Susan Cho, Ph.D.
AceOne RS, Inc.
5903 Hampton Forest Way
Fairfax, VA 22030

Re: GRAS Notice No. GRN 001118

Dear Dr. Cho:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001118. We received the notice that you submitted on behalf of Zhejiang Medicine Co., Ltd. (ZMC, they) on October 11, 2022 and filed it on March 22, 2023. ZMC submitted amendments on May 31, 2023 and June 20, 2023, that clarified the specifications, production strain, product purity, and provided additional safety information.

The subject of the notice is pyrroloquinoline quinone disodium salt (PQQ disodium salt) for use as an ingredient at a level up to 20 mg/serving in "enhanced and fortified" waters; up to 12 mg/serving in "energy" drinks; and up to 8 mg/serving in "sports" and "electrolyte" drinks, bottled waters, and non-milk-based meal replacement beverages[1]. The notice informs us of ZMC's view that these uses of PQQ disodium salt are GRAS through scientific procedures.

ZMC provides information about the identity and composition of PQQ disodium salt. PQQ disodium salt is a red or reddish-brown powder. PQQ disodium salt is designated by the CAS Registry Number 122628-50-6 and has the molecular formula $C_{14}H_4N_2Na_2O_8$.

ZMC provides a description of the method of manufacture for PQQ disodium salt, which is produced through a fermentation process utilizing a strain of *Methylovorus glucosotrophus*, a nonpathogenic and non-toxicogenic microorganism. ZMC states that the original *M. glucosotrophus* strain is deposited with the China General Microbiological Culture Collection Center as CGMCC No. 4096. ZMC describes the production of the *M. glucosotrophus* culture, growth medium, and fermentation process. The *M. glucosotrophus* inoculum is added to the fermentation medium and fermented under controlled conditions. After fermentation is complete, the culture is filtered to separate the biomass from the supernatant. The supernatant is subjected to

[1] ZMC states that PQQ disodium salt is not intended for use in infant formula or any products under the jurisdiction of the United States Department of Agriculture.

ion exchange chromatography and optionally concentrated by nanofiltration. Sodium chloride is added to the solution to form a crystallized product. The crystallized product is dissolved in water and subjected to additional ion exchange chromatography, crystallization, and filtration to obtain a crude PQQ disodium salt. The crude product is then dissolved in water, treated with hydrochloric acid, and cooled to crystalize and then filtered. The crystalline product is dried under vacuum, milled, and sieved to obtain the final PQQ disodium salt. ZMC states that PQQ disodium salt is produced in accordance with current good manufacturing practices and that all raw materials, processing aids, and fermentation medium ingredients are food grade, are used in accordance with U.S. regulations, or are previously concluded to be GRAS for their respective uses.

ZMC provides specifications for PQQ disodium salt that include the minimum content of PQQ disodium salt (≥ 98% on a dry weight basis (DM)) and PQQ (≥ 85% DM). Specifications also include limits for water (≤ 13%), sodium (10.5 – 12.9% DM), total organic impurities (≤ 1%), any individual organic impurity (≤ 0.1%),[2] lead (≤ 0.1 mg/kg) and microorganisms. ZMC provides the results of the analyses of six batches, including three non-consecutive batches, to demonstrate that PQQ disodium salt can be manufactured to meet these specifications.

ZMC provides the results of a stability study and stated that PQQ disodium salt is stable for 12 months when stored in polyethylene bags at 25 °C and 60% relative humidity.

ZMC states that the intended uses of PQQ disodium salt are the same as described in GRN 000709.[3] ZMC provides an estimate of the dietary exposure to PQQ disodium salt based on the intended uses in food and food consumption and body weight data from the 2015-2018 National Health and Nutrition Examination Surveys (NHANES). ZMC estimates the mean and 90th percentile eaters-only dietary exposure for the U.S. population aged 2 years and older to be 21.3 and 45.8 mg/person/d (0.30 and 0.62 mg/kg body weight (bw)/d), respectively. ZMC states that the intended uses of PQQ disodium salt will be substitutional for other dietary sources, and its use is not anticipated to increase the overall dietary exposure to PQQ disodium salt.

ZMC discusses publicly available data and information supporting the safety of PQQ disodium salt and its production organism *Methylovorus glucosotrophus*. ZMC also states that FDA has previously evaluated PQQ disodium salt produced synthetically or by *Hyphomicrobium denitrificans*[4]. ZMC conducted a comprehensive literature search of new publications through July 2022 to identify recently available safety information

[2] ZMC discusses the potential presence of imidazolopyrroloquinoline (IPQ) in PQQ disodium salt, which is a secondary metabolite of the fermentation process. ZMC provides the results of the analyses of the production intermediates and the final product for three non-consecutive batches to demonstrate that IPQ is removed during the purification process and is not detected in PQQ disodium salt.

[3] The subject of GRN 000709 is PQQ disodium salt intended for use in the same foods and at the same use levels described in GRN 001118. We evaluated GRN 000709 and responded in a letter dated March 6, 2018, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

[4] The subjects of GRNs 000625, 000641, 000694, 000701 and 000709 are pyrroloquinoline quinone disodium salt (PQQ). We evaluated these notices and responded in letters dated August 18, 2016, October 14, 2016, September 28, 2017, September 8, 2017, and March 6, 2018, respectively, stating that we had no questions at that time regarding the notifiers' GRAS conclusions.

relevant to PQQ disodium salt. ZMC did not identify any safety concerns or information that would contradict its GRAS conclusion.

ZMC describes published studies investigating the absorption, distribution, metabolism, and excretion (ADME) characteristics of PQQ disodium salt. ZMC concludes that PQQ disodium salt is non-mutagenic and non-genotoxic based on the results of published bacterial reverse mutation, *in vitro* chromosomal aberration, and *in vivo* rat micronucleus assays. ZMC provides a summary of published safety studies including acute, sub-chronic, and developmental toxicity studies to support the safety of the intended use of PQQ disodium salt. ZMC notes the safety of the intended use of PQQ disodium salt is corroborated by the results of a published 90-day sub-chronic oral toxicity study in rats administered PQQ disodium salt produced by *M. glucosotrophus*. Additionally, ZMC describes several published human studies to further support the safety of the intended use of PQQ.

Based on the totality of the data and information, ZMC concludes that PQQ disodium salt is GRAS for its intended use.

Standard of Identity

In the notice, ZMC states its intention to use PQQ disodium salt in several food categories, including foods for which standards of identity exist, located in Title 21 of the Code of Federal Regulations. 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, & 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 PQQ disodium salt 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 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.

Potential Requirement for a Color Additive Petition

There is no GRAS provision for color additives. In the notice, ZMC notes that PQQ disodium salt has color. As such, the use of PQQ disodium salt 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 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 001118 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 the Office of Food Additive Safety.

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 ZMC's notice concluding that PQQ disodium salt 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 PQQ disodium salt. Accordingly, our response should not be construed to be a statement that foods containing PQQ disodium salt, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that ZMC provided, as well as other information available to FDA, we have no questions at this time regarding ZMC's conclusion that PQQ disodium salt is GRAS under its intended conditions of use. This letter is not an affirmation that PQQ disodium salt 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 001118 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2023.07.31 18:13:50 -04'00'

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