Safety Considerations with Omega-3 Fatty Acid Therapy

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It has been suggested that the potential antithrombotic effect of fish oils may theoretically increase the risk for bleeding, which may be a safety concern for individual patients. However, clinical trial evidence has not supported increased bleeding with omega-3 fatty acid intake, even when combined with other agents that might also increase bleeding (such as aspirin and warfarin). Another potential safety concern is the susceptibility of omega-3 fatty acid preparations to undergo oxidation, which contributes to patient intolerance and potential toxicity. Finally, large amounts of fish consumption may result in adverse experiences due to the potential presence of environmental toxins such as mercury, polychlorinated biphenyls, dioxins, and other contaminants. The risks of exposure to environmental toxins and hypervitaminosis with fish consumption are substantially reduced through purification processes used to develop selected concentrated fish oil supplements and prescription preparations. Thus, in choosing which fish oil therapies to recommend, clinicians should be aware of available information to best assess their relative safety, which includes the US Food and Drug Administration (FDA) and Environmental Protection Agency (EPA) advisory statement regarding fish consumption, the meaning of certain labeling (such as “verification” through the US Pharmacopeia) and the differences in FDA regulatory requirements between nonprescription fish oil supplements and prescription fish oil preparations, and how all of this is important to the optimal treatment of patients. © 2007 Elsevier Inc. All rights reserved. (Am J Cardiol 2007;99[suppl]:35C–43C)

Does Therapy with Fish Oils Rich in Omega-3 Fatty Acids Increase the Risk for Bleeding, and Are They Contraindicated in Patients Treated with Antiplatelet and Anticoagulant Therapies?

Response: No.

Confidence/level of evidence: 2C (Table 1).

Rationale: Because of the cardiovascular benefits of omega-3 fatty acids, the American Heart Association (AHA) has recommended omega-3 fatty acid intake in the form of routine fatty fish (as well as foods rich in α-linolenic acid) for patients without atherosclerotic coronary artery disease (CAD), fish or fish oil supplements for patients with CAD, and high-dose fish oil capsules for patients with hypertriglyceridemia. However, as with all pharmaceuticals, potential adverse experiences exist.

Fish oils rich in omega-3 fatty acids inhibit thrombosis, which has sometimes been suggested to account partially for the associated reduced risk for sudden cardiac death and reduced all-cause mortality. In vitro, fish oils competitively inhibit cyclooxygenase (and thus decrease the synthesis of thromboxane A2 from arachidonic acid in platelets), which leads to decreased platelet aggregation. Blood rheologic features and flow are also improved. Platelet-derived, growth factor–like protein is decreased, and synthesis of the platelet activation factor is decreased as well, all potentially contributing to a decrease in clinical atherothrombosis. Data regarding the effects of fish oils on fibrinogen and clotting factors are more limited.

In contrast to this in vitro data, the in vivo human data are less definitive, and even the most common antithrombotic effects attributable to fish oils, such as a decrease in platelet aggregation, have not yet been definitively demonstrated in clinical trials. In fact, some human studies have demonstrated that fish oil omega-3 administration has no effect on platelet aggregation. Furthermore, low-dose fish oil therapy (<1 g/day of omega-3 fatty acids) appears to have little effect on atherothrombotic factors such as platelet-derived growth factor. Given that omega-3 fatty acid therapy has been shown to have favorable effects on cardiovascular end points with doses as low as 1 g/day, this suggests that the cardiovascular clinical benefits of fish oils are more likely related to antidysrhythmic effects compared with antithrombotic effects.

Nonetheless, because an antithrombotic effect is possible, it has been suggested that fish oils could potentially increase the risk for bleeding. Furthermore, although the consumption of fish high in omega-3 fatty acids may decrease the risk for thrombotic stroke, it has been suggested that fish oil omega-3 therapy may actually result in a slightly higher risk for hemorrhagic stroke.
So the question is as follows: Do the potential antithrombotic effects of fish oils rich in omega-3 fatty acids pose a significant risk for increased bleeding in clinical practice, particularly when combined with other antiplatelet or anticoagulant therapies? In short, the clinical trial evidence suggests that if such an increased bleeding risk exists, the risk is very small and not of clinical significance.

