

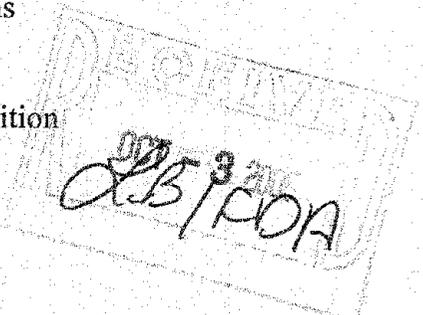


WASHINGTON

September 30, 2005

1101 17th Street, N.W.
Suite 500
Washington, D.C. 20036
Telephone 202 223-4392
Fax 202 872-0745

Vicky Lutwak
Division of Dietary Supplement Programs
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
Room 4D011
5100 Paint Branch Parkway
College Park, MD 20740



SACRAMENTO

Re:Pre-Market Notification for Geranti Bio-Ge Yeast as New Dietary Ingredient.

712 Fifth Street
Suite A
Davis, CA 95616
Telephone 530 757-1298
Fax 530 757-1299

Dear Ms. Lutwak:

Attached please find four copies of the Pre-Market Notification for Geranti Bio-Ge Yeast. This submission is made on behalf of Mr. Tsang-Uk Sohn of Geranti USA, Inc. of Los Angeles California.

I believe that we have addressed all issues that have been previously raised by the FDA in their review of this product. Please don't hesitate to contact me if there are any questions or if further information is needed.

CANADA

275 Slater Street
Suite 900
Ottawa, Ontario
K1P 5H9
Telephone 613 247-6285
Fax 613 236-3754

Best regards,

Gary J. Burin, Ph.D., DABT

2005-6572
AIMS

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

COMPANY INFORMATION

COMPANY NAME:

Geranti USA, Inc.

COMPANY ADDRESS:

765 S. Harvard Blvd.
Los Angeles California
90005

AB/ROA

MANUFACTURING SITES:

Geranti USA, Inc.
765 S. Harvard Blvd.
Los Angeles California
90005

Geranti Pharma Ltd.
678-20 Yoksam-dong, Kangnam-ku
Seoul, Korea

NEW DIETARY INGREDIENT INFORMATION

NEW DIETARY INGREDIENT NAME: Geranti Bio-Ge Yeast

INTENDED USE OF NEW DIETARY INGREDIENT: Geranti Bio-Ge Yeast is intended for use as a dietary ingredient in dietary supplement products. Such dietary supplement products will contain from 3 to 250 mg Geranti Bio-Ge Yeast (and from 0.009 mg to 0.75 mg germanium) per capsule/tablet with the higher dosage capsule/tablets to be taken no more than twice per day. The maximum intake of Geranti Bio-Ge Yeast would be 500 mg/day (1.5 mg germanium). Geranti Bio-Ge Yeast strengthens the immune system and promotes health and well being.

DESCRIPTION OF THE NEW DIETARY INGREDIENT

Background

The element Germanium was predicted by Mendeleev in 1871 and discovered in 1886 by Clemens Winkler. It is a Group IV metal and has similar properties as other elements in the group, especially silicon. It is found in valance states of +2 and +4 and in organic and inorganic forms. Germanium (³²Ge) is a trace element found in common food sources such as tuna, milk, butter, and beans with relatively high levels found in ginseng and green tea (Fisher et al., 1991).

Dietary Intake of Germanium

Dietary intakes of germanium in various forms have been reported to vary between 400 micrograms and 3500 micrograms per day in the United States (Schroeder and Balassa, 1967), and more recently, a review article by Tao and Bolger cited an estimated dietary intake of 1.5 mg/day (Tao and Bolger, 1997). Dietary intake estimates in the United Kingdom have ranged from 0.370 mg/day (Hamilton and Minski, 1972) to 0.004 mg/day excluding drinking water (Ysart et al., 1999). Volatile germanium compounds may be lost with certain analytical procedures (Kaplan et al., 2004) and this may at least partially explain the variability that has been reported in studies of dietary intake of germanium.

