DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Ave
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Silver Spring, MD 20993

FEB 21 2014

John H. Fuson
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1001 Pennsylvania Avenue, NW
Washington, DC 20004

Re: Docket No. FDA-2013-P-0148

Dear Mr. Fuson:

This responds to your citizen petition dated February 6, 2013 (Petition) regarding Lovaza (omega-3-acid ethyl esters) Capsules. You request that the Food and Drug Administration (FDA or the Agency) amend the strength listing for Lovaza, including the strength listing in the *Orange Book*.[1] Specifically, you request that FDA:

(1) Amend its listed strength for Lovaza (omega-3-acid ethyl esters) Capsules, including the strength listing in the *Orange Book*, to 900 milligrams (mg), so that the strength "appropriately identifies the amount of active ingredient per administration unit without reference to any other capsule properties such as product weight/fill weight, excipients, or other inactive ingredients" (Petition at 1); or, alternatively,
(2) Adopt a strength of 840 mg for Lovaza based upon the fixed amount of major omega-3-acid ethyl esters specified in the Lovaza new drug application (NDA) reviews and labeling (Petition at 6).

In support of your request, you state that a revision to the strength for Lovaza is necessary to (1) conform the listed strength to FDA's well-established definition of strength, (2) make the *Orange Book* listing consistent with thousands of similarly situated strengths that FDA has adopted and published since 1984, and (3) conform FDA's adopted strength to publicly available data on Lovaza, the Lovaza labeling, and the drug listings submitted by the NDA holder and published in the National Drug Code (NDC) Directory (Petition at 1).

We have carefully reviewed the Petition, the comments filed in this docket, and other relevant information available to the Agency. Lovaza contains a naturally derived, partially-purified fish oil concentrate mainly consisting of a mixture of fatty acids. The clinical studies that supported the approval of Lovaza tested the fish oil as a whole to establish the safety and effectiveness of the product. At the time of approval, the fish oil mixture in Lovaza had not been fully characterized, and the available data did not adequately demonstrate the activity or inactivity of all components in

[1] See FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly known as the *Orange Book*), at 3-318 (33rd Ed., 2013), available at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf.

the mixture. In accordance with the Agency's practice regarding naturally derived mixtures that are not fully characterized, FDA identified the entire fish oil mixture as the active ingredient of Lovaza. You have provided no new information or data that would cause us to revise that initial determination, and the Petition is therefore denied.

I. BACKGROUND

A. FDA Specifications for Strength

FDA's regulations in Title 21 of the Code of Federal Regulations (CFR) establish a definition for drug strength. Specifically, section 210.3(b)(16), in relevant part, defines "strength" as "[t]he concentration of the drug substance (for example, weight/weight, weight/volume, or unit dose/volume basis)." Section 314.3(b) defines "drug substance" as "an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body . . . ." Thus, "drug strength" is defined in terms of the amount (or concentration) of active ingredient(s) in a drug product.

B. Lovaza

GlaxoSmithKline is the holder of NDA 21-654 for Lovaza (omega-3-acid ethyl esters) Capsules, which the FDA approved on November 10, 2004.[2] Lovaza is approved as an adjunct therapy to diet for reducing triglyceride (TG) levels in adult patients with severe (≥ 500 mg/deciliter (dL)) hypertriglyceridemia.

Lovaza consists of partially-purified fish oil that predominantly (i.e., at least 90%) contains a mixture of seven different omega-3 fatty acid ethyl esters (the omega-3 component).[3] Eicosapentaenoic acid ethyl ester (EPAee) and docosahexaenoic acid ethyl ester (DHAee) are the principal ethyl esters of the omega-3 component. In addition to the omega-3 component, the fish oil mixture in Lovaza also contains omega-6 fatty acid ethyl esters and other components, some of which have not been characterized (the non-omega-3 component).

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[2] See FDA November 10, 2004, approval letter for Omacor, available at, http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2004/21654ltr.pdf. The Lovaza NDA was originally approved under the name of Omacor. This name was changed to Lovaza in 2008. See FDA June 3, 2008, letter approving the trade name change supplement, available at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2008/021654s021ltr.pdf. In this response, we refer to Lovaza to mean both Lovaza and its originally marketed name Omacor, where applicable.

[3] The seven omega-3-acid ethyl esters are: Eicosapentaenoic acid ethyl ester (EPAee), Docosahexaenoic acid ethyl ester (DHAee), Alpha-linolenic acid ethyl ester, Moroctic acid ethyl ester, Eicosatetraenoic acid ethyl ester, Heneicosapentaenoic acid ethyl ester, and Docosapentaenoic acid ethyl ester. See United States Pharmacopeia (USP), Omega-3-Acid Ethyl Esters, 36 USP-NF 1 at 4571 (Dec. 1, 2013).