Clinical trials have shown high-dose fish oil omega-3 fatty acid consumption to be safe, even when concurrently administered with other agents that may increase bleeding, such as aspirin and warfarin.\textsuperscript{12,19,20} In fact, in certain clinical settings, it could be argued that the reported antithrombotic effects of fish oils rich in omega-3 fatty acids are a benefit that outweighs the unproved bleeding risks, especially in select patients at high risk for thrombosis,\textsuperscript{11,21,22} which may include patients with acute atherosclerotic CAD.\textsuperscript{23} Finally, it is important to note that on the basis of existing clinical trial outcomes data, the AHA has recommended omega-3 fatty acid consumption (about 1 g of eicosapentaenoic acid [EPA] plus docosahexaenoic acid [DHA] per day in the form of fatty fish or fish oil supplements) in patients with documented atherosclerotic CAD,\textsuperscript{1} most of whom also would likely be treated with antithrombotic agents such as aspirin.

Recommendations to healthcare professionals (Table 2): Clinical trial data are lacking for every conceivable patient situation. From a practical standpoint, clinicians should be aware of regulatory recommendations included in the prescribing information of Omacor (Solvay Pharmaceuticals, Inc., Marietta, GA),\textsuperscript{24} the only prescription fish oil preparation.\textsuperscript{25} The drug interaction with anticoagulant section states, “Some studies with omega-3-acids demonstrated prolongation of bleeding time. The prolongation of bleeding time reported in these studies has not exceeded normal limits and did not produce clinically significant bleeding episodes. Clinical studies have not been done to thoroughly examine the effect of Omacor\textsuperscript{®} and concomitant anticoagulants. Patients receiving treatment with both Omacor\textsuperscript{®} and anticoagulants should be monitored periodically.”

Thus, a commonsense approach in treating patients routinely consuming significant amounts of fish oils, including prescription fish oils or supplements (in each case >1 g/day of EPA and DHA), would be to use similar general guidelines applicable to other anticoagulants. For example, it
The clinical trial evidence does not support an increased bleeding risk with fish oil therapy, even when used in combination with other agents that may increase bleeding (such as aspirin and warfarin).

It is reasonable to monitor patients treated with fish oils and anticoagulants for potential bleeding adverse experiences; however, it is unclear if more monitoring is required than what would otherwise be done with patients administered anticoagulants alone.

Fish oils should probably be discontinued during acute bleeding episodes, such as hemorrhagic stroke.

The decision to discontinue fish oils days before an invasive procedure at high risk for bleeding complications should be based on weighing the unproved potential increase in bleeding risk versus the potential reduction in atrial fibrillation before certain procedures, such as coronary artery bypass surgery.

Rigorous purification processes involved in fish oil manufacturing reduce the risk of fatty acid oxidation, hypervitaminosis, and exposure to environmental toxins.

Clinicians and patients should be aware of the variance in the purification processes among different fish oil manufacturers.

Because fish oil supplements are generally regarded as safe, they are not subject to FDA premarket and approval requirements.

If a product has the “USP-Verified” mark on its label, the manufacturer has met voluntary USP standards, which include initial and ongoing determinations to ensure that (1) what is on the label is in fact in the bottle (all the listed ingredients in the declared amounts), (2) the supplement does not contain harmful levels of contaminants, (3) the supplement will break down and release ingredients in the body, and (4) the supplement has been made under current good manufacturing practices.

Some fish oil manufacturers advertise voluntary compliance with the standards set by the CRN, which suggests that the fish oil manufacturers are adhering to a voluntary monograph developed by an association of manufacturers in the dietary supplement industry that specifies quality standards for fish oil supplements marketed in the United States.

Claims of a fish oil supplement being “pharmaceutical grade” have little meaning regarding safety and have even less meaning with regard to efficacy, unless the fish oil preparation has been approved by the FDA as a prescription pharmaceutical.

Prescription fish oil preparations undergo the same rigorous FDA regulatory requirements as other prescription pharmaceuticals, with regard to both efficacy and safety.

One of the most common pitfalls in the day-to-day, clinical use of fish oil therapy is the sense among patients that all fish oil therapies are the same. Clinicians need to educate patients of the wide variance in fish oil therapies regarding efficacy, tolerability, and perhaps even safety. For example, the efficacy of fish oil therapy is most dependent on the amount of omega-3 fatty acids (such as EPA and DHA) in each capsule, not the total amount of fish oil concentrate. Thus, to achieve the same level of omega-3 fatty acid intake, patients may have to take as many as 11 capsules of some fish oil supplements to match the same amount of omega-3 fatty acid intake as 4 fish oil capsules of prescription fish oil.

