IWADE RESEARCH INSTITUTE OF MYCOLOGY CO.,LTD.
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June 21, 2006

Susan Walker, Ph.D.
Division of Dietary Supplement Programs
Office of Nutritional Products Labeling and Dietary Supplements (HFS-800)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740

Subject: Notification for New Dietary Ingredient
Freeze-Dried Extract of *Agaricus blazei* Murrill (ABM-FD)

Dear Dr. Walker,

This notification is in accordance with the 21 USC 350(b)(2) and 21 CFR 190.6, Requirement for premarket notification by Iwade Research Institute of Mycology Co. Ltd., Japan.

The new dietary ingredient is a freeze dried extract of *Agaricus blazei* Murrill (fruiting bodies) also referred to as ABM-FD. Iwade Research Institute has submitted notification for very similar new dietary ingredient in 1999 and 2000 (RPT 49 and 76), and another very similar product was submitted by Japan Applied Microbiology Research Institute Ltd. (RPT 276). This notification makes reference to all the safety studies that support these notifications, as the subject of this notification is similar and encompass the same constituents. However, any specific studies that are relied are particularly discussed in our safety review.

Iwade Research has concluded that ABM-FD is safe for use as a new dietary ingredient and is providing safety data to support this use.

2006-5416

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Portions of the notification are considered commercial and confidential and fall within the exemptions established in 21 CFR 20.61. All these sections are found in the attachment section described as Manufacturing (Tab 1), and should not be placed on public display.

If there are any questions this notification please contact Kristi Smedley or William Olson, Center for Regulatory Services, Inc at. 703-590-7337 or at cfrsrv@aol.com.

Sincerely,

Toshimitsu Sumiya

Toshimitsu Sumiya, President
Iwade Research Institute
of Mycology Co.,Ltd.

Enclosure: Notification for Dietary Ingredient—ABM-FD (original and two copies)

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75-Day Notification for New Dietary Ingredient ABM-FD

1.Name and Address:

Manufacturer: Iwade Research Institute of Mycology Co., Ltd.
1-9 Suehiro-cho, Tsushi, Mie 514-0012, Japan

2. Name of the New Dietary Ingredient

ABM-FD (*Agaricus blazei* Murrill Freeze Dry)
Vacuum Freeze-Dried *Agaricus blazei* Murrill (also known as Himematsutake) Extract

3. Description of the New Dietary Ingredient

- 100% vacuum freeze-dreid water extract of *Agaricus blazei* Murrill (Himematsutake). (No other ingredients.)
- ABM-FD is a simple water extraction and freeze dried product, of the fruiting body of *Agaricus blazeii* Murrill. No carriers or other ingredients are introduced. Tab 1 provides a schematic of the manufacturing process.
- ABM-FD is marketed in a glass bottle.
- Directions state that the consumer dissolves AMB-FD in water in the marketed bottle, by filling the bottle between half to seven-tenths in the bottle, shake, and then drink on an empty stomach, prior to a meal.
- A typical certificate of analysis (original in Japanese, with an English translation) is provided in Tab 1.

3(i). Level of Use

- Each bottle contains 3.0 grams of ABM-FD.
- For adults (non-pregnant and non-lactating) are instructed to consume the dissolved contents of one bottle (3.0 grams) each day
- The commercial product is sold in a box containing 10 bottles of ABM-FD (a vacuum of Freeze-Dry of *Agaricus blazei* Murrill (Himematsutake) Extracts. Each bottle contains 3.0g of ABM-FD.

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3(ii) Conditions of use:

- Intended for use by adults.
- Not intended for use by pregnant females, lactating females, or infants, or children.
- Product is to be dissolved in water and consumed on an empty stomach (before meals or several hours after a meal.

4. Evidence to Establish Safety

There have been previous premarket notifications submitted for dietary supplements derived from *Agaricus blazei* Murrill. These include the following:

Iwade Research Institute 1999 (RPT 49) (spray dried extract of mycelia of *Agaricus blazei* Murrill mixed with guar gum)

Iwade Research Institute 2000 (RPT 76) (dried water extract of fruiting bodies and mycelia of *Agaricus blazei* Murrill mixed with guar gum),

Japan Applied Microbiology Research Institute Ltd. 2005 (RPT 276) (enzyme-treated *Agaricus blazei* Murill mycelia mixed with brewer's yeast)

The recommendations for use are 3 grams of the freeze-dry material 1X/day, which is a dosage for a 60 kg person of 50 mg/kg/day.

Previous submitted information included: subchronic feeding studies in experimental animals, reproductive studies in mice, and human clinical studies with no remarkable adverse effects observed (see RPT 76).