Lovaza's active ingredient, omega-3 acid ethyl esters,[4] is defined in the USP as being derived from "transesterification [sic] of the body oil obtained from fish"[5] and containing, among other things, "[not less than] 90% (w/w) of the sum of [seven different omega-3 fatty acid ethyl ester components]."[6]

At the time of approval, Lovaza's strength was designated as 1 gram, a measure which denoted the total amount of fish oil concentrate (meeting the USP definition of Omega-3 Acid Ethyl Esters) in the capsule.[7] The dosage form and strength listed in the current labeling for Lovaza states that "Lovaza (omega-3-acid ethyl esters) capsules are supplied as 1-gram transparent soft-gelatin capsules filled with light-yellow oil and bearing the designation Lovaza."[8] The Highlights of Prescribing Information Section states the dosage and strength as "Capsules: 1-gram."[9] In addition, section 11 of the labeling describes Lovaza as follows:

> Each 1-gram capsule of Lovaza contains at least 900 mg of the ethyl esters of omega-3 fatty acids sourced from fish oils. These are predominantly a combination of ethyl esters of eicosapentaenoic acid (EPA – approximately 465 mg) and docosahexaenoic acid (DHA – approximately 375 mg) . . . .
>
> Lovaza capsules also contain the following inactive ingredients: 4 mg α-tocopherol (in a carrier of soybean oil), and gelatin, glycerol, and purified water (components of the capsule shell).[10]

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[4] We note that the established name for Lovaza "omega-3-acid ethyl esters" does not mean that Lovaza's active ingredient is its omega-3 component. As explained herein, the Lovaza labeling and relevant files in the drug's NDA establish that FDA defined the drug's active ingredient as the entire mixture at the time of approval. Moreover, at the time of approval, FDA rejected the suggestion that Lovaza's established name should consist of the names for EPAee and DHAee. Instead the Agency determined that the name "omega-3 acid ethyl esters" would be suitable because it "was designed to correspond to the mixture (natural product containing EPA and DHA ethyl esters, among other compounds)." CDER, Approval Package for NDA 21-654, Administrative/Correspondence, Omacor Action Letters (Nov. 1, 2004) (emphasis added).

[5] The fish oil from which the drug substance is obtained originates from ocean fish families such as *Engaulidae, Carangidae, Clupeidae, Osmeridae, Salmonidae,* and *Scrombroidae.* USP, Omega-3-Acid Ethyl Esters, 36 USP-NF 1 at 4571 (2013); see Haber, M., NDA 021654, Chemistry Review at 7, November 1, 2004, available at, http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-654_Omacor_Chemr.pdf.

[6] USP 36-NF 1 at 4571.

[7] Omacor labeling, at 1 (2004) available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/21654lbl.pdf. ("Each one gram capsule of Omacor® (omega-3 acid ethyl esters) contains at least 900 mg of the ethyl esters of omega-3 fatty acids."). Id. at 8 ("Each capsule contains 1 gram omega-3-acid ethyl ester liquid concentrate consisting of at least 900 mg omega-3-acid ethyl esters.").

[8] Lovaza labeling at 2, DOSAGE FORMS AND STRENGTHS section, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021654s039lbl.pdf.

[9] Id. at 1.

[10] Id. at 5-6 (DESCRIPTION section).

Lovaza's strength is currently listed in the Orange Book as: "1gm contains at least 900mg of the ethyl esters of omega-3 fatty acids."[11]

II. DISCUSSION

A. FDA's Regulatory Framework for the Definition of "Strength" is Based on the Amount of Active Ingredient per Administration Unit

In the Petition, you reference Drugs@FDA, the NDC Directory, the International Conference on Harmonisation (ICH) Consensus Guidelines, and FDA's regulation at 21 CFR 210.3(b)(16), among others, to support your contention that FDA has a well-established regulatory framework that defines the strength of a drug product to refer to the amount of active ingredient per administration unit (Petition at 2-3). You also observe that for similarly situated drugs listed in the *Orange Book*, strength is a fixed figure identifying the amount of active ingredient contained in each dose of the product (Petition at 3). You state that FDA applies this regulatory framework regardless of product origin (chemical vs. biotechnology), derivation (synthetic vs. naturally derived), or sourcing of ingredients or their complexity (Id.).

Next, you assert that "formulation-related factors"[12] unrelated to the amount of active ingredient in a drug product dose and only relevant to product weight are not part of the strength calculus (Petition at 3). You state that although formulation-related properties of a drug product can impact its safety and efficacy profile and may require additional studies, these considerations do not affect a product's strength, and they have no bearing on the comparative assessment of strength vis-à-vis a reference listed drug (RLD) if an RLD is evaluated in development and/or relied upon in the application process (Petition at 5).

