



(51) International Patent Classification:

A61K 31/20 (2006.01) *A61K 9/16* (2006.01)
A61K 31/185 (2006.01) *A61P 3/10* (2006.01)
A61K 9/20 (2006.01) *A61P 9/00* (2006.01)

(21) International Application Number:

PCT/US2012/042489

(22) International Filing Date:

14 June 2012 (14.06.2012)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/496,893 14 June 2011 (14.06.2011) US

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(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

(54) Title: FORMULATIONS AND METHODS OF TREATING SUBJECTS HAVING CENTRAL NERVOUS SYSTEM, ENDOCRINE, INFLAMMATORY OR CARDIOVASCULAR DISORDERS OR AT-RISK THEREOF WITH HIGHLY PURIFIED OMEGA-3 FATTY ACID FORMULATIONS

(57) Abstract: The present invention provides highly purified omega-3 fatty acid formulations. Unit dosage forms of the omega-3 fatty acid formulations are also provided herein. The invention also provides methods of using the dosage forms to treat a variety of cardiovascular system, central nervous, endocrine or inflammatory disorders by providing a formulation of the invention to a patient in need thereof.



**FORMULATIONS AND METHODS OF TREATING SUBJECTS HAVING
CENTRAL NERVOUS SYSTEM, ENDOCRINE, INFLAMMATORY OR
CARDIOVASCULAR DISORDERS OR AT-RISK THEREOF WITH HIGHLY
PURIFIED OMEGA-3 FATTY ACID FORMULATIONS**

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RELATED APPLICATIONS

This application claims priority to US provisional application 61/496,893 filed on June 14, 2011, which is herein incorporated by reference in its entirety.

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FIELD OF THE INVENTION

The present invention provides highly purified omega-3 fatty acid formulations. Unit dosage forms of the omega-3 fatty acid formulations are also provided herein. The invention also provides methods of using the dosage forms to treat a variety of cardiovascular system, central nervous, endocrine or inflammatory disorders by providing a formulation of the invention to a patient in need thereof.

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A method of identifying subjects for treatment with omega-3 fatty acid formulations is also provided, wherein the population is selected on the basis of polyunsaturated fatty acid status to prevent diseases or treat diseases of the central nervous system, cardiovascular system, endocrine system or disorders associated with excessive inflammation. Such methods are intended to reduce major events associated with such diseases and improve outcome in patients with such diseases. Such biomarker targets that include polyunsaturated status in the subject can be used as therapeutic targets for omega-3 fatty acid treatment such that the treatment acts to modulate the status of various polyunsaturated fatty acids in the body with the goal of preventing or mitigating the risk of developing various diseases or in actually modifying (i.e., treating) existing disease.

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BACKGROUND

Omega-3 fatty acids are often referred to as "essential" fatty acids ("EFAs") because they are needed for human health but are not sufficiently produced by the body alone. The two major health promoting omega-3 polyunsaturated fatty acids are eicosapentaenoic acid ("EPA") and docosahexaenoic acid ("DHA"). EPA and DHA are naturally found in certain cold-water fatty fish, such as, salmon, tuna, and mackerel. They can also be derived in the body from alpha-linolenic acid ("ALA"), which is an omega-3 fatty acid found in certain

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seeds and plant-based oils. However, the body is very inefficient at converting ALA into EPA and DHA.

The modern diet is typically deficient in omega-3 essential fatty acids and has become overloaded with pro-inflammatory omega-6 fatty acids, especially arachidonic acid. This heavy imbalance of omega-6 to omega-3 fatty acids in the modern diet is thought to lead to an overall inflammatory state that contributes to certain diseases. The increased consumption of vegetable oils and shortenings, beef, and dairy is one of the major reasons for the high amount of omega-6 fatty acids in the diet and the imbalance between omega-6 to omega-3 fatty acids. The North American population, in particular, has among the lowest dietary intake of omega-3 fatty acids found in the world and the highest amount of the pro-inflammatory omega-6 fatty acids.

Recent scientific developments have shown that the omega-3 fatty acids, in particular EPA and DHA, play a vital role in central nervous system, cognitive, cardiovascular, joint, immune and metabolic function. EPA and DHA not only protect good overall physical and emotional health, but also can reduce the risk of cardiac disease and exert powerful anti-inflammatory effects that can help treat certain diseases. The benefits of EPA and DHA have been studied across a wide range of illnesses, including, but not limited to heart disease, high cholesterol, hypertension, arthritis, back pain, osteoporosis, psoriasis, lupus, Crohn's Disease, back pain, dry eyes, depression, bipolar disorder, ADHD, and stress-related disorders. Omega-3 fatty acids have also been shown to be important in pregnant women and infants, where their depletion can lead to visual or central nervous system problems.

Adequate amounts of omega-3 fatty acids including EPA and DHA can be obtained in the diet by regularly eating cold-water fatty fish, such as, salmon, tuna, and mackerel. However larger fish species can contain high levels of mercury, polychlorinated biphenyls (PCBs), dioxins or other contaminants. Thus achieving an optimal amount of omega-3 fatty acids through the intake of fish alone raises a number of practical and safety concerns. Fatty acids supplements are available. However, conventional over-the-counter omega-3 fatty acid supplements contain relatively impure material and are typically only about 30%-60% omega-3 fatty acids. This low purity leads to inadequate dosing of essential fatty acids unless a large number of dosage units are consumed each day. Although omega-3s are generally regarded as safe below 3 grams per day, many individuals consume 4-8 softgels (>3grams per day) of low purity products in order to obtain sufficient amounts of omega-3s or EPA/DHA per day—this can lead to safety concerns. Additionally research suggests that the EPA:DHA ratio is important for efficacy. Currently available omega-3 fatty acid preparations, such as,

the prescription omega-3 medication LOVAZA(formerly known as OMACOR) are formulated for cardiovascular use and contain EPA and DHA in an approximate 3:2 ratio. Other omega-3 formulations are intended primarily for treatment of mental health disorders and have very high levels of EPA and little or no DHA. The EPA:DHA ratio for these omega-3 formulations is 7:1 or higher.

Polyunsaturated fatty acids, including both omega-3 and omega-6 fatty acids, have important physiologic roles in human cells. In particular, omega-3 fatty acids are incorporated into prostaglandins, leukotrienes, phospholipids, triglycerides, cholesterol esters, and other molecules that have function roles in cellular membranes, inflammatory cascade (i.e., namely the arachidonic acid cascade), and neurotransmission. Low dietary intake of omega-3 polyunsaturated fatty acids have been associated with an increased risk of various diseases including coronary heart disease, fatal arrhythmias, and depression. Studies examining serum fatty acid concentrations of various omega-3 and omega-6 fatty acids have demonstrated a potential relationship to illness.

