DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, MD 20740

JUL 2 2 2008

Donald J. Cox, Ph.D.
Vice President of R&D
and Business Development
Healthcare Group
Biothera, Inc
3388 Mike Collins Drive
Eagan, MN 55121

Re: GRAS Notice No. GRN 000239

Dear Dr. Cox:

The Food and Drug Administration (FDA) is responding to the notice, dated January 11, 2008, that you submitted in accordance with the agency's proposed regulation, proposed 21 CFR 170.36 (62 FR 18938; April 17, 1997; Substances Generally Recognized as Safe (GRAS); the GRAS proposal). FDA received the notice on January 16, 2008, filed it on January 24, 2008, and designated it as GRAS Notice No. GRN 000239.

The subject of the notice is bakers yeast beta-glucan. The notice informs FDA of the view of Biothera, Inc. (Biothera) that bakers yeast beta-glucan is GRAS, through scientific procedures, for use as an ingredient in a variety of food products including baked goods and baking mixes, beverages and beverage bases, cereals and cereal products, dairy product analogs, milk and milk products, plant protein products, processed fruits and fruit juices, soft candy, soups and soup mixes at a level of up to 200 milligrams per serving.

21 CFR 101.4 states that all ingredients must be declared by their common or usual name. In addition, 21 CFR 102.5 outlines general principles to use when establishing common or usual names for nonstandardized foods. FDA's Office of Nutrition, Labeling, and Dietary Supplements (ONLDS) in the Center for Food Safety and Applied Nutrition, considers the name "bakers yeast beta-glucan" to be an appropriate name for this substance. ONLDS considered that this name adequately and accurately describes the substance and is specific to beta-glucan derived from bakers yeast, understanding that beta-glucans can be derived from other sources, including cereal grains and that the composition of such beta-glucans may vary depending on the source material. ONLDS also notes that "bakers yeast beta-glucan" is consistent with other terms used in our GRAS and food additive regulations for substances derived from bakers yeast, such as "bakers yeast glycan," "bakers yeast protein," and "bakers yeast extract." ONLDS notes that Biothera makes a statement about yeast sensitivity/allergy and considers that "bakers yeast beta-glucan" provides clear and accurate information to such consumers.

As part of its notice, Biothera includes the report of a panel of individuals (Biothera's GRAS panel) who evaluated the data and information that are the basis for Biothera's GRAS determination. Biothera considers the members of its GRAS panel to be qualified by scientific training and experience to evaluate the safety of substances added to food. Biothera's GRAS

panel evaluated identity, method of manufacture, product specifications, estimated daily intake, and generally available safety data for the intended use of bakers yeast beta-glucan as a food ingredient. Based on this review, Biothera's GRAS panel concluded that bakers yeast beta-glucan that meets its established food grade specifications and produced in accordance with current good manufacturing practices (cGMP), is GRAS under the conditions of its intended use.

Biothera describes the identity of bakers yeast beta-glucan. Bakers yeast beta-glucan is a beige-to-tan colored powder obtained from bakers yeast (*Saccharomyces cerevisiae*) cell walls. The product contains at least 70% insoluble beta-(1,3),(1,6)-D-glucan. In addition, small amounts of beta-1,6-glucan, chitin, protein, and lipids are present in the product. Biothera produces bakers yeast beta-glucan in two forms: one with at least 70% beta-glucan, the other with at least 75% beta-glucan. Biothera uses only one manufacturing process to produce both forms of bakers yeast beta-glucan.

Biothera describes the method of manufacture and provides specifications for bakers yeast beta-glucan. Biothera manufactures bakers yeast beta-glucan from food-grade bakers yeast (*S. cerevisiae*) grown at Biothera's production plant under controlled conditions in stainless steel fermentation vessels. To extract the cell walls, Biothera lyses the yeast cells using a thermal process and separates the cell wall component from the yeast extract using centrifugation. To strip the mannosylated cell wall proteins that are linked to the cell wall, the cell wall isolate undergoes a caustic treatment. This step also removes residual cellular lipids trapped within the cell wall. Subsequently, the ingredient undergoes an acid treatment, which results in the depolymerization and deacetylation of chitin to form free glucosamine hydrochloride, resulting in the removal of most of the chitin. Next, the yeast wall slurry undergoes flash sterilization, followed by pH adjustment steps, resulting in a sterile solution with an approximate pH range of 5-6. The resulting mixture contains between 6 to 12% of the original solids. The mixture is then spray-dried. Once dry, the powder is sieved through a mesh sifter. Biothera provides product specifications for bakers yeast beta-glucan, including specifications for total carbohydrates ($\geq$80%) composed primarily of beta-(1,3),(1,6)-glucan ($\geq$70%), protein, fat, ash, moisture, lead, and microbiological specifications.

