



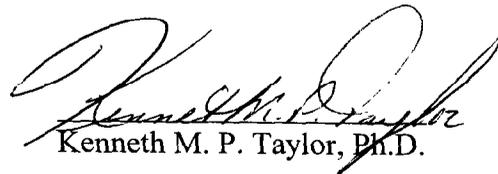
Memorandum

0439 '03 JAN 27 P2:25

Date: January 23, 2003
From: Chemist, Division of Standards and Labeling Regulations, Office of Nutritional Products, Labeling and Dietary Supplements, HFS-821
Subject: 75-Day Premarket Notification of New Dietary Ingredients
To: Dockets Management Branch, HFA-305

Subject of the Notification: Geranti Bio-Ge
(bio-germanium yeast)
Firm: Geranti Pharm Ltd.
McKenna, Long & Aldrich
Date Received by FDA: August 30, 2002
90-Day Date: November 28, 2002

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.



Kenneth M. P. Taylor, Ph.D.

Attachments

95S 0316

RPT155



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, MD

OCT 17 2002

Stuart Kim
McKenna Long & Aldrich LLP
Attorneys at Law
1900 K Street, NW
Washington, DC 20006

Dear Mr. Kim:

This is to inform you that the notification, dated August 30, 2002, which you submitted on behalf of your client, Geranti Pharm Ltd. of Seoul, South Korea, pursuant to 21 U.S.C. 350b(a)(2) was received and filed by the Food and Drug Administration (FDA) on August 30, 2002. Your notification concerns the substance Geranti Bio-Ge that you assert is a new dietary ingredient.

Your notification further states that Geranti Bio-Ge is a bio-germanium yeast product intended for use in dietary supplements. The dietary supplement products are expected to contain from 10 to 300 mg bio-germanium yeast per capsule/tablet for a maximum daily intake of 500 mg bio-germanium yeast (1.5 mg total germanium).

In accordance with 21 C.F.R 190.6(c), FDA must acknowledge its receipt of a notification for a new dietary ingredient. For 75 days after the filing date (i.e., after November 13, 2002), your client must not introduce or deliver for introduction into interstate commerce any dietary supplement that contains Geranti Bio-Ge.

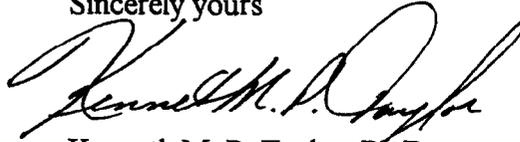
Please note that acceptance of this notification for filing is a procedural matter and, thus, does not constitute a finding by FDA that the new dietary ingredient or supplement that contains the new dietary ingredient is safe or is not adulterated under 21 U.S.C. 342. FDA is not precluded from taking action in the future against any dietary supplement containing Geranti Bio-Ge if it is found to be unsafe, adulterated, or misbranded. As another procedural matter,

Page 2 – Mr. Stuart Kim

your notification will be kept confidential for 90 days after the filing date. After November 28, 2002, the notification will be placed on public display at FDA's Docket Management Branch in docket number 95S-0316. However, any trade secret or otherwise confidential commercial information in the notification will not be disclosed to the public.

Please contact me at (301) 436-2371, if you have any questions concerning this matter.

Sincerely yours

A handwritten signature in black ink, appearing to read "Kenneth M. P. Taylor". The signature is fluid and cursive, with a large initial "K" and "T".

Kenneth M. P. Taylor, Ph.D.

Chemist

Division of Standards

and Labeling Regulations

Office of Nutritional Products, Labeling

and Dietary Supplements

Center for Food Safety

and Applied Nutrition



NOV 13 2002

Stuart Kim
McKenna Long & Aldrich LLP
Attorneys at Law
1900 K Street, NW
Washington, DC 20006

Dear Mr. Kim:

This is in response to your submission of a new dietary ingredient notification, dated August 30, 2002, to the Food and Drug Administration (FDA) pursuant to 21 U.S.C. 350b(a)(2) and 21 Code of Federal Regulations (CFR) Part 190.6. FDA received your notification on August 30, 2002, of your intent to market the ingredient Geranti Bio-Ge.

