



Ashish Talati, J.D., M.S., RAC
Amin Talati & Upadhye, LLC
100 South Wacker Drive, Suite 2000
Chicago, IL 60606

Re: GRAS Notice No. GRN 000666

Dear Mr. Talati:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000666. We received the notice, dated August 16, 2016, that you submitted on behalf of Gnosis S.p.A. (Gnosis), in accordance with the agency's proposed regulation, proposed 21 Code of Federal Regulations (CFR) 170.36 (62 FR 18938; April 17, 1997; Substances Generally Recognized as Safe (GRAS); the GRAS proposal) on August 17, 2016, and filed it on September 13, 2016. We received an amendment containing additional dietary exposure information on November 23, 2016.

FDA published the GRAS final rule on August 17, 2016 (81 FR 54960), with an effective date of October 17, 2016. As GRN 000666 was pending on the effective date of the GRAS final rule, we requested additional information consistent with the format and requirements of the final rule. We received an amendment responding to this request on November 1, 2016.

The subject of the notice is chondroitin sulfate sodium derived from *Escherichia coli* (*E. coli*-derived chondroitin sulfate sodium). The notice informs us of Gnosis' view that *E. coli*-derived chondroitin sulfate sodium is GRAS, through scientific procedures, for use as an ingredient in conventional foods such as beverages and beverage bases, milk and milk products, and chewing gum at levels from 50 to 200 mg/serving.¹

Our use of the term, "*E. coli*-derived chondroitin sulfate sodium," in this letter is not our recommendation of that term as an appropriate common or usual name for declaring the substance in accordance with FDA's labeling requirements. Under 21 CFR 101.4, each ingredient must be declared by its common or usual name. In addition, 21 CFR 102.5 outlines general principles to use when establishing common or usual names for nonstandardized foods. Issues associated with labeling and the common or usual name of a food ingredient are under the purview of the Office of Nutrition and Food Labeling (ONFL) in the Center for Food Safety and Applied Nutrition (CFSAN). The Office of Food additive Safety (OFAS) did not consult with ONFL regarding the appropriate common or usual name for "*E. coli*-derived chondroitin sulfate sodium."

Gnosis discusses the identity of *E. coli*-derived chondroitin sulfate sodium. The notifier states that *E. coli*-derived chondroitin sulfate sodium with chemical formula $(C_{14}H_{19}NNa_2O_{14}S)_n$ is an amorphous white to off-white powder that is soluble in water and 96% insoluble in acetone and

¹ Gnosis states that the intended uses of *E. coli*-derived chondroitin sulfate sodium exclude infant formula, foods formulated for infants and toddlers, and meat and poultry products.

U.S. Food & Drug Administration
Center for Food Safety & Applied Nutrition
5001 Campus Drive
College Park, MD 20740

ethanol. Gnosis describes *E. coli*-derived chondroitin sulfate sodium as an amino sugar polymer (glucosaminoglycan) with structure $\rightarrow[4)\text{-}\beta\text{-D-GlcA-(1}\rightarrow\text{3)-}\beta\text{-D-GalNAc(1}\rightarrow\text{)}_n$. Gnosis states that the chondroitin sulfate described in this notice is identical to the chondroitin sulfate derived from animal sources.

Gnosis describes the manufacturing of *E. coli*-derived chondroitin sulfate sodium as a two-step process. The first step uses *E. coli* O5:K4:H4 strain U1-41 (ATCC 23502) to produce K4 polysaccharide via fermentation.² In the second step, the K4 polysaccharide is chemically transformed to chondroitin sulfate sodium from chondroitin sodium. Positively charged sodium ions are removed under acidic conditions and alkyl-ammonium hydroxide is then added to form the chondroitin salt. This is followed by sulphation, ultrafiltration, and spray-drying to recover solid chondroitin sulfate sodium. All processing agents and materials used in the production of *E. coli*-derived chondroitin sulfate sodium are high-grade pure chemicals used in accordance with current good manufacturing practices.

Gnosis provides specifications for *E. coli*-derived chondroitin sulfate sodium. These specifications are for assay (95.0-105.0%), and include limits for lead (≤ 0.5 mg/kg), cadmium (≤ 0.5 mg/kg), mercury (≤ 0.1 mg/kg), arsenic (≤ 1.5 mg/kg), microbial contaminants, and endotoxin (≤ 100 endotoxin units/mg). Gnosis presented analyses of three non-consecutive batches of *E. coli*-derived chondroitin sulfate sodium to demonstrate conformance with the specifications.

