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February 6, 2013

Via Hand Delivery

Division of Dockets Management
U.S. Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

The undersigned submits this Petition pursuant to the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 *et seq.* ("FDCA"), and in accordance with the procedural requirements specified in 21 C.F.R. § 10.30, to request that the Commissioner of Food and Drugs ("the Commissioner") amend the strength adopted by the Food and Drug Administration ("FDA" or the "Agency") for Lovaza (omega-3-acid ethyl esters) Capsules, including the strength listing in the *Orange Book.*

On or about May 2011, FDA adopted a strength for Lovaza, which it listed in the *Orange Book* as follows: "1GM CONTAINS AT LEAST 900MG OF THE ETHYL ESTERS OF OMEGA-3 FATTY ACIDS." Unique from other entries in the *Orange Book*, and contrary to the Agency's well-established definition of "strength," this listing describes not just the strength of Lovaza – that is, the amount of active ingredient per administration unit – but also the overall weight of an individual capsule, including excipients.

As explained in greater detail below, the Commissioner should correct this aberration and amend FDA's adopted strength for Lovaza so it describes only the amount of active ingredient per administration unit. This is necessary to (1) conform the adopted 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 New Drug Application ("NDA") holder and published in the *NDC Directory*.

A. ACTION REQUESTED

Petitioner requests that the Commissioner amend FDA's adopted strength for Lovaza (omega-3-acid ethyl esters) Capsules, including the strength listing in the *Orange Book*, 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. As set forth in this Petition, and consistent with Agency

definitions, guidance, and precedent, an appropriate strength listing for Lovaza would identify only the total amount of active ingredient (omega-3-acid ethyl esters), *e.g.*, 0.9GM, per administration unit.

B. STATEMENT OF GROUNDS

I. Strength Means the Amount of Active Ingredient Per Administration Unit

A. *Under FDA's Well Established Regulatory Framework, Strength Means the Amount of Active Ingredient Per Administration Unit*

Repeatedly and unambiguously, FDA instructs stakeholders that the "strength of a drug product tells how much of the active ingredient is present in each dosage" (emphasis added).

This definition appears prominently on the Agency's website under both the Glossary of Terms and Instructions at Drugs@FDA.[1] It also appears in the *NDC Directory* Product File Definitions.[2]

This same definition is embodied in Agency guidance promulgated as part of the International Conference on Harmonization ("ICH") process. The ICH Consensus Guideline, which expressly aims to harmonize regulatory terms across jurisdictions globally, defines strength as the "content of the active ingredient expressed quantitatively per dosage unit, per unit of volume or per unit of weight, according to the pharmaceutical dose form."[3] The Guideline

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1 Drugs@FDA, Glossary of Terms, *available at* http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm (last accessed February 6, 2013); Drugs@FDA, Instructions: Regulatory Information, *available at* http://www.fda.gov/Drugs/InformationOnDrugs/ucm079811.htm (last accessed February 6, 2013).

2 NDC Product File Definitions, NDC Directory – eLIST, Product File Data Elements, Definitions, and Notes, *available at* http://www.fda.gov/Drugs/InformationOnDrugs/ucm254527.htm (last accessed February 6, 2013).

3 *Data Elements and Standards for Drug Dictionaries (M5)*, Recommended for Adoption at Step 2 of the ICH Process by the ICH Steering Committee (10 May 2005), at Section 2.3.6.3 Strength Section, *available at* http://www.fda.gov/downloads/Drugs/GuidanceCompliance/RegulatoryInformation/Guidances/UCM073307.pdf (last accessed February 6, 2013).

The Agency's Current Good Manufacturing Practice regulations define strength as "(i) The concentration of the drug substance (for example, weight/weight, weight/volume, or unit dose/volume basis), and/or (ii) The potency, that is, the therapeutic activity of the drug product

goes on to explain that, in solid forms, "strength is … the amount of active ingredient per unit dose."

In short, the term "strength" identifies the amount of active ingredient contained in an administration unit. Formulation-related factors unrelated to the amount of active ingredient in a drug product dose and only relevant to product weight – factors such as excipients in an oral dosage form, buffers in an intravenous dosage form, or the film in a transdermal dosage form – are not part of the strength calculus; and in no other case known to this Petitioner have formulation-related factors unrelated to the amount of active ingredient been expressed in a product's adopted strength or its identification in the *Orange Book.*

B. *Longstanding Agency Precedent Applies a Definition of Strength Identifying the Amount of Active Ingredient Per Administration Unit*