Your submission indicates that Geranti Bio-Ge is a bio-germanium yeast product intended for use in dietary supplements. The dietary supplement products are expected to contain from 10 to 300 mg bio-germanium yeast per capsule/tablet for a maximum daily intake of 500 mg bio-germanium yeast (1.5 mg total germanium). You state in the notification that the dietary supplement products that contain Geranti Bio-Ge are expected to contain from 0.03 mg to 0.9 mg germanium per capsule/tablet, with the recommended maximum daily intake of germanium not to exceed 1.5 mg per day. However, no specific dosage is given, and a dose of two capsule/tablets of the products containing 0.9 mg germanium would exceed the maximum daily limit stated in the notification.

In accordance with 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 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 new 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 dietary supplements containing Geranti Bio-Ge, when used under the conditions recommended or suggested, will reasonably be expected to be safe. Specifically, FDA continues to have concerns about the use of germanium and germanium-containing compounds in dietary supplements and nothing in your submission provides a basis to conclude that germanium use is safe. Prolonged intake of products containing germanium has been reported to be associated with various adverse effects including renal dysfunction, anemia, myopathy, neurotoxicity, and nephrotoxicity in several human cases¹⁻⁴. The studies referenced in your notification are not sufficient to demonstrate that use of your Geranti Bio-Ge would not cause the adverse effects noted in the literature to be associated with the intake of germanium.

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that Geranti Bio-Ge, 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 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. After November 28, 2002, the notification and related correspondence from FDA will be placed on public display at FDA's Dockets Management Branch in docket number 95S-0316. However, any trade secret or otherwise confidential commercial information that is in the notification will not be disclosed to the public. Commercial and confidential information in the notification will not be made available to the public. Prior to November 28, 2002, you may wish to identify in writing specifically what information you believe is proprietary.

¹ Schauss, AG (1991) *Biol Trace Elem Res* **29**(3):267-280.

² Deseus, FH *et al* (1986) *Cancer Treat Rep* **70**(9):1129-1130.

³ Eisenhauer, E. *et al* (1985) *Invest New Drugs* **3**(3):307-310.

⁴ Nagata, N. *et al* (1985) *J Toxicol Sci* **10**(4):333-334.

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Nevertheless, our Center's Freedom of Information Officer has the authority to make the final decision about what information in the notification should be redacted before it is posted at Dockets.

If you have any questions concerning this letter, please contact me at (301) 436-2371.

Sincerely yours,

A handwritten signature in cursive script that reads "Felicia B. Satchell for".

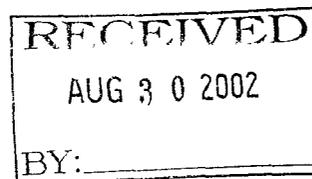
Felicia B. Satchell
Director
Division of Standards
and Labeling Regulations
Office of Nutritional Products, Labeling
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August 30, 2002

VIA HAND DELIVERY

Stuart Kim
202-496-7534
skim@mckennalong.com

Division of Standards and Labeling Regulations
Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-820)
Center for Food Safety and Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, Maryland 20740-3835

Re: 75-Day Pre-Market Notification for New Dietary Ingredient - Geranti Bio-Ge

Dear Sir or Madam:

Pursuant to Section 413 of the Federal Food, Drug, and Cosmetic Act ("the Act") and 21 C.F.R. § 190.6, please find enclosed a pre-market notification for *Geranti Bio-Ge*, which McKenna Long & Aldridge, L.L.P. is forwarding as counsel to the submitter, Geranti Pharm Ltd. of Seoul, South Korea.

Geranti Bio-Ge is a bio-germanium yeast product intended for use as a dietary ingredient in dietary supplements. We have enclosed a discussion of the scientific data and information showing that *Geranti Bio-Ge*, when used under the conditions suggested in the labeling of the dietary supplement, is reasonably expected to be safe. Therefore, Geranti Pharm Ltd. believes *Geranti Bio-Ge*, when used as intended, would not present a significant or unreasonable risk of illness or injury and would reasonably be expected to be safe.

In accordance with 21 C.F.R. § 190.6(a), we have enclosed the original and two copies of this pre-market notification submission. If you have any questions concerning this notification, please contact me.

