



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

6656 '04 MAR -1 P1:51

Date: FEB 25 2004

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: **Tsumura Tokaku-joki-to Extract**

Firm: **Tsumura USA, Inc.**

Date Received by FDA: **8/07/03**

90-Day Date: **11/06/2003**

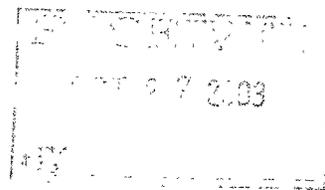
In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification and related correspondence for the aforementioned substance should be placed on public display in docket number 95S-0316 as soon possible since it is past the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

Gloria Chung

955-0316

RPT207

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



Dear Dr. Walker,

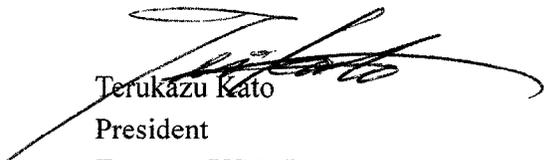
This is a response to your notification dated October 16, 2003 with respect to the subject, "Status of New Dietary Notification Application- TSUMURA Tokaku-joki-to- extract granules (TJ-61)."

TJ-61 has been used traditionally over centuries in Japan and it is considered as a safe herbal product based on its long-using experience. We have made efforts to accumulate data on the above product including safety ones. However, we don't possess sufficient data, of which FDA requires us this time.

We decided to refrain from marketing TJ-61 as a dietary supplement this time and to develop it as an ethical drug in the US complying with the IND submission procedure. The document for notification of a new dietary ingredient, "New Dietary Ingredient Notification of TSUMURA Tokaku-joki-to Extract Granules", contains our trade secrets, such as manufacturing conditions and specifications etc. of the above product, so we hope the above documents not to be placed on public display.

From above circumstances, Tsumura USA, Inc. hopes to withdraw the submission of this application if FDA can permit it.

Sincerely yours,


Terukazu Kato
President
Tsumura USA, Inc.

86300



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, Maryland 20740

OCT 16 2003

Terukazu Kato
President
TSUMURA USA, INC.
20910 Normandie Avenue, #C
Torrance, California 90502

Dear Mr. Kato:

This is to inform you that the notification, dated August 5, 2003, you submitted pursuant to 21 U.S.C. 350b(a)(2)(section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)) was filed by the Food and Drug Administration (FDA) on August 7, 2003. Your notification concerns the substance called "TSUMURA Tokaku-joki-to extract granules (TJ-61)", that you intend to market as a new dietary ingredient.

The notification describes the following components in your new dietary ingredient called TJ-61: peach kernel, cinnamon bark, rhubarb, glycyrrhiza, and anhydrous mirabilium ($\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$). The cover letter includes light anhydrous silicic acid as a component of your new dietary ingredient, TJ-61. Thus, FDA is unclear regarding the specific description and composition of your intended new dietary ingredient, TJ-61. According to the notification, "The usual adult dose is 7.5 grams (g)/day orally in 2 to 3 divided doses before or between meals. The dosage may be adjusted according to the patient's age and body weight."

Under 21 U.S.C. 350b(a)(2), 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 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 section 350b(a)(2), there must be a history of use or other evidence of safety establishing that the new 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 TJ-61 (peach kernel, cinnamon bark, rhubarb, glycyrrhiza, anhydrous mirabilitum ($\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$), and possibly light anhydrous silicic acid) will reasonably be expected to be safe.

The notification does not clearly describe the specific components in the new dietary ingredient, TJ-61. In addition, the notification does not provide an explanation for the inclusion of anhydrous mirabilitum ($\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$) and silicic acid as components of the new dietary ingredient, TJ-61. For example, your cover letter includes silicic acid as a component of the new dietary ingredient, TJ-61. However, the notification identifies silicic acid as a vehicle. Thus, the notification does not clearly identify the new dietary ingredient, TJ-61 or the components contained in the new dietary ingredient, TJ-61. Moreover, the notification did not identify the type of silicic acid in TJ-61. According to the notification, syloid 244 was tested in the published chronic and carcinogenicity studies, however the notification does not clearly state that syloid 244 is contained in TJ-61.

According to the notification, TJ-61 contains two marker compounds, glycyrrhetic acid from licorice root and Sennoside A from rhubarb. However, the notification does not provide sufficient information to determine the actual concentrations of glycyrrhetic acid and Sennoside A in TJ-61.

