powder was precisely weighed (about equivalent to *Radix Angelicae Dahuricae* 0.9g dried herd/90 mg liquid extract/or 9 capsules) into a 100mL Erlenmeyer flask with ground cap and 50mL ethanol was added. The mixture was extracted by refluxing for 40min in water bath, then the mixture was cooled down to room temperature and was filtered. 25mL continuous filtrate was precisely measured into a 50mL volumetric bottle, ethanol was added to the scale and the bottle was shaken evenly. A little was taken from the volumetric bottle and filtered through a 0.45µm membrane. An aliquot of 10µL was injected into the HPLC system, the peak of imperatorin was recorded and its amount was calculated by the standard method. Three batch samples were determined, and the results of imperatorin were 0.66, 0.71 and 0.72 mg/capsule respectively. These results all met the manufacturer's specification of 0.7mg plus or minus 10% of imperatorin per capsule.

Approved: 12/20/02 *Signature On File*

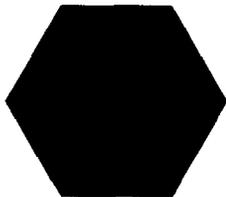
Quality System,

Tianjing Zhongxin Pharmaceutical Group Co., Ltd.

Lerentang Pharmaceutical Factory

Qing Guang Bei, Beichin District, Tianjin, China,

Phone: 011-86-20-6232-8629, Fax: 011-86-20-6232-8426



Tianjing Zhongxin Pharmaceutical Group Co., Ltd.

Lerentang Pharmaceutical Factory

Laboratory Centre

CERTIFICATE OF ANALYSIS

CUMARIS CAPSULE

250 mg X 60 Capsules¹, Cat #: 021112- S1, Lot #: 3666999, Expiration Date: 02/04

SPECIFICATIONS:

Chemical classification: Organic Nutritive

Physical classification: Powder

Color: Light yellow

Storage: Store in dark and dry place at room temperature.

Dosage: Two capsules twice daily, in morning and evening.



TEST	SPECIFICATION	RESULT
The product should match the reference solution of <i>Rhizoma Chuanxiong</i> in position and color on fluorescent light point in Thin Layer Chromatogram		Conforms
The product should match the reference solution of <i>Radix Angelicae Dahuricae</i> in position and color on fluorescent light point in Thin Layer Chromatogram		Conforms
Disintegration Limit	<30 minutes	13 minutes
Moisture	<9%	2%

Heavy Metals

Total heavy metals	not to exceed 6 ppm	0.95 ppm
Pb	not to exceed 2 ppm	0.33 ppm
As	not to exceed 2 ppm	0.195 ppm
Hg	not to exceed 1 ppm	0.20 ppm
Cd	not to exceed 1 ppm	0.225 ppm

Microbiological assays

Total Plate Count \leq 1000 cfu/g	260
Yeast and Mold \leq 50 cfu/g	15
Staphylococcus aureus (Negative)	Negative
E.Coli (Negative)	Negative
Salmonella (Negative)	Negative

Conclusion

Cumaris® Capsule product meets the specifications set by Beijing Tong Yuan Pharmaceutical Company, Ltd.

Approved: 12/06/02

Quality Systems

Tianjing Zhongxin Pharmaceutical Group Co., Ltd.

Lerentang Pharmaceutical Factory

Qing Guang Bei, Beichin District

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Signature On File