Sincerely,

Stuart Kim

SK/clb
Enclosures
cc: Geranti Pharm Ltd.

**PRE-MARKET NOTIFICATION FOR NEW DIETARY INGREDIENT
GERANTI BIO-GE (BIO-GERMANIUM YEAST)**

COMPANY INFORMATION

COMPANY NAME: Geranti Pharm Ltd.

COMPANY ADDRESS: Geranti Building 678-20
Yoksam-dong, Kangnam-gu
Seoul, SOUTH KOREA

NEW DIETARY INGREDIENT INFORMATION

NEW DIETARY INGREDIENT NAME: *Geranti Bio-Ge* (bio-germanium yeast)

INTENDED USE OF NEW DIETARY INGREDIENT: *Geranti Bio-Ge* is intended for use as a dietary ingredient in dietary supplement products. Such dietary supplement products are expected to contain from 10 to 300 mg bio-germanium yeast (and from 0.03 mg to 0.9 mg germanium) per capsule/tablet for daily intake up to 500 mg bio-germanium yeast (and 1.5 mg germanium).

DESCRIPTION OF THE NEW DIETARY INGREDIENT

Germanium (³²Ge) is an ultratrace element¹ found in common food sources such as beans, garlic, ginseng, shitake mushrooms, tuna, and water chestnuts.² Germanium is available in both *inorganic* and *organic* forms. Typical daily dietary intakes of germanium range from 0.4 to 1.5 mg.³

¹ For humans, the term *ultratrace element* is often used to indicate elements with an established, estimated, or suspected requirement of < 1 mg/day, or generally indicated by µg/day. See Nielsen, F.H. 1996. *How Should Dietary Guidance Be Given for Mineral Elements with Beneficial Actions or Suspected of Being Essential?* JOURNAL OF NUTRITION 126: 2377S-2385S.

² See Schroeder, H.A., and J.J. Balassa. 1966. *Abnormal trace elements in man: Germanium.* JOURNAL OF CHRONIC DISEASES 20: 211-224.

³ See Nielsen, F.H. 1996. *How Should Dietary Guidance Be Given for Mineral Elements with Beneficial Actions or Suspected of Being Essential?* JOURNAL OF NUTRITION 126: 2377S-2385S and PDR FOR NUTRITIONAL SUPPLEMENTS 181 (Medical Economics/Thomson Healthcare 2001). For comparison, many commercially available dietary supplement products containing *Bis-Beta Carboxyethyl Germanium Sesquioxide* (Ge-132) contain amounts of germanium greater than 1.5 mg.

PRE-MARKET NOTIFICATION FOR NEW DIETARY INGREDIENT GERANTI BIO-GE (BIO-GERMANIUM YEAST)

The dietary intake of germanium is recognized but not well understood. The absorption, distribution, and elimination of organic germanium has been described.⁴ Preliminary evidence has shown that:

1. germanium deficiency in rats is observed as “altered bone and liver mineral composition, and decreased tibial DNA”;⁵
2. germanium reverses changes in rats caused by silicon deprivation;⁶
3. several organic germanium compounds may have antitumor activity;⁷ and
4. one form of *organic* germanium, Ge-132 (bis-beta carboxyethyl germanium sesquioxide), may have both antiproliferative activity and antioxidant activity.⁸

Germanium is one of eighteen *ultratrace elements* for which increased attention in future editions of the Recommended Dietary Allowances (“RDAs”) is appropriate.⁹ The reasons for this increased attention are:

- “... responsible information about the usefulness of the ultratrace elements for health and well-being is needed.”
- “Authoritative advice is required to prevent standards that obstruct the achievement of beneficial intakes of ultratrace elements.”

⁴ See Lekim, D, and H. Kehlbeck. 1985. *The biological activity of germanium*. In: 1ST INTERNATIONAL CONFERENCE ON GERMANIUM. Hanover, October 1984. Lekim and Samochowiec, eds. Semmelweis-Verlag cited in Goodman, S. 1988. *Therapeutic effects of organic germanium*. MEDICAL HYPOTHESES 26: 207-215.

⁵ See Nielsen, F.H. 1996. *How Should Dietary Guidance Be Given for Mineral Elements with Beneficial Actions or Suspected of Being Essential?* JOURNAL OF NUTRITION 126: 2377S-2385S.

