

COD LIVER 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. It is a referenced document to be used as a labelling standard.

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 are synonyms or that the statements are synonymous. Either term or statement may be selected by the applicant.
- ▶ Vitamin E is an optional medicinal ingredient in cod liver oil products. However, no use or purpose statements may be associated with vitamin E. See Appendix 4 for vitamin E proper name, common name, source material, and dose information.
- ▶ The use(s) or purpose(s) statements in this monograph are based on the efficacy of vitamins A and D, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) that are present in cod liver oil. The references used to support these statements refer to the efficacy of these individual constituents and are not specific to cod liver oil.
- ▶ See Appendix 1 for Adequate Intake (AI), Recommended Dietary Allowance (RDA) and Tolerable Upper Intake Level (UL) definitions for nutrient intake. See also Table 8 in Appendix 2 for RDA and AI values for vitamin A, and Table 9 in Appendix 3 for AI values for vitamin D.

Date: February 24, 2010

Proper name(s): Cod liver oil (USP 32; Ph. Eur. 2007)

Common name(s): Cod liver oil (USP 32; Ph. Eur. 2007)

Source material(s):

- ▶ Liver of Atlantic cod, *Gadus morhua* L. (Gadidae) (ITIS 2004); Arctic and Maritimes populations only (EC 2009)
- ▶ Liver of Greenland cod, *Gadus ogac* Richardson (Gadidae) (ITIS 2004)
- ▶ Liver of Pacific cod, *Gadus macrocephalus* Tilesius (Gadidae) (ITIS 2004)

Note:

- “Arctic population” and/or “Maritimes population” is not required on the label, but must be indicated on the Animal

Tissue Form (ATF) when the source material is liver of Atlantic cod.

- “Atlantic cod, *Gadus morhua*”, “Greenland cod, *Gadus ogac*” or “Pacific cod, *Gadus macrocephalus*” must be indicated on the PLA and label as source material information.

Route(s) of administration: Oral

Dosage form(s): The acceptable pharmaceutical dosage forms for oral administration include, but are not limited to, chewables (e.g. gummies, tablets), caplets, capsules, strips, lozenges, powders or liquids where the dose is measured in drops, teaspoons or tablespoons. This monograph is not intended to include foods or food-like dosage forms such as bars, chewing gums or beverages.

Use(s) or Purpose(s): Statement(s) to the effect of:

For products providing 138-3,000 µg retinol activity equivalents (RAE) (µg vitamin A/all-*trans* retinol (palmitate)), per day:

- ▶ Helps to maintain eyesight, skin membranes and immune function (IOM 2006; Shils et al. 2006; Groff and Gropper 2000).
- ▶ Helps in the development and maintenance of night vision (IOM 2006; Shils et al. 2006; Groff and Gropper 2000).

For products providing daily doses of vitamin A at or above the Recommended Dietary Allowance (RDA) or Adequate Intake (AI) (adjusted for the life stage groups), the following use or purpose is acceptable:

Helps to prevent vitamin A deficiency (IOM 2006; Shils et al. 2006; Groff and Gropper 2000).

For products providing 1.15-25 µg vitamin D₃ (cholecalciferol), per day:

- ▶ Helps in the development and maintenance of bones (IOM 2006; Shils et al. 2006; Groff and Gropper 2000).
- ▶ Helps in the development and maintenance of teeth (IOM 2006; Shils et al. 2006; Groff and Gropper 2000).
- ▶ Helps in the absorption and use of calcium and phosphorus (IOM 2006; Shils et al. 2006; Groff and Gropper 2000; IOM 1997).

For products providing daily doses of vitamin D at or above the Adequate Intake (AI) (adjusted for the life stage groups), the following use or purpose is acceptable:

Helps to prevent vitamin D deficiency (IOM 2006; Shils et al. 2006; Groff and Gropper 2000; IOM 1997).