Dietary intakes can also be approximated by assessing intake from individual commodities or quantifying the excretion of germanium. The average intake of milk in the United States is 224 grams/person/day (USDA, 1993) and the reported concentration of 1.51 micrograms of Ge/gram reported in milk (Schroeder and Balassa, 1967) would result in a dietary intake of 338 micrograms from milk alone. The highest levels of germanium have been reported in canned tomato juice (5.76 ug/g) and the consumption of 200 grams of tomato juice at this concentration would thus result in a daily exposure of 1.152 mg of germanium. Urinary excretion has been reported to range from 0.56 to 3.0 mg in adults (Venugopol and Luckey, 1978 in Fisher et al., 1991) with a mean concentration of 1.26 mg/liter (Schroeder and Balassa, 1967). Based upon an average daily urinary volume of 1,200 ml and a mean concentration of 1.26 mg/liter, the daily average amount of germanium excreted in the urine in the United States is approximately 1.5 mg and, assuming excretion primarily in the urine, this rate of excretion is consistent with published estimates of daily dietary intake of germanium in the United States.

Absorption, Distribution and Metabolism

Inorganic germanium is readily absorbed and is excreted primarily in the urine in laboratory animals and humans (Tao and Bolger, 1997). An oral dose of sodium germinate given to rats was 96.4% excreted in 8 hours (Rosenfeld, 1954 reported in Tao and Bolger, 1997). In humans, inorganic germanium is widely distributed in the body with the greatest accumulations in the spleen, vertebra, renal cortex, brain and skeletal muscle (Nagata et al., 1985). Absorption and excretion of germanium appears to be similar in rats and humans (Tao and Bolger, 1997).

The difference in toxicity between organogermanium compounds and inorganic germanium may be due to the lower bioavailability and reduced potential for organogermanium compounds to accumulate in renal tissue. The absorption of trace metals such as germanium from the diet is complicated and is influenced by a number of factors including the form of the element including whether the metal is in an organic complex, the composition of the diet, gut microflora, and the nutritional state of the individual (see Southon et al., 1988). In addition to poorer absorption, organogermanium appears to be less readily absorbed and is metabolized via C-hydroxylation by microsomal enzymes and excreted primarily via the kidney (Prough et al., 1981). Ge-132

has been shown to be only 30% absorbed after oral administration (Goodman, 1988; Tao and Bolger, 1997). Absorbed Ge-132 has been shown to be more rapidly excreted than inorganic germanium and shows no potential for tissue-binding or accumulation in the kidney (Schauss, 1991).

PROPERTIES, BENEFITS AND SAFETY OF THE NEW DIETARY INGREDIENT

Properties of the New Dietary Ingredient

Geranti Pharm Ltd. has developed a form of yeast called *Geranti Bio-Ge Yeast* that consists of 99.7% yeast and 0.3% germanium bound to components of the yeast. The manufacturing process for this yeast is described in the attached patent application (Appendix A) and is shown in Figure 1 of the quality control process (Appendix B). The Certificate of Analysis for this yeast is also attached (Appendix C). Geranti Pharm Ltd. is in the process of updating its manufacturing facility to comply with the Korean requirement that functional food manufacturers be compliant with Good Manufacturing Practices. Geranti Pharm Ltd. expects to be fully compliant by the deadline of February, 2006 required by Korean law.

Geranti Bio-GeYeast contains organic germanium processed by fermentation in adapted *Saccharomyces cerevisiae* yeast. The use of *S. cerevisiae* in converting an ultratrace element from its toxic form to a safe, organic form occurs 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 (Ramsey and Gadd, 1997). In addition, this process of mineral conversion by yeast is commonly used by other dietary supplement manufacturers to synthesize the organic forms of other ultratrace elements such as selenium-yeast.

