DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, MD 20740

Mary M. Murphy, MS, RD
Exponent
1150 Connecticut Avenue, N.W., Suite 1100
Washington, D.C. 20036

NOV 21 2011

Re: GRAS Notice No. GRN 000382

Dear Ms. Murphy:

The Food and Drug Administration (FDA) is responding to the notice, dated May 12, 2011, that you submitted on behalf of Baolingbao Biology Co., Ltd. (Baolingbao) 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 May 13, 2011, filed it on June 2, 2011, and designated it as GRAS Notice No. GRN 000382.

The subject of the notice is erythritol produced through fermentation of glucose by a microorganism known as *Yarrowia lipolytica* (erythritol). The notice informs FDA of the view of Baolingbao that erythritol is GRAS, through scientific procedures, for use as a flavor enhancer, formulation aid, humectant, nutritive sweetener, stabilizer and thickener, sequestrant, and texturizer in a variety of foods as described in Table 1 (below).

Table 1
Baolingbao's intended conditions of use

Food	**Level of Use (percent by weight)**
Reduced and low-calorie and non-carbonated beverages; Dairy drinks (chocolate and flavored milks)	3.5
Frozen dairy desserts (regular ice cream, soft serve, sorbet); Puddings (instant, phosphate set); Yogurt (regular and frozen)	10
Bakery fillings (fruit, custard, cream, pudding); Cakes and cookies (regular and dietetic)	15
Fat-based cream used in modified fat/calorie cookies, cakes, and pastries; Chewing gum; Soft candies (non-chocolate, plain chocolate, chocolate coated)	60
Hard candies (including pressed candy and mints)	99
Sugar substitutes (carrier)	100

Baolingbao provides information about the chemical identity and specifications for erythritol. Erythritol is a naturally occurring four carbon sugar. Baolingbao notes that erythritol is a white, crystalline powder with a sweet and cooling taste. Erythritol's CAS Registry No. is 149-32-6 and the empirical formula is $C_4H_{10}O_4$. Baolingbao provides specifications for its erythritol, including purity (> 99.5%), reducing sugars (< 0.3%), microbial limits, and limits on lead (< 0.1 milligram

per kilogram (mg/kg)). Baolingbao also provided batch analysis for five batches of its product, which demonstrate compliance with these specifications.

Baolingbao states that its erythritol complies with the Food Chemicals Codex, 6th Edition (2008) specification for erythritol and notes that erythritol was the subject of two previous GRAS notices (GRN 000076 and GRN 000208). Baolingbao states that the only difference among GRN 000076, GRN 000208, and 000382 is the production organism used (*Moniliella pollinis*, *Trichosporonoides megachiliensis*, and *Y. lipolytica*, respectively).

Baolingbao states that its erythritol is manufactured through fermentation of glucose using a pure culture of *Y. lipolytica* strain 1431. Following fermentation, the culture is filtered to remove microbial cells. The filtrate is then concentrated, cooled, and erythritol crystals are removed by centrifugation. These crystals are redissolved and activated carbon is added; the resulting solution is then demineralized using an ion-exchange resin. The solution is then concentrated and the erythritol recrystallized. The resulting erythritol crystals are then separated by centrifugation. The crystals are dried and screened to achieve the appropriate particle size for the finished product.

Baolingbao states that its erythritol is GRAS under the same conditions of use (Table 1) as described in GRN 000076 and GRN 000208. Consequently, the uses of erythritol in GRN 000382 will not result in any additional exposure to erythritol beyond what was estimated previously. Baolingbao states that the estimated daily intake (EDI) per user of erythritol from the intended uses in GRN 000382 is therefore identical to the EDI calculated in GRN 000076 and GRN 000208, which is 13 grams per person per day (g/p/d) at the mean and 30 g/p/d at the 90th percentile. Baolingbao notes that this exposure estimate for these uses of erythritol was originally calculated by FDA in its response to GRN 000076.

Baolingbao discusses information supporting the safety of the yeast *Y. lipolytica* as a production microbe for erythritol. Baolingbao states that *Y. lipolytica* has a history of consumption due to its presence in commonly consumed foods. Baolingbao states that *Y. lipolytica* is found in foods such as soy sauce, poultry products, sausage, salads containing meat or shrimp, and cheese. Baolingbao states that no evidence of pathogenic or toxigenic potential from the use of *Y. lipolytica* in the production of food ingredients has been identified in the literature.

In addition, Baolingbao states that *Y. lipolytica* is described as a nonpathogenic organism in 21 CFR 173.165 (listed as *Candida lipolytica*), under which it is permitted as a secondary direct food additive for use in the production of citric acid for human consumption. Baolingbao also states that FDA had no questions in response to a GRAS Notice (GRN 000355) describing the intended use of eicosapentaenoic acid (EPA)-rich triglyceride oil from *Y. lipolytica*.

Baolingbao states that the erythritol production strain was derived by chemical and UV mutagenesis of parental strain *Y. lipolytica* strain 1675 followed by growth at high osmolarity. A strain producing a high level of erythritol during fermentation was selected and designated as *Y. lipolytica* strain 1431.

Baolingbao notes that the safety of erythritol as a food ingredient has been extensively reviewed and evaluated, citing previous reviews that were conducted as part of GRN 000208 and GRN 000076, as well as a review conducted by the Joint FAO/WHO Expert Committee on Food Additives where erythritol was assigned an acceptable daily intake of "not specified."[1]

[1] JECFA describes an acceptable daily intake of "not specified" as a term applicable to a food component of very low toxicity for which the total dietary intake of the substance does not, in the opinion of the Committee, represent a hazard to health.

Baolingbao states that these reviews included reviews of published and unpublished *in vivo, in vitro* and clinical data that provided no evidence of adverse toxicological effects associated with erythritol.

Baolingbao also reviewed the scientific literature regarding erythritol safety published since 2006. Baolingbao noted that several studies observed an increase in the occurrence of transient, mild and self-limiting gastrointestinal effects, predominantly laxation and borborygmi associated with large, aqueous, bolus administrations of erythritol above approximately 1 g/kg of body weight. Baolingbao notes however that exposure estimates support the conclusion that intakes of erythritol from these proposed uses will be below any levels associated with gastrointestinal effects.

Standards of Identity

In the notice, Baolingbao states its intention to use erythritol 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 (FD&C Act)

The Food and Drug Administration Amendments Act of 2007, which was signed into law on September 27, 2007, amends the FD&C Act to, among other things, add section 301(ll). Section 301(ll) of the FD&C Act prohibits the introduction or delivery for introduction into interstate commerce of any food that contains a drug approved under section 505 of the FD&C Act, 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 Baolingbao's notice that erythritol is GRAS for the intended uses, FDA did not consider whether section 301(ll) or any of its exemptions apply to foods containing erythritol. Accordingly, this response should not be construed to be a statement that foods that contain erythritol, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information provided by Baolingbao, as well as other information available to FDA, the agency has no questions at this time regarding Baolingbao's conclusion that erythritol produced by *Y. lipolytica* 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 erythritol. As always, it is the continuing responsibility of Baolingbao 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 000382, as well as a copy of the information in this notice that conforms to the information in the GRAS exemption claim (proposed 21 CFR 170.36(c)(1)), is available for public review and copying at http://www.fda.gov/grasnoticeinventory.

Sincerely,

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