⁶ *Id.*

⁷ See Goodman, S. 1988. *Therapeutic effects of organic germanium*. MEDICAL HYPOTHESES 26: 207-215 and Marczynski, B. 1988. *Carcinogenesis as the result of the deficiency of some essential trace elements*. MEDICAL HYPOTHESES 26: 239-249.

⁸ See PDR FOR NUTRITIONAL SUPPLEMENTS 181 (Medical Economics/Thomson Healthcare 2001).

⁹ See Nielsen, F.H. 1996. *How should dietary guidance Be given for mineral elements with beneficial actions or suspected of being essential?* JOURNAL OF NUTRITION 126: 2377S-2385S.

PRE-MARKET NOTIFICATION FOR NEW DIETARY INGREDIENT GERANTI BIO-GE (BIO-GERMANIUM YEAST)

- "... the determination of nutritional requirements should include consideration of the total effects of nutrients, not just their roles in preventing deficiency pathology ..."¹⁰

Some *inorganic* forms of germanium (e.g., germanium dioxide) have been shown to be toxic to the liver and kidneys. The safety of dietary supplement products containing or consisting of the non-toxic forms of organic germanium (e.g., Ge-132) has been compromised by contamination with toxic forms of *inorganic* germanium.¹¹

Geranti Pharm Ltd. ("Company"), through its biotechnology research efforts, has developed a form of bio-germanium yeast called *Geranti Bio-Ge* that consists of 99.7% yeast and 0.3% germanium. *Geranti Bio-Ge* contains organic germanium processed by fermentation in adapted *Saccharomyces cerevisiae* yeast.¹²

The use of *S. cerevisiae* in converting an ultratrace element from its toxic, low availability *inorganic* form to its safe, high availability *organic* form is not unique because yeast (1) replicates the mineral conversion process performed by most plants for improved nutrient utilization, and (2) has a role in toxic metal ion detoxification.¹³ In addition, this process is commonly used by other dietary supplement manufacturers to synthesize the organic forms of other ultratrace elements such as selenium-yeast (e.g., SelenoSource™ "All-Natural, High Selenium Yeast" manufactured by DV Technologies, Inc. of Cedar Rapids, Iowa).

SAFETY OF THE NEW DIETARY INGREDIENT

Some inorganic forms of germanium have been associated with some toxic effects of germanium. However, some organic forms of germanium may be contaminated by the presence of inorganic germanium. The purity of *Geranti Bio-Ge* manufactured by the Company is unique and distinguished from other forms of commercially prepared organic germanium.

¹⁰ *Id.*

¹¹ On its web site <http://www.nnfa.org/services/science/bg_germanium.htm>, the National Nutritional Foods Association reiterated this concern: The "known toxicity of germanium dioxide makes the purity of Ge-132 a critical factor in determining propriety of its uses as a dietary supplement."

¹² See Geranti Pharm Ltd. 1995. *Preparation of organic germanium by yeast cell*. KOREAN JOURNAL OF APPLIED MICROBIOLOGY AND BIOTECHNOLOGY 1: 87-90.

¹³ See Ramsay, L.M., and G.M. Gadd. 1997. *Mutants of Saccharomyces cerevisiae defective in vacuolar function confirm a role for the vacuole in toxic metal ion detoxification*. FEMS MICROBIOLOGY LETTERS 152: 293-298.

**PRE-MARKET NOTIFICATION FOR NEW DIETARY INGREDIENT
GERANTI BIO-GE (BIO-GERMANIUM YEAST)**

The Food and Drug Administration (“FDA”) has expressed safety concerns regarding germanium related to (1) contamination of the organic form with the inorganic form and (2) the nutritional value of this ultratrace element. According to its 1988 (revised 1995) Import Alert,

Germanium ... has caused nephrotoxicity (kidney injury) and death when used chronically by humans ... Germanium-containing products have been labeled for drug use (e.g., with claims that they are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of diseases such as AIDS or cancer) ... Germanium containing products also have been offered for entry as food products such as dietary supplements.¹⁴

This statement regarding toxicity in humans is applicable only to products that contain *inorganic* germanium, either as an ingredient or as a contaminant. The FDA did not to make the distinction between *organic* and *inorganic* germanium in its Import Alert. Moreover, various *organic* germanium dietary supplement products have been and are in commercial distribution without any reports of adverse events.