Several studies have shown that major depression or various forms of cardiovascular disease can be associated with lower blood levels of long chain omega-3 fatty acids. Such studies have characteristically measured EPA and/or DHA in plasma or serum phospholipids. Other studies have suggested high arachidonic acid status, a pro-inflammatory Omega-6 fatty acid, in relation to EPA status, can be associated with depressive symptomatology. Research to date has aimed at establishing a correlation between omega-3 and/or omega-6 fatty acid status to depressive or cardiovascular risk but has not been associated with either selecting patients for treatment or for identifying the appropriate fatty acid formulation for treatment. There is an important, unmet clinical need for targeting patients in need of treatment with omega-3 fatty acid formulations thereof, whereby the subjects can be selected for being at risk for potential polyunsaturated deficiencies, be effectively treated with appropriate omega-3 fatty acid formulations, and demonstrative improvement in polyunsaturated fatty acid status. The goal of such treatment is for the prevention or treatment of a variety of diseases of the central nervous system, cardiovascular system, endocrine system or disorders associated with excessive inflammation

A method of identifying subjects for treatment with omega-3 fatty acid formulations is also provided, wherein the population is selected on the basis of polyunsaturated fatty acid status to prevent diseases or treat diseases of the central nervous system, cardiovascular system, endocrine system or disorders associated with excessive inflammation. Such methods are intended to reduce major events associated with such diseases, improve outcome

in patients with such diseases. Such biomarker targets that include polyunsaturated status in the subject can be used as therapeutic targets for omega-3 fatty acid treatment such that the treatment acts to modulate the status of polyunsaturated fatty acids in the body with the goal of preventing or mitigating the risk of developing various diseases.

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SUMMARY OF THE INVENTION

The invention provides a highly purified omega-3 fatty acid formulation comprising EPA and DHA in a weight to weight ratio from about 3.5:1 to about 5.5:1, and, more particularly, in a weight ratio from about 3.5:1 to about 5:1, from about 3.7:1 to about 5:1, and, most particularly, from about 4:1 to about 5:1. Formulations having other EPA to DHA weight to weight ratios are also provided and are described in greater detail below. The invention also provides highly purified omega-3 fatty acid formulations in which the content of EPA and DHA, taken together, is greater than 84% of the formulation by weight, and the omega-3 fatty acids comprise greater than 90% of the formulation by weight.

The invention also provides dosage forms of such formulations comprising at least 50 mg DHA and at least 300 mg EPA in a unit dosage form. Dosage forms containing other amount of EPA and DHA are also described herein.

Packed omega-3 formulations comprising one or more omega-3 unit dosage forms of the invention together with instructions for using the formulation to treat or prevent a cardiovascular disorder, feeding disorder, central nervous system disorder, autoimmune disorder, inflammatory disorder or chronic pain are provided by the invention.

Methods of using the highly purified omega-3 fatty acid formulations described herein to treat or prevent a cardiovascular disorder, feeding disorder, central nervous system disorder, autoimmune disorder, inflammatory disorder or chronic pain are provided by the invention.

DETAILED DESCRIPTION OF THE INVENTION

Terminology

The terms "a" and "an" do not denote a limitation of quantity, but rather denote the presence of at least one of the referenced item. The term "or" means "and/or". The terms "comprising", "having", "including", and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to"). Recitation of ranges of values are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is

incorporated into the specification as if it were individually recited herein. The endpoints of all ranges are included within the range and independently combinable. All methods described herein can be performed in a suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as"), is intended merely to better illustrate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention as used herein. Unless defined otherwise, technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs.

An "active agent" means a compound (including EPA or DHA), element, or mixture that when administered to a patient, alone or in combination with another compound, element, or mixture, confers, directly or indirectly, a physiological effect on the patient. The indirect physiological effect can occur via a metabolite or other indirect mechanism. When the active agent is a compound, then salts, solvates (including hydrates) of the free compound or salt, crystalline forms, non-crystalline forms, and any polymorphs of the compound are included. Compounds can contain one or more asymmetric elements, such as, stereogenic centers, stereogenic axes and similar ingredients, e.g., asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. These compounds can be, for example, racemates or optically active forms. For compounds with two or more asymmetric elements, these compounds can additionally be mixtures of diastereomers. For compounds having asymmetric centers, all optical isomers in pure form and mixtures thereof are encompassed. In addition, compounds with carbon-carbon double bonds can occur in Z- and E-forms, with all isomeric forms of the compounds. In these situations, the single enantiomers, i.e., optically active forms can be obtained by asymmetric synthesis, synthesis from optically pure precursors, or by resolution of the racemates. Resolution of the racemates can also be accomplished, for example, by conventional methods, such as, crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral HPLC column. All forms are contemplated herein regardless of the methods used to obtain them.

A "cardiovascular surgical procedure" is any surgery on the heart, veins or arteries. Such procedures includes coronary artery bypass surgery, heart transplant, heart valve surgery, valve replacement, mitral valve repair or replacement, tricuspid valve repair or

replacement, septal myectomy, aortic valve repair, repair of congenital heart anomalies, ventricular restoration, and surgical procedures to treat aneurysms and thromboses.

"Cardiotomy" is any surgical procedure in which an incision is made in the heart.

"DHA" is docosahexaenoic acid and "EPA" is eicosapentaenoic acid. The terms EPA
5 and DHA are used to indicate both the triglyceride and esterified forms of these fatty acids unless the triglyceride or esterified form is clearly indicated by the context. DHA and EPA also include pharmaceutically acceptable fatty acid salts.

A "dosage form" means a unit of administration of an active agent. Examples of dosage forms include tablets, capsules, particularly gel and liquid capsules, suspensions,
10 liquids, candy and chewable formulations, emulsions, creams, ointments, suppositories, and similar ingredients.

The term "effective amount" or "therapeutically effective amount" means an amount effective, when administered to a patient, to provide any therapeutic benefit. A therapeutic benefit can be an amelioration of symptoms, e.g., an amount effective to decrease the
15 symptoms of a central nervous system disorder, an autoimmune disorder, chronic pain, an inflammatory disorder, or cardiovascular disease. In certain circumstances a patient may not present symptoms of a condition for which the patient is being treated. A therapeutically effective amount of an active agent can also be an amount sufficient to provide a significant positive effect on any indicium of a disease, disorder, or condition, e.g. an amount sufficient
20 to significantly reduce the frequency and severity of symptoms. A significant effect on an indicium of a disease, disorder, or condition is statistically significant in a standard parametric test of statistical significance, for example Student's T-test, where $p \leq 0.05$. An "effective amount or "therapeutically effective amount" of the omega-3 formulations provided herein can also be an amount of about of the formulation or of any dosage amount
25 approved by a governmental authority, such as, the U.S. FDA, for use in treatment. In some embodiments amounts an amount of the formulations provided herein sufficient to provide 900 mg EPA and 150 mg DHA daily, or 990 mg EPA and 190 mg DHA daily, or 1050 mg EPA and 240 mg DHA daily or 1125 mg EPA and 250 mg DHA daily of omega-3 fatty acids in an adult human patient is an "effective amount" or "therapeutically effective amount."