The notification contains the results of an acute toxicity study in rats and mice, a 7-day study in ovariectomized rats, genetic toxicity tests and a 6-month study in 8 perimenopausal women. Based on the notification, the acute studies were of single or short duration exposure to TJ-61 and limited parameters were assessed. For example, the study "Acute toxicity study of TSUMURA Tokaku-joki-to extract granules (TJ-61) after oral administration in mice and rats" did not provide adequate information regarding the number of animals in the study, the dose groups, the tissues examined, or any information regarding individual animal observations. Based upon the single exposure used in this study, and limited information, it is unclear how these animal studies would establish a reasonable expectation of safety. It is also unclear how the 6-month study in 8 perimenopausal women would establish a reasonable expectation of safety.

The notification did not address the potential laxative effect of TJ-61 in the general population under chronic conditions of use. For example, the notification states that TJ-61 contains Sennoside A, an anthracene laxative. According to the notification, TJ-61 also contains sodium sulfate (anhydrous mirabilitum ($\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$)), an osmotic laxative. Finally the notification states that radix glycyrrhizae has purgative properties and that peach kernel may have laxative properties. In addition, the notification did not discuss the potential inclusion of cyanogenic glycoside compounds from the peach kernel component in TJ-61. Nor did the notification discuss the potential inclusion of oxalic acid and calcium oxalate from the rhubarb and root of glycyrrhiza components of the new dietary ingredient, TJ-61.

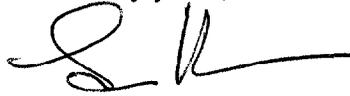
Page - 3 - Terukazu Kato, President

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that Tokaku-joki-to extract granules (TJ-61), 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 an ingredient does not present a significant or unreasonable risk of illness or injury. Introduction of such a 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 August 7, 2003. After the 90-day date, the notification will be placed on public display at FDA's Docket Management Branch in docket number 95S-0316. Prior to that date, you may wish to identify in writing specifically what information you believe is proprietary, trade secret or otherwise confidential for FDA's consideration.

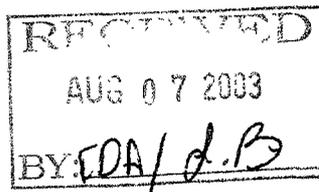
If you have any questions concerning this matter, please contact Victoria Lutwak at (301) 436-2375.

Sincerely yours,

A handwritten signature in black ink, appearing to be 'S. Walker', written over a horizontal line.

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

August 5, 2003



Ms. Victoria Lutwak
Division of Dietary Supplement
Programs and Compliance
Food and Drug Administration Center for Food Safety and Applied Nutrition
Office of Nutritional Products, Labeling and Dietary Supplements
5100 Paint Branch Parkway
College Park, MD, 20740-3835

Dear Ms. Lutwak,

Enclosed please kindly find two copies of our 75-day notification for a new dietary ingredient. According to 21 CFR 190.6, I just sent an original copy dated July 8, 2003. I apologize for making a mistake to send it without two copies and thank you very much for your kind phone-calls and facsimile.

If you have any questions, please contact me via e-mail at tkato@pmaiusa.com or fax at (310)328-5805.

Sincerely,

A handwritten signature in black ink, appearing to read "Terukazu Kato".

Terukazu Kato

President

TSUMURA USA, INC.

85'



TSUMURA USA
www.tsumura.com

TSUMURA USA
www.tsumura.com

FACSIMILE TRANSMISSION

DATE: 8 / 5 / 2003

ATTN: Ms. Victoria Lutwak

**TO: Division of Dietary Supplement, Programs and Compliance
Food and Drug Administration**

Fax Number: 301-436-2636

Phone Number: 301-436-1775

From: Terukazu Kato, c/o Tsumura & Co.

T-K

Fax Number: +81-3-3221-0016

Phone Number: +81-3-3221-0197

Pages including this: 1

Subject: 75-day Notification

Note: Thank you very much for your kind phone-calls and fax. I apologize for delay to respond to your phone-calls and fax because I have been staying in Japan to get a new VISA since the beginning of July 2003. I might have to stay in Japan for a couple more weeks.

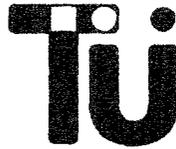
Today, 5th of August, I have sent two more copies of our 75-day notification for a new dietary ingredient to you via FedEx. Please kindly find the package very soon.

Since I will be in Japan more for a while, please contact me via e-mail at tkato@pmaiusa.com or fax at 310-328-5805 / +81-3-310-328-5805.

Again, I appreciate your great assistance.