For products providing 100-1,360 mg eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA), per day:

- ▶ A factor in the maintenance of good health (IOM 2006)
- ▶ Source of omega-3 fatty acids for the maintenance of good health (Simopoulos 2007; Oh 2005; IOM 2002; Simopoulos 1999)
- ▶ Source of eicosapentaenoic acid / EPA and docosahexaenoic acid / DHA for the maintenance of good health (Simopoulos 2007; Oh 2005; IOM 2002; Simopoulos 1999)

For products providing 100-1,360 mg EPA + DHA including at least 100 mg DHA, per day:
Helps support cognitive health and/or brain function (van de Rest et al. 2008; Freund-Levi et al. 2006; Fontani et al. 2005a; Fontani et al. 2005b; Haag 2003; Morris et al. 2003; IOM 2002).

For products providing 150-1,360 mg EPA + DHA including at least 150 mg DHA, per day (maximum doses of EPA + DHA in Table 4 below will apply):
Helps support the development of the brain, eyes and nerves in children up to 12 years of age (Agostini 2008; Helland et al. 2008; Ryan and Nelson 2008; Marszalek and Lodish 2005; Haag 2003; IOM 2002; Giedd et al. 1999; Mills 1999).

Dose(s):

Note:

The potencies of vitamin A, vitamin D₃ and/or EPA/DHA must be indicated on the PLA and label, in addition to the dose of Cod liver oil.

Quantities:

Table 1: Dose information for cod liver oil¹ presented as dose per day

| Life stage group | | Cod liver oil | | | |
|---------------------|---------|-----------------------|---------|------------------------|---------|
| | | Minimum ² | | Maximum ^{3,4} | |
| | | (ml/day) ⁵ | (g/day) | (ml/day) | (g/day) |
| Infants | 0-12 mo | 0.83 | 0.77 | 0.87 | 0.80 |
| Children | 1-3 y | 0.83 | 0.77 | 0.87 | 0.80 |
| | 4-8 y | 0.83 | 0.77 | 1.3 | 1.2 |
| Adolescents | 9-13 y | 0.83 | 0.77 | 2.4 | 2.2 |
| | 14-18 y | 0.83 | 0.77 | 4.0 | 3.7 |
| Adults ³ | ≥ 19 y | 0.83 | 0.77 | 4.3 | 4.0 |

¹ USP 32, Ph. Eur. 2007, or BP 2008 grade Cod liver oil must be used to ensure that potencies of vitamin A, vitamin D₃, and EPA + DHA listed in Tables 2, 3 and 4 are met.

² The minimum dose of Cod liver oil is based on the minimum quantities of EPA + DHA required for efficacy.

³ Includes pregnant and breastfeeding women.

⁴ For all subpopulations, the maximum dose is based on the quantity of Cod liver oil providing the maximum daily amount of vitamin A, in µg RAE, according to the UL (IOM 2006).

⁵ Based on the specific gravity of Cod liver oil (USP 32)

Potencies:

Table 2: Potency information for vitamin A/all-*trans* retinol (palmitate) in cod liver oil (BP 2008; Ph. Eur. 2007; Tischer 1938)

| Life stage group | | Vitamin A (µg RAE/day) | |
|---------------------|---------|------------------------|----------------------|
| | | Minimum ¹ | Maximum ² |
| Infants | 0-12 mo | 138 | 600 |
| Children | 1-3 y | 138 | 600 |
| | 4-8 y | 138 | 900 |
| Adolescents | 9-13 y | 138 | 1,700 |
| | 14-18 y | 138 | 2,800 |
| Adults ³ | ≥ 19 y | 138 | 3,000 |

¹ Calculated as the minimum amount of vitamin A available in 0.77 g Cod liver oil, which is based on the minimum quantities of EPA + DHA required for efficacy.

² Maximum potency based on the UL (IOM 2006).

³ Includes pregnant and breastfeeding women.

