



Madhu G. Soni, Ph.D.  
Soni & Associates Inc.  
749 46th Square  
Vero Beach, FL 32968

Re: GRAS Notice No. GRN 000797

Dear Dr. Soni:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000797. We received the notice that you submitted on behalf of New Francesco Biotechnology Corporation (NFBC) on July 2, 2018, and filed it on August 10, 2018. NFBC submitted amendments to the notice on October 15, 2018, and October 17, 2018, that provided additional data and information on the ion exchange resin used in the manufacturing process and clarified text from the notice.

The subject of the notice is fructooligosaccharides (FOS) for use as an ingredient in non-exempt infant formulas for term infants, as consumed, at a level up to 400 mg FOS/100 mL formula for infants 0-6 months and up to 500 mg FOS/100 mL formula for infants >6 months. The notice informs us of NFBC's view that these uses of FOS are GRAS through scientific procedures.

NFBC provides information about the identity and composition of FOS (CAS Registry No. 308066-66-2). FOS is a white to light yellow syrup or off-white to light yellow powder with a slightly sweet taste and no odor. NFBC describes FOS as fructan oligosaccharides consisting of linear chains of fructose linked by  $\beta$  (2-1) linkages with a terminal glucose residue. FOS primarily contains three fructans that have 2, 3, or 4 fructose units referred to as 1-kestose, nystose, and fructofuranosylnystose, respectively.

NFBC describes the manufacturing process for FOS, which it states is identical to that detailed in GRN 000623 (which is for the intended use of FOS in conventional foods).<sup>1</sup> Food-grade sucrose is dissolved in deionized water at elevated temperature and  $\beta$ -fructofuranosidase<sup>2</sup> is added in a fermenter. The pH is adjusted with sodium carbonate and the enzyme is inactivated by adding citric acid to the fermenter solution. This process results in a solution containing at least 50% FOS. The 50% FOS solution is decolorized, filtered, and evaporated. The FOS purity is increased through chromatographic separation to remove glucose, fructose, and sucrose. After purification,

<sup>1</sup> FOS was the subject of GRNs 000044, 000537, 000605, 000623, and 000717. We evaluated these notices and responded in letters dated November 22, 2000, February 6, 2015, March 17, 2016, August 1, 2016, and February 13, 2018, respectively, stating that we had no questions at that time regarding the notifiers' GRAS conclusions.

<sup>2</sup> NFBC states that *Aspergillus oryzae*, the soil bacterium used to produce the  $\beta$ -fructofuranosidase enzyme, is non-toxigenic and non-pathogenic.

the syrup form is packaged and the powder form is obtained by evaporation and spray drying, and then packaged. NFBC states that all ingredients are food-grade and FOS is manufactured according to current good manufacturing practices.

NFBC provides specifications for the syrup and powder forms of FOS. These specifications include ≥95% FOS and limits on sugars ( $\leq 5\%$ ), ash ( $\leq 0.1\%$ ), lead ( $\leq 0.02$  mg/kg), total arsenic ( $\leq 0.05$  mg/kg), cadmium ( $\leq 0.1$  mg/kg), total mercury ( $\leq 0.01$  mg/kg), and microorganisms (no detectable *Cronobacter sakazakii* or *Salmonella* serovars in 100 g or 25 g samples, respectively). NFBC provides the results of five non-consecutive batch analyses to show that FOS can be manufactured to meet these specifications.

NFBC estimates the dietary exposure to FOS, and states that the intended uses and use levels are identical to those described in GRN 000537.<sup>1</sup> NFBC estimates that the 90<sup>th</sup> percentile exposures are 828 mg FOS/kg body weight (bw)/day (d) from 0-1 month of age and about 800 mg/kg bw/d from >1 month of age.

NFBC discusses the safety of FOS and incorporates into the notice published toxicity studies cited in GRNs 000044, 000537, 000605, 000623, and 000717.<sup>1</sup> These published toxicity studies on FOS include acute, short-term (6-8 weeks), subchronic, chronic, carcinogenicity, developmental, and reproductive, as well as *in vitro* genotoxicity assays. NFBC states that these studies did not reveal any toxicologically relevant treatment-related adverse effects, including a 104-week study where male and female rats were fed FOS through the diet at up to 2170 mg/kg bw/d and 2664 mg/kg bw/d, respectively. NFBC states that an updated literature search was conducted through March 2018 and did not reveal any new data or information on the effects of FOS in adults or children.

NFBC includes the statement of a panel of individuals (NFBC's GRAS panel). Based on its review, NFBC's GRAS panel concluded that FOS is safe under the conditions of its intended use.

Based on the totality of the evidence, NFBC concludes that the intended use of FOS is GRAS.

### Potential Labeling Issues

Under section 403(a) of the Federal Food, Drug, and Cosmetic (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). The notice raises a potential issue under these labeling provisions. NFBC cites studies that describe FOS as having certain health benefits. If products containing FOS bear any nutrient content or health claims on the label or in labeling, such claims are subject to the applicable requirements and are under the purview of the Office of Nutrition and Food Labeling (ONFL) in the Center for Food Safety and Applied Nutrition. The Office of Food 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.

### **Intended Use in Infant Formula**

Under section 412 of the FD&C Act, a manufacturer of a new infant formula must make a submission to FDA providing required assurances about the formula at least 90 days before the formula is marketed. Our response to NFBC's GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing FOS to make the submission required by section 412. Infant formulas are the purview of ONFL.

### **Section 301(l) of the FD&C Act**

Section 301(l) 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(l)(1)-(4) applies. In our evaluation of NFBC's notice concluding that FOS is GRAS under its intended conditions of use, we did not consider whether section 301(l) or any of its exemptions apply to foods containing FOS. Accordingly, our response should not be construed to be a statement that foods containing FOS, if introduced or delivered for introduction into interstate commerce, would not violate section 301(l).

### **Conclusions**

Based on the information that NFBC provided, as well as other information available to FDA, we have no questions at this time regarding NFBC's conclusion that FOS is GRAS under its intended conditions of use. This letter is not an affirmation that FOS 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 000797 is accessible to the public at [www.fda.gov/grasnoticeinventory](http://www.fda.gov/grasnoticeinventory).

Sincerely,

Michael A. Adams -S

Digitally signed by Michael A.  
Adams -S  
Date: 2018.11.15 13:41:07 -05'00'

Dennis M. Keefe, Ph.D.

Director

Office of Food Additive Safety  
Center for Food Safety  
and Applied Nutrition