NATURAL HEALTH PRODUCT

FISH OIL

This monograph is intended to serve as a guide to industry for the preparation of Product Licence Applications (PLAs) and labels for natural health product market authorization. It is not intended to be a comprehensive review of the medicinal ingredient.

There are many N-3 polyunsaturated fatty acids, popularly known as omega-3 acids/ω-3 fatty acids (Ph.Eur. 2012). This monograph is specific to eicosapentaenoic acid (C20:5 n-3; EPA) and docosahexaenoic acid (C22:6 n-3; DHA).

Notes
- Text in parentheses is additional optional information which can be included on the PLA and product label at the applicant’s discretion.
- The solidus (/) indicates that the terms or the statements are synonymous. Either term or statement may be selected by the applicant.

Date: July 18, 2017

Proper name(s):
Fish oil (BP 2012; Ph.Eur. 2012)

Common name(s):
Fish oil (BP 2012; Ph.Eur. 2012)

Source material(s):
- Engraulidae – Whole
- Carangidae – Whole
- Clupeidae – Whole
- Osmeridae – Whole
- Scombridae – Whole
- Ammodytidae – Whole
- Salmonidae – Whole

The above corresponds to oil from the body of one or more of the following species in its natural and/or concentrated triglyceride/triacylglycerol form and/or its concentrated esterified form (BP 2012; Ph.Eur. 2012; Froese and Pauly 2011; Martindale 2011):
Anchovy (any species of Engraulidae)
Jack or pompano (any species of Carangidae)
Herring, shad, sardine, or menhaden (any species of Clupeidae)
Smelt (any species of Osmeridae)
Mackerel, tuna, or bonito (any species of Scombridae)
Sand lance (any species of Ammodytidae)
Salmonids (any species of Salmonidae)

Route(s) of administration:
Oral

Dosage form(s):
This monograph is not intended to include foods or food-like dosage forms such as bars, chewing gums or beverages.

Dosage forms by age group:

- **Children 1-2 years**: The acceptable dosage forms are limited to emulsion/suspension and solution/drops (Giacoia et al. 2008; EMEA/CHMP 2006).
- **Children 3-5 years**: The acceptable dosage forms are limited to chewables, emulsion/suspension, powders and solution/drops (Giacoia et al. 2008; EMEA/CHMP 2006).
- **Children 6-12 years, Adolescents 13-17 years, and Adults ≥ 18 years**: The acceptable dosage forms include, but are not limited to capsules, chewables (e.g., gummies, tablets), liquids, powders, strips or tablets.

Use(s) or Purpose(s):

For products providing 100-5,000 mg eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA), per day:
- Source of omega-3 fatty acids (EFSA 2012; Simopoulos 2007; Oh 2005; IOM 2002; Simopoulos 1999) for the maintenance of good health
- Source of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (EFSA 2012; Simopoulos 2007; Oh 2005; IOM 2002; Simopoulos 1999) for the maintenance of good health

For products providing 100-5,000 mg EPA + DHA including at least 100 mg DHA, per day:
Helps support cognitive health and/or brain function (EFSA 2012; van de Rest et al. 2008; Freund-Levi et al. 2006; Fontani et al. 2005a,b; Haag 2003; Morris et al. 2003; IOM 2002).
For products providing 150-2,000 mg EPA + DHA including at least 150 mg DHA, per day (maximum doses of EPA + DHA in Table 1 below will apply): Helps support the development of the brain, eyes and nerves in children up to 12 years of age (Marszalek and Lodish 2005; Haag 2003; IOM 2002; Giedd et al. 1999; Mills 1999).

For products providing 200-5,000 mg EPA + DHA, per day and containing a ratio of EPA:DHA between 0.5:1 and 2:1: Helps maintain/support cardiovascular health (EFSA 2012; Oh 2005; Wang et al. 2004; Leaf et al. 2003; Kris-Etherton et al. 2002).

For products providing 1,000-5,000 mg EPA + DHA, per day and containing a ratio of EPA:DHA between 0.5:1 and 2:1: Helps to reduce serum triglycerides/triacylglycerols (EFSA 2012; Oh 2005; Balk et al. 2004; Hooper et al. 2004; Nilsen et al. 2001; Sirtori et al. 1998).

For products providing 2,800-5,000 mg EPA + DHA, per day and containing a ratio of EPA:DHA between 0.5:1 and 2:1: In conjunction with conventional therapy, helps to reduce the pain of rheumatoid arthritis in adults (EFSA 2012; Volker et al. 2000; Sköldstam et al. 1992).

For products providing 1,500-5,000 mg EPA + DHA including at least 1000 mg EPA, per day and a ratio of EPA:DHA of 1.75:1 to 2:1: Helps to promote healthy mood balance (EFSA 2012; Nemets et al. 2006; Sontrop and Campbell 2006; Fontani et al. 2005a,b; Zanarini and Frankenburg 2003; Peet and Horrobin 2002; Stoll et al. 1999).

Dose(s):

Potency must be expressed as the quantity (mg) and/or percent (%) of EPA and DHA (% w/w) relative to the total quantity of fish oil.

Table 1 Daily dose for eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) in fish oil

<table>
<thead>
<tr>
<th>Subpopulation</th>
<th>EPA + DHA (mg/day)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minimum¹</td>
<td>Maximum²</td>
</tr>
<tr>
<td>Children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-8 y</td>
<td>100</td>
<td>1,500</td>
</tr>
<tr>
<td>Adolescents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9-13 y</td>
<td>100</td>
<td>2,000</td>
</tr>
<tr>
<td>14-18 y</td>
<td>100</td>
<td>2,500</td>
</tr>
<tr>
<td>Adults³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 19 y</td>
<td>100</td>
<td>5,000</td>
</tr>
</tbody>
</table>

¹ Restrictions to minimum dose may apply according to Use(s) or Purpose(s) section above.
² Adult maximum dose supported by US FDA 1997. Children and adolescent maximum doses, calculated as a fraction of the adult dose, are relative to body weight and caloric intake.
³ Includes pregnant and breastfeeding women.