We agree that FDA has a well-established framework for the definition of strength under which the Agency defines the strength of a drug product as the amount of the drug substance (i.e., active ingredient) per administration unit, and that FDA's regulatory framework for defining strength in terms of the drug substance is an established convention in the *Orange Book*. It is also true that, although inactive ingredients or excipients can potentially impact the safety and efficacy of a drug, they generally do not influence the designation of its strength. Nor do inactive ingredients or other formulation-related components of the drug product factor into a comparative assessment of

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[11] *Orange Book*, *supra* note 1, at 3-318.

[12] Throughout the Petition, you allude variously to "formulation-related factors," (Petition at 3) "formulation-specific factors," (Id. at 5) and "excipients and other factors" (Id. at 6) without identifying any component(s) of the fish oil mixture that fits this description. By claiming that these "factors" should be discounted in determining Lovaza's strength, you are in essence asserting that "factors" refers to certain components of the fish oil mixture which should be considered to be inactive ingredients. Therefore, in your request to revise Lovaza's strength to 900mg, you appear to be asserting that the non-omega-3 component of the fish oil mixture are inactive ingredients. As to your alternative request to revise the strength to 840 mg, you appear to suggest that all components of the fish oil mixture other than EPAee and DHAee (including the omega-3 acid ethyl esters other than EPAee and DHAee) are inactive ingredients.

strength between a generic product and an RLD. The only component of a drug product that determines its strength is the amount of its active ingredient.

B. FDA does not have Sufficient Information that would Support a Decision to Revise the Strength Listing for Lovaza

1. Lovaza's Strength Listing in the Orange Book is Consistent with its Labeling and FDA's Regulatory Framework for the Definition of "Strength"

In the Petition, you assert an inconsistency between FDA's current listed strength for Lovaza and the strength certified by the NDA holder in drug listing submissions made in accordance with the Drug Listing Act of 1972, 12 U.S.C. § 360 (Petition at 4). You also claim that Lovaza's strength as listed in the *Orange Book*, is inconsistent with the identification of the product's strength set forth in the currently approved labeling for Lovaza (Petition at 5, n.5).

We do not agree that the current strength for Lovaza listed in the *Orange Book* and the identification of Lovaza's strength in its currently approved labeling are inconsistent. According to the *Orange Book*, the strength listing for Lovaza is "1gm contains at least 900mg of the ethyl esters of omega-3 fatty acids."[13] The DOSAGE FORMS AND STRENGTHS section in the approved drug labeling for Lovaza describes the capsules as "supplied as 1-gram transparent soft-gelatin capsules filled with light-yellow oil and bearing the designation LOVAZA," and the DESCRIPTION section of the approved drug labeling states "Each 1-gram capsule of LOVAZA contains at least 900 mg of the ethyl esters of the omega-3 fatty acids sourced from fish oils,"[14] which conforms with the strength displayed in the *Orange Book* listing for Lovaza.[15]

You maintain that FDA's current strength listing for Lovaza gives undue prominence and inappropriate importance to the 1-gram product weight/fill weight of the Lovaza Capsule, and the weight/fill weight is a parameter that is driven by excipients and other factors[16] that are not relevant to product strength (Petition at 6). You state that the current strength for Lovaza does not plainly (and singularly) identify the amount of active ingredient per capsule (Id.).

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[13] Id.

[14] See labeling for Lovaza, DOSAGE FORM AND STRENGTHS and DESCRIPTION sections, available at Drugs@FDA http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021654s034lbl.pdf, pp. 2 and 5-6.

[15] The current strength for Lovaza listed in the Orange Book and the strength certified by the NDA holder in the NDC Directory do not appear, on their face, to be identical. The current strength listing for Lovaza in the Orange Book is "1gm contains at least 900mg of the ethyl esters of omega-3 fatty acids." The NDC Directory lists the strength as "900 mg/1." As you also recognize (Petition at 4), GSK, the NDA holder, submits this information to the NDC Directory, not FDA. In its comments to the docket, GSK explains that "900 mg/1" is a shorthand that reflects the current strength of Lovaza as listed in its labeling and the *Orange Book*. See Comments filed by GlaxoSmithKline, LLC and Pronova BioPharma Norge AS at 9, fn. 41, Docket No. FDA-2013-P-0148 (August 6, 2013).

[16] See note 12, *supra*.

