NEW DIETARY INGREDIENT NOTIFICATION FOR OMEGA-3 FISH OIL

PREPARED BY

Spirit Pharmaceuticals LLC.

Address: 2004-02 Orville Dr N,

Ronkonkoma, NY 11779.

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New Dietary Ingredient Notification for Omega-3 Fish oil in Omega-3, Fish oil, and Triple Omega.

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1. Information of the New Dietary Ingredient

1.1 Description of the identity of the NDI

The proposed new dietary ingredient is Omega-3 Fatty acid is key ingredient in dietary supplements, namely Omega-3, Fish Oil, and Triple Omega, are distributed by Spirit Pharmaceuticals LLC ("SPL"). The dietary supplement strengths and quantities are tabulated below.

Name of the Dietary Supplement	Strength (mg)	Count
Omega-3	500	180, 120 and 60
Omega-3	1000	60
Omega-3	2000	180
Fish oil	1000	60, 300
Triple Omega	800	120

To submit a New Dietary Ingredient Notification (NDIN) for the respective dietary supplements, the ingredients are summarized as follows:

(b) (4)

The term “dietary supplement” is defined in 21 U.S.C. 321 (ff) (U.S. FDA, 2022) as, among other things:

“a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: (A) a vitamin; (B) a mineral; (C) an herb or other botanical; (D) an amino acid; (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E).”

The Fish Oil, Omega-3, and Triple Omega are dietary supplements deemed lawful for use in dietary supplements, in accordance with 21 U.S.C. 321(ff) (1)(E) (U.S. FDA, 2022). Specifically, these supplements fall under category (E) as dietary substances for use by humans to supplement the diet by increasing the total dietary intake. They are recognized as essential dietary components, meeting the regulatory standards set forth by the U.S. FDA.

1.2 Description of the evidence verifying the identity of the NDI

The verification of the identity of the proposed Dietary Supplements by Spirit Pharmaceuticals LLC. ("SPL") encompasses detailed information on the composition and specifications of (b) (4)

(b) (4)

1.3 NDI manufacture

(b) (4) . "Spirit Pharmaceuticals LLC (SPL) acknowledges that certain information within the New Dietary Ingredient Notification (NDIN) dossier, specifically related to the chemical composition, manufacturing details, specifications, certificates of analysis, test methods, and unpublished safety data of Omega-3, Fish Oil, and Triple Omega, is classified as confidential trade secret and/or confidential commercial information under 21 CFR §20.61(d) and 190.6(e) (U.S. FDA, 2021b, c). SPL is aware that, per FDA regulations, this confidential information will be treated as such for 90 days after the filing date of this Notice. However, SPL respectfully requests continued confidentiality for the specific information outlined in Table 1.3-1 beyond the initial 90-day period."

Table 1.3-1 Confidential Chapters and Sections of the New Dietary Ingredient Notification

Confidential Chapters and Sections	Explanation
Sections 1.2, 1.3.1 and 1.3.3 Manufacturing process which includes process flow charts and relevant in Appendices regarding manufacturing process.	Trade Secret under 21 CFR §20.61(a) (U.S. FDA, 2021b), as Sections 1.2, 1.3.1 and 1.3.3 contain SPL exact composition of the supplements and manufacturing process. These documents must be kept confidential because the information is proprietary and commercially valuable. Confidential Commercial Information under 21 CFR §20.61(b) (U.S. FDA, 2021b), as Sections 1.2 and 1.3.3 contain confidential information used in SPL's business and this information is customarily held in strict confidence or regarded as privileged.
Sections 1.3.4, 1.3.5 and 1.3.6 and information in relevant appendices regarding the product specifications, Method of Analysis, certificate of Analysis and stability of the dietary Supplement.	Trade Secret under 21 CFR §20.61(a) (U.S. FDA, 2021b), as Sections 1.3.4, 1.3.5 and 1.3.6 and the associated data in the appendices contain the product specifications, certificates of analyses, methods of analysis, and stability of the dietary Supplement. Ingredient that must be kept confidential because the information is proprietary and commercially valuable. Product specifications and certificates of analyses contain trade secret compositional information. Confidential Commercial Information under 21 CFR §20.61(b) (U.S. FDA, 2012b), as Sections 1.3.4, 1.3.5 and 1.3.6 and the associated appendices contain confidential information used in SPL's business and this information is customarily held in strict confidence or regarded as privileged. Disclosure of this information would allow competitors to copy SPL's new dietary supplement and would likely cause substantial harm to SPL's competitive position.
Sections 3.3.1 Safety study type	Trade Secret under 21 CFR §20.61(a) (U.S. FDA, 2021b), as section 3.3.1contain reference to SPL's product-specific safety studies on Omega-3 Fish oil. The data are regarded as proprietary information that is not publicly available. Therefore, the information presented in this section is a product of research and innovation that required substantial effort. Accordingly, these sections are trade secret and must not be disclosed, as the information is proprietary and commercially valuable. Confidential Commercial Information under 21 CFR §20.61(b) {U.S. FDA, 2021b), as Sections 3.3.1 contain confidential information used in SPL's business and this information is customarily held in strict confidence or regarded as privileged. Disclosure is likely to cause substantial harm to SPL's competitive position.

