Summary of the application: Extracted oil derived from *Nannochloropsis oculata*

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The novel food supplement subject to the authorization is an extract of the microalgae *Nannochloropsis oculata*. The novel food supplement (Ultra*Nanno*) contains 25% wt. omega-3 polyunsaturated fatty acids (PUFA), primarily the omega-3 (n-3) fatty acid (n-3 LCPUFA) eicosapentaenoic acid (EPA). Ultra*Nanno* is intended for use in the European Union as a source of the naturally occurring n-3 LCPUFA, EPA, in food supplement products for the general population, which is safe when consumed at the recommended intake of 1,250 mg Ultra*Nanno*/day, which will provide a maximum of 312.5 mg/day omega-3 fatty acids.

Three independent, industrial-scale batches of Ultra*Nanno* were produced and fully characterized, which included proximate analysis, physical characteristics, oxidation stability, and the fatty acids profile. Analyses also demonstrated that potential contaminants [residual solvents, pesticides (organochlorine and organophosphorus), and toxins] were non-detectable. The analytical results demonstrate that the production process is robust and reproducible to produce Ultra*Nanno*, which is compliant with the proposed regulatory specifications. Stability studies demonstrated that Ultra*Nanno* is stable for four months under accelerated conditions (40°C/75% relative humidity) from the date of manufacture and up to 18 months when stored under an inert atmosphere in tight containers in a cool, dry environment at less than 5°C, away from direct sunlight.

Ultra*Nanno* is composed of the LCPUFA EPA at an average of 25%, palmitic acid at an average of approximately 7% and palmitoleic acid at an average of approximately 9% wt. Ultra*Nanno* also contains about 3% chlorophyll and 15% polar lipids (phospho-lipids & glyco-lipids). Other components of Ultra*Nanno* were also quantified, which include phospholipid and glycolipid content, containing an average of approximately 3.9% wt. of Phosphatidylcholine, 4.8% wt. of total phospho-lipids, and 8.2% wt. glycolipids, which includes monogalactosyldiacylglycerols and digalactosyldiacylglycerols. These are normal dietary components which are metabolized by humans via established biochemical processes. A comprehensive evaluation of published literature indicated that EPA is rapidly absorbed and metabolized by humans and laboratory animals.

A series of toxicological studies were conducted on Almega®PL, following EFSA's recommendations for establishing the safety of novel foods and food additives in the EU. Almega®PL from Qualitas Health has been notified to the FDA as a New Dietary Ingredient (NDI) (NDIN #826), and recently VAXA evaluated the publicly available information for Almega®PL and found Ultra*Nanno* to be substantially equivalent to Almega®PL. To demonstrate that Ultra*Nanno* was substantially similar to Almega®PL (as described in NDIN #826), VAXA evaluated the composition, nutritional value, metabolic fate of the identifying components, intended use, and level of undesirable substances between UltraNanno and Almega®PL. The source and specifications stated in the publication are consistent with the specifications stated in the NDIN #826 for Almega®PL and for the stated source and specifications for the Ultra*Nanno* produced by VAXA. Therefore, Almega®PL and Ultra*Nanno* are substantially equivalent, and safety studies from both oils establish the safety of oil derived from *N. oculata* for use as a food supplement.

A comprehensive evaluation of publicly available toxicological studies using the algal biomass, algal extracts, or algal residues corroborated the overall safety of *N. oculata.* The results of an in vitro bacterial reverse mutation assay and in vitro micronucleus assay were negative indicating that Ultra*Nanno* is not genotoxic. Results of the 90-day toxicity study in rats fed Almega®PL by gavage established a no observed adverse effect level (NOAEL) of 2,000 mg/kg bw/day for both male and female rats. The subchronic study utilizing an *N. oculata* biomass determined the NOAEL to be 6000 mg/kg bw/day. Compared to the maximum proposed use level of Ultra*Nanno* in food supplements of 1,250 mg/person/day a safety factor of 112 can be calculated based off the Almega®PL study and of

336 for the algal biomass subchronic study. Acute and short term/subacute toxicity studies also demonstrated that Almega®PL is well tolerated and safe up to 2,500 mg/kg bw/day, indicated the median lethal dose (LD50) was higher than this concentration. The reported LD50 for studies utilizing *N. oculata* biomass or algal extract (including Almega®PL) were above the highest dose tested (ranging from 2,500 mg/kg bw/day – 12,000 mg/kg bw/day). These acute and short term/subacute toxicity studies indicated that *N. oculata* did not induce mortality, clinically adverse effects, or any signs of toxicity.

Although there were no studies investigating the chronic toxicity or carcinogenicity of *N. oculata*, there were no studies indicating that *N. oculata* would potentially possess chronic toxicity or carcinogenic potential and one study reported *N. oculata* may possesses potential anticarcinogenic activity. There were no studies examining the potential carcinogenic of Almega®PL or Ultra*Nanno* found within the literature; however, its primary constituent, EPA, and its role in cancer has been thoroughly investigated, and there is no indication that the levels of EPA consumed at the maximum recommended dose would have carcinogenic potential. Moreover, the additional intake of EPA from Ultra*Nanno* will not exceed the safe levels of EPA consumption set forth by EFSA (1,800 mg EPA/day). Therefore, Ultra*Nanno* does not possess carcinogenic potential and is safe under the intended conditions of use for the general population. *N. oculata* also does not possess the potential for reproductive or developmental toxicity up to 10,000 mg/kg.

N. oculata also poses no concern for allergenicity and is well tolerated in humans, which is corroborated by its current approval status as a food supplement in a member of the EU, France, and by human safety studies. Ultra*Nanno* is a purified oil that lacks protein and does not possess any known allergens that are listed in Annex II of Regulation (EU) No 1169/2011; therefore, Ultra*Nanno* also possesses a very low probability for allergenicity. In France, *N. oculata* is approved for the general population and has no limitations in use as a food supplement. Multiple human studies have also confirmed that *N. oculata* is well tolerated, and no serious adverse events were reported, even at doses that would exceed those for which Ultra*Nanno* would be intended as a food supplement. Human studies also indicated that Almega®PL can potentially provide nutritional and health benefits, including a hepato-protective role, a source of EPA, and increases in plasma levels of DHA.

Therefore, based on the analytical data, the evaluation of the production process, composition, specifications, and the publicly available toxicological information and safety studies, the maximum proposed use level of Ultra*Nanno* in food supplements (1,250 mg/day) is safe under the conditions of its intended use and does not pose a safety risk to human health.