30 "Efficacy" means the ability of an active agent administered to a patient to produce a therapeutic effect in the patient.

"Gel capsule" means any soft gelatin, liquid-filled capsule that contains a liquid, liquid suspension, solution, gel, or emulsion.

"Liquid capsule" is a capsule with a hard or soft capsule shell filled with a non-solid formulation. The formulation can be for example a liquid, solution, suspension, emulsion or gel.

A "patient" means a human or non-human animal in need of medical treatment.

5 Medical treatment can include treatment of an existing condition, such as, a disease or disorder, prophylactic or preventative treatment, or diagnostic treatment. In some embodiments the patient is a human patient. Patients also include veterinary patients; dogs, cats and horses are particularly included.

10 "Providing" means giving, administering, selling, distributing, transferring (for profit or not), manufacturing, compounding, or dispensing.

"Salts" as used herein describes "pharmaceutically acceptable salts" of omega-3 fatty acids and other active agents discussed herein and also includes solvates and hydrates of such active agents. The active agent can be modified by making non-toxic acid or base addition salt thereof. Examples of pharmaceutically acceptable salts include mineral or organic acid
15 addition salts of basic residues, such as, amines; alkali or organic addition salts of acidic residues; and similar ingredients, and combinations comprising one or more of the foregoing salts. The pharmaceutically acceptable salts include non-toxic salts and the quaternary ammonium salts of the active agent. For example, non-toxic acid salts include those derived from inorganic acids, such as, hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric,
20 nitric and similar ingredients; other acceptable inorganic salts include metal salts, such as, sodium salt, potassium salt, cesium salt, and similar ingredients; and alkaline earth metal salts, such as, calcium salt, magnesium salt, and similar ingredients, and combinations comprising one or more of the foregoing salts. Pharmaceutically acceptable organic salts include salts prepared from organic acids, such as, acetic, propionic, succinic, glycolic, stearic, lactic,
25 malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, mesylic, esylic, besylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, $\text{HOOC}-(\text{CH}_2)_n-\text{COOH}$ where n is 0-4, and similar ingredients; organic amine salts, such as, triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt,
30 N,N'-dibenzylethylenediamine salt, and similar ingredients; and amino acid salts, such as, arginate, asparaginate, glutamate, and similar ingredients; and combinations comprising one or more of the foregoing salts.

A "second myocardial infarction" is any myocardial infarction that is not the initial or first myocardial infarction experienced by the patient.

Pharmaceutical Formulations

The omega-3 fatty acid formulations provided herein can be provided to a patient in any of number of pharmaceutically acceptable oral dosage forms. The omega-3 fatty acids can be orally administered in the form of pills, tablets, or gel capsules or similar ingredients. However, administering omega-3 fatty acid formulations can also be through any other route where the active ingredients is efficiently absorbed and utilized, e.g. intravenously, subcutaneously, rectally, vaginally or topically. Also included herein are pharmaceutical compositions, comprising pharmaceutical formulations in a unit dosage form. In such dosage forms, the formulation is subdivided into suitably sized unit doses containing appropriate quantities of the omega-3 fatty acids, an effective amount to achieve the desired purpose.

Accordingly the invention provides capsule, tablet, liquid, syrup, suspensions, sublingual, candy, and chewable dosage forms of the omega-3 fatty acid formulations. The invention includes dosage forms in which the EPA and DHA fatty acids are in the triglyceride form, the esterified form, particularly the ethyl ester form, and in which the fatty acids are in the form of acid salts.

The invention also includes methods for making pharmaceutical compositions comprising the omega-3 formulations described herein.

Pharmaceutical dosage forms can contain excipients. Excipients include fillers, stabilizers, extenders, binders, humidifiers, surfactants, lubricants, and similar ingredients. Excipients must be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the animal being treated. An excipient can be inert or it can possess pharmaceutical benefits.

Excipients are selected with respect to the intended form of administration, e.g. oral tablets, capsules, powders, syrups, suspensions, and similar ingredients, and consistent with conventional pharmaceutical practices. For example, for oral administration in the form of gel capsule, the omega-3 fatty acid formulation can be combined with a preservative, flavorant, colorant or other ingredients.

The amount of omega-3 formulation contained in an oral unit dose form for an adult human patient can be generally varied or adjusted from about 400 mg to about 1000 mg of omega-3 fatty acids. The amount of omega-3 formulation contained in an oral unit dose form for a pediatric patient can be generally varied or adjusted from about 10 mg/kg to about 30 mg/kg omega-3 fatty acid per day in one or two oral unit dosage forms. Thus, a unit dosage form for a child aged 2 to 6 years contains about 50 mg to about 500 mg, or preferably about

150 to about 180 mg, omega-3 fatty acids. One or two unit dosage forms are provided daily to the pediatric patient. Particularly the invention includes oral dosage forms for use in adult humans in which the unit dosage form comprises at least 50 mg DHA and at least 300 mg EPA, at least 65 mg DHA and at least 330 mg EPA, at least 80 mg DHA and 350 mg EPA, at least 100 mg DHA and 400 mg EPA, or 125 mg DHA and 600 mg EPA. Dosage units prepared for human use can be used for veterinary purposes. However the invention also includes unit dosage forms prepared especially for veterinary use. Generally about 10 mg/kg to about 30 mg/kg should be administered daily for veterinary purposes. Thus unit dosage forms prepared for equine use having about 5 to about 15 g omega-3 fatty acids are included in the invention.

The invention provides a highly purified omega-3 fatty acid formulation comprising EPA and DHA in a weight to weight ratio from about 3.5:1 to about 5.5 to 1, and, more particularly, from about 4:1 to about 5.5:1, or from about 4:1 to about 5:1. The invention also provides a highly purified omega-3 fatty acid formulation in which the weight to weight ratio of EPA:DHA is approximately 4.1:1. The EPA and DHA can be present in the formulation in either the triglyceride form or in the form of esterified fatty acid. Capsules typically contain the ethyl esters forms of EPA and DHA. Candy formulations typically contain the triglyceride forms of EPA and DHA.

The invention also provides highly purified omega-3 fatty acid formulations in which the content of EPA and DHA, taken together, is greater than 70%, greater than 75%, greater than 84%, or greater than 85% of the formulation by weight, and the omega-3 fatty acids comprise greater than 85%, greater than 90%, or greater than 91% of the formulation by weight. Additionally the invention provides omega-3 fatty acid formulations in which the amount of cholesterol in the formulation is less than 5% by weight, less than 2.5% by weight, or less than 1% by weight. The invention also includes omega-3 fatty acid formulations in which the formulation comprises less than 20 milliequivalents per kg peroxides, less than 10 milliequivalents per kg peroxides, or less than 5 milliequivalents per kg peroxides.