The toxicity of germanium dioxide (i.e., *inorganic* germanium) has been documented in humans,¹⁵ but few adverse effects have been reported for Ge-132 or germanium sesquioxide (i.e., *organic* germanium).¹⁶ The mere representation that the “evidence of Ge-132 toxicity is inconclusive” is insufficient to warrant a conclusion, as stated in the paper by CFSAN scientists, that *organic* germanium “presents a potential health hazard.”¹⁷ General statements of this type confirm that “... responsible information about the usefulness of the ultratrace elements for health and well-being is needed.”¹⁸

In general, prolonged intake of many ultratrace elements, not just germanium, is toxic.¹⁹ In 27 cases of toxicity associated with the prolonged intake of germanium-containing products, only

¹⁴ The FDA Import Alert is available at <http://www.fda.gov/ora/fiars/ora_import_ia5407.html>.

¹⁵ See e.g., Obara, K. 1991. *Germanium poisoning: Clinical symptoms and renal damage caused by long-term intake of germanium*. JAPANESE JOURNAL OF MEDICINE 30: 67-72.

¹⁶ See e.g., Stricker, B.H. 1990. *Dietary germanium supplements*. LANCET 336: 117 and Stricker, B.H. 1991. *Dietary germanium supplements*. LANCET 337: 864.

¹⁷ See Tao, S.-H. and P.M. Bolger. 1997. *Hazard assessment of germanium supplements*. REGULATORY TOXICOLOGY AND PHARMACOLOGY 25: 211-219.

¹⁸ See Nielsen, F.H. 1996. *How should dietary guidance Be given for mineral elements with beneficial actions or suspected of being essential?* JOURNAL OF NUTRITION 126: 2377S-2385S.

¹⁹ See e.g., Mosby, D.W. 2000. CLINICIAN'S COMPLETE REFERENCE TO COMPLEMENTARY AND ALTERNATIVE MEDICINE (2nd Edition), p. 586 and Koller, L.D., and J.H. Exon. 1986. *The two faces of*

(Footnote cont'd on next page.)

**PRE-MARKET NOTIFICATION FOR NEW DIETARY INGREDIENT
GERANTI BIO-GE (BIO-GERMANIUM YEAST)**

six cases involved products containing organic germanium,²⁰ and two of those cases involved a product containing both inorganic and organic germanium (i.e., GeO₂ and Ge-132).²¹ Although “evidence of Ge-132 toxicity is inconclusive,” the more important need for a distinction between the *inorganic* and *organic* forms of germanium in assessing the hazard of germanium dietary supplement products has been expressed.

Specifically, the safety concerns regarding *Geranti Bio-Ge* as a new dietary ingredient focus on:

1. the purity of the bio-germanium yeast;
2. the toxicity of the bio-germanium yeast; and
3. the recommended daily intake of the organic germanium yeast product.

These concerns will be addressed individually.

1. **PURITY OF THE BIO-GERMANIUM YEAST:** *Geranti Bio-Ge* contains *organic* germanium synthesized by fermentation in adapted *S. cerevisiae* yeast.²² *Geranti Bio-Ge* consists of 99.7% yeast and 0.3% germanium. The Company applies a manufacturing process to eliminate all by-products (specifically *inorganic* germanium) of the fermentation process. The Company has confirmed that, using standard biochemical and molecular biological methods to identify and purify the organic germanium, *Geranti Bio-Ge* contains organic germanium bound with yeast.²³

(Footnote cont'd from previous page.)

selenium-deficiency and toxicity-are similar in animals and man. CANADIAN JOURNAL OF VETERINARY RESEARCH 50: 297-306.

²⁰ Two cases involved carboxyethyl germanium sesquioxide (a.k.a. Ge-132), and four cases involved sanumgerman (a.k.a. germanium-lactate-citrate).

²¹ See Tao, S.-H. and P.M. Bolger. 1997. *Hazard assessment of germanium supplements.* REGULATORY TOXICOLOGY AND PHARMACOLOGY 25: 211-219.