CRN = Council for Responsible Nutrition; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; FDA = US Food and Drug Administration; USP = United States Pharmacopoeia.

would seem prudent to discontinue high-dose fish oil consumption or supplementation in the setting of an acute bleeding illness, such as during and immediately after a hemorrhagic stroke, or in patients at high risk for hemorrhagic stroke. Another practical clinical example might be the perioperative management of patients who undergo some major surgeries. It is true that the even infusion of fish oils after major abdominal surgery (as occurs through total parenteral nutrition) does not appear to result in clinically significant bleeding and has been suggested to be safe with specific regard to coagulation and platelet function. Nonetheless, some clinicians might consider discontinuing fish oil therapy 4–7 days before planned invasive procedures with the highest risk for bleeding complications, as is often recommended with aspirin, warfarin, and clopidogrel.

However, in the case of fish oils, the unproved benefit of stopping fish oil therapy to reduce a theoretical increase in bleeding risk should be weighed against the potential benefits of fish oil therapy in reducing atrial fibrillation, when administered ≥5 days before major procedures such as coronary artery bypass surgery.

Postoperatively, clinicians should consider the potential antithrombotic and cardiovascular advantages of restarting fish oil therapies, given that thrombotic and cardiovascular events are often among the most common complications following many major surgeries.
and particularly the potential toxicities of fish oil therapy involve the manner in which the fish oil products are manufactured, specifically regarding purification processes directed at the removal of toxins, non–omega-3 fatty acids, oxidized substances, and other undesirable byproducts. In fact, it could be argued that when a patient describes a fish oil supplement as having a strong, rancid fishy smell and taste, this may suggest that the supplement was poorly purified by the manufacturer or has expired or become oxidized and is potentially toxic.

**Hypervitaminosis:** Hypervitaminosis is another potential toxicity that may occur with the excessive consumption of fish oils containing high concentrations of fat-soluble vitamins D and A, as might occur with excessive cod liver oil consumption. Very high vitamin D intake can cause hypercalcemia, but this has not been a widely described consequence of any fish oil consumption, including cod liver oil ingestion. Similarly, studies suggest that vitamin A toxicity is rare when fish oils are administered in oil-based preparations. Nonetheless, the excessive intake of vitamin A (particularly in water-miscible, emulsified, and solid forms) has been described to cause yellowish discoloration of the skin (carotenemia); possibly an increased risk for lung cancer; teratogenic effects in pregnant women; severe anemia and thrombocytopenia in infants; toxicities to the musculoskeletal, neurologic, and gastrointestinal system in children; bone pain; and osteoporosis, with an increased risk for bone fractures in older subjects.

In the early 1900s, rickets (a bone disease due to vitamin D deficiency) was rampant among poor children in the United States and England who were living in industrialized cities amid polluted, smoky skies. Vitamin D deficiency ensued because sunlight is needed to metabolize vitamin D. Around this same time, cod liver oil (an omega-3 fatty acid) was found to be useful to prevent rickets because it contained substantial amounts of vitamin D. Cod liver oil also was used as a supplement to treat a variety of many pediatric ailments, partly because it also contained high doses of vitamin A, and vitamin A deficiency was thought to contribute to blindness and immune deficiencies and thus an increased risk for infections. Thus, it was not uncommon for parents to administer cod liver oil routinely to their children and for pediatricians to recommend infant formulas that included cod liver oil.

However, since the fortification of infant milk preparations with vitamins D and A in the 1930s, the use of cod liver oil to prevent rickets is no longer common in the United States. US pediatricians no longer routinely recommend cod liver oil for infants, although cod liver oil remains a component of some “homemade” infant formulas. Thus, clinicians should be made aware that cod liver oil supplementation is still common in some populations, such as those in northern Europe, and thus may represent at least a potential risk for hypervitaminosis.