The invention includes solid dosages forms, such as, tablets and capsules. A capsule can be prepared, e.g., by placing the omega-3 fatty acid formulation, described above, inside a capsule shell. A capsule is a dosage form administered in a special container or enclosure containing an active agent. In some embodiments the omega-3 fatty acid is in liquid form and is filled into hard or soft capsules. A capsule shell can be made of methylcellulose, hydroxypropylmethyl cellulose, polyvinyl alcohols, or denatured gelatins or starch or other material. Hard shell capsules are typically made of blends of relatively high gel strength

bone and pork skin gelatins. In some embodiments the unit dosage form is a gel capsule. In some embodiments the capsule shell is a glycerin capsule shell, for example product no. GSU0051 manufactured by SwissCaps and which meets USP 25 requirements (SwissCaps, USA 14193 SW 119th Ave., Miami/Fla., U.S. 33186). In other embodiments the capsule is a bovine gelatin shell, for example SwissCaps product no. GSU0708. Other suitable capsule shell materials include polyethylene, polypropylene, poly(methylmethacrylate), polyvinylchloride, polystyrene, polyurethanes, polytetrafluoroethylene, nylons, polyformaldehydes, polyesters, cellulose acetate, and nitrocellulose. The capsule shell itself can contain small amounts of dyes, opaquing agents, plasticizers, and preservatives.

Conventional methods for preparing other solid dosage forms, for example, capsules, suppositories, and similar ingredients are also well known. Gelatin capsule shells can be made of tapioca, grass, vegetable derived or fish derived gelatin. For example, K-CAPS (Capsuline, Inc. Pompano Beach, Fla.) is a certified Kosher soft capsule shell of vegetable origin. Other vegetarian derived gelatin capsules can be made of vegetable derived hydroxypropylmethyl cellulose (HPMC). Capsules shells can also contain Modified Maize Starch, Glycerol, and Carrageenan as a gelling agent.

In other embodiments the capsule has a shell comprising the material of a rate-limiting membrane, including coating materials, and filled with Omega-3 fatty acids. Capsule shells can be made of a porous or a pH-sensitive polymer made by a thermal forming process. In certain embodiments the capsule shell in the form of an asymmetric membrane; i.e., a membrane that has a thin skin on one surface and most of whose thickness is constituted of a highly permeable porous material.

Yet another useful capsule, a "swelling plug device", can be used. Omega-3 fatty acids can be incorporated into a non-dissolving capsule-half of the device which is sealed at one end by a hydrogel plug. This hydrogel plug swells in an aqueous environment, and, after swelling for a predetermined time, exits the capsule thus opening a port through which the active agent can leave the capsule and be delivered to the aqueous environment. Preferred hydrogel-plugged capsules are those which exhibit substantially no release of active agent from the dosage form until the dosage form has exited the stomach and has resided in the small intestine for about 15 minutes or more, preferably about 30 minutes or more, thus assuring that minimal omega-3 fatty acid is released in the stomach. Hydrogel-plugged capsules of this type have been described in patent application WO90/19168, which is incorporated herein by reference.

Conventional methods for preparing tablets are known. Such methods include dry methods, such as, direct compression and compression of granulation produced by compaction, or wet methods or other special procedures.

Liquid form preparations include solutions, suspensions and emulsions. Examples of liquid pharmaceutical preparations include propylene glycol solutions and solutions containing sweeteners for oral solutions, suspensions and emulsions.

Omega-3 dosage forms can contain a plasticizer, particularly in a capsule shell. Suitable plasticizers include, e.g., polyethylene glycols, such as, PEG 300, PEG 400, PEG 600, PEG 800, PEG 1450, and PEG 3350, stearic acid, propylene glycol, oleic acid, triethyl cellulose, and triacetin.

Omega-3 dosage forms described herein can be coated. The coating can be an enteric coating, i.e. a coating that is predominantly soluble in the intestinal fluid, but substantially insoluble in the gastric fluids. Examples of coating materials included polyvinyl acetate phthalate (PVAP), commercially available under trade names of Opadry®, enteric from Colorcon®, hydroxypropylmethylcellulose acetate succinate (HPMCAS), cellulose acetate phthalate (CAP), methacrylic acid copolymer, hydroxypropylmethylcellulose succinate, cellulose acetate succinate, cellulose acetate hexahydrophthalate, hydroxypropylmethylcellulose hexahydrophthalate, hydroxypropylmethylcellulose phthalate (HPMCP), cellulose propionate phthalate, cellulose acetate maleate, cellulose acetate trimellitate, cellulose acetate butyrate, cellulose acetate propionate, methacrylic acid/methacrylate polymer, methacrylic acid-methyl methacrylate copolymer, ethyl methacrylate-methylmethacrylate-chlorotrimethylammonium ethyl methacrylate copolymer, and similar ingredients, and combinations comprising one or more of the foregoing enteric polymers. Other examples include natural resins, such as, shellac, SANDARAC, copal colophonium, and combinations comprising one or more of the foregoing polymers. Yet other examples of enteric polymers include synthetic resin bearing carboxyl groups. The methacrylic acid : acrylic acid ethyl ester copolymers are commercially available under the trade names of "Eudragit®", such as, Eudragit® L 30-D55 from Degussa.

Omega-3 formulations described herein can include a stabilizer. "Stabilizers" include compounds which maintain a desirable attribute of the formulation over a time interval including but not limited to mechanical, chemical and temperature stressing that can be tested in a laboratory setting. Such attributes include stabilizing homogeneity resulting in concentrations consistent with the labeled potency, maintaining specified purity and dispersibility in simulated gastric and intestinal fluids without significant degradation of the

attributes for which the stabilizer was employed. In some embodiments the stabilizer is an antioxidant, such as, vitamin E. Other suitable antioxidants include hydroxytoluene, butyrate, quinone, ascorbic acid.

Omega-3 formulations described herein can contain a preservative. Preservatives are compounds that inhibit microbial growth and are typically added to dispersions to prevent microbes from growing. Typically amounts of preservatives needed to pass anti-microbial effectiveness testing as described by USP and EU methodology are used to test appropriate preservative levels. Preservatives include but are not limited to potassium sorbate, methylparaben, propylparaben, benzoic acid and its salts, other esters of parahydroxybenzoic acid, such as, butylparaben, alcohols, such as, ethyl or benzyl alcohol, phenolic compounds, such as, phenol, or quaternary compounds, such as, benzalkonium chloride.