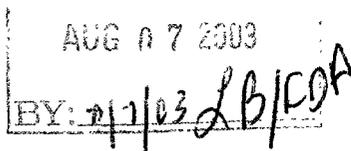
Terukazu Kato
TSUMURA USA, INC.

TSUMURA USA, INC.



TSUMURA USA

www.tsumura.com



July 8, 2003

Division of Standards and Labeling Regulations
Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-820)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD, 20740-3835
Telephone Number: (301) 436-2371

To whom it may concern,

In accordance with 21 CFR 190.6, TSUMURA USA INC. is hereby notifying the Food and Drug Administration that we intend to market a dietary supplement containing a new dietary ingredient, TSUMURA Tokaku-joki-to extract granules which is particularly useful for women's health.

1. The name and complete address of applicant

TSUMURA USA INC.
20910 Normandie Avenue, Unit C, Torrance,
CA 90502 U.S.A

2. The name of the new dietary ingredient

Peach Kernel, Cinnamon Bark, Rhubarb, Glycyrrhiza,
Anhydrous Mirabilitum ($\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$)
Light anhydrous silicic acid

3. The description of TSUMURA Tokaku-joki-to extract granules

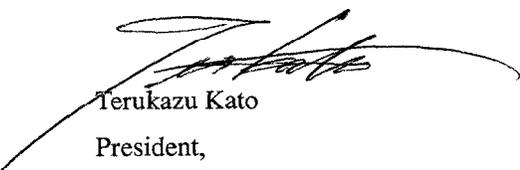
The usual adult dose is 7.5g/day orally in 2 or 3 divided doses before or between meals. The dosage may be adjusted according to the patient's age and body weight.



Detailed information on the conditions of use of the product, history of use or other evidence of safety of TSUMURA Tokaku-joki-to extract granules are summarized in the attached documents.

Based on the scientific studies and other information, TSUMURA USA INC. concludes that TSUMURA Tokaku-joki-to extract granules, when used under the conditions recommended, is reasonably expected to be safe.

Sincerely,



Terukazu Kato

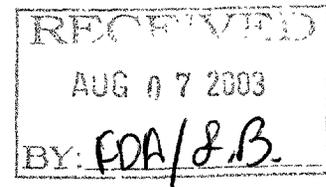
President,

TSUMURA USA INC.

TSUMURA TOKAKU-JOKI-TO EXTRACT GRANULES (TJ-61)

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I. INTRODUCTION

Tsumura Tokaku-joki-to Extract Granules (TJ-61) is an aqueous extract preparation from natural herbs, which was modernly standardized based on the traditional formula used for the Japanese Phytotherapy.

The raw herbs of TJ-61 are verified botanically and satisfy the requirement of Japanese Pharmacopoeia, the approved specifications and the additional self-imposed specifications.

Dried extract powder is formulated to granules by adding appropriate excipients. The amount of 2.5 g of granules is packaged in an aluminum laminated pouch. The specifications of this preparation for quality control include an assay of marker compounds by HPLC, description, identification test by TLC, purity test, heavy metals (arsenic), water content, ash, acid-insoluble ash, ethanol-soluble extract, disintegration, particle size and weight variation. The stability study has been conducted at room temperature.

Tsumura's production facilities meet the Good Manufacturing Practice (GMP) standards of the Ministry of Health and Welfare as set forth in the World Health Organization's GMP guidelines. Researchers, engineers and others involved in the production process work closely together to achieve a high-level of synergy in the integration of research and production, and this enabled to produce herbal extract preparations of good quality under optimum GMP standards. Moreover, Tsumura has taken the lead in this area by establishing a set of Self-imposed Standards for GMP of Extract Products in Herbal Product Formulations for Prescription Use¹⁾.

II. COMPONENTS AND COMPOSITION

A. Herbs

An active substance, Tokaku-joki-to extract powder, is made of 3.0g of the dry extract of the mixed raw herbs and 0.33g of light anhydrous silicic acid as a vehicle. The addition of 11% of light anhydrous silicic acid by weight to the extract increase the recovery rate when being dried by the spray-dry method. Also additional light anhydrous silicic acid, when manufacturing extract granules, improves fluidity and prevents coalescence.

