Ashit Vora
Synergia Life Sciences Pvt. Ltd.
6/312, Jogani Industrial Complex
V.N. Purav Marg, Chunabhatti
Mumbai - 400022
INDIA

Re: GRAS Notice No. GRN 000887

Dear Mr. Vora:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000887. We received Synergia Life Sciences Pvt. Ltd. (Synergia)'s notice on October 21, 2019, and filed it on December 5, 2019. Synergia submitted amendments to the notice on February 21, 2020, March 22, 2020, March 27, 2020, April 1, 2020, and May 29, 2020, that clarified the intended use, manufacturing, specifications, safety narrative, and cited references.

The subject of the notice is menaquinone-7 (MK-7) for use as an ingredient and as a nutrient according to 21 CFR 170.3(o)(20) in nutritional beverage products intended for consumers ages 1-13 years at a use level of 4 µg/serving.[1] The notice informs us of Synergia's view that this use of MK-7 is GRAS through scientific procedures.

Synergia discusses the identity of MK-7 (CAS No. 2124-57-4) and states that it is a pale yellow to yellow oil extracted from *Bacillus licheniformis* DSM 24722.[2] MK-7 is a vitamin K2 subtype with the molecular formula $C_{46}H_{64}O_2$.

Synergia describes the method of manufacture for MK-7, which is produced by fermentation of the non-pathogenic and non-toxicogenic strain *B. licheniformis* DSM 24722. Fermentation occurs until a desired cell density is reached using gram flour and dextrin as carbon and nitrogen sources. MK-7 in the fermentation broth is then spray dried and extracted using hexane. The resulting concentrated oil is mixed with glycerol monostearate, cooled, and milled to a powder. Alternatively, the concentrated oil can be blended in a vegetable oil as needed. Synergia states that all chemicals and processing aids used in the manufacture of MK-7 are food grade.

[1] Synergia uses "mcg" to refer to micrograms in the notice.
[2] Synergia states that *B. licheniformis* DSM 24722 is deposited in the strain collection of the Leibniz Institute DSMZ-German Collection of Microorganisms and Cell Cultures GmbH in Braunschweig, Germany, and is designated as DSM 24722.

Synergia provides specifications for MK-7 that include a minimum content of MK-7 (>1500 μg/g), arsenic (<0.5 μg/g), mercury (<0.1 μg/g), lead (<0.5 μg/g), cadmium (<0.5 μg/g), and limits for microorganisms. Synergia provides results from five non-consecutive batch analyses to demonstrate that MK-7 can be manufactured to meet these specifications.

Synergia estimates the exposure to MK-7, vitamin K1, vitamin K2, and vitamin K (vitamin K1 and vitamin K2) from existing dietary sources (total diet and dietary supplements), the intended uses, and a cumulative dietary exposure from the existing dietary sources and intended uses using food consumption data from the 2011-2014 National Health and Nutrition Examination Surveys. Synergia estimates exposure to MK-7 from the intended use at the maximum use level to range from 20 μg/person (p)/day (d) for children aged 12-23 months to 44 μg/p/d for males aged 9-13 years. The cumulative eaters-only mean and 90th percentile dietary exposure for vitamin K (vitamin K1 and vitamin K2) ranged from 317 to 449 μg/p/d and 486 to 682 μg/p/d, respectively, for the various population groups.

Synergia discusses published data and information identified in a literature search through April 2019 to support the safety of the intended use of long-chain menaquinone or MK-7. Synergia states that menaquinones are absorbed unchanged from the small intestines and distributed to the liver. The available published studies demonstrate higher serum bioavailability and longer half-life of MK-7 when compared to the short-chain MK-4 or phylloquinone (Vitamin K1).

Synergia describes two published acute and subchronic (90-day) oral toxicity studies in rats where no compound-related toxicities were reported. Synergia states that MK-7 is neither mutagenic nor genotoxic based on the results of the published genotoxicity studies. Synergia summarizes two published subchronic and chronic (1-year) toxicity studies with structurally similar MK-4 conducted in both rats and dogs and states that no adverse effects were observed. Synergia also describes developmental toxicity studies with MK-4, reviewed by the European Food Safety Authority (EFSA) panel (2008) that concluded there were no significant adverse effects observed on reproductive and developmental parameters measured. Synergia states that the studies with MK-4 support the safety of MK-7.