Gnosis provides dietary exposure estimates for *E. coli*-derived chondroitin sulfate sodium for its intended uses using the 1994-1996 U.S. Department of Agriculture Continuing Survey of Food Intakes by Individuals data for food consumption. The exposures to *E. coli*-derived chondroitin sulfate sodium for the U.S. population aged 2 years or older are estimated to be 593 mg/person (p)/day (d) (10 mg/kg bodyweight (bw)/d) at the mean and 1187 mg/p/d (20 mg/kg bw/d) at the 90th percentile for a 60 kg individual.

Gnosis discusses the data and information supporting the safety of *E. coli*-derived chondroitin sulfate sodium. Gnosis describes the metabolic fate of chondroitin sulfate of animal origin after oral administration in studies with rats, dogs, and humans. The published pharmacokinetic studies in rats and dogs revealed that chondroitin sulfate was partially absorbed from the gut as relatively low molecular weight fractions of the depolymerized material. In humans, it was reported that more than 50% of the intravenously administered chondroitin sulfate was excreted in urine during the first 24 h as high and low molecular weight derivatives. Following ingestion of 3 g of chondroitin sulfate in humans, the absolute bioavailability calculated from the area under the curve of plasma concentration is 13.2%. A peak for oligo- and polysaccharides of lower molecular weight was also present in the plasma suggesting that the metabolic fate of chondroitin sulfate is similar in humans and in animals.

Gnosis discusses published studies specifically conducted with *E. coli*-derived chondroitin sulfate sodium to support its safe use. These studies include a 90-day subchronic oral (gavage) toxicity study performed in Sprague-Dawley rats, *in vitro* genotoxicity studies, and a human pharmacokinetic study. Gnosis states that the results of the human pharmacokinetic study conducted with *E. coli*-derived chondroitin sulfate sodium demonstrate that its metabolic fate is

² Gnosis provides information showing that the strain is fully characterized and does not contain genes involved in pathogenicity or toxicity. Following fermentation, the bacteria are heat-inactivated, separated from K4 polysaccharide, and are not part of the final ingredient.

similar to the more commonly consumed chondroitin sulfate of bovine origin. The results of the subchronic toxicity study showed that no adverse effects were observed at 1000 mg/kg bw/d, the highest dose tested. *In vitro* genotoxicity studies did not reveal any mutagenic or clastogenic potential. In addition, Gnosis discusses published human clinical studies that indicate no adverse effects at levels up to 1200 mg/day for up to 3 years. Gnosis states that the results of all the studies with *E.coli*-derived chondroitin sulfate sodium support its safe use.

Gnosis includes the statement of a panel of individuals (Gnosis' GRAS panel). Based on its review, Gnosis' GRAS panel concluded that *E. coli*-derived chondroitin sulfate sodium is safe under the conditions of its intended use.

Based on the totality of data and information discussed above, Gnosis concludes that *E. coli*-derived chondroitin sulfate sodium is GRAS under the conditions of its intended use.

Standards of Identity

In the notice, Gnosis states its intention to use *E. coli*-derived chondroitin sulfate sodium 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 (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. In the notice, Gnosis cites studies that describe *E. coli*-derived chondroitin sulfate sodium as having certain health benefits. If products containing *E. coli*-derived chondroitin sulfate sodium bear any nutrient content or health claims on the label or in labeling, such claims are the subject to the applicable requirements and are under the purview of ONFL in CFSAN. OFAS 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(II) of the FD&C Act

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

Conclusions

Based on the information that Gnosis provided, as well as other information available to FDA, we have no questions at this time regarding Gnosis' conclusion that *E. coli*-derived chondroitin sulfate sodium is GRAS under its intended conditions of use. This letter is not an affirmation that *E. coli*-derived chondroitin sulfate sodium 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 000666 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Michael A. Adams

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Dennis M. Keefe, Ph.D.

Director

Office of Food Additive Safety

Center for Food Safety

and Applied Nutrition

Digitally signed by Michael A. Adams -S
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