U.S. FOOD & DRUG ADMINISTRATION

Human Foods Program

Wing Yu
CIRS Group USA, Inc.
4250 Fairfax Drive, Suite 600
Arlington, VA 22203

Re: GRAS Notice No. GRN 001198

Dear Ms. Yu:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001198. We received the notice that you submitted on behalf of Sichuan Bohaoda Biological Technology Co., Ltd. (Sichuan Bohaoda) on May 21, 2024 and filed it on August 16, 2024. Sichuan Bohaoda submitted amendments to the notice on November 20, 2024 and December 11, 2024 that clarified the production strain identity, manufacturing process, specifications, dietary exposure, and safety information.

The subject of the notice is inositol for use as a nutrient supplement at a level up to 120 mg/kg in flavored and enhanced waters, soft drinks, fruit and vegetable juices, and fruit drinks, and at a level up to 250 mg/kg in dry milks.[1] The notice informs us of Sichuan Bohaoda's view that this use of inositol is GRAS through scientific procedures.

Sichuan Bohaoda describes inositol (also known as *myo*-inositol) as a white crystalline powder containing 97.0% – 99.3% inositol on an anhydrous basis. Inositol is a polyol, a type of carbohydrate, consisting of a six-carbon ring structure with a hydroxyl group at each carbon position, with a molecular weight of 180.16 g/mol and the CAS Registry No. 87-89-8.

Sichuan Bohaoda describes the method of manufacture of inositol. Inositol is manufactured from starch or maltodextrin by a one-step non-fermentative multi-enzyme reaction in the presence of isoamylase, glucan phosphorylase, phosphoglucomutase, inositol-1-phosphate synthase and inositol monophosphatase preparations produced by fermentation of genetically engineered *Escherichia coli* BL21(DE3) strains "BHD-STIA", "BHD-TMαGP", "BHD-TKPGM", "BHD-AFIPS" and "BHD-TMIMP", respectively. Sichuan Bohaoda describes that each of the production strains is a strain of *E. coli* BL21(DE3) carrying a plasmid for expression of a *de novo* synthesized gene encoding the respective enzyme. Sichuan Bohaoda states that the

[1] Sichuan Bohaoda states that inositol is not intended for use in infant formula, products under the jurisdiction of the United States Department of Agriculture, or in any food for which standards of identity would preclude its use.

production strains are non-pathogenic and non-toxigenic. Sichuan Bohaoda states that the parent strain *E. coli* BL21(DE3) has safely been used in the production of human milk oligosaccharides. Sichuan Bohaoda confirms that whole genome sequencing of *E. coli* BL21(DE3) revealed the absence of genes encoding invasion factors, adhesion molecules, and enterotoxins associated with virulence.

The enzyme-catalyzed reaction is carried out at 70°C in a phosphate buffer in the presence of magnesium sulfate. The process is stopped by filtering the bacteria when the conversion rate is ≥80%. The resulting solution is decolorized using activated carbon and concentrated. The crude inositol is further purified through crystallization, centrifugation, washing, and drying. Sichuan Bohaoda states that inositol is manufactured in accordance with current good manufacturing practices and that all raw materials and processing aids are food grade, are used in accordance with applicable U.S. regulations, are GRAS for their intended uses, or are the subject of an effective food contact notification. Sichuan Bohaoda states that none of the raw materials used in the manufacture of inositol are major allergens or are derived from major allergens.

Sichuan Bohaoda provides specifications for inositol that include assay (≥97% on the anhydrous basis), water (≤0.5%); organic impurities (glucose and maltose) (≤0.3% individual impurities or ≤ 1.0% total impurities), arsenic (≤ 0.1 mg/kg), lead (≤ 0.1 mg/kg), mercury (≤ 0.1 mg/kg), cadmium (≤ 0.1 mg/kg), and limits for microorganisms including *Salmonella* serovars (negative in 10 g). Sichuan Bohaoda provides the results from the analyses of five non-consecutive batches to demonstrate that inositol can be manufactured to meet these specifications. Shichuan Bohaoda indicates that the shelf life of inositol is 2 years when it is stored sealed in a cool and dry place.

Sichuan Bohaoda estimates the eaters-only dietary exposure to inositol from the intended uses to be 55.1 mg/person (p)/day (d) (0.85 mg/kg body weight (bw)/d) at the mean and 119.0 mg/p/d (1.83 mg/kg bw/d) at the 90th percentile for the U.S. population aged one year and older based on food consumption data from the 2017-2020 National Health and Examination Survey (NHANES). Sichuan Bohaoda notes that the intended uses of inositol are substitutional for those specified in §184.1370 and therefore, there will be no increase in cumulative dietary exposure to inositol.