1.3.1 Raw materials

(b) (4)

1.3.2 Formulation ingredients

The formulation ingredients are identical to the raw materials specified in the **Table 1.3.1.1**.

1.3.3 Manufacturing process

(b) (4)

1.3.4 NDI specifications

(b) (4)

(b) (4)

1.3.5 Methods of analysis

(b) (4)

2. Dietary Supplement Manufacture

Identical as in section 1

3. History of Safe Use

3.1 History of use

Fish oil, Omega-3, and Triple Omega supplements are popular dietary supplements that contain essential fatty acids, particularly omega-3 fatty acids[1]. These supplements are widely used for their potential health benefits, including cardiovascular health, brain function, and inflammation reduction[2].

Omega-3

Omega-3 fatty acids, including Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are essential for various physiological functions. The history of omega-3 supplements is closely tied to the recognition of the health benefits of these fatty acids[5]. Omega-3 supplements gained popularity in the late 20th century, with increasing research highlighting their role in cardiovascular health, brain function, and inflammation modulation[6].

Fish Oil

Fish oil has been consumed for centuries, and its health benefits have been recognized in various cultures. The traditional diet of some coastal communities, such as the Inuit in Greenland and the Japanese, included a significant amount of fish, providing a natural source of omega-3 fatty acids[3]. The use of fish oil as a dietary supplement gained popularity in the latter half of the 20th century as researchers began to uncover the health benefits associated with omega-3 fatty acids found in fish oil[4].

Triple Omega

Triple Omega supplements typically combine fish oil, flaxseed oil, and borage oil to provide a comprehensive mix of omega-3, omega-6, and omega-9 fatty acids[7]. The idea behind these combinations is to offer a broad spectrum of essential fatty acids, each with its own health benefits. The use of triple omega supplements has emerged as a convenient way for individuals to obtain a diverse range of fatty acids in a single supplement[8].

3.2 Adverse events associated with historically consumed material

No adverse effects have been reported that can be associated with the chronic consumption of Omega-3 Fatty acids. Detailed analysis of relevant studies follows.

3.3 Other evidence of safety

3.3.1 Safety study type

Omega-3s, which are short for omega-3 fatty acids, represent a category of fats present in both food and the human body. They are also available in the form of dietary supplements.

Varieties of Omega-3s and their Food Sources

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), known as long-chain omega-3s due to their chemical structure, can be sourced from seafood, including fish and shellfish.

Alpha-linolenic acid (ALA), another type of omega-3, is found in specific plant oils like flaxseed, soybean, and canola oils. Additionally, it occurs in various plant-based foods such as chia seeds and black walnuts. The majority of the research discussed in this fact sheet primarily focuses on EPA and DHA.

Various dietary supplements contain omega-3s, offering different sources and combinations of these fatty acids:

Fish oil supplements: These supplements include both EPA and DHA.

Fish liver oil supplements: Examples like cod liver oil contain EPA and DHA along with varying amounts of vitamins A and D. Caution is advised as excessive amounts of vitamins A and D can be harmful.

Krill oil: This supplement contains both EPA and DHA.

Algal oils: Sourced from algae, these are vegetarian supplements providing DHA, and some may also contain EPA.

Flaxseed oil: This supplement contains ALA.

When considering the benefits of omega-3s, it's noted that for certain health conditions, evidence supporting the advantages of obtaining omega-3s from seafood (fish and shellfish) is stronger compared to omega-3 supplements. This could be due to various factors:

Seafood might naturally provide sufficient omega-3s, and an excess may not necessarily be beneficial. Other nutrients present in seafood, apart from omega-3s, may contribute to its health benefits. Some benefits of seafood consumption may arise from individuals choosing it over less healthy food options. People who regularly consume seafood may generally lead healthier lifestyles.

The Dietary Guidelines for Americans (2015–2020) recommend that adults consume 8 or more ounces of a variety of seafood per week for the comprehensive nutritional benefits it offers. Additionally, it suggests including seafood choices with higher levels of EPA and DHA. Smaller amounts of seafood are recommended for young children.

As per the 2012 National Health Interview Survey, a comprehensive study on the adoption of complementary health practices in the United States, fish oil supplements stand out as the most frequently consumed non-vitamin/non-mineral natural product among both adults and children.

Survey results revealed that approximately 7.8 percent of adults (equivalent to 18.8 million individuals) and 1.1 percent of children aged 4 to 17 (amounting to 664,000) had used a fish oil supplement within the previous 30 days.

Conditions Affecting the Circulatory System

Heart Disease[7]

In a 2011 evaluation encompassing 17 studies, individuals consuming seafood (fish and shellfish) one to four times a week demonstrated a lower likelihood of succumbing to heart disease compared to those who rarely or never included seafood in their diet.