**Environmental toxins:** High fish oil intake through the consumption of large amounts of fish may present a risk for increased environmental toxin exposure. For example, excessive mercury exposure may originate from industrial sources (such as coal-fired power plants, waste incinerators, and certain factories and mining operations). Once airborne, the mercury pollutants fall to the ground in rain or snow, become deposited in water bodies, and are subsequently converted by bacteria into methylmercury, which is highly toxic to humans. Larger and older fish may have more time to bioaccumulate mercury from their food (and through their gills) than smaller and younger fish. Furthermore, large predatory fish near the top of marine food chains may accumulate more mercury than fish lower in the marine food chain through the consumption of small fish, resulting in biomagnification. Mercury poisoning through fish consumption has resulted in various neuropsychiatric signs and symptoms, including constriction of the bilateral visual fields, parasthesias of the extremities and mouth, ataxia, incoordination, tremor dysarthria and auditory impairments, severe neurologic damage to children born to mothers with toxic mercury exposure, and other signs and symptoms. As a testament that mercury exposure poses real risks to populations, in 2004, the US Food and Drug Administration (FDA) and the Environmental Protection Agency (EPA) issued an advisory statement recommending that women who may become pregnant, women who are pregnant, breast-feeding mothers, and young children avoid eating some types of fish and eat fish and shellfish that are lower in mercury. However, the totality of evidence supports that the benefits of fish intake generally exceeds the potential risks, including intake in women of childbearing age, except for a few selected fish species. It is noteworthy that these recommendations apply only to fish oil intake through the consumption of fish. With regard to fish oil intake through select fish oil supplements, testing has shown that the level of mercury (and other environmental toxins) is very low or negligible. This is probably due to 2 factors. First, the oxidized mercury released from power plants and potentially washed into local water bodies by rainfall is water soluble. Thus, although mercury toxicity may sometimes be a potential issue with the consumption of the flesh of fish, oxidized mercury is insoluble in oil and thus would not be expected to represent a significant toxicity risk with the intake of the oils of fish. Second, selected fish oil supplements undergo extensive purification processes to remove environmental and other toxins, with prescription fish oil preparations undergoing even more rigorous regulatory processes to achieve FDA approval as prescription pharmaceuticals.

Before 1980, polychlorinated biphenyls (PCBs), colorless and odorless chemicals, were used widely in flame retardants, pesticides, paints, varnishes, inks, lubricants, and insulation related to electrical equipment, such as transformers. Since then, PCBs have been banned by most countries. As with mercury, PCBs are toxic to humans as well
Other environmental toxins include organochlorine (OC) pesticides, which were sprayed on crops and forests and released into the air, water, and soil. One of the best known OCs is dichlorodiphenyltrichloroethane (DDT), which has been banned in the United States since the 1970s. DDT is highly toxic to fish, and its widespread use was a major reason for the near extinction of the bald eagle in the 1950s. Although the clinical manifestations of OC toxicity may not be as clear as other toxins, OCs may cause abnormalities in liver enzymes and chloracne and contribute to neurologic impairment, such as Alzheimer disease.

Dioxins, which are another family of chemical compounds called polychlorodibenzo(dioxins (sometimes grouped as part of OCs), are a byproduct of industrial processes involving chlorine, such as waste incineration, chemical and pesticide manufacturing, and pulp and paper bleaching. Dioxin was the primary toxic component of Agent Orange, a defoliant used during the Vietnam War, and is considered a likely carcinogen. Dioxin toxicity is commonly manifested by chloracne and has also been suggested to contribute to the onset of diabetes mellitus, endometriosis with infertility, abnormalities in thyroid function, and impaired neurodevelopment of infants.

Just as with mercury, fish consumption has sometimes been associated with toxicities from all of these environmental toxins. Thus, manufacturers of selected fish oil supplements have implemented various purification processes and quality controls designed to reduce the risk for exposure to environmental toxins. Largely through these quality measures, reviews of 5 commercial fish oil supplements have concluded that some of the more common fish oil supplements contain fewer toxins than fish and that fish oil supplements may be preferable to fish consumption as a therapeutic source of omega-3 fatty acids.

Recently, a prescription omega-3 fatty acid fish oil preparation has been approved for the treatment of hypertriglyceridemia (Omacor). In multiple clinical trials of this prescription omega-3 fatty acid agent, no cases of hypervitaminosis or illnesses due to exposure to environmental toxins were reported. This safety profile is likely owing to an extensive purification process resulting in no detectable concentrations of heavy metals, halogenated polycarbons, and dioxins, as well as <0.05% of trans-fatty acids.