Uniformity in how FDA adopts strengths and, by extension, lists them in the *Orange Book,* is essential. Applicants and other stakeholders who utilize the *Orange Book* – including pharmacists, other healthcare providers, and payors – rely on being able to readily ascertain from each strength listing a precise, unambiguous amount of active ingredient that is delivered in each administration unit of a drug product. Indeed, ever since the Hatch-Waxman Amendments were added to the FDCA, strength has been one of the very exact, "black and white" data elements included in every drug product listing in the *Orange Book.* Each strength listing known to this Petitioner and published in the *Orange Book* over the past 28 years has identified only the amount of active ingredient per administration unit. Accordingly, for thousands of similarly-situated drugs, including thousands of reference listed drugs, the listed strength is a fixed figure identifying the amount of active ingredient contained in each dose of the product. This is true regardless of product origin (chemical *vs.* biotechnology), derivation (synthetic *vs.* naturally-derived), or even sourcing of natural ingredients or their complexity.

Consideration of thousands of other strength listings in the current or prior editions of the *Orange Book* demonstrates unambiguously that such strength listings comport with the regulatory framework described in Part A above. To illustrate this point, Appendix A to this Petition lists a diverse array of complex products, including several whose complexity has triggered petition proceedings and/or litigation, and in each case the listed strength provides a straightforward identification of the amount of active ingredient per administration unit.

FDA applies the same regulatory framework when a drug product's strength is listed in the *Orange Book* as a proportional measure – *e.g.*, 0.4MG/SPRAY, 17GM/SCOOPFUL, 8,500

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as indicated by appropriate laboratory tests or by adequately developed and controlled clinical data (expressed, for example, in terms of units by reference to a standard)." 21 C.F.R. § 210.3(16).

IU/ML, EQ 90MG BASE, and EQ 500MG BASE/VIAL. (*See* Appendix B). Each of these examples describes product strength in accordance with the amount of active ingredient per administration unit.

FDA also applies this regulatory framework to naturally-sourced products, products of biotechnology origin, and complex mixtures. One notable example is the Agency's recent approval of a related drug product, Vascepa (icosapent ethyl), whose active ingredient is the same as the more prominent of the two major omega-3-acid ethyl esters in Lovaza. For Vascepa, as reflected in the *Orange Book*, FDA adopted a strength of 1GM, which is the amount of active ingredient in an administration unit as identified in the drug labeling.[4]

In these and all other cases, the strength adopted by FDA adheres to the established regulatory framework, that is, strength expresses the amount of active ingredient per administration unit. The Commissioner should amend the current strength for Lovaza, including how it is reported in the *Orange Book*, to conform to this well-established and widely relied upon precedent.

C. *Filings by the NDA Holder Recognize that Strength Is Defined By the Amount of Active Ingredient Per Administration Unit*

There is a notable inconsistency between FDA's current adopted 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, 21 U.S.C. § 360. According to the current *NDC Directory*, whose entries are pulled directly from such submissions, the NDA holder certified the strength of Lovaza to be 900 mg. (*See* Appendix C).

The strength for Lovaza certified by the NDA holder is consistent with the publicly-available NDA reviews posted online at Drugs@FDA. At the conclusion of its reviews of the Lovaza NDA, FDA approved labeling that expresses the total omega-3-acid ethyl esters content as 900 mg of the active ingredient concentrate, consisting of at least 900 mg of the ethyl esters of omega-3 fatty acids. For this reason too, FDA should amend its adopted strength for Lovaza, including its listing in the *Orange Book*, to similarly describe the amount of active ingredient per administration unit.

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[4] Prescribing Information for Vascepa (icosapent ethyl), Section 11, Description ("Each VASCEPA capsule contains 1 gram of icosapent ethyl. Icosapent ethyl is an ethyl ester of omega-3 fatty acid eicosapentaenoic acid (EPA).") (emphasis added), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202057S000lbl.pdf (last accessed February 6, 2013).

D. *Formulation Factors Are Unrelated to Product Strength*

Although formulation-related properties of a drug product can impact a product's safety and efficacy profile, and thus approvability and post-approval interchangeability as an A-rated product in the *Orange Book*, they are distinct from product strength. Such formulation-specific considerations may thus require a sponsor to perform additional preclinical safety studies in animals, conduct clinical trials to evaluate clinical safety and efficacy in patients, or conduct comparative bioavailability studies when developing a follow-on version of a previously-approved reference listed drug ("RLD"). These considerations, however, do not affect a product's strength, and they have no bearing on the comparative assessment of strength vis-à-vis an RLD if an RLD is evaluated in development and/or relied upon in the application process. Instead, the strength of both such products, like the strength of all other products, simply reflects the amount of active ingredient per administration unit.