Duration(s) of use:

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No statement required.

**Risk information:**

**Caution(s) and warning(s)**

No statement required.

**Contraindication(s)**

No statement required.

**Known adverse reaction(s)**

No statement required.

**Storage conditions:**

For all products:
Store in airtight container, protected from light (Ph.Eur. 2012; USP 35).

For all products, except those encapsulated:
Refrigerate after opening (Wille and Gonus 1989).

**Non-medicinal ingredients:**

Must be chosen from the current Natural Health Products Ingredients Database (NHPID) and must meet the limitations outlined in the database.

**Specifications:**

- The finished product specifications must be established in accordance with the requirements described in the Natural and Non-prescription Health Products Directorate (NNHPD) *Quality of Natural Health Products Guide*.
- The medicinal ingredient must comply with the requirements outlined in the NHPID.
- The medicinal ingredient may comply with the specifications outlined in the pharmacopoeial monographs listed in Table 2 below.
- Peroxide, anisidine, and totox values of fish oil and omega-3 fatty acids derived from fish oil must be in accordance with the methods set out by the Association of Analytical Community (AOAC) and/or Pharmacopoeial analytical methods. These specifications are necessary to ensure the oxidative stability of the fish oil and the omega-3 fatty acids from fish oil (HC 2007). Refer to Table 3 below.
The dioxins, polychlorinated dibenzo-para-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs); the dioxin-like polychlorinated biphenyls (DL PCBs); and the polychlorinated biphenyls (PCBs) are contaminants in oils from marine sources. Testing for these contaminants are required and must be performed using either the analytical method of the European Commission Regulation EU 252/2012 (EU 2012) or the U.S. Environmental Protection Agency’s method 1613B for PCDDs and PCDFs and method 1668A for PCBs (USP 35; US EPA 2010, 2008, 1994). Applicants are advised to consult the Council of the European Union document on these contaminants for further information (EU 2011). Refer to Table 4 below.

### Table 2  Fish Oil Monographs published in the American (USP), British (BP) and European (Ph.Eur.) Pharmacopoeias

<table>
<thead>
<tr>
<th>Pharmacopoeia</th>
<th>Monograph</th>
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<tbody>
<tr>
<td>BP</td>
<td>Fish Oil, Rich in Omega-3-Acids</td>
</tr>
<tr>
<td>Ph.Eur.</td>
<td>Fish Oil, Rich in Omega-3-Acids</td>
</tr>
<tr>
<td>USP</td>
<td>Fish Oil Containing Omega-3 Acids</td>
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</tbody>
</table>

### Table 3  Maximum values of oxidative stability parameters for fish oil (HC 2007)

<table>
<thead>
<tr>
<th>Oxidative stability parameter</th>
<th>Maximum value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peroxide value (PV)</td>
<td>5 mEq/kg</td>
</tr>
<tr>
<td>p-Anisidine value (AV)</td>
<td>20</td>
</tr>
<tr>
<td>Totox value</td>
<td>26 (calculated as (2 x PV) + AV)</td>
</tr>
</tbody>
</table>

### Table 4  Maximum levels of dioxins, dioxin-like polychlorinated biphenyls (DL PCB) and polychlorinated biphenyls (PCBs) in oils from marine sources

<table>
<thead>
<tr>
<th>Dioxin, DL PCB, and PCB contaminants</th>
<th>Maximum level</th>
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<tbody>
<tr>
<td></td>
<td>EU 1259/2011</td>
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<tr>
<td>Dioxins (sum of PCDDs + PCDFs)(^1)</td>
<td>1.75 pg/g</td>
</tr>
<tr>
<td>Sum of dioxins and DL PCBs(^1,3)</td>
<td>6 pg/g</td>
</tr>
<tr>
<td>PCBs(^4)</td>
<td>200 ng/g</td>
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</table>

1. Expressed in World Health Organization (WHO 2005) toxic equivalents using WHO-toxic equivalent factors (TEFs). Analytical results relating to 17 individual dioxin congeners of toxicological concern are expressed in a single quantifiable unit: 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) toxic equivalent concentration (TEQ) (USP 35; EU 2011).
2. Sum of dioxins: WHO-PCDD/F-TEQ (USP 35; EU 2011)
3. Sum of dioxins and dioxin-like PCBs: WHO-PCDD/F-PCB-TEQ (EU 2011)
5. Equivalence: 0.5 ppm = 500 ng/g

### References cited:


References reviewed:


European Food Safety Authority. 2008. Scientific substantiation of a health claim related to Docosahexaenoic Acid (DHA) and Arachidonic Acid (ARA) and support of the neural development of the brain and eyes pursuant to Article 14 of Regulation (EC) No 1924/2006. The EFSA Journal 794:1-11.


Frais AT. 2007. Depression and the causal role of specific memory system degenerations: Link may be supported by reported therapeutic benefits of omega 3 fatty acids. Medical Hypothesis 69(1):67-69.


Peat JK, Mihrshahi S, Marks GB, Tovey ER, Webb K, Mellis CM, Leeder SR. 2004. Three-year outcomes of dietary fatty acid modification and house dust mite reduction in the Childhood Asthma Prevention Study. The Journal of Allergy and Clinical Immunology 114(4):807-813.


Sagredos AN. 1991. [Fatty Acid Composition of Fish Oil Capsules]. Fett Wissenschaft Technologie 93(5):184-191 [article in German].