Synergia discusses several published human studies with MK-7 to support safety. Synergia states that these studies did not report any significant adverse effects when consumed at levels up to 180 μg/d for 3 years. Additionally, Synergia discusses multiple published long-term (up to 2 years) human studies that show high doses (up to 90 mg/d for 24 weeks) of MK-4 were well tolerated and further corroborate the safety of MK-7 for the intended use.

Synergia addresses concerns related to MK-7 and vitamin K antagonists (anticoagulant therapy), dietary intake of vitamin K, and drug interactions. Synergia states that the available information suggests that different vitamin K homologs differ in their mode or extent of action in disturbing vitamin K antagonist-induced anticoagulation. Synergia discusses studies and reviews indicating MK-7 at doses ≤50 μg/day are unlikely to affect

levels of vitamin K in a clinically relevant way. Despite having higher bioavailability and longer half-life when compared to vitamin K1 or another short-chain K2 (MK-4), Synergia concludes that regular or daily low dose supplementation of MK-7 (4 µg/serving) and restricted use in specific nutritional beverage products for children ensures that it does not pose increased risk to children, including those undergoing anticoagulation therapy. Furthermore, Synergia emphasizes that children undergoing anticoagulation therapy are a relatively small percentage of the general child population and would likely be under the supervision of a hematologist who is aware of the fact that dietary vitamin K interacts with anticoagulation medication and would track the child's International Normalized Ratio to ensure a therapeutic dosage is provided. Further, Synergia states that the historical consumption of MK-7-containing foods like natto and different cheeses supports the intended use of MK-7. Synergia also provides EFSA's safety evaluation (2008) that MK-7 is safe to consume in foods for the general population at use levels of 10 µg/serving as further evidence of general recognition.

Synergia includes the report of a panel of individuals (Synergia's GRAS panel). Based on its review, Synergia's GRAS panel concluded that MK-7 is safe under the conditions of its intended use.

Based on the totality of information discussed above, Synergia concludes that MK-7 is GRAS for its intended use.

Potential Labeling Issues

Under section 403(a) of the Federal Food, Drug, & 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). If products containing MK-7 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 (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.[3]

Potential Requirement for a Color Additive Petition

There is no GRAS provision for color additives. In the notice, Synergia describes MK-7 as a pale yellow to yellow oil. As such, the use of MK-7 in food products may constitute a color additive use under section 201(t)(1) of the FD&C Act and FDA's implementing regulations in 21 CFR Part 70. Under section 201(t)(1) and 21 CFR 70.3(f), a color

[3] As discussed in the "Food Labeling: Revision of the Nutrition and Supplement Facts Labels" Final Rule (81 FR 33742), menaquinones are not included in the definition of Vitamin K and would not be declared in the Nutrition Facts Label as Vitamin K.

additive is a material that is a dye, pigment, or other substance made by a synthetic process or similar artifice, or is extracted, isolated, or otherwise derived from a vegetable, animal, mineral, or other source. Under 21 CFR 70.3(g), a material that otherwise meets the definition of a color additive can be exempt from that definition if it is used (or is intended to be used) solely for a purpose or purposes other than coloring. Our response to GRN 000887 is not an approval for use as a color additive nor is it a finding of the Secretary of the Department of Health and Human Services within the meaning of section 721(b)(4) of the FD&C Act. Questions about color additives should be directed to the Division of Food Ingredients in OFAS.

Section 301(ll) of the 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 Synergia's notice concluding that MK-7 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 MK-7. Accordingly, our response should not be construed to be a statement that foods containing MK-7, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Synergia provided, as well as other information available to FDA, we have no questions at this time regarding Synergia's conclusion that MK-7 is GRAS under its intended conditions of use. This letter is not an affirmation that MK-7 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 000887 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2020.06.12 17:02:19 -04'00'

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