Table 3: Potency information for vitamin D₃ (cholecalciferol) in cod liver oil (BP 2008; Ph. Eur. 2007; Green 1951)

| Life stage group | | Vitamin D ₃ (µg/day) | |
|---------------------|---------|---------------------------------|----------------------|
| | | Minimum ¹ | Maximum ² |
| Infants | 0-12 mo | 1.15 | 5.00 |
| Children | 1-3 y | 1.15 | 5.00 |
| | 4-8 y | 1.15 | 7.50 |
| Adolescents | 9-13 y | 1.15 | 14.06 |
| | 14-18 y | 1.15 | 23.12 |
| Adults ³ | ≥ 19 y | 1.15 | 25.00 |

¹ Based on the minimum amount of vitamin D₃ available in 0.77 g Cod liver oil, and supported by the AI for vitamin D₃ (IOM 2006). See Appendix 1 for definitions and Table 1 in Appendix 3 for AI values.

² For all subpopulations, the maximum potencies are based on the amount of vitamin D₃ available in the quantity of Cod liver oil which provides the maximum daily amount of vitamin A, in µg RAE, according to the UL (IOM 2006).

³ Includes pregnant and breastfeeding women.

Table 4: Potency information for EPA + DHA in cod liver oil (BP 2008; Ph. Eur. 2007)

| Life stage group | | EPA + DHA (mg/day) | |
|----------------------|---------|----------------------|----------------------|
| | | Minimum ¹ | Maximum ² |
| Infants ³ | 0-12 mo | 100 | 272 |
| Children | 1-3 y | 100 | 272 |
| | 4-8 y | 100 | 408 |
| Adolescents | 9-13 y | 100 | 765 |
| | 14-18 y | 100 | 1,258 |
| Adults ⁴ | ≥ 19 y | 100 | 1,360 |

¹ Restrictions to minimum potency may apply according to Use(s) or Purpose(s) section above.

² For all subpopulations, the maximum potencies are based on the amount of EPA + DHA available in the quantity of Cod liver oil which provides the maximum daily amount of vitamin A, in µg RAE, according to the UL (IOM 2006).

³ USP 32; Rajakumar and Thomas 2005; Stene et al 2003; Linday et al. 2002.

⁴ Includes pregnant and breastfeeding women.

Duration(s) of use: 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 condition(s): Statement(s) to the effect of:

For all products, except those encapsulated:

Refrigerate after opening (USP 32; Ph. Eur. 2007; Wille and Gonus 1989).

Non-medicinal ingredients:

- ▶ Must be chosen from the current NHPD *Natural Health Products Ingredients Database* and must meet the limitations outlined in the database.
- ▶ For products providing vitamin E at doses lower than the minima specified in Table 2 of Appendix 2, vitamin E must be declared as a non-medicinal ingredient.

Specifications:

- ▶ The finished product must comply with the minimum specifications outlined in the current NHPD *Compendium of Monographs*.
- ▶ The medicinal ingredient may comply with the specifications outlined in the pharmacopoeial monographs listed in Table 5 below.

Table 5: Monographs published in the British Pharmacopoeia (BP), European Pharmacopoeia (Ph. Eur.) and the U.S. Pharmacopoeia (USP)

| Pharmacopoeia | Monograph |
|---------------|------------------------|
| BP | Cod-Liver Oil (Type A) |

| Pharmacopoeia | Monograph |
|---------------|---|
| | Cod-Liver Oil (Type B) |
| Ph. Eur. | Cod-Liver Oil, Farmed Cod-Liver Oil (Type A) Cod-Liver Oil (Type B) |
| USP | Cod Liver Oil |

- ▶ Peroxide, anisidine, and totox values of cod liver oil must meet their respective values from Table 6, and must be performed using methods in accordance with those established by the Association of Analytical Communities (AOAC) and/or pharmacopoeial analytical methods. These specifications are necessary to ensure the oxidative stability of the cod liver oil (HC 2007).
- ▶ Polychlorinated dibenzo-para-dioxins (PCDD), polychlorinated dibenzofurans (PCDF) and polychlorinated biphenyls (PCB) are contaminants in oils from fish. Testing for PCDD, PCDF and PCB is required, and must be performed using appropriate analytical methods. Applicants are advised to consult the *Evidence for Quality of Finished Natural Health Products* Guidance Document (HC 2007). See Table 7 below.