Coloring agents provide coloration to the composition or dosage form. Such excipients can include food grade dyes and food grade dyes adsorbed onto a suitable adsorbent, such as, clay or aluminum oxide. The amount of the coloring agent can vary, for example from about 0.1 to about 5% by weight of the composition or from about 0.1 to about 1%.

Packaged Formulations

Packaged pharmaceutical formulations are included herein. Such packaged formulations include one or more omega-3 unit dosage forms in a container and instructions for using the dosage form to treat a patient having a disease or disorder responsive to omega-3 fatty acid treatment or in need of prophylactic omega-3 fatty acid therapy.

The invention includes providing prescribing information, over the counter medical use information, or nutritional information for the dosage form, for example, to a patient or health care provider, or as a label in a packaged pharmaceutical formulation. Information included in the pharmaceutical package can include, for example, efficacy, dosage and administration, contraindication and adverse reaction information pertaining to the omega-3 dosage form.

In certain embodiments, the omega-3 dosage forms provided herein are omega-3 capsules provided in blister packages together with over the counter medical use information and/or nutritional information. Such packages can contain, for example 30, 60, or 180 omega-3 fatty acid unit dosage forms.

Packaged pharmaceutical formulations in which an omega-3 formulation described herein is the only active agent or in which an omega-3 formulation as described herein is packaged in combination with one or more other active agents are included in the invention.

5 Methods of Treatment

The invention includes methods of preventing and treating of depression and related disorders by providing an omega-3 formulation as described herein to a patient in need thereof. The patient can be a human or non-human patient. Non-human patients include livestock animals, such as, cattle, sheep, and horses and domestic companion animals, such as, cats and dogs. In certain embodiments the non-human patient is a horse or dog.

While the omega-3 fatty acid formulation and method described herein are particularly suited for the treatment of depression and related disorders, various diseases and disorders that can be treated with the omega-3 fatty acid formulations described herein include alopecia, Alzheimer's dementia, anxiety disorders, asthma, attention deficit disorder, attention-deficit hyperactivity disorder, atopic dermatitis, autism, bipolar disorder, borderline personality disorder, cardiovascular disease, chronic fatigue syndrome, chronic obstructive pulmonary disease, chronic pain, chronic polyarthritis, cognitive disorders, communication disorders, Crohn's disease, cystic fibrosis, dementia, depression, diabetes (of the non-insulin dependent or insulin dependent forms), diabetes-related sequelae, diabetic neuropathy, dry eyes and other inflammatory eye disorders, dry skin, dyslexia, dysmenorrhea, eating disorders (such as anorexia nervosa or bulimia nervosa and obesity), eczema, fibromyalgia, gout, learning disorders (e.g. reading, spelling, mathematics, receptive, and expressive language, and motor skills disorders), lupus, macular degeneration (including age-related and wet macular degeneration), male infertility (including oligozoospermia, oligospermia, impaired semen viscosity, impaired sperm motility, impaired CK-parameters), metabolic syndrome, melanoma, mild cognitive impairment, migraine, mood disorders, multiple sclerosis, obsessive-compulsive disorder, oppositional-defiant disorder, osteoarthritis, osteoporosis, pervasive developmental disorders, polyarteritis nodosa, psoriasis, psoriatic arthritis, rheumatoid arthritis, schizophrenia, sclerodermia, self-injurious behavior, sickle cell anemia, tic disorders, ulcerative colitis, or vasculitic disorders (such as polyarteritis nodosa and temporal arthritis. Cardiovascular disease and disorders that can be treated with the omega-3 fatty acid formulations described herein include angina, atherosclerosis, hypercholesterolemia, hypertriglyceridemia, low HDL, high blood pressure, Raynaud's disease, and cardiac arrhythmias. Methods of treatment with the omega-3 fatty acid

formulations described herein include prophylaxis with Omega-3 formulations to prevent post-cardiotomy (including but not limited to coronary artery bypass graft surgery and valve surgery) complications (including but not limited to depression, neuro-cognitive decline, congestive heart failure and infarction, clotting events, and arrhythmias) as well as for the treatment for such complications. The invention includes a method of preventing or reducing the risk a second myocardial infarction by providing an omega-3 formulation as described herein at least one time per day for at least 60 days, 180 days, 360 days, or in perpetuity to a patient following a first myocardial infarction.

The omega-3 fatty acid formulations described herein can be used to treat basal cell carcinomas. In certain embodiments the omega-3 fatty acid formulations described herein are given to patients in remission from basal cell carcinoma, to reduce the risk of recurrence. The omega-3 fatty acid formulations described herein can be used to diminish weight loss cachexia associated with cancer treatment and to augment the effects of cancer chemotherapy.

The omega-3 formulations described herein can also be used in humans and animals for cosmetic purposes. For example the formulations can be used to improve skin quality and clarity and hair or coat shine.

Dosage levels of the order of from about 10 mg to about 35 mg per kilogram of body weight per day, about 14 mg to about 30 mg per kilogram of body weight per day, or 15 mg to about 25 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 500 mg to about 3 g per adult human patient per day or preferably about 1000 mg to about 200 mg per adult human patient per day). The amount of omega-3 fatty acid that can be combined with the carrier materials to produce a single unit dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms for adult human patients will generally contain between from about 500 mg to about 1500 mg of purified EPA and DHA. Dosage forms for pediatric or veterinary patients will contain different amounts of Omega-3 fatty acids. Frequency of dosage can also vary depending on the route of administration and the particular disease treated. However, for treatment of most cardiovascular, central nervous system disorders, autoimmune system disorders and inflammatory disorders a dosage regimen of 4 times daily or less is preferred and a dosage regimen of 1 or 2 times daily or less is particularly preferred.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of

administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

When the omega-3 formulations provided herein are used to treat central nervous system disorders, particularly psychiatric disorders, patients should be evaluated on a regular basis over an extended period of time, e.g. 1 to 12 weeks. One good method of carrying out evaluations is for patients to keep a daily diary in which they chart their moods. For example, patients can keep a daily record in which they rate their best and worst moods as either normal, mildly, moderately or severely depressed. These records should help the patient and their physician determine if depression occurs less frequently or becomes less extreme intensity. Ideally, such a diary should be kept both before and after the administration of omega-3 fatty acid is begun. The evaluation of mood alterations by the patient should also be supplemented with periodic clinical evaluations carried out by a physician. In some cases, the evaluation discussed above can indicate that mood fluctuations have become so stabilized in a patient as the result of administering omega-3 fatty acid at the initial concentration that no further adjustment in dosage is necessary. In other cases, the dosage of omega-3 fatty acid can be increased in order to obtain a more efficacious result. In general, dosage should not be increased beyond the point at which further stabilization of patient mood is observed. If patients experience adverse side effects, then dosages can be adjusted in a downward direction accordingly.

