Timothy Murbach, ND, DABT
AIBMR Life Sciences, Inc
1425 Broadway, Suite 458
Seattle, WA 98122

Re: GRAS Notice No. GRN 000960

Dear Dr. Murbach:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000960. We received the notice that you submitted on behalf of Shin-Etsu Chemical Col, Ltd. (Shin-Etsu) on June 24, 2020 and filed it on November 16, 2020. Shin-Etsu submitted amendments to the notice on February 19, 2021, June 1, 2021, and July 27, 2021 that clarified information related to batch compliance with specifications, raw materials and the manufacturing process, dietary exposure, and safety studies.

The subject of the notice is hypromellose acetate succinate (HPMCAS) for use as an enteric coating agent, and an enteric agent in dietary supplement tablets/caplets (5-10%), granules (10-50%), pellets, and capsules (including gel caps, pills, soft gels, and vegi caps) (5-27.5%). The notice informs us of Shin-Etsu's view that these uses of HPMCAS are GRAS through scientific procedures.

Our use of the term, "HPMCAS," 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. The Office of Food Additive Safety did not consult with ONFL regarding the appropriate common or usual name for "HPMCAS."

Shin-Etsu states that hypromellose acetate succinate (HPMCAS) is a tasteless, white to yellowish powder or granules with a faint acetic-acid-like odor. HPMCAS consists of methyl and hydroxypropyl side groups ether-linked to hydroxyl groups on a cellulose backbone, with intermittent acetyl and succinyl group substitutions. HPMCAS is identified by the CAS # 71138-97-1.

Shin-Etsu describes the method of manufacture for HPMCAS. Shin-Etsu states that first, hypromellose is dissolved in glacial acetic acid in a reactor; then acetic and succinic anhydride are added with sodium acetate as a catalyst and the mixture is heated. The resulting paste is transferred to a water tank and HPMCAS polymer is precipitated out

by agitation. The polymer is then washed with more water and centrifuged to decant the supernatant, dehydrated and dried. The product is then sieved, blended, and packed into three grades of different particle sizes: granular, mid-sized or fine. Shin-Etsu states that the entire process complies with current good manufacturing practices. Shin-Etsu states that all raw materials and processing aids are food grade and are used in accordance with all applicable U.S. regulations, have been previously determined to be GRAS for their intended use, or have been the subject of an effective food contact notification.

Shin-Etsu provides specifications for HPMCAS for acetyl content (7.0 – 11.0%), succinyl content (10.0 – 14.0%), methoxy content (21.0 – 25.0%), hydroxypropoxy content (5.0 – 9.0%), particle size, viscosity, limit of free acetic and succinic acids (<1.0%), lead (< 0.15 mg/kg), loss on drying (<5.0%), and residue on ignition (<0.2%). Shin-Etsu provides results from the analyses of three non-consecutive batches to demonstrate that HPMCAS can be manufactured to meet these specifications. Shin-Etsu states that all methods used for the analyses are validated methods that are fit for purpose. Shin-Etsu states that HPMCAS has been shown to be stable over four years when stored in a double-layer polyethylene bag with a fiber drum.

Shin-Etsu estimates the dietary exposure to HPMCAS from its intended uses in dietary supplements with data from the 2011-2012 National Health and Nutrition Examination Survey. Shin-Etsu applied the maximum use levels intended for the applications in the tablet, granule, and capsule categories of dietary supplements. Shin-Etsu estimates the eaters-only dietary exposure to HPMCAS from the intended uses to be 219.0 mg/p/d (2.83 mg/kg bw/d) at the mean, and 550.0 mg/p/d (6.15 mg/kg bw/d) at the 90th percentile for the U.S. population aged 2 years and older.

Shin-Etsu discusses several published studies on HPMCAS including acute (rats and rabbits), subchronic (rats), and chronic (rats) studies, as well as several reproductive and developmental toxicity studies conducted in rats and New Zealand (NZ) white rabbits. All long-term toxicity studies used 6 days/week treatment schedule. Shin-Etsu concluded that there were no treatment-related adverse effects up to 1.25 g/kg bw 6 days /week (equivalent to 1.071 g/kg bw/day).

Shin-Etsu discussed several published studies focused on the effects of HPMCAS in fertility, reproductive function, and early embryonic development in both male and female rats and New Zealand (NZ) white rabbits. Shin-Etsu concluded that there were no treatment-related adverse effects on reproductive performance, paternal and maternal toxicities, maternal and developmental toxicities, and teratogenicity of HPMCAS at up to 1.071 g/kg bw/day.

Shin-Etsu corroborated the safety of HPMCAS by noting that JECFA allocated an acceptable daily intake (ADI) “not specified” to seven modified celluloses; HPMCAS is structurally similar to one of the modified celluloses.

Based on the available data and information, Shin-Etsu concludes that its HPMCAS is GRAS under the intended conditions of 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 Shin-Etsu's notice concluding that HPMCAS 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 HPMCAS. Accordingly, our response should not be construed to be a statement that foods containing HPMCAS, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Shin-Etsu provided, as well as other information available to FDA, we have no questions at this time regarding Shin-Etsu's conclusion that HPMCAS is GRAS under its intended conditions of use. This letter is not an affirmation that HPMCAS 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 000960 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2021.12.21 11:28:37 -05'00'

Susan Carlson, Ph.D.
Director
Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety
and Applied Nutrition