Weight ratio of the raw herbs of Tokaku-joki-to extract 3.0 g:

Name of herbal drug	Unit
Peach Kernel (Persicae Semen)	5.0g
Cinnamon Bark (Cinnamomi Cortex)	4.0g
Rhubarb (Rhei Rhizoma)	3.0g
Glycyrrhiza (Glycyrrhizae Radix)	1.5g
Anhydrous Mirabilitum	0.9g

B. Excipients²⁾

In a daily dose, 7.5 g of TJ-61:

Name of component	Unit
Active substance:	
Tokaku-joki-to extract powder	3.33g
Excipients:	
Lactose monohydrate (vehicle)	Quantum sufficit
Magnesium stearate (lubricant)	0.1125g
Light anhydrous silicic acid (lubricant)	0.0375g

III.HISTORICAL USE

A. Herbs and light anhydrous silicic acid

A-1.Persicae Semen

The common peach is effective against high blood pressure and chronic appendicitis. It also promotes circulation, dissolves clots, and acts as a laxative, emollient, and anti-tussive. The seed is used.

A-2.Cinnamomi Cortex

Recent studies indicate that cinnamon contains a substance that kills fungi, bacteria, and other microorganisms, including the one that causes botulism, and another that causes a staph infection. Cinnamon is a heady spice, too, and is used in the cuisine of East India, Morocco, Indonesia, Arabia, Mexico, Hungary, China, Greece, and many other countries around the world. The bark is used.

A-3.Rhei Rhizoma

This herbal, native to the mountainous areas of China and Tibet, has been used medicinally for more than 2,000 years. Depending upon the size of the dose and the way it is given, the rhizome is effective in treating both constipation and diarrhea. In Kampo it is used primarily as a laxative. The root is used.

A-4.Glycyrrhizae Radix

The licorice root was mentioned in the very first Chinese herbal, thousands of years ago, and was introduced into Europe centuries later. The Blackfoot Indians used licorice to cure earaches. Other uses in various cultures include treatment of dropsy, fever, menstrual cramps, flu; hypoglycemia, and coughs. The chief component is 50 times sweeter than sugar. For a plant known primarily as a candy flavoring it has a remarkably long list of pharmacological properties. The root is used in Japanese herbal medicine.

A-5.Mirabilitum

Usage of Mirabilitum according to Japanese classics:

Used mainly to soften hardness. Used to treat hardness of the epigastrium, severe pain upon pressure in the lower left abdomen, pain and distention of the epigastrium, dry hard stools, stagnant food in the digestive tract, abdominal distention, discomfort and tension of the lower abdomen, and other illness caused by stagnant pathogens.

A-6.Light anhydrous silicic acid

Light anhydrous silicic acid is used as an adsorbent and an anticaking agent in the preparation of the extract powder.

B. TJ-61

TJ-61, Japanese traditional herbal product, is based on know-how and experience going back to ancient times in China on the utilization and combining of herbs to exhibit their

effectiveness.

TJ-61 consists of Persicae Semen, Rhei Rhizoma, Cinnamomi Cortex, Glycyhizae Radix and Mirabilitum and light anhydrous silicic acid, and helps maintain women's health.

IV. TOXICITY STUDIES

A. Acute toxicity of TJ-61³⁾

Acute toxicity studies of TJ-61 were examined in mice and rats. Both rats and mice showed sedation and diarrhea. In addition, one and two dead animals were observed in male and females rats in the 15-g/kg treatment group, respectively, but the LD₅₀ value could not be calculated. There was no remarkable finding in mice and rats at any dose.

B. Acute toxicity of light anhydrous silicic acid⁴⁾

Experiments using mice and rats indicated that Syloid, a food additive consisting of amorphous silica, has a very low toxicity with LD₅₀ higher than 4,500 mg/kg for oral administration. Although studies on chronic toxicity will be needed to establish the safety of Syloid as a food additive, the results are expected to indicate a very low toxicity.

C. Chronic toxicity and carcinogenicity of light anhydrous silicic acid⁵⁾

Based on the results of oral ingestion of Syloid to mice and rats, the use of Syloid as an anti-caking agent is safe for human consumption.

D. Genotoxicity of TJ-61⁶⁾

Herbal products were investigated using a bacterial reverse mutation test (the Ames test), an in vivo micronucleus test (MN test) in mouse bone marrow cells and an unscheduled DNA synthesis test (UDS test) in rat hepatocytes. TJ-61 was investigated using the Ames test.

From the results of genotoxicity studies, it was suggested that herbal products pose little or no risk for human health from the viewpoint of genotoxicity. under the conditions of intended use.

V. MANUFACTURING CONDITIONS

A. Method of preparation

TJ-61 is manufactured based on the following 4 standard codes according to the GMP:

1. Drug product standard code
2. Manufacturing control standard code
3. Quality control standard code
4. Manufacturing hygiene control standard code

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information