²² See Geranti Pharm Ltd. 1995. *Preparation of organic germanium by yeast cell.* KOREAN JOURNAL OF APPLIED MICROBIOLOGY AND BIOTECHNOLOGY 1: 87-90.

²³ See National Instrumentation Center for Environmental Management, College of Agriculture and Life Sciences, Seoul National University. 2001. *Identification and purification of Dried Yeast-G (Geranti Bio-Ge, dried yeast containing organic germanium).*

**PRE-MARKET NOTIFICATION FOR NEW DIETARY INGREDIENT
GERANTI BIO-GE (BIO-GERMANIUM YEAST)**

2. TOXICITY OF THE BIO-GERMANIUM YEAST: The Company has conducted both acute (in mice and rats)²⁴ and chronic (in rats and beagles)²⁵ toxicity tests to show that *Geranti Bio-Ge* is safe. The acute oral toxicity for *Geranti Bio-Ge* is low (> 5000 mg/kg body weight for the ICR mouse and Sprague-Dawley rat). In chronic toxicity tests, a maximum of 5000 mg (Sprague-Dawley rats) and 1500 mg (beagles) *Geranti Bio-Ge* were administered per kg body weight of the test animals. There was no evidence of carcinogenicity.

Germanium is rapidly absorbed and eliminated from the body without undergoing metabolic alteration. Studies have been performed which trace the route that organic germanium follows in its “trip” through the body.²⁶ A summary of this “trip” follows:

- Within one hour of administration, 50% of organic germanium is in the gastrointestinal tract. After 12 hours, the figure falls to 5%.
- Organic germanium is resorbed by the vena portae. One hour after administration, 50% is in the vena portae. After eight hours, this figure rises to 85%. By 12 hours, organic germanium is quasi-complexed.
- Two hours after administration, serum plasma levels reach a maximum. In eight hours, this figure is reduced by 80% of the maximum.
- Organic germanium, when administered orally, has been shown to be absorbed by about 30%, and is ubiquitously distributed in all organs. After 12 hours, almost no residual concentration is detected.
- Organic germanium is excreted (and unchanged metabolically) in the urine after 24 hours.

²⁴ See Experimental Animal Laboratory, Research Institute of Animal Medicine College of Veterinary Medicine, Chungbuk National University, Korea. 1994. *An acute toxicity test of bio-synthesized organic germanium: 1. Mouse – An acute oral toxicity test; 2. Rat – An acute oral toxicity test.* and Biological Test Center, Irvine, California. 1996. *Organic Germanium Fortified Dried Yeast – Acute Oral Toxicity Test.*

²⁵ See Ahn, D.-C., *et al.* 2001. Chronic toxicity of Dry Yeast-G (Biogermanium) orally administered to rats for 10 consecutive months. *KOREAN JOURNAL OF LABORATORY ANIMAL SCIENCE* 17: 109-118 and Ahn, D.-C., *et al.* 2001. Chronic toxicity of Dry Yeast-G (Biogermanium) orally administered to beagle dogs for 10 consecutive months. *KOREAN JOURNAL OF LABORATORY ANIMAL SCIENCE* 17: 99-108.

²⁶ See Lekim, D, and H. Kehlbeck. 1985. *The biological activity of germanium.* In: 1ST INTERNATIONAL CONFERENCE ON GERMANIUM. Hanover, October 1984. Lekim and Samochowiec, eds. Semmelweis-Verlag cited in Goodman, S. 1988. *Therapeutic effects of organic germanium.* *MEDICAL HYPOTHESES* 26: 207-215.

