

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204977Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 204977	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Omtryg Established/Proper Name: omega-3-acid ethyl esters A Dosage Form: Capsule Strengths: 1.2 grams		
Applicant: Trygg Pharma, Inc.		
Date of Receipt: 1/31/2013		
PDUFA Goal Date: 11/30/2013	Action Goal Date (if different): 11/22/2013	
RPM: Kati Johnson		
Proposed Indication: Adjunct to diet to reduce triglyceride levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 21654 (Lovaza (omega-3-acid ethyl esters) Capsules	FDA's previous finding of safety and effectiveness (Clinical and nonclinical)

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The company conducted a 28-day bridging toxicity study. There were 4 bioequivalence studies performed linking Omtryg to Lovaza. There was one Phase 3 efficacy/safety study comparing placebo, Lovaza, and Omtryg.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If “NO,” proceed to question #5.

If “YES”, list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Lovaza (omega-3-acid ethyl esters) Capsules	21654	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a final OTC drug monograph?

YES NO

If “**YES**”, please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES NO

If “**YES**”, please list which drug(s) and answer question d) i. below.

If “**NO**”, proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

Omtryg is a less concentrated in omega-3 fatty acid ethyl esters as compared to Lovaza. Therefore the Omtryg capsule is bigger (1160 mg) vs a Lovaza capsule (1000 mg) of fish oil to compensate but still calculated to give about the same total omega-3 fatty acid ethyl ester amounts for both products. Because Omtryg is less concentrated in the omega-3 fatty acid ethyl esters, it contains more of other fatty acids, (b) (4)

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity,*

disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "NO" to (a) proceed to question #11.
If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A YES NO

*If this application relies only on non product-specific published literature, answer "N/A"
If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A YES NO

*If this application relies only on non product-specific published literature, answer "N/A"
If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS
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- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): 5502077
5656667
7732488

No patents listed *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES X NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): 5656667
7732488
5502077

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?
YES X NO

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.
YES X NO

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): 4/3/2013

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above? No

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KATI JOHNSON
04/28/2014

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title¹	OMTRYG (non-proprietary name pending) capsules, for oral use
Applicant	Trygg Pharma, Inc.
Application/Supplement Number	NDA 204977
Type of Application	Original Submission
Indication(s)	An adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia
Office/Division	ODE II/DMEP
Division Project Manager	Kati Johnson
Date FDA Received Application	January 31, 2013
Goal Date	November 30, 2013
Date PI Received by SEALD	November 7, 2013
SEALD Review Date	November 7, 2013
SEALD Labeling Reviewer	Jeanne M. Delasko
Acting SEALD Division Director	Sandra Kweder

¹ Product Title that appears in draft agreed-upon prescribing information (PI)

This Study Endpoