Susan S. Cho, Ph.D.
NutraSource, Inc.
6309 Morning Dew Court
Clarksville, MD 21029

Re: GRAS Notice No. GRN 000709

Dear Dr. Cho:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000709. We received the notice that you submitted on behalf of Shandong JinCheng Bio-Pharmaceutical Co., Ltd. (JinCheng) on May 25, 2017, and filed it on July 12, 2017. You submitted amendments on July 19, August 20, and November 25, 2017, which contain additional discussion of safety information and clarification of details regarding the method of manufacture, identity, and exposure.

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

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

JinCheng provides a description of the method of manufacture for PQQ disodium salt, which is produced through a fermentation process utilizing a strain of *Hyphomicrobium denitrificans*, a nonpathogenic and nontoxicogenic microorganism. JinCheng states that all materials and processing aids used in the manufacture of PQQ disodium salt are food-grade. JinCheng describes the production of the *H. denitrificans* culture, growth medium, and fermentation process. The *H. denitrificans* culture is added to fermentation medium and fermented under specific conditions. After fermentation is complete, the culture is filtered to separate the biomass from the supernatant. The supernatant is adsorbed, eluted, and crystallized to produce PQQ disodium salt. The crystalline product is first dissolved, filtered, and recrystallized; and then dried, milled and sieved to form the final PQQ disodium salt product.

JinCheng provides specifications for PQQ disodium salt that include the minimum content of PQQ disodium salt (≥ 99 %), limits on water (≤ 12 %), ethanol (≤ 5000 mg/kg), lead (≤ 0.5 mg/kg), arsenic (≤ 0.5 mg/kg), cadmium (≤ 0.3 mg/kg), and mercury (≤ 0.2 mg/kg), as well as limits on microbial contaminants. JinCheng provides the results of the analysis of three, non-consecutive batches to demonstrate that PQQ disodium salt can be manufactured to meet these specifications.

JinCheng 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 National Health and Nutrition Examination Survey (NHANES, 2011-2014). JinCheng estimates the mean and 90th percentile, users-only, dietary exposures to the general population to be 28.2 and 63.1 mg/person/d (0.41 and 0.89 mg/kg bw/d), respectively.

JinCheng discusses published and unpublished studies pertaining to the safety of PQQ disodium salt. As part of the narrative in its notice, JinCheng references toxicological and clinical studies discussed in previous notices concerning PQQ disodium salt.[1] JinCheng's updated literature search for the period ending in April 2017 did not include any relevant safety data that had not been discussed in one or more previous notices. Published and unpublished toxicity studies in rats and mice were presented to support the view that PQQ disodium salt exhibits low oral toxicity. In published 14-day, 28-day, and 13-week gavage studies, no toxicity was reported for PQQ disodium salt at up to 100 mg/kg bw/d, the highest dose tested in the 13-week study. The results of published Ames tests, *in vitro* chromosome aberration tests, and *in vivo* micronucleus tests indicate that PQQ disodium salt is neither mutagenic nor genotoxic.

Based on the totality of the data and information described above, JinCheng concludes that PQQ disodium salt is GRAS for its intended use in food.

Standards of Identity

In the notice, JinCheng states its intention to use PQQ disodium salt in several food categories, including food 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, and Cosmetic Act (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). In the notice, JinCheng cites studies that describe PQQ disodium salt as having certain health benefits. If products

[1] FDA has previously evaluated similar uses of PQQ in GRNs 000625, 000641, 000694, and 000701 and responded with letters stating that we had no questions at those times regarding the notifiers' GRAS conclusions.

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 (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.

Potential Requirement for a Color Additive Petition

There is no GRAS provision for color additives. In the notice, JinCheng 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 000709 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 Petition Review 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 JinCheng'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 JinCheng provided, as well as other information available to FDA, we have no questions at this time regarding JinCheng'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 000709 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Michael A. Adams -S

Digitally signed by Michael A. Adams -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300042713, cn=Michael A. Adams -S
Date: 2018.03.06 13:26:16 -05'00'

Dennis M. Keefe, Ph.D.
Director
Office of Food Additive Safety
Center for Food Safety
and Applied Nutrition