Recommendations to healthcare professionals: In choosing the most appropriate fish oil therapy to recommend to patients, clinicians should be aware of potential fish oil toxicities and know which fish oil manufacturers have adequate purification processes to minimize these potential toxicities. This can present a challenge, because although the FDA has regulatory mechanisms to ensure the safety of prescription products, no such FDA regulatory mechanisms are in place for “dietary supplements.” Agents classified as dietary supplements do not require product registration, manufacturer registration, premarket approval, or the mandatory reporting of adverse events and require only limited safety-related labeling. From a practical standpoint, this means that manufacturers of dietary supplements are not required to provide evidence of efficacy, safety, or manufacturing standards before marketing products. Although it has been suggested that this lack of oversight and inadequate regulation may pose a risk to the health and safety of the public, and although organizations such as the American Medical Association (AMA) have advocated that dietary supplements be regulated to the same standards as prescription and over-the-counter drugs, in the current regulatory environment, clinicians should be aware of the quality assurance practice guidelines for fish oil products, self-established by their manufacturers, before recommending any dietary supplement.

For example, specific FDA current good manufacturing practices are required for the prescription pharmaceuticals and describe procedural protocols that help ensure acceptable quality. Current good manufacturing practices are currently under development for dietary supplements (Table 3). In the interim, fish oil supplements are included on the list of substances that the FDA designates as “generally regarded as safe,” which means that according to qualified experts, fish oils have adequately been shown to be safe under the conditions of their intended use. As with other products generally regarded as safe, fish oils supplements are not subject to the premarket review and approval requirements of the FDA. Nonetheless, some fish oil manufacturers include in their advertisements that fish oil supplements have been designated by the FDA as generally regarded as safe and that their manufacturing processes are in voluntary compliance with current good manufacturing practices. With regard to efficacy (and safety) in the clinical use of fish oil supplements, the FDA has determined that the following statement is acceptable, provided that fish oil supplement manufacturers do not recommend or suggest in their labeling a daily intake that exceeds 2 g/day of EPA and DHA: “Consumption of omega-3 fatty acids may reduce the risk of coronary heart disease. The FDA evaluated the data and determined that, although there is scientific evidence supporting the claim, the evidence is not conclusive.”

Because of the recognition that “faith” alone is not sufficiently reassuring to many clinicians or patients regarding medicinal product quality and safety, some fish oil supplement manufacturers elect to pursue “USP-Verified” marks.
on their labels. A USP-Verified mark indicates compliance with standards set by the United States Pharmacopeia (USP), an independent, not-for-profit organization established in 1820 that has quality standards enforceable by the FDA and sets the legally recognized standards for identity, strength, quality, purity, packaging, and labeling. Many clinicians are aware of USP monographs, mostly issued for prescription or over-the-counter products and sometimes for dietary supplements as well. A USP monograph is a descriptive document that typically contains the following information about a product: descriptive information (graphic formula, chemical formula, molecular weight, chemical name, and chemical abstracts registry number), percentage of the active ingredient in the product, a discussion of product packaging and storage, USP reference standards, any official revisions to the monograph, tests used to identify the product, melting temperature range, amount of water, residue on ignition, and a list of tests and procedures to assess toxins and impurities. No official USP monograph currently exists for nonprescription fish oil supplements.

Beyond describing monograph specifications of products, the USP is also engaged with the verification of products, such as through the voluntary Dietary Supplement Verification Program. The presence of the distinctive USP-Verified mark on its label signifies that the USP has rigorously tested and verified a supplement to ensure that (1) what is on the label is in fact in the bottle (all the listed ingredients in the declared amounts), (2) the supplement does not contain harmful levels of contaminants, (3) the supplement will break down and release ingredients in the body, and (4) the supplement has been made under current good manufacturing practices. If a product has a USP-Verified mark on its label, the manufacturer is legally responsible for meeting USP standards. Two separate USP verifications exist. One distinctive USP-Verified mark is “Ingredient Verified.” In this case, the USP has performed testing at the request of the manufacturer to verify the consistent quality of active and inactive ingredients. This mark is used mainly by manufacturers. The other distinctive USP-Verified mark is “Dietary Supplement Verified,” indicating that testing has been done to ensure the integrity, purity, dissolution, and safe manufacturing of a dietary supplement. This mark is for mainly for consumers. At the time of this writing, only a few fish oil supplement manufacturers have voluntarily requested and subsequently received either of these USP-Verified designations.