Petitioner recognizes that when FDA made the current adoption of strength for Lovaza and listed it in the *Orange Book*, there might not have been sufficient data to determine whether formulation-specific factors impacted the safety and efficacy profile of new omega-3-acid ethyl esters product. However, 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.

II. An Appropriate Strength Listing for Lovaza Would Identify Only the Total Amount of Active Ingredient

As demonstrated by the regulatory overview presented in the preceding section, the strength FDA adopted for Lovaza around May 2011 and listed in the *Orange Book* – "1GM CONTAINS AT LEAST 900MG OF THE ETHYL ESTERS OF OMEGA-3 FATTY ACIDS" – is not consistent with FDA's well-established regulatory framework. Although the reference to 900MG – standing alone – would be consistent with that framework, the other properties FDA included in the description of the product strength are not.[5]

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[5] It also is worth noting that the strength currently adopted by FDA, as listed in the *Orange Book*, is not consistent with the identification of the product's strength set forth in the currently-approved labeling for Lovaza, which, in the "Strengths" section of the Prescribing Information, identifies the product strength as "1Gram". (*See* Appendix D). It is also noteworthy that, for a related NDA for Omacor (omega-3 acid ethyl esters), FDA identifies the strength of Omacor as "1G" in the Omacor listing on Drugs@FDA. (*See* Appendix E).

Instead, the current strength listing gives undue prominence and inappropriate importance to the 1GM product weight/fill weight of the Lovaza Capsule – a parameter which is driven by excipients and other factors presumably delineated in the Lovaza NDA that are not relevant to product strength. As a result, the current strength adopted by FDA does not plainly (and singularly) identify the amount of active ingredient per capsule.

For the reasons set forth above, the Commissioner should amend the strength adopted by FDA for Lovaza, including the strength listing in the *Orange Book*, to reflect the amount of active ingredient per administration unit. Specifically, the Commissioner should amend the strength adopted for Lovaza to "0.9GM" (or "900MG"). Identifying the strength of Lovaza in this manner would conform the Agency's treatment of this product to FDA's well-established regulatory framework as well all other strengths adopted by FDA.

Alternatively, the Commissioner could adopt a strength for Lovaza based upon the fixed amount of major omega-3-acid ethyl esters specified in the Lovaza reviews and labeling. According to its currently-approved labeling, "at least 900 mg of the ethyl esters of omega-3 fatty acids sourced from fish oils" "are predominantly a combination of ethyl esters of eicosapentaenoic acid (EPA - approximately 465 mg) and docosahexaenoic acid (DHA - approximately 375 mg)." Adopting a strength of 840 mg would be consistent with the emphasis (reflected in the publicly-accessible NDA reviews) on the 840 mg mixture of the major omega-3-acid ethyl esters in Lovaza.[6] Agency's reviews reflect that the 840 mg of the major omega-3 fatty acids is further supplemented by the minor omega-3-acid ethyl esters, such as alpha-linoleic acid, moroctic acid, eicosatetraenoic acid, heneicodapentaenoic acid, and clupanodonic acid.[7] The carton, however, only expresses the EPA and DHA content of Lovaza Capsules in fixed terms amounting to 840 mg:

> Each capsule provides:
> Eicosapentaenoic acid (EPA) ethyl ester: 465 mg
> Docosahexaenoic acid (DHA) ethyl ester: 375 mg

Based upon the Agency's prior emphasis on the 840 mg of the major omega-3-acid ethyl esters, the Commissioner could also choose "840MG" as FDA's adopted strength for Lovaza.

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[6] Lovaza Clinical Pharmacology and Biopharmaceutics Review at 6/64, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-654_Omacor_BioPharmr.pdf (last accessed February 6, 2013); Lovaza Pharmacology Review at 11/80, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-654_Omacor_Pharmr.pdf (last accessed February 6, 2013).

[7] Lovaza Pharmacology Review at 12/80-13/80, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-654_Omacor_Pharmr.pdf (last accessed February 6, 2013).

C. ENVIRONMENTAL IMPACT

An environmental assessment report on the action requested in this Petition is not required, as Petition claims a categorical exclusion under 21 C.F.R. § 25.31(a).

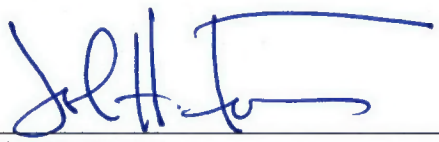
D. ECONOMIC IMPACT

A statement of the economic impact of the requested action will be provided if required by the Commissioner following review of this Petition, in accordance with 21 C.F.R. § 10.30

E. CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this Citizen's Petition includes all information and views on which the Petition relies, and that it includes representative data and information known to the Petitioner that are unfavorable to the Petition.

Respectfully submitted,



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