**PRE-MARKET NOTIFICATION FOR NEW DIETARY INGREDIENT
GERANTI BIO-GE (BIO-GERMANIUM YEAST)**

- Organic germanium is eliminated at quite a rapid, linear rate (approximately 8% of the dose per hour) during the first eight hours. It is completely eliminated after three days, mainly via the kidneys (85%).
3. RECOMMENDED DAILY INTAKE OF THE BIO-GERMANIUM YEAST: The Company has followed the range of typical daily dietary intake of germanium (from 0.4 to 1.5 mg) in recommending the daily intake of *Geranti Bio-Ge* (and germanium) should not exceed 500 mg (and 1.5 mg). This recommended daily intake of germanium in *Geranti Bio-Ge* is much lower than that of commercially available germanium dietary supplement products.²⁷

SUMMARY

Pursuant to Section 413 of the Federal Food, Drug, and Cosmetic Act and 21 C.F.R. § 190.6, Geranti Pharm Ltd. has submitted a pre-market notification for *Geranti Bio-Ge*, a bio-germanium yeast product intended for use as a dietary ingredient in dietary supplements. The Company believes *Geranti Bio-Ge*, when used as intended, would not present a significant or unreasonable risk of illness or injury and would reasonably be expected to be safe when used as intended.

REFERENCES CITED

- | | |
|--|-------|
| Experimental Animal Laboratory, Research Institute of Animal Medicine College of Veterinary Medicine, Chungbuk National University, Korea. 1994. <i>An acute toxicity test of bio-synthesized organic germanium: 1. Mouse – An acute oral toxicity test; 2. Rat – An acute oral toxicity test.</i> | TAB A |
| FDA Import Alert #54-07. 1995. <i>Germanium Products</i> . Available on the Internet at http://www.fda.gov/ora/fiars/ora_import_ia5407.html . | TAB B |
| Geranti Pharm Ltd. 1995. <i>Preparation of organic germanium by yeast cell</i> . KOREAN JOURNAL OF APPLIED MICROBIOLOGY AND BIOTECHNOLOGY 1: 87-90. (abstract only) | TAB C |
| Goodman, S. 1988. <i>Therapeutic effects of organic germanium</i> . MEDICAL HYPOTHESES 26: 207-215. | TAB D |
| Ahn, D.-C., et al. 2001. Chronic toxicity of Dry Yeast-G (Biogermanium) orally administered to rats for 10 consecutive months. KOREAN JOURNAL OF LABORATORY ANIMAL SCIENCE 17: 109-118 and Ahn, D.-C., et al. 2001. Chronic toxicity of Dry | TAB E |

²⁷ By comparison, the recommended daily intake for *Bis-Beta Carboxyethyl Germanium Sesquioxide* (a.k.a. Ge-132) by Jarrow Formulas is one (1) 30 mg capsule which contains 12.84 mg germanium, a difference of 475%. [The germanium dose was converted from Ge-132 by a factor of 0.428. See Tao, S.-H. and P.M. Bolger. 1997. *Hazard assessment of germanium supplements*. REGULATORY TOXICOLOGY AND PHARMACOLOGY 25: 211-219.]

**PRE-MARKET NOTIFICATION FOR NEW DIETARY INGREDIENT
GERANTI BIO-GE (BIO-GERMANIUM YEAST)**

- Yeast-G (Biogermanium) orally administered to beagle dogs for 10 consecutive months. KOREAN JOURNAL OF LABORATORY ANIMAL SCIENCE 17: 99-108.
- Marczynski, B. 1988. *Carcinogenesis as the result of the deficiency of some essential trace elements*. MEDICAL HYPOTHESES 26: 239-249. TAB F
- National Instrumentation Center for Environmental Management, College of Agriculture and Life Sciences, Seoul National University. 2001. *Identification and purification of Dried Yeast-G (Geranti Bio-Ge, dried yeast containing organic germanium)*. TAB G
- National Nutritional Foods Association. *Scientific Backgrounders – Germanium*. Available on the Internet at http://www.nnfa.org/services/science/bg_germanium.htm. TAB H
- Nielsen, F.H. 1996. *How should dietary guidance Be given for mineral elements with beneficial actions or suspected of being essential?* JOURNAL OF NUTRITION 126: 2377S-2385S. TAB I
- PDR FOR NUTRITIONAL SUPPLEMENTS 181 (Medical Economics/Thomson Healthcare 2001). TAB J
- Ramsay, L.M., and G.M. Gadd. 1997. *Mutants of Saccharomyces cerevisiae defective in vacuolar function confirm a role for the vacuole in toxic metal ion detoxification*. FEMS MICROBIOLOGY LETTERS 152: 293-298. TAB K
- Schroeder, H.A., and J.J. Balassa. 1966. *Abnormal trace elements in man: Germanium*. JOURNAL OF CHRONIC DISEASES 20: 211-224. TAB L
- Tao, S.-H. and P.M. Bolger. 1997. *Hazard assessment of germanium supplements*. REGULATORY TOXICOLOGY AND PHARMACOLOGY 25: 211-219. TAB M