To assist in the establishment of quality and safety standards that might form the basis of an official USP monograph for the class of nonprescription fish oil supplements, the Council for Responsible Nutrition (CRN) developed a voluntary monograph aimed at the goal of “raising the bar” through quality standards for fish oil supplements marketed in the United States. The CRN is an association of ingredient suppliers and manufacturers in the dietary supplement industry founded in 1973 for the purpose of “improving the environment for member companies to responsibly market

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| Product Class | Product Registration | Manufacturer Approval | Premarket Approval | Specific Good Manufacturing Practices | Mandatory Manufacturer Reporting | Voluntary Postmarket Reporting System | Under Development | Some
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| Dietary supplement | Food additive | Monograph drugs | New drug application drugs | Infant formula | | | |

* The FDA does not collect or evaluate all adverse events on all conventional food. Excluded from this system are the investigations the FDA conducts after food-borne illness outbreaks.

† Monograph drugs are typically over-the-counter drugs that must adhere to specific safety standards set out for each ingredient and do not undergo clinical testing.

‡ A new drug application must be submitted to the FDA for all prescription drugs and some over-the-counter drugs before market. This application must include data that demonstrate the safety and efficacy of the product.

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dietary supplements by enhancing confidence among media, healthcare professionals, decision makers and consumers" and has encouraged the incorporation of this voluntary monograph into existing standards established by organizations such as the USP, as well as other organizations such as the American Oil Chemists Society and the Association of Official Analytical Chemists International. Some fish oil manufacturers claim voluntary compliance with the proposed CRN fish oil monograph.

Currently, the USP is providing its verification mark on the basis of a proposed monograph, which was derived from the CRN monograph, as well as other resources. The establishment of an official USP monograph for fish oil therapy is imminent. However, even with the establishment of an official USP monograph, clinicians and patients should understand that no USP designation exists to qualify omega-3 fish oil supplements as “pharmaceutical grade,” as claimed by some fish oil manufacturers in their advertisements. The USP has no standards that defined the term “pharmaceutical grade”; thus, any labeling of an omega-3 fish oil supplement as “pharmaceutical grade” as it pertains to the USP is misleading. In fact, it might better be considered as blatantly inaccurate, unless the fish oil formulation has gone through the rigorous processes and oversight required to receive approval as a prescription pharmaceutical from an established regulatory agency such as the FDA (Table 1).

So the answer as to whether prescription and/or supplement omega-3 fatty acid products may contain excessive vitamins or environmental toxins in sufficient concentrations to pose a potential health risk is dependent almost entirely on the purification process. With nonprescription fish oil supplements, because no FDA regulatory oversight exists to ensure a lack of included toxins, clinicians and patients must rely on their faith in the voluntary commitment to quality on the part of manufacturers or ensure that the fish oil supplement manufacturers have complied with accepted quality assurance standards, as denoted by labeling such as “USP-Verified.” The only caveat here is that any such labeling does not verify, or even address, the degree of efficacy of a supplement. For efficacy information, a label must be read to assess the amount of EPA and DHA within a fish oil dietary supplement, which can then be used to determine the anticipated therapeutic response. This is important because although the front of the bottles of some fish oil supplements may list the contents as having “1,000 mg of fish oil concentrate,” the labeling on the back of the bottles may reveal that the amounts of the actual omega-3 fatty acids (e.g., EPA and DHA) are much less, often as low as 300 mg per fish oil capsule. In this case, from a practical standpoint, a patient would have to consume 11 fish oil capsules containing 300 mg EPA and DHA to achieve the same omega-3 fatty acid intake as 4 tablets of prescription fish oil (which contains 840 mg of EPA and DHA).

If a fish oil preparation has received FDA approval as a prescription pharmaceutical, clinicians and patients can be assured that the manufacturer has met rigorous FDA regulatory requirements with regard to both efficacy and safety when used in the clinical setting and at the doses in compliance with the prescribing information.

17. O’Keefe JH Jr, Abusia H, Sastre A, Steinhaus DM, Harris WS. Effects of omega-3 fatty acids on resting heart rate, heart rate recovery after exercise, and heart rate variability in men with healed myocardial