Sichuan Bohaoda states that inositol is GRAS affirmed[2] and discusses publicly available data and information pertaining to the safety of dietary inositol, including a report by FDA's Select Committee on GRAS Substances (SCOGS)[3]. Sichuan Bohaoda describes background consumer dietary exposure to inositol and notes that inositol is naturally present in commonly consumed foods like cow's milk, fruits, beans, grains, and nuts. Further, Sichuan Bohaoda discusses that inositol is endogenous to the human body and

[2] Per 21 CFR 184.1370 – Inositol. Available at: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-B/part-184/subpart-B/section-184.1370

[3] SCOGS (1975). Evaluation of the Health Aspects of Inositol as a Food Ingredient - Final Report. (PB262660; SCOGS-51; Contract No. FDA-223-75-2004). Prepared by: Federation of American Societies for Experimental Biology (FASEB), Life Sciences Research Office (LSRO), Select Committee on GRAS Substances (SCOGS). Bethesda (MD). Available at: https://ntrl.ntis.gov/NTRL/dashboard/searchResults.xhtml?searchQuery=PB262660

is naturally produced by the kidney at a level far exceeding dietary exposure estimates from the intended uses.[4]

Sichuan Bohaoda describes data on the absorption, distribution, metabolism, and excretion of inositol in humans and rats that was reviewed by SCOGS, which indicates inositol is slowly absorbed in the gastrointestinal tract, mainly metabolized in the kidney, and excreted in urine. Sichuan Bohaoda notes that any non-excreted inositol is likely to undergo catabolism and be incorporated into microsomal phospholipids. Further, the *in vitro* mutagenicity and genotoxicity data outlined in the SCOGS report, as discussed by Sichuan Bohaoda, indicates that inositol is non-mutagenic and unlikely to be genotoxic. Sichuan Bohaoda describes pivotal published toxicology data on oral exposure (via dietary incorporation or gavage) to inositol, or *myo*-inositol, which share the same chemical formula as the article of commerce. These data were sourced from their search of the scientific literature through October 2024, and include a subchronic (9 months) study in male rats where no adverse findings were noted at a maximum dose of approximately 1,000 mg/kg bw/d (2% of the diet), and multiple developmental and reproductive toxicity studies in rodents, including one in rats where inositol was administered to the mother during pregnancy, lactation, and then to the offspring for 3 months post-weaning and no adverse effects were noted at doses up to 500 mg/kg bw/d. Sichuan Bohaoda further discusses multiple human clinical studies supportive of the safety of dietary inositol, but note that these studies use substantially higher doses of inositol (up to 20,000 mg/p/d) compared to dietary exposure estimates from the intended uses. Given this, Sichuan Bohaoda notes that no non-nutritive physiological or medicinal effects, as reported in the literature, would be expected from the intended uses.

Based on the totality of data and information described above, Sichuan Bohaoda concludes that inositol is GRAS for its intended uses.

Standards of Identity

In the notice, Sichuan Bohaoda states its intention to use inositol in several food categories, including foods for which standards of identity exist, located in Title 21 of the CFR. 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.

Potential Labeling Issues

Under section 403(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), a food is misbranded if its labeling is false or misleading in any way. Section 403(r) of the FD&C Act lays out the statutory framework for labeling claims characterizing a nutrient level in a food or the relationship of a nutrient to a disease or health-related condition (also referred to as nutrient content claims and health claims). If products containing inositol bear any nutrient content or health claims on the label or in labeling, such claims are

[4] Sichuan Bohaoda reports via publicly available data and information, that the adult human kidney produces an estimated 4,000 mg of inositol per day.

subject to the applicable requirements and are under the purview of the Office of Nutrition and Food Labeling (ONFL) in the Nutrition Center of Excellence. The Office of Pre-Market Additive Safety did not consult with ONFL on this issue or evaluate any information in terms of labeling claims. Questions related to food labeling should be directed to ONFL.

Section 301(ll) of the FD&C Act

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 our evaluation of Sichuan Bohaoda's notice concluding that inositol is GRAS under its intended conditions of use, we did not consider whether section 301(ll) or any of its exemptions apply to foods containing inositol. Accordingly, our response should not be construed to be a statement that foods containing inositol, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Sichuan Bohaoda provided, as well as other information available to FDA, we have no questions at this time regarding Sichuan Bohaoda's conclusion that inositol is GRAS under its intended conditions of use. This letter is not an affirmation that inositol is GRAS under 21 CFR 170.35. Unless noted above, our review did not address other provisions of the FD&C Act. Food ingredient manufacturers and food producers are responsible for ensuring that marketed products are safe and compliant with all applicable legal and regulatory requirements.

In accordance with 21 CFR 170.275(b)(2), the text of this letter responding to GRN 001198 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2025.02.03 17:55:32 -05'00'

Susan J. Carlson, Ph.D.
Director
Division of Food Ingredients
Office of Pre-Market Additive Safety
Office of Food Chemical Safety, Dietary Supplements, and Innovation
Human Foods Program