BIOLOGICAL TEST CENTER

December 29, 1996

YUN HO CHUNG
B & C CORPORATION
ROOM NO. 506, HYUNDAI BUILDING
35-1, MAPO-DONG, MAPO-KU
SEOUL, KOREA

BTC Number: 44105

Material Description: DAIJY CORP ORGANIC GERMANIUM FORTIFIED DRIED YEAST

Lot Number: N/A

RESULTS SUMMARY:

1. 220 - ACUTE ORAL TOXICITY-LIMIT TEST (10 RATS)
Sample Prep: SEE COMMENTS
RESULTS: PASSES TEST

NOTES: N/A

APPROVED BY:

Richard Velasco

DATE: 12/26/96

IA #54-07 - Revised 9/13/95, "GERMANIUM PRODUCTS"

****NOTE: Import Alert #62-02, "Germanium Products" dated 06/28/88, is cancelled simultaneously with the issuance of this alert. The alert is revised to remove the food additive charge in accordance with the requirements of the Dietary Supplement, Health, and Education Act (DSHEA) of 1994.****

TYPE OF ALERT: AUTOMATIC DETENTION

Note: This import alert contains guidance to FDA field personnel only. It does not establish any requirements, or create any rights or obligations on FDA or on regulated entities.

PRODUCT : Germanium products

PRODUCT CODE : 54YY-09
66V--99

PROBLEM : Poisonous and deleterious substance (PSNC) or
Unapproved new drug (DRND)

PAC : 21008
56008H

COUNTRY : All

MANUFACTURER
or SHIPPER : All

CHARGES : "The article is subject to refusal of admission pursuant to
Section 801(a)(3) in that it appears to contain a poisonous
and deleterious substance which may render it injurious to
health [Adulteration, 402(a)(1)]."

or

"The article is subject to refusal of admission pursuant to
Section 801(a)(3) in that it appears to be a new drug within
the meaning of Section 201(p) without an approved new drug
application [Unapproved new drug, Section 505(a)]."

RECOMMENDING

OFFICE : CFSAN: Division of Program and Enforcement Policy, Regulatory
Branch (HFS-456); Division of Field Program Planning and
Evaluation, Import Programs Branch (HFS-637).

REASON FOR

ALERT : Germanium is a nonessential trace element that has caused
nephrotoxicity (kidney injury) and death when used chronically
by humans, even at recommended levels of use. Germanium
containing products have been labeled for drug use (e.g., with
claims that they are intended for use in the diagnosis, cure,

mitigation, treatment, or prevention of diseases such as AIDS or cancer), although there are no approved new drug applications (NDAs) or current investigational new drug applications (INDs) on file. Germanium containing products also have been offered for entry as food products such as dietary supplements.

GUIDANCE : Districts may detain all Germanium products offered for entry, without physical examination, including unlabeled bulk entries, except for semiconductor use as discussed below. If the product claims to be useful in the diagnosis, cure, mitigation, treatment, or prevention of disease, use the drug charge; otherwise use the "poisonous and deleterious" charge.

There are legitimate uses for germanium in the semiconductor industry. If an importer shows that the intended use of the product is other than for human consumption, the entry should be released with comment. If possible, appropriate follow up should be made to assure the ultimate disposition is as indicated by the importer.

Germanium may be offered for entry under a variety of names including:

Germanium Sesquioxide
GE-132
GE-OXY-132
Vitamin "O"
Pro-Oxygen
Nutrigel 132
Immune Multiple
Germax

PRIORITIZATION

GUIDANCE : I

FOI : No purging required.

KEYWORDS : Germanium, Germax, Immune Multiple, Nutrigel 132, Pro-Oxygen, Vitamin "O", GE-OXY-132, GE-132.

PREPARED BY: The Drugs, Devices, & Biologics SDWG, DIOP, HFC-170,
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