Biothera notes that small amounts of volatile organic compounds (methanol, ethanol, isopropanol, acetone and hexane) can be detected in the final bakers yeast beta-glucan product even though no organic solvents are used during the manufacturing process. Biothera determined that these compounds are the result of fatty acid decomposition during the manufacturing process. Based on their levels in the final product, Biothera concludes that the volatile organic compounds are not expected to produce adverse effects on human health.

Biothera estimates the all-user mean intake of bakers yeast beta-glucan from its intended use in the food categories listed above. These estimates were derived from the USDA Continuing Survey of Food Intakes by Individuals (CSFII) 1994-1996. Biothera estimates that the intake of bakers yeast beta-glucan under the conditions of its intended use would be ca. 413 milligrams per person per day (mg/p/d) (8.90 mg per kilogram body weight per day) (mg/kg bw/d) and the 90th percentile intake as ca. 827 mg/person/day (20.66 mg/kg bw/d).

Biothera asserts that the safety of bakers yeast beta-glucan is partly supported by the compositional similarity of the substance to bakers yeast glycan, which is listed in 21 CFR 172.898. Biothera notes that bakers yeast beta-glucan and bakers yeast glycan are both manufactured from cell walls of *S. cerevisiae,* are composed almost entirely of carbohydrates, and their specifications include similar limits for chemical and microbiological parameters.

Biothera summarizes published and unpublished rodent and human studies, including acute toxicity studies in rats and mice, a subchronic oral toxicity study in rats, and double-blind, placebo-controlled studies for 10 and 30 days in humans. Biothera notes that no adverse effects were observed in any of the studies. Biothera concludes that the rodents in the acute toxicity studies had no evidence of clinical chemistry or histopathological toxicity. In the subchronic oral toxicity study, the rats showed no evidence of systemic or gastrointestinal toxicity at the highest level (100 mg/kg bw/d) of bakers yeast beta-glucan. Biothera discusses the results of the human clinical studies, and concludes that levels up to 500 mg/p/d of bakers yeast beta-glucan were well-tolerated and that there were no significant differences in blood biochemistry parameters.

Standards of Identity

In the notice, Biothera states its intention to use yeast beta-glucan in several food categories, including foods for which standards of identity exist, located in Title 21 of the Code of Federal Regulations. We note that an ingredient that is lawfully added to food products may be used in a standardized food only if it is permitted by the applicable standard of identity.

Section 301(ll) of the Federal Food, Drug, and Cosmetic Act (FFDCA)

The Food and Drug Administration Amendments Act of 2007, which was signed into law on September 27, 2007, amends the FFDCA to, among other things, add section 301(ll). Section 301(ll) of the FFDCA prohibits the introduction or delivery for introduction into interstate commerce of any food that contains a drug approved under section 505 of the FFDCA, a biological product licensed under section 351 of the Public Health Service Act, or a drug or a biological product for which substantial clinical investigations have been instituted and their existence made public, unless one of the exemptions in section 301(ll)(1)-(4) applies. In its review of Biothera's notice that bakers yeast beta-glucan is GRAS for use in a variety of food products, FDA did not consider whether section 301(ll) or any of its exemptions apply to foods containing bakers yeast beta-glucan. Accordingly, this response should not be construed to be a statement that foods that contain bakers yeast beta-glucan, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information provided by Biothera, as well as other information available to FDA, the agency has no questions at this time regarding Biothera's conclusion that bakers yeast beta-glucan is GRAS under the intended conditions of use. The agency has not, however, made its own determination regarding the GRAS status of the subject use of bakers yeast beta-glucan. As always, it is the continuing responsibility of Biothera to ensure that food ingredients that the firm markets are safe, and are otherwise in compliance with all applicable legal and regulatory requirements.

In accordance with proposed 21 CFR 170.36(f), a copy of the text of this letter responding to GRN 000239, as well as a copy of the information in this notice that conforms to the information in the proposed GRAS exemption claim (proposed 21 CFR 170.36(c)(1)), is available for public review and copying on the homepage of the Office of Food Additive Safety (on the Internet at http://www.cfsan.fda.gov/~lrd/foodadd.html).

Sincerely,

Laura M. Tarantino, Ph.D.
Director
Office of Food Additive Safety
Center for Food Safety
and Applied Nutrition