When treating depression in a human patient, an effective amount of an omega-3 fatty acid formulation as described herein, in certain embodiments, is an amount sufficient to decrease the patient's HAM-D scores. The HAM-D (Hamilton Depression) rate scale is a numerical scoring of depression symptoms that provides an indication of depression and over time provides a guide to treatment progress. A HAM-D score of 10-13 indicates mild depression, 14-17 indicates mild to moderate depression and a score of greater than 17 indicates severe depression.

When treating a cardiovascular disorder an effective amount of an omega-3 fatty acid formulation as described herein is, for example, an amount sufficient to decrease diastolic blood pressure, systolic blood pressure, decrease pulse rate, decrease serum cholesterol, reduce serum triglycerides, or reduce the activity of coagulation factor VII is considered and effective amount of the formulation.

The process of adjusting dosage in an upward or downward direction and evaluating the effect of the adjustment on mood changes should be continued until an optimum dosage is discovered, i.e. the dosage at which the patient experiences the best balance between

therapeutic effectiveness and discomfort due to side effects. In cases where adverse side effects are not experienced, the optimal dosage is the lowest dose resulting in maximum reduction in psychiatric episodes.

5 Combination Administration

The Omega-3 fatty acid formulations and dosage forms provided herein can be used alone or in combination with one or more other active agents. For example the omega-3 fatty acid formulations provided herein can be used with other psychotropic agents including, for example, lithium, pharmaceutical antidepressants, herbal antidepressants (e.g., St. John's
10 Wort, S-adenosylmethionine), anti-convulsants, mood stabilizers, antipsychotic agents, benzodiazepines, psychostimulants, and alpha-2 agonists. These other agents can either be given together with omega-3 fatty acid in a single dosage form, or they can be administered separately.

An antidepressant, an anxiolytic, a selective serotonin reuptake inhibitor, a serotonin
15 5HT receptor partial agonist or antagonist, a norepinephrine dopamine reuptake inhibitor, a serotonin norepinephrine dopamine reuptake inhibitor, a serotonin 5-HT1a partial agonist, a serotonin 5-HT1b agonist, a serotonin 5-HT2 antagonist, a serotonin 5-HT6 antagonist, a serotonin-2 antagonist reuptake inhibitor, a serotonin-1 agonist reuptake inhibitor, a mixed serotonin antagonist reuptake inhibitor/partial agonist/dopamine agonist, an alpha-2
20 antagonist/serotonin 5HT2-3 receptor antagonist, a serotonin modulator or stimulator, a mixed serotonin antagonist/melatonin agonist, a mixed serotonin dopamine antagonist, a tricyclic antidepressant, a tetracyclic antidepressant, a bis-aryl-sulphonyl modulator, a beta-3 adrenoreceptor stimulator or agonist, a beta-3 adrenoreceptor antagonist, a nicotinic acetylcholine receptor agonist or antagonist, an enkephalinergic modulator, an aprepitant, a
25 neurokinin (NK) antagonist, a NK1, 2, or 3 antagonist, a neuropeptide (NP) Y antagonist, a NPY1, 2, or 3, or 5 antagonist, a substance P antagonist, a corticotrophin-releasing hormone (CRH or CRF) antagonist, a CRH(or CRF)-1 antagonist, a glucocorticoid receptor agonist or partial agonist, a glucocorticoid receptor antagonist, a glucocorticoid receptor type II antagonist, an anti-convulsant, a GABA modulator, a GABA inverse agonist or partial
30 agonist, a GABA receptor antagonist, a GABA channel antagonist, a GABA reuptake inhibitor, a glutamate modulator, an mGluR receptor modulator, agonist or antagonist, an mGluR2/3 agonist, an mGluR5 antagonist, an estrogen receptor agonist or antagonist, a melatonin receptor agonist or antagonist, a glycine transporter inhibitor, an alpha-1 receptor agonist, an alpha-1 receptor antagonist, an alpha-2 receptor agonist, an alpha-2 receptor

antagonist, a vasopressin-1B (V1B) agonist or antagonist, an NMDA receptor modulator (i.e., a partial agonist, agonist, or antagonist), an ampakine modulating agent, an opioid antagonist, an opioid partial agonist, a benzodiazepine, an anti-psychotic, a dopamine receptor agonist or analog, a wakefulness promoting agent, an anti-manic agent, a mood
5 modulating (i.e., stabilizing) agent, a cholinesterase inhibitor, an anti-amyloid agent, an anti-aggregant, a beta-secretase inhibitor, a beta-amyloid antagonist, a monoamine oxidase inhibitor, an anti-migraine agent, a melanocyte inhibiting factor, or a combination of the foregoing.

The omega-3 formulations described herein may also be provided in combination
10 with other active agents used to treat cardiovascular disorders. Particularly the omega-3 formulations may be used in combination with agents used to treat dyslipidemia, for example the formulations may be used in combination with statins, fibrates, and bile acid binding resins, including atorvastatin calcium (tradename, LIPITOR), fenofibrate (tradename, TRICOR), gemfibrozil (LOPID), simvastatin (tradename, ZOCOR), rosuvastatin calcium
15 (tradename, CRESTOR), pravastatin (tradename, PRAVACHOL), lovastatin (MEVACOR), rovastatin, fluvastatin, ezetimibe (tradename, ZETIA), ezetimibe/simvastatin (tradename, VYTORIN), and clopidogrel bisulfate (tradename, PLAVIX). The omega-3 formulations described herein may also be used in combination with other classes of agents used to treat cardiovascular disorders including niacin, niacin derivatives, aspirin, diuretics, calcium
20 channel blockers, antianginal drugs, anticoagulants, antithrombotic agents, cardiac ionotropic agents, such as, digoxin, antihypertensive, and antiarrhythmics, such as, Amiodarone, beta blockers, and ACE inhibitors.

In certain embodiments, patients taking anti-depressants will continue taking other active agents they have been taking prior to omega-3 fatty acid treatment during the time at
25 which omega-3 fatty acid treatment is begun. Optimal dosages for each of the drugs can then be determined sequentially. For example, administration of one agent can be initiated and then optimized followed by the initiation and optimization of omega-3 fatty acid treatment. The problem of adjusting the dosages of multiple therapeutic agents is one that is routinely encountered by physicians and can be solved using well-established procedures similar to
30 those discussed herein.

The omega-3 fatty acid formulations described herein can also be provided in combination with vitamins or herbal supplements either in a single unit dosage form or in separate unit dosage forms. For example the omega-3 fatty acid formulations can be provided in combination with ascorbic acid, folic acid, Vitamin A, Vitamin C, Vitamin D,

Vitamin E, Vitamin B12, Vitamin K, Thiamin, Riboflavin, Niacin, Vitamin B6, Biotin, or pantothenic acid.