Yeast appears to readily bind germanium on the outer face of the cell envelope (Klapcinska and Chmielowski, 1986). In the case of *Geranti Bio-Ge Yeast*, the germanium is tightly bound as evidenced by the inability of dialysis to release germanium from *Sacharomyces cerevisiae* (Song et al., 1995). Research sponsored by Geranti has shown that germanium is tightly bound to a 34 KDa protein and that this protein can be sequence matched with enolase, the enzyme that transforms 2-phosphoglycrate into phosphoenolpyruvate (Park, 2004).

The stability of the complex has recently been investigated with simulated gastric fluid (Ahn, 2005). *Geranti Bio-Ge Yeast* (300 mg in 20 ml) was dissolved in either simulated gastric fluid or germanium-free water. Dialysis tubing with a molecular weight limit of 1200 daltons was used and concentrations of germanium were determined in the dialysis tubes both before and after two hours of dialysis at 37°C. Germanium concentrations were similar in both water and gastric fluid after dialysis. This indicates that incubation with simulated gastric juice does not result in significant release of unbound germanium. NMR analyses of yeast before and after incubation with germanium show modification of proteins or peptides by germanium (this research will be published soon in a scientific

journal). The modification of the protein or peptides by germanium was shown to remain stable after incubation with simulated gastric fluid at an elevated temperature. This study indicates that protein/ germanium complex is likely to be stable under the conditions found in the human gastrointestinal tract.

Benefits of Geranti Bio-Ge Yeast and Other Organic Germanium Compounds

Organic germanium has been reported to have a variety of beneficial effects on human health (Goodman, 1988). The deficiency of germanium has been reported to be associated the development of neoplasia (Marczynski, 1988) and other adverse effects (Kaplan et al., 2004).

Organic germanium has been associated with anti-viral and enhanced immune response (Goodman, 1988). Fisher et al., (1991) note that germanium compounds act as immunomodulators due to effects on several immune system components. Interleuken 1 production was enhanced and interleukin 2 and 3 depressed in mice administered organogermanium (Demartino et al., 1986). Cytotoxic macrophages were induced 48 hours after oral dosing with Ge-132 (carboxylethyl-Ge sesquioxide) in mice (Aso et al., 1985). Germanium compounds have shown protection against methylcholanthrene-induced tumors (Kumano et al., 1978). Lymphokines are thought to mediate the anticancer properties of Ge-132 (Suzuki et al., 1985). Spirogermanium (4,4-dialkyl-4-germacyclohexanone) has been reported to act synergistically with antitumor drugs such as cys-platin and 5-fluorouricil (Hill et al., 1984). The administration of Ge-132 to healthy volunteers was shown to result interferon induction and enhanced Natural Killer cell activity (Aso, 1985).

Safety of the New Dietary Ingredient

As with many beneficial elements, excess exposure to germanium can result in toxicity. Inorganic forms of germanium (e.g., germanium dioxide) have been shown to be toxic to the kidneys and at least 31 human cases of human poisoning and 9 deaths have occurred after intentional ingestion of germanium (Tao and Bolger, 1996). All of these cases resulted from the ingestion of inorganic germanium or organic germanium compounds contaminated with the inorganic germanium. The purity of *Geranti Bio-Ge Yeast* manufactured by the Company is unique and distinguished from other forms of commercially prepared organic germanium. It is important to distinguish between the toxicity of inorganic germanium, organic germanium of low or unknown purity and the high purity organic *Geranti Bio-Ge Yeast* because there are major differences in the nephrotoxicity of organic and inorganic germanium and other trace elements (Vanholder et al., 2002).

The six reports of toxicity in humans after the intake of dietary supplements containing organogermanium compounds have been subsequently attributed to the presence of germanium dioxide in the supplements. Four cases of renal toxicity in Europe that were initially reported to be associated with an organogermanium compound were later found to be due to the intake of inorganic germanium (Krapf et al., 1992). Two cases of renal

toxicity were originally attributed to Ge-132 exposure (Okuda et al., 1987 cited in Tao and Bolger, 1996) but were later shown to be due to inorganic germanium contamination of Ge-132 (Sanai et al., 1990). In summary, all cases of human poisoning initially attributed to organogermanium were later found to be due to exposure to inorganic germanium.