The preparation which is the subject of this premarket notification has been subjected to a subchronic study in rats by oral gavage for 13-weeks (Tab 2). This is a comprehensive study with detailed in life observations, as well as hematology, blood chemistry, urinalysis, observation of organs, and histopathology.

The test substance used in this study was the same material that is the subject of this

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premarket notification and was prepared in the freeze dry material in water with the concentrations being adjusted so that a 10 ml/kg dosage resulted in a dosage of the test substance being 500, 1000, and 2000 mg/kg/day. The dosage was given daily to be consistent with the dosage recommendation in this premarket notification.

All of the dosages were well tolerated, with no evidence of any toxicological significant change, and no treatment related histopathology findings. The observed adverse effect level of this substance was determined to be 2000 mg/kg/day.

The equivalent dosage with no observable adverse effects therefore was 40X that of the dosage recommended(50 mg/Kg/day) for use as a dietary supplement in man.

In addition a battery of mutagenicity studies were conducted to evaluate the potential genotoxicity of the substance. These were:

Bacterial reverse mutation test (Tab 3)
In vitro mutation test using mouse lymphoma L5178Y cells (Tab 4)
Micronucleus Test in Rats (Tab 5)

The results of these studies indicated that there was no evidence of genotoxicity of the substances.

A clinical study has also been conducted using Freeze-Dry Agaricus blazei Murrill (Iwade strain 101) Himematsutake extracts. An English language report of this study is enclosed (Tab 6--Kajimoto, et al.). In this case the fruiting body and the mycelia were extracted and freeze-dried in a manner similar to the preparation of the substance used in this premarket notification.

The substance was administered to normal adults or to adults with slightly altered hepatic function. The study was conducted for 12-weeks with three grams of the freeze-dried substance being consumed 2X per day. The preparation used in this clinical study was composed of 70% extracts from the fruiting body and 30% from the mycelia, thus there was

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approximately 2 grams of freeze-dried fruiting bodies being consumed 2X per day. The dosage on a daily basis was 4 grams of freeze-dried fruiting body extractives, i.e., an excess of the recommended dosage of the dietary supplement. The subjects were followed carefully with respect to hematology, blood chemistry, urinalysis, and medical and physical examinations.

The conclusion of the study was that the freeze-dried extract when administered continuously for 12-weeks by adult male and female subjects including those with slightly altered hepatic function did not result in any adverse events and supported the conclusion that the use of the extract was safe and health in subjects with slightly altered hepatic function.

A 90-day feeding study (levels up to 5%) in rats (Tab 7) confirmed a lack of toxicity, of the ABM-FD. The researchers concluded a NOAEL at the highest concentration tested.

It is concluded from the publicly available information and from the previously submitted safety and clinical studies together with the studies as conducted specifically with the product that is the subject of this dietary ingredient notification, that the freeze-dry extract of *Agaricus blazei* Murrill fruiting bodies is safe for use under the conditions as proposed for use in the description of the new dietary ingredient.

There is no evidence from the studies for use in human subjects, or in the toxicological evaluations of this substance that would suggest that the product is unsafe when used as directed.

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REFERENCES

Tab 1. Manufacturing Information--**CONFIDENTIAL**

A. Schematic of Manufacturing
B. Certificate of Analysis
C. Chemical Specifications

TAB 2. ABM-FD: Toxicity Study By Oral Gavage Administration To CD Rats For 13 Weeks. Huntingdon Life Sciences

TAB 3. ABM-FD (EXTRACT OF HIMEMATSUTAKE): Bacterial Reverse Mutation Test.-- Huntingdon Life Sciences

TAB 4. ABM-FD (EXTRACT OF HIMEMATSUTAKE): *In Vitro* Mutation Test Using Mouse Lymphoma L5178Y Cells.-- Huntingdon Life Sciences

TAB 5. ABM-FD (EXTRACT OF HIMEMATSUTAKE): Rat Micronucleus Test.-- Huntingdon Life Sciences

Tab 6. The Safety of Extended Consumption of Freeze-Dry of *Agaricus blazei* Murrill (Iwade strain 101) Himematsutake Extracts. Osami Kajimoto[1)], Yutaka Ikeda[2)], Mitsuharu Yabune[3)], Akane Sakamoto[3)], Yoshitaka Kajimoto[3)]

Tab 7. Lack of subchronic toxicity of an aqueous extract of *Agaricus blazei* Murrill in F344 rats. Y. Kuroiwa, et al.: Food and Chemical Toxicology 43, 1047-1053, 2005.