Table 1

LIST OF BIOMARKERS

Activator Protein 1
Adamalysin
Adenosine monophosphate (cAMP)-dependent protein kinase A
A-Disintegrin
ADAM
Agouti-Related Protein (AGRP)
AKT
Alpha-1chymotrypsin
Angioproteins (ANG), including ANG-1, 2, 3, and 4
Antiapoptotic factor, including bcl-2, bcl-xL
Anti-Brain Derived Neurotrophic Factor Antibody
Arachidonic Acid
Astacin
Beta-catenin
Brain-Derived Neurotrophic Factor (BDNF), including pro-BDNF, BDNF antibodies, and Val66Met (BDNF Gene)
Calcitonin-gene-related peptide (CGRP)
Ca ²⁺ /calmodulin-dependent protein kinase
Catalase (CAT)
Cellular fibronectin (c-Fn)
CD-40 ligand
C-reactive protein (CRP), including hs-CRP
COX-2
Creatine kinase
Cyclooxygenase
Cystatin C
D-Dimer
Desaturase, including delta5 and delta6
Diacylglycerolkinase
E-selectin
Early Growth Response 2 (Egr2)
ERK 1/2
Endothelial-Derived Relaxing Factor (EDRF)
Eotaxin
Epidermal Growth Factors (EGFs)
Eukaryotic initiation factor (eIF), including eIF2B

Extracellular regulated kinase (ERK)
Fibrinogen
Fibroblast growth factor (FGF)
Flk receptors, including Flk 1
Flt receptors, including Flt4
F2 isoprostanes
Fractalkine
Glial fibrillary acidic protein (GFAP)
Glucocorticoid-regulated kinase 1 (SGK1)
Glutathione peroxidase
Glutathione transferase
Glycerol-3-phosphate dehydrogenase (Gpd3)
Glycogen synthase
Glycogen synthase kinase (GSK), including GSK 3
GPCR 88 (GPR88)
GRO-alpha
Haptoglobin
HDL cholesterol
Heart type fatty acid binding protein
Heat shock protein, including HSP-1 and HSPb1
Hepatocyte growth factor (HGF)
Histone deacetylase (HDAC)
Homocysteine
Homer1
Hs-CRP
Insulin-like growth factors, including IGF-I
Insulin receptor substrate (IRS), including IRS-1
Interferon-inducible protein 10 (IP-10)
Interferon-alpha
Interferon-gamma
Interleukin (IL), including 1, 1a, 1b, 2, 5, 6, 7, 8, 10, 18
Inter cellular Adhesion Molecule (ICAM), including ICAM1 and sICAM1
Jun N-terminal kinases (JNKs)
Leptin
LDL, Oxidized LDL, Oxidized-LDL antibodies, Anti-oxidized LDL, Anti-oxidized LDL antibodies
Leukotriene (including LTA4, LTA5, LTB4, LTB5, LTC4, LTC5, LTD5)
Leukocyte count
5-Lipoxygenase
Lipoprotein(a)

Liver X receptor (LXR)
LTA-synthase
Melanocortin 4 Receptor (MC4R)
Metalloproteinase (MMP), including MMP 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and Tissue Inhibitors of Metalloproteinase (TIMP)
Metzincins
Mitogen-activated protein kinase (MAPK)
Monocyte Chemo-attractant protein(s) (MCP), including MCP-1, MCP-2, MCP-3, and MCP-4
Monocyte superoxide
Myeloperoxidase(s)
Nitrous Oxide
Neuropeptide Y
Neurotransmitter-induced early gene
Neurotrophins, including NGF, BDNF, NT-3 and NT-4/5
Neurotrophic protein, including BCL-2
Neurotrophic tyrosine kinase, including (NTRK2)
Nitric Oxide
Nitric Oxide Synthase, including neuronal NOS (nNOS or NOS1) and Endothelial Nitric Oxide Synthase 3 (eNOS or NOS3)
Nuclear factor kappa-beta (NF-KB)
Nuclear factor of activated T cells (NFAT)
Oncostatin-M
Osteopontin
Osteoprotegerin
PAI-1(plasminogen activator inhibitor)
Pappalysin, including PAPP-2 and PAPP-A
Phospholipase (including A2)
Parathyroid hormone related protein (PHRP)
Peroxynitrate
Phosphatidylinositol glycan anchor biosynthesis, class F, (PIGF)
Phosphatidylinositol 3-kinase (PI3K)
Phospholipase A2 (including lipoprotein-associated Phospholipase A2; lp-PA2)
Plasminogen
Platelet activating factor
Platelet derived growth factor (PDGF), including A and B
Peroxisome proliferators activated receptor (PPAR), including PPAR-alpha, -beta, -delta, -gamma
Prostacyclin/Prostaglandin (including, PGE2, PGE3, PGH2,PGH3, PGI2, PGI3)
Protein Kinase C
P-selectin

RANTIS protein
Ret proto-oncogene (Ret)
Retinoid X receptor (RXR)
SAA (circulating amyloid)
sCD40 ligand
Ser-473
Serralysin
Silencing mediator of retinoic acid and thyroid receptor (SMRT)
Soluble thrombomodulin
STAT6
sTNF-R1, sNTF-R2
Substance P
Sulfotransferase 1a (Sult1a)
Superoxide dismutase (SOD)
Tau
Thr-308
Thromboxane (including TXA2, TXA3)
Tissue Plasminogen Activator (t-PA)
TNF-related activation-induced cytokine (TRANCE)
Toll-like receptors, including TLR3 and TL4
Transcription factor cAMP response element binding protein (CREB)
Triglycerides
Troponins, including I, T
Tumor necrosis factor (including TNF-alpha)
Tyrosine receptor kinase (TRK), including A, B, and C
Urinary nitrotyrosine
Vasoactive intestinal peptide
Vascular cell adhesion molecule (VCAM), including VCAM 1, sVCAM
Vascular Endothelial Growth Factor (VEGF), including VEGF-A, PIGFm VEGF-B, EGF-C, VEGF-D, and VEGFxxx proteins
Zincins