Tao and Bolger (1997) noted that "While nephrotoxicity similar to that reported in human cases was consistently induced by oral administration of GeO₂ in animals, results of animal studies with Ge-132 do not give a clear picture." Subsequent to this review, however, additional studies have become available that show that little or no nephrotoxicity is associated with organogermanium administration to laboratory animals (see summary of *Geranti Bio-Ge Yeast* studies, below, and Appendix D). Although there is some variability in toxicity between the various forms of organogermanium, the results of repeat dose studies of these compounds clearly show little or no toxicity, even at relatively high dose levels. This is in contrast to germanium dioxide, which results in significant and irreversible renal toxicity at low dose levels in studies in laboratory animals and which has been associated with renal toxicity in humans.

Toxicology studies of organogermanium compounds (other than *Geranti Bio-Ge Yeast*) are described in Appendix A and toxicology studies of inorganic germanium were summarized and critiqued in the review article by Tao and Bolger (1997).

The following are summaries of toxicology studies conducted with *Geranti Bio-Ge Yeast*:

Acute Oral/Rat: Five rats per sex received 2,000 mg/kg by oral gavage administration. All animals survived after dosing for 14 days until they were sacrificed. The only treatment-related effect was a suppression of body weight after 14 days (Lee et al., 2004a).

Acute Oral/Dog: Two dogs per sex received 2,000 mg/kg by oral gavage administration. All animals survived and no toxicity was observed (Lee et al., 2004b).

Repeat Dose Oral/Rat: Rats received dose levels of 0, 500, 1,000 and 2,000 mg/kg by oral gavage for 90 days. Clinical signs, body weight, food and water consumption, hematology, blood chemistry, urinalysis, gross findings at necropsy and histopathology were examined in all animals. No effects were observed at any dose levels that were considered to be treatment-related. Kidney samples taken from high dose male and female rats in this study showed no detectable germanium. (Lee et al., 2004a)

Chronic Dose Oral/Rat: Rats received dietary dose levels of 0, 30, 300 and 3,000 mg/kg by oral gavage for ten months. Clinical signs, body weight, food and water consumption, hematology, blood chemistry, urinalysis, gross findings at necropsy

and histopathology were examined in all animals. No effects were observed in rats at any dose level (Lee et al., 2004b).

Repeat Dose Oral/Dog: Beagle dogs received dietary concentrations of 0, 500, 1,000 and 2,000 mg/kg by oral gavage for 90 days. Clinical signs, body weight, food and water consumption, hematology, electrocardiography, blood chemistry, urinalysis, gross findings at necropsy and histopathology were examined in all animals. No effects were observed at any dose levels that were considered to be treatment-related (Ahn, 2001).

Chronic Dose Oral/Dog: Beagle dogs received diets containing concentrations of 0, 30, 300 and 3,000 mg/kg in water for ten months. Clinical signs, body weight, food and water consumption, hematology, electrocardiography, blood chemistry, urinalysis, gross findings at necropsy and histopathology were examined in all animals. No effects were observed at any dose level (Ahn, 2001).

In vitro reverse Mutation Assay: Negative for genotoxicity in *Salmonella typhimurium* strains TA 1535, 1537, 98 and 100 and *Escherichia coli* WP2uvrA (pKM101) with and without metabolic activation at concentrations of 312.5, 625, 1,250, 2,500 and 5,000 ug/plate (Min et al., 2004).

In vitro Chromosomal Aberration Assay: Negative for genotoxicity in Chinese hamster lung fibroblasts at treatment levels of 1,250, 2,500 and 5,000 ug/ml with and without metabolic activation (Min et al., 2004).

Mouse Micronucleus Assay: Negative after intraperitoneal administration of 125, 250, 500, 1,000, 2,000 or 5,000 mg/kg to mice (Min et al., 2004).