However, a 2018 analysis examining 10 major studies involving omega-3 supplementation (involving 77,917 participants at high risk of heart disease, each with a minimum treatment duration of one year and at least 500 participants) found no evidence supporting the reduction of fatal or nonfatal coronary heart disease through omega-3 supplementation.

A comprehensive 2016 evaluation by the U.S. Government's Agency for Healthcare Research and Quality (AHRQ) considered 98 studies on omega-3s and heart disease, encompassing both dietary and supplementation studies. The conclusion was that there is no evidence supporting the ability of omega-3s to decrease the risk of heart attacks or death from heart disease.

Recent analyses, conducted from 2012 onwards, align with the 2018 analysis and the AHRQ report, showing limited or no evidence for a protective effect of omega-3 supplements against heart disease. This shift in conclusions over time may be attributed to increased public awareness promoting higher seafood consumption, potentially rendering additional omega-3s from supplements less beneficial. Additionally, the prevalence of medications like statins for heart attack risk reduction may diminish any extra benefits offered by omega-3s.

Stroke [8, 9]

Consumption of seafood has been associated with a modest reduction in the risk of stroke. The AHRQ report suggests some evidence supporting the notion that omega-3s from marine sources, such as fish oil, may lower the risk of ischemic stroke (resulting from blood vessel narrowing or blockage in the brain). However, omega-3s have not shown conclusive evidence of reducing total strokes or stroke-related mortality.

Triglycerides [9, 10]

High levels of triglycerides in the blood may elevate the risk of heart disease. Dietary adjustments, weight management, and exercise are conventional methods to lower triglyceride levels. Omega-3 fatty acids, particularly in high doses, have been proven to reduce triglyceride levels.

Certain prescription drugs containing omega-3s have been approved to be used in conjunction with diet to lower triglyceride levels in individuals with markedly elevated levels. It's essential to note that the composition of these prescription products differs from typical omega-3 supplements, and their

effects may not be equivalent due to variations in testing and regulation between prescription drugs and dietary supplements.

Conditions Affecting the Brain, Nervous System, or Mental Health

Depression[11]

The effectiveness of omega-3 fatty acid supplements in alleviating depression remains uncertain. While some studies have shown promising outcomes, a comprehensive 2015 evaluation of 26 studies involving over 1,400 individuals concluded that if there is any effect, it might be too minimal to be clinically significant. Other analyses have suggested that, if omega-3s do exhibit an effect, EPA (Eicosapentaenoic acid) may be more advantageous than DHA (Docosahexaenoic acid), and that omega-3s may be most beneficial when used in conjunction with antidepressant medication rather than as a standalone treatment.

It's worth noting that omega-3s have not demonstrated efficacy in relieving depression symptoms during pregnancy or postpartum. Depression is a serious condition, and if there are concerns about depression in yourself or a family member, it is advisable to consult a healthcare provider.

Attention-Deficit Hyperactivity Disorder (ADHD)

Research on the use of omega-3s for ADHD has yielded conflicting results. The potential benefits of omega-3s for alleviating symptoms associated with this condition remain uncertain.

Alzheimer’s Disease/Cognitive Impairment[12]

While some research suggests that increased seafood consumption may lower the risk of cognitive decline, omega-3 supplements have not demonstrated efficacy in preventing cognitive impairment or Alzheimer's disease or improving symptoms associated with these conditions. A notable NIH-sponsored study completed in 2015 found that taking EPA and DHA supplements did not impede cognitive decline in older adults participating in a larger eye disease study, all of whom had age-related macular degeneration (AMD).

There is a possibility that the effects of omega-3s may vary among individuals with different genetic backgrounds. A 2017 research review proposed that individuals carrying the APOE4 gene, associated with an increased risk of Alzheimer’s disease, might benefit from taking DHA before displaying signs of Alzheimer's.

Other Conditions Affecting the Brain, Nervous System, or Mental Health[13, 14]

Omega-3s have been investigated for conditions such as autism spectrum disorders, borderline personality disorder, multiple sclerosis, and schizophrenia. However, the evidence regarding their effects on these conditions is inconclusive.

Eye Diseases

Age-Related Macular Degeneration (AMD) [15]

AMD, an eye disease causing vision loss in older individuals, was studied in major NIH-sponsored projects, AREDS and AREDS2. These studies revealed that dietary supplements containing specific combinations of vitamins, antioxidants, and zinc slowed AMD progression in those at high risk. However, adding EPA and DHA to the supplement formulation in AREDS2 did not provide additional benefits. Smaller studies on omega-3 supplements have also not demonstrated a beneficial effect on AMD progression.

Dry Eye Disease[16]

While earlier small studies suggested that omega-3 supplements might alleviate dry eye disease symptoms, a 2018 NIH-sponsored study with a larger group (535 participants) found that these supplements, tested over a full year, were no more effective than a placebo.

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