Gary Yingling
Morgan Lewis Bockius LLP
1111 Pennsylvania Ave., NW
Washington, D.C. 20004

Re: GRAS Notice No. GRN 000214

Dear Mr. Yingling:

The Food and Drug Administration (FDA, we) completed our evaluation of the supplement to GRN 000214 that you submitted on behalf of DSM Nutritional Products (formerly known as DSM Food Specialties; DSM). We received the supplement on June 28, 2016. The supplement addresses additional uses of asparaginase enzyme preparation from *Aspergillus niger* expressing a gene encoding asparaginase from *A. niger* (asparaginase enzyme preparation).

We previously responded to GRN 000214 on March 12, 2007. We stated that we had no questions at that time regarding DSM's conclusion that asparaginase enzyme preparation is GRAS through scientific procedures, for use as an enzyme to lower free L-asparagine levels in breads, cereal-based products, potato-based products, and reaction flavors, at levels up to 562 milligrams Total Organic Solids per kilogram (mg TOS/kg) of final food.

In the supplement dated June 28, 2016, DSM informs us of its view that asparaginase enzyme preparation is GRAS, through scientific procedures, for use as an enzyme in the manufacture of infant biscuits, cookies, and infant cereals at a maximum use level of 562 mg TOS/kg of final food, to reduce acrylamide.[1]

As part of this supplement, DSM confirms that the manufacture of asparaginase enzyme preparation has not changed from that described in the original notice, GRN 000214, and that asparaginase enzyme preparation meets the specifications established for enzyme preparations in the current Food Chemicals Codex (FCC)[2] and the General Specifications and Considerations for Enzyme Preparations Used in Food Processing established by the FAO/WHO Joint Expert Committee on Food Additives (JECFA, 2006).

DSM discussed the impact of the additional intended uses on the estimated dietary exposure of asparaginase enzyme preparation. DSM states that the enzyme is denatured during the baking process and is not expected to be active in the final food. However, DSM estimates the maximum mean and 90th percentile dietary exposures to be 0.214 mg TOS per kg bodyweight per day (mg TOS/kg bw/d), and 0.638 mg TOS/kg bw/d, respectively from consumption of the additional intended foods by infants and toddlers 6-24 months of age; DSM assumed a bodyweight of 10.3 kg for these calculations.

[1] Acrylamide forms when foods containing L-asparagine and reducing sugars are baked or fried at temperatures above 120°C. DSM intends to use asparaginase enzyme preparation in the manufacture of the intended additional foods, to reduce L-asparagine levels thereby reducing acrylamide levels in these foods. FDA has not evaluated the efficacy of the asparaginase enzyme preparation for the intended use.

[2] FDA notes that the most current FCC is the 10th edition (FCC, 2016).

DSM states that the safety data discussed in the original notice, GRN 000214, are still applicable to these intended additional uses. The No Observe Adverse Effect Level (NOAEL) in the 90-day oral toxicity study was reported in GRN 000214 to be 271 mg TOS/kg bw/d, which was the highest dose tested. In particular, DSM determined the prenatal development study described in GRN 000214 to be relevant given that the intended consumers of the additional intended uses would be infants and toddlers. DSM reports that the NOAEL in the prenatal developmental study is 1003 mg TOS/kg bw/d, which was the highest dose tested. DSM calculates a margin of safety of 325, based on the 90th percentile exposure and the NOAEL from the 90-day oral toxicity study. DSM concludes that all the NOAEL levels tested in the toxicity studies are far above the consumption levels expected given the additional intended uses.

DSM also confirms performing a search of current scientific literature regarding the asparaginase enzyme preparation that is the subject of GRN 000214 through June 2016. DSM reports no new safety data.

Based on the data and information summarized above, DSM concludes that asparaginase enzyme preparation is GRAS for its intended use.

Section 301(ll) of the Federal Food, Drug, and Cosmetic Act (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 DSM's supplement concluding that asparaginase enzyme preparation 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 asparaginase enzyme preparation. Accordingly, our response should not be construed to be a statement that foods containing asparaginase enzyme preparation, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that DSM provided, as well as other information available to FDA, we have no questions at this time regarding DSM's conclusion that asparaginase enzyme preparation from *A. niger* expressing a gene encoding asparaginase from *A. niger* is GRAS under the intended conditions of use. This letter is not an affirmation that asparaginase enzyme preparation from *A. niger* expressing a gene encoding asparaginase from *A. niger* 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 the supplement to GRN 000214, is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
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