These studies show that *Geranti Bio-Ge Yeast* yeast is not toxic after acute or repeat dosing at the highest levels that can be practically administered to laboratory animals without compromising the nutritional composition of the diet. It is significant that no renal toxicity was seen in these studies in either the dog or the rat. The maximum dose of *Geranti Bio-Ge Yeast* that has been administered without evidence of renal toxicity was 3,000 mg/kg/day. This is equivalent to a dose level of 9 mg/kg/day of germanium. *Geranti Bio-Ge Yeast* is not genotoxic in a battery of genotoxicity studies.

The toxicity of *Geranti Bio-Ge Yeast* is clearly less, based on equivalent germanium content, than that of germanium dioxide. A 50% mortality rate was found in young rats receiving 17 mg/kg/day of germanium dioxide (equal to 11.7 mg/kg/day of germanium) in drinking water (Rosenfeld and Wallace, 1953). In a feeding study in rats, Sanai et al., (1991) found decreased growth, anemia renal dysfunction, and renal tubular degeneration at a dose of 37.5 mg/kg/day of germanium dioxide, equivalent to 26 mg/kg/day of germanium. Renal dysfunction and abnormalities of the mitochondria of kidney and skeletal muscle were found after the dosing of rats in drinking water for 9-10 months

with germanium dioxide at a dose level of 13 mg/kg/day of germanium dioxide, equivalent to 9 mg/kg/day of germanium (Schroeder et al., 1968)¹

HISTORY OF SAFE USE OF GERANTI BIO-GE YEAST

Geranti Bio-Ge Yeast was approved as a health supplement, food additive and special nutrient in Korea in 1996. In 1998, it was approved in Korea as a medicinal ingredient and in 2004, Geranti Bio-Ge Yeast was approved as a functional food.

Geranti Bio-Ge Yeast was registered with the Singapore Ministry of Health in 1999.

In 2002, Geranti Bio-Ge Yeast was approved for import into Japan.

There have been no reports of adverse effects in users of Geranti Bio-Ge in any of the countries in which Geranti Bio-Ge Yeast is sold.

CONCLUSIONS

Based upon all of the above data and published information as well as our inability to find contradictory information we believe the Bio-Ge yeast is safe for human consumption as a dietary ingredient at the levels that we propose for this product.

REFERENCES

- Aso H., Suzuki F, Ebina, and N Ishida (1985). Antiviral activity of carboxyethylgermanium sesquioxide (Ge-132) in mice infected with influenza virus. *J Biol Resonse Mod* 8:180-189.
- Ahn DC (2005). Chronic Toxicity of Dry Yeast-G (Bio-Germanium) Orally Administered to Beagle Dogs for 10 Consecutive Months. Kang-Won National University.
- Ahn SD (2005). NMR and ICP Assay Report. Chung-Ang University.
- Demartino MJ, JC Lee, AM Badger KA Muirhead, CK Mirabelli, and N Hann (1986). Antiarthritic and immunoregulatory activity of spirogermanium. *J Pharmacol Exp Ther* 235:103-110.
- Fisher BR, PL Goering and BA Fowler (1991). Germanium. In "Metals and Their Compounds in the Environment. VCH, Weinheim.
- Goodman S (1988). Therapeutic effects of organic germanium. *Medical Hypotheses* 26:207-215.

¹ The germanium equivalents of 26 and 9 mg/kg/day were the lowest dose levels used in the studies.