We disagree. The 1-gram specification is consistent with FDA conventions of designating strength, which denotes the amount of active pharmaceutical ingredient (API) in each dosage form. As explained above, when Lovaza was approved, the Agency concluded that the API of Lovaza was the fish oil mixture in its entirety. Thus, the strength of Lovaza was labeled as 1 gram of the fish oil concentrate (the amount of fish oil concentrate in the capsule).

The Agency's recognition of the entire fish oil mixture as Lovaza's active ingredient is consistent with the Agency's approach to naturally derived mixtures that are not fully characterized. As the Agency has stated in several instances, when naturally derived mixtures are not sufficiently characterized to precisely identify every molecule that meaningfully contributes to the activity of the mixture, it is difficult to define the active ingredient in terms of the specific components of such a mixture.[17] In such cases, the Agency may identify the entire mixture as the active ingredient of the product.[18] Examples that are consistent with this approach include two recently approved botanical products — Fulyzaq (crofelemer) Tablets and Veregen (sinecatechins) ointment.[19]

2. Amending the Strength Listing for Lovaza

In the Petition, you request that FDA amend the strength for Lovaza, including the strength listing in the *Orange Book*, to 900 mg (Petition at 6). Alternatively, you assert that FDA could revise Lovaza's strength to 840 mg based on the fixed amount of major omega-3-acid ethyl esters (EPAee and DHAee) specified in the Lovaza reviews and labeling (Id.).

We do not agree that a designation of a strength of 900 mg or 840 mg for Lovaza would be consistent with FDA's general approach to defining the strength of a drug product such as Lovaza. Your request to revise the strength to 900 mg necessarily requires us to conclude that the non-omega 3 component of the fish oil mixture is composed solely of inactive ingredients. But you have not provided any new information or data that would identify the omega-3-component as being solely responsible for Lovaza's pharmacological effect. Similarly, you have not provided any new information or data to support a conclusion that all components of the Lovaza mixture other than EPAee and DHAee are inactive ingredients. Thus, FDA also lacks sufficient evidence to conclude that the strength of Lovaza should be revised to 840 mg.

You appear to recognize that when FDA adopted a strength of 1 gram for Lovaza at the time of approval, the Agency did not have sufficient data to conclude that certain components of the fish

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[17] See, e.g., Conjugated Estrogens FR Notice, 62 FR 42562 at 42566 (Aug. 7, 1997) ("At the time of marketing, products such as Premarin, that are derived from natural source material, frequently are not characterized as completely as synthetic products would be. The term 'adequate characterization' is intended to mean an amount of scientific information on a product that is sufficient to determine what constituents in the product are responsible for making clinically meaningful contributions to its therapeutic effects.")

[18] A naturally derived mixture that constitutes the active ingredient of a drug product may contain more than one active moiety. That issue is not before us here.

[19] See Approval History for Veregen (NDA 021902), available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021902s000TOC.cfm; see also Approval History for Fulyzaq (NDA 202292), available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202292Orig1s000TOC.cfm.

oil mixture were inactive ingredients (Petition at 5). But you claim that FDA now possesses new data that would demonstrate that certain components of Lovaza are inactive ingredients because

> new preclinical, clinical, and bioavailability data before the Agency demonstrates that those formulation-related factors do not impact safety and effectiveness of at least one new omega-3-acid ethyl esters product that has been shown to have the same safety and efficacy profile in animals, in the target patient population, as well as in healthy volunteers in both the fed and the fasted state. (Id.).

We do not agree that FDA has new data that would support a conclusion that certain components of Lovaza "do not impact [its] safety or effectiveness." We are aware of no new studies that have ruled out the possibility that the non-omega 3 components (or the omega 3 components other than EPAee or DHAee) make a meaningful contribution to Lovaza's activity. Even assuming that a different "omega-3-acid ethyl esters product," were also to be shown to be safe and effective for the same indication as Lovaza, that would still not be sufficient to conclude that certain components of Lovaza do not contribute meaningfully to its pharmacological effect.

Because the clinical studies to establish Lovaza's safety and efficacy were based on the entire mixture — not just on the omega-3 component or a combination of just EPAee and DHAee — and because FDA does not have a sufficient basis to conclude that the other components of the drug do not meaningfully contribute to Lovaza's pharmacological effect, there is no basis to change the characterization of the entire mixture as the active ingredient in Lovaza.

In sum, at the time of Lovaza's approval, the Agency identified the entire fish oil mixture as the active ingredient of Lovaza. At that time, the strength of Lovaza was labeled as 1 gram based on the fact that 1 gram of its active ingredient, a naturally derived, partially-purified fish oil mixture, is provided in each Lovaza capsule. As described above, we believe the Agency does not currently have a sufficient basis to revise that strength listing.

III. CONCLUSION

For the reasons discussed above, your Petition is denied.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research