100 S. Wacker Dr. | Suite 2000
Chicago, IL 60606

312.466.1033 PHONE
312.884.7352 FAX

AminTalati.com

AMIN TALATI UPADHYE

November 22, 2016

RECEIVED
NOV 23 2016
OFFICE OF
FOOD ADDITIVE SAFETY

Eric Sause
Biologist, Division of Biotechnology and GRAS Notice Review
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5001 Campus Drive
College Park, MD 20740

RE: Gnosis S.p.A. GRAS Notice No. GRN 000666

Dear Mr. Sause,

As you know, we represent Gnosis S.p.A. ("Gnosis") in regulatory matters. We are in receipt of FDA's request for additional information via electronic mail on November 14, 2016). Enclosed is the additional information requested from Gnosis. Please do not hesitate to contact me if there are any further questions or concerns.

Sincerely,

Ashish R. Talati
Amin Talati & Upadhye, LLP
100 South Wacker Drive, Suite 2000
Chicago, IL 60606
(312) 327-3381 (direct)
(312) 884-7352 (fax)
Email: Ashish@AminTalati.com

Encl: Responses and Statements from Gnosis S.p.A. Regarding GRN 000666

Responses and Statements from Gnosis S.p.A. Regarding GRN 000666

Gnosis did not include the dietary supplement related uses in the exposure assessment for the following reasons:

(1) In clinical trials with chondroitin sulfate, a dose of 1200 mg/day is commonly used[1], [2]. Although there is no evidence of an optimum level of chondroitin to be consumed beyond which no benefit is expected, the available information indicate that for a short term dietary supplement use, the recommended dose of chondroitin sulfate appears to be 1200 to 1800 mg/day, with a maintenance dose of 600 to 750 mg/day to improve clinical signs of osteoarthritis. As described in the GRAS dossier, for food uses, the intended use level of chondroitin sulfate is 50 to 200 mg/serving in different foods, resulting in daily estimated intake of 1200 mg/person/day. These estimates from intended food uses are very conservative and many consumers are unlikely to consume many different foods containing added chondroitin sulfate. The proposed use of chondroitin sulfate in food will be marketed to target population that is likely to be aware of their existing intake of chondroitin sulfate as a dietary supplement. It is anticipated that these individuals are likely to use the food containing chondroitin sulfate as a maintenance dose in place of dietary supplement. For those individuals consuming chondroitin sulfate from dietary supplement use, and from a food source, the total intake levels could vary between 1400 - 2000 mg/day. Even at these levels, we do not believe there is a safety concern.

(2) We do not anticipate substantial dietary changes in the general population but do expect there to be some increase in consumer taking chondroitin as a dietary supplement who may also consume food containing chondroitin.

(3) In a review article, Hathcock and Shao (2007)[3] noted a nearly complete absence of any adverse effects of chondroitin sulfate within the range of the clinical trials reviewed (800 - 1200 mg/day) suggesting that the highest level, 1200 mg/day, is not a true no-observed adverse effect level (NOAEL) and that any low-observed adverse effect level (LOAEL) is likely to be much higher. This also indicates that a marginal increase in the exposure to chondroitin by the combined use of dietary supplement and its use as a food ingredient is unlikely to raise any safety concern.

(4) Although dietary supplement use has been increased during the past few decades, only about 50% of the adult population takes dietary supplements on a frequent basis[4]. Among the users, multivitamin-multimineral use was the most frequently reported dietary supplement (33%). Thus, it is not possible to extrapolate dietary supplement use to the continuous use by the general population.

---

[1] Adebowale, A.O., Cox, D.S., Liang, Z., Eddington, N.D., 2000. Analysis of glucosamine and chondroitin sulfate content in marketed products and the Caco-2 permaebility of chondroitin sulfate raw materials. J. Am. Nutraceutical Assoc. 3:37-44.

[2] Hendler, S.S., Rorvik, D., 2001. Chondroitin sulfate. In: PDR for Nutritional Supplements. Medical Economics™ Thomson Healthcare, Montvale, NJ, pp. 93-96.

[3] Hathcock, J.N., Shao, A., 2007. Risk assessment for glucosamine and chondroitin sulfate. Regul. Toxicol. Pharmacol. 47:78-83.

[4] Bailey, R.L., Gahche, J.J., Lentino, C.V., Dwyer, J.T., Engel, J.S., Thomas, P.R., Betz, J.M., Sempos, C.T., Picciano, M.F., 2011. Dietary supplement use in the United States, 2003-2006. J. Nutr. 141(2):261-266.