Table 6: Maximum values of oxidative stability parameters for oils from cod liver (HC 2007)

| Oxidative stability parameter | Maximum value |
|--------------------------------|--------------------------------|
| Peroxide value (PV) | 5 mEq/kg |
| <i>p</i> -Anisidine value (AV) | 20 |
| Totox value | 26 (calculated as 2 x PV + AV) |

Table 7: Tolerance limits for specific contaminants in oils from cod liver (HC 2007)

| Contaminant | Tolerance limit |
|--------------|---------------------------|
| PCDD PCDF | Dioxin < 2 pg/kg b.w./day |
| PCB | PCB < 0.10 µg/kg b.w./day |

Note: Information detailed in this section is not to be submitted with the compendial PLA, although it may be requested at the NHPD's discretion.

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Appendix 1: Definitions

Adequate Intake (AI): The recommended average daily intake level based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of apparently healthy people that are assumed to be adequate. An AI is used when a Recommended Dietary Allowance (RDA) cannot be determined (IOM 2006).

Recommended Dietary Allowance (RDA): The average daily dietary nutrient intake level sufficient to meet the nutrient requirements of nearly all (97-98%) healthy individuals in a particular life stage and gender group (IOM 2006).

Tolerable Upper Intake Level (UL): The highest average daily nutrient intake level that is likely to pose no risk of adverse health effects to almost all individuals in the general population. As intake increases above the UL, the potential risk of adverse effects may increase (IOM 2006).

Appendix 2: Recommended Dietary Allowance (RDA) and Adequate Intake (AI)¹ Values for vitamin A

Table 8: RDA and AI¹ values for vitamin A based on life stage group (IOM 2006)

| Life stage group | | Vitamin A (µg RAE/day) |
|--------------------|---------|------------------------|
| Infants | 0-6 mo | 400* |
| | 7-12 mo | 500* |
| Children | 1-3 y | 300 |
| | 4-8 y | 400 |
| Adolescent males | 9-13 y | 600 |
| | 14-18 y | 900 |
| Adult males | ≥ 19 y | 900 |
| Adolescent females | 9-13 y | 600 |
| | 14-18 y | 700 |
| Adult females | ≥ 19 y | 700 |
| Pregnancy | 14-18 y | 750 |
| | 19-50 y | 770 |
| Breastfeeding | 14-18 y | 1,200 |
| | 19-50 y | 1,300 |

1. The AI is indicated by an asterisk.

Appendix 3: Adequate Intake (AI) Values for vitamin D

Table 9: AI values for vitamin D based on life stage group (IOM 2006)

| Life stage group | | Vitamin D ($\mu\text{g}/\text{day}$) |
|------------------|---------|--|
| Infants | 0-12 mo | 5 |
| Children | 1-3 y | 5 |
| | 4-8 y | 5 |
| Adolescents | 9-13 y | 5 |
| | 14-18 y | 5 |
| Adults | 19-50 y | 5 |
| | 51-70 y | 10 |
| | >70 y | 15 |
| Pregnancy | 14-50 y | 5 |
| Breastfeeding | 14-50 y | 5 |