CLAIMS

1. A method for identifying subjects at risk for central nervous system illness, cardiovascular disease, endocrine disorders or inflammatory disorders for treatment with Omega-3 fatty acid formulations, wherein the population is selected on the basis of polyunsaturated fatty acid status.
2. A method of identifying and diagnosing diseases and disease states of the central nervous system, cardiovascular system, endocrine disorders, inflammatory disorders, pain disorders via polyunsaturated fatty acid status.
3. The method of Claim 1 wherein cardiovascular disease includes coronary heart disease, coronary atherosclerosis, arteriosclerosis, myocardial infarction, stroke, cardiac arrhythmias, congestive heart failure, high triglycerides, high LDL, and low HDL or hypertension.
4. The method of Claim 1 wherein central nervous system disorders include Alzheimer's dementia, anxiety disorders, attention deficit disorder, attention-deficit hyperactivity disorder, autism, bipolar disorder, bipolar depression, borderline personality disorder, cognitive disorders, communication disorders, dementia, depression, dyslexia, eating disorders, fibromyalgia, learning disorders, lupus, mild cognitive impairment, migraine, mood disorders, multiple sclerosis, obsessive-compulsive disorder, oppositional-defiant disorder, pervasive developmental disorders, schizophrenia, self-injurious behavior, and tic disorders.
5. The method of Claim 1 wherein endocrine disorders include diabetes, diabetes-related sequelae, diabetic neuropathy, dysmenorrhea, and metabolic syndrome.
6. The method of Claim 1 wherein the inflammatory disorders are atopic dermatitis, chronic pain, chronic polyarthritis, Crohn's disease, dry eyes, macular degeneration, wet macular degeneration, dry skin, eczema, gout, osteoarthritis, osteoporosis, polyarteritis nodosa, psoriasis, psoriatic arthritis, rheumatoid arthritis, chronic

obstructive pulmonary disease, asthma, scleroderma, ulcerative colitis, and vasculitic disorders.

7. The method of Claim 1 wherein serum fatty acid status is determined by omega-3 serum phospholipids composition.
8. The method of Claim 1 wherein serum fatty acid status is determined by Omega-6 serum phospholipid composition.
9. The method of Claim 1 wherein serum fatty acid status is determined by a ratio of omega-3 to Omega-6 serum phospholipid composition.
10. The method of Claim 9 further combining the use of any of the biomarkers listed in Table 1.
11. The method of Claim 1 wherein omega-3 polyunsaturated fatty acids are selected from any one or combination of the following of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), alpha linolenic acid (ALA), stearidonic acid (SA), or eicosatetraenoic acid.
12. The method of Claim 1 wherein omega-6 polyunsaturated fatty acids are selected from any one or combination of arachidonic acid (AA), linolenic acid (LA), gamma-linoleic acid (GLA), dihommogammalinolenic acid, and aredenic acid.
13. The method of Claim 1 wherein omega-3 serum phospholipid compositions are a target for modulation by omega-3 fatty acid treatment
14. The method of Claim 1 wherein omega-6 serum phospholipids composition are a target for modulation by omega-3 fatty acid treatment
15. The method of Claim 1 wherein a ratio of omega-6:omega-3 serum phospholipids composition are a target for modulation by Omega-3 fatty acid treatment

16. The method of Claim 1 wherein Omega-3 serum phospholipid compositions are used as a modifiable target to prevent or treat cardiovascular disease, reduce major events associated with cardiovascular disease, and improve outcome in patients with existing cardiovascular disease.
17. The method of Claim 1 wherein a ratio of Omega-6:Omega-3 serum phospholipids compositions are used as a modifiable target to prevent or treat cardiovascular disease, reduce major events associated with cardiovascular disease, or improve outcome in patients with existing cardiovascular disease.
18. The method of Claim 1 wherein a ratio of Omega-6:Omega-3 serum phospholipids composition are used as a modifiable target to prevent or treat cardiovascular disease, reduce major events associated with cardiovascular disease, or improve outcome in patients with existing cardiovascular disease.
19. The method of Claim 1 wherein Omega-3 serum phospholipid compositions are used as a modifiable target to prevent or treat central nervous system disorders, reduce major events associated with central nervous system disorders, and improve outcome in patients with one or more existing central nervous system disorders.
20. The method of Claim 1 wherein a ratio of Omega-6:Omega-3 serum phospholipids compositions are used as a modifiable target to prevent or treat central nervous system disorders, reduce major events associated with central nervous system disorders, or improve outcome in patients with one or more existing central nervous system disorders.
21. The method of Claim 1 wherein a ratio of Omega-6:Omega-3 serum phospholipids composition are used as a modifiable target to prevent or treat central nervous system disorders, reduce major events associated with central nervous system disorders, or improve outcome in patients with one or more existing central nervous system disorders.
22. The method of Claim 1 wherein Omega-3 serum phospholipid compositions are used as a modifiable target to prevent or treat endocrine disorders, reduce major events

associated with endocrine disorders, and improve outcome in patients with one or more existing endocrine disorders.

23. The method of Claim 1 wherein a ratio of Omega-6:Omega-3 serum phospholipids compositions are used as a modifiable target to prevent or treat endocrine disorders, reduce major events associated with endocrine disorders, or improve outcome in patients with one or more existing endocrine disorders.
24. The method of Claim 1 wherein a ratio of Omega-6:Omega-3 serum phospholipids composition are used as a modifiable target to prevent or treat endocrine disorders, reduce major events associated with endocrine disorders, or improve outcome in patients with one or more existing endocrine disorders.
25. The method of Claim 1, further comprising administering an Omega-3 fatty acid formulation comprising EPA and DHA in a weight ratio of EPA:DHA of approximately 3.5:1 to approximately 5.5:1.
26. The method of Claim 25, wherein the formulation comprises at least 50% weight EPA and DHA as compared to the total fatty acid content of the formulation.
27. The method of Claim 25, wherein the formulation comprises at least 60% weight EPA and DHA as compared to the total fatty acid content of the formulation.
28. The method of Claim 25, wherein the formulation comprises at least 65% weight EPA and DHA as compared to the total fatty acid content of the formulation.
29. The method of Claim 25, wherein the formulation comprises at least 70% weight EPA and DHA as compared to the total fatty acid content of the formulation.
30. The method of Claim 25, wherein the formulation comprises at least 75% weight EPA and DHA as compared to the total fatty acid content of the formulation.
31. The method of Claim 25, wherein the formulation comprises at least 80% weight EPA and DHA as compared to the total fatty acid content of the formulation.

32. The method of Claim 25, wherein the formulation comprises at least 85% weight EPA and DHA as compared to the total fatty acid content of the formulation.
33. The method of Claim 25, wherein the formulation comprises at least 90% weight EPA and DHA as compared to the total fatty acid content of the formulation.
34. The method of Claim 25, wherein the formulation comprises at least 95% weight EPA and DHA as compared to the total fatty acid content of the formulation.
35. The method of Claim 25, wherein the formulation comprises at least 99% weight EPA and DHA as compared to the total fatty acid content of the formulation.
36. The method of Claim 35, wherein the method comprises delivering at least 1000mg of total EPA plus DHA per day.
37. The method Claim 35, wherein the method comprises delivering at least 1200mg of total EPA plus DHA per day.
38. The method of Claim 35, wherein the method comprises delivering at least 1400mg of total EPA plus DHA per day.
39. The method of Claim 35, wherein the formulation comprises a weight ratio of EPA:DHA of approximately 3.5:1 to approximately 5:1.