- Hamilton EI, MJ Minski and JJ Clearly (1972). The concentration and distribution of some stable elements in healthy human tissues from the United Kingdom. *Sci. Total Environ* 1:341-374.
- Hill BT, AS Bellamy, S Metcalfe, PJ Hepburn, JR Masters and RD Whelan (1984). Identification of Synergistic Combinations of Spirogermanium with 5-Fluorouracil or Cisplatin Using a Range of Human Tumor Cell Lines in vitro. *Invest. New Drugs* 2:29-33.
- Kaplan BJ, WW Parish, M Andrus, JSA Simpson and CJ Field (2004). Germane Facts About Germanium Sesquioxide: I. Chemistry and Anticancer Properties. *J Alt Compl Med* 10: 337-344.
- Krapf R, T Schaffner, and PX Iten (1992). Abuse of germanium associated with fatal lactic acidosis. *Nephron*. 62:351-356.
- Lee JS, JI Park, SH Kim, HY Lee, Z Hwang, C Park, TU Sohn, S Shin, JK Kang and YB Kim (2004a). Oral and single and repeated dose toxicity studies on Geranti Bio-Ge Yeast Organic Germanium fortified yeasts, in rats. *J Tox Sciences* 29: 541-553.
- Lee JS, JI Park, SH Kim, HY Lee, Z Hwang, C Park, TU Sohn, S Shin, JK Kang, YB Kim (2004b). Oral and single and repeated dose toxicity studies on Geranti Bio-Ge Yeast Organic Germanium fortified yeasts, in rats. *J Tox Sciences* 29: 555-569.
- Marczynski B (1988). Carcinogenesis as the results of the deficiency of some essential trace elements. *Medical Hypotheses* 26:239-248.
- Min SJ, MS Zheng, JI Park, JS Lee, YB Kim, JK Kang, TU Sohn and Cheol-Beom Park (2004). Genotoxicity studies on Geranti Bio-Ge Yeast, an Organic Germanium Synthesized in Yeasts. *Korean J of Lab An Science* 20:81-88.
- Nagata N, T Yoneyama, K Yanagida, K Ushio, S Yanagihar, O Matsubara and Y Eishi (1985). Accumulation of Germanium in the Tissues of a Long-Term User of Germanium Preparation Died of Acute Renal Failure. *J Tox Sciences* 10:333-341.
- Park, E.W. (2004). Identification and Purification of Geranti Bio-Ge Yeast. Seoul National University.
- Prough RA, MA Stalmach, P Wiebkin and JW Bridges (1981). The Microsomal Metabolism of the Organometallic Derivatives of the Group IV Elements, Germanium, Tin and Lead. *Biochem J*. 196:763-770.
- Ramsey LM and GM 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.

Sanai T, N Oochi, S Okuda, S Osato, S Kiyama, T Komota, K Onoyama and M Fujishima (1990). Subacute Nephrotoxicity of Germanium Dioxide in Experimental Animals. *Tox App Pharm* 103:345-353.

Schauss AG (1991). Nephrotoxicity and Neurotoxicity in Humans from Organogermanium Compounds and Germanium Dioxide. *Bio Trace Element Res* 29:267-280.

Schroeder HA and JJ Balassa (1967). Abnormal Trace Metals in Man: Germanium. *J Chronic Disease* 20:211-224.

Schroeder HA, M Kanisawa, DV Frost, and M Mitchener (1968). Germanium, tin and arsenic in rats: Effects on Growth, Survival, Pathological Lesions and Lifespan. *J Nutrit* 96:37-45.

Southon S, SJ Fairweather-Tait and T Hazell (1988). Trace element availability from the human diet. *Proceeding of the Nutrition Society* 47:27-35.

Tao HS and PM Bolger (1997). Hazard Assessment of Germanium Supplements. *Reg Tox Pharm* 25:211-219.

Vanholder R., R Cornelis, A Dhondt and N Lameire (2002). The role of trace elements in uraemic toxicity. *Nephrol Dial Transplant* 17:2-8.

Ysart G, P Miller, H Crews, P Robb, M Baxter, C Delargy, S Lofthouse, C Sargent and N Harrison (1990). Dietary Exposure Estimates of 30 Elements from UK Total Diet Study. *Food Add Contam* 16:391-403.

APPENDIXES

Appendix A. Process for Preparing *S. Cerevisiae* Containing Organically Bound Germanium. US Patent Number 5,792,646. August 11, 1998

Appendix B. Quality Control.

Appendix C. Certificate of Analysis.

Appendix D. Evaluation of the Toxicity of Organogermanium Compounds. G. Burin. September 28, 2005.