Appendix 4: Vitamin E

Table 10: Vitamin E proper name(s), common name(s) and source material(s)

| Proper name(s) | Common name(s) | Source material(s) |
|--|--|---|
| Vitamin E (Sweetman 2007; IOM 2003; O'Neil et al. 2001) | Alpha-Tocopherol / α -Tocopherol (Sweetman 2007; O'Neil et al. 2001) Vitamin E (Sweetman 2007; IOM 2003; O'Neil et al. 2001) | All <i>racemic-α-Tocopherol</i> /all <i>rac-α-Tocopherol</i> / <i>dl-α-Tocopherol</i> (Sweetman 2007; IOM 2003) All <i>racemic α-Tocopheryl acetate</i> /all- <i>rac-α-</i> <i>Tocopheryl acetate</i> / <i>dl-α-Tocopheryl acetate</i> (Sweetman 2007; IOM 2003) All <i>racemic-α-Tocopheryl succinate</i> /all <i>rac-α-</i> <i>Tocopheryl succinate</i> / <i>dl-α-Tocopheryl acid</i> <i>succinate</i> / <i>dl-α-Tocopheryl succinate</i> (Sweetman 2007) <i>RRR-α-Tocopherol</i> / <i>d-α-Tocopherol</i> (Sweetman 2007; IOM 2003; O'Neil et al. 2001) <i>RRR-α-Tocopheryl acetate</i> / <i>d-α-Tocopheryl</i> <i>acetate</i> (Sweetman 2007; IOM 2003) <i>RRR-α-Tocopheryl succinate</i> / <i>d-α-Tocopheryl</i> <i>acid succinate</i> / <i>d-α-Tocopheryl succinate</i> (Sweetman 2007; IOM 2003) |

Quantity:

The quantity of vitamin E must always be provided in terms of α -Tocopherol (AT) (i.e. mg *RRR- α -Tocopherol*), irrespective of the source material used.

IUs may be provided as optional additional information on the PLA form in the "potency" field and on product labels.

Table 11: Dose information for vitamin E presented as dose per day

| Subpopulation | | Vitamin E (mg AT/day) | |
|---------------|-------------|-----------------------|---------|
| | | Minimum | Maximum |
| Children | 1-8 y | 2.2 | 179 |
| Adolescents | 9-13 y | 4.5 | 179 |
| | 14-18 y | 4.5 | 179 |
| Adults | ≥ 19 y | 4.5 | 179 |

Conversion factors:

Table 12 : Conversion of vitamin E source material quantity into vitamin E quantity in terms of α -Tocopherol (AT) and vitamin E activity in terms of International Unit (IU) (IOM 2006)

| Source material (1 mg) | Vitamin E quantity (mg AT) | Vitamin E activity (IU) |
|---|-------------------------------|----------------------------|
| <i>RRR</i> - α -Tocopherol | 1.00 | 1.49 |
| <i>RRR</i> - α -Tocopheryl acetate | 0.91 | 1.36 |
| <i>RRR</i> - α -Tocopheryl succinate | 0.81 | 1.21 |
| All <i>rac</i> - α -tocopherol | 0.50 | 1.10 |
| All <i>rac</i> - α -tocopheryl acetate | 0.46 | 1.00 |
| All <i>rac</i> - α -tocopheryl succinate | 0.41 | 0.89 |

Table 13 : Conversion of vitamin E source material activity into vitamin E quantity in terms of α -Tocopherol (AT) (IOM 2006)

| Source material (1 IU) | Vitamin E quantity (mg AT) |
|---|-------------------------------|
| <i>RRR</i> - α -Tocopherol | 0.67 |
| <i>RRR</i> - α -Tocopheryl acetate | 0.67 |
| <i>RRR</i> - α -Tocopheryl succinate | 0.67 |
| All <i>rac</i> - α -tocopherol | 0.45 |
| All <i>rac</i> - α -tocopheryl acetate | 0.45 |
| All <i>rac</i> - α -tocopheryl succinate | 0.45 |

Examples using the vitamin E conversion factors:

- a) Converting vitamin E activity into quantity of AT (mg)

Convert 400 IU of *RRR*- α -Tocopheryl succinate activity into mg AT:
= 400 IU x 0.67 mg AT/IU
= 268 mg AT

- b) Converting vitamin E source material quantity into quantity of AT (mg)

Convert 200 mg of all *rac*- α -Tocopheryl acetate into mg AT:
= 200 mg x 0.46 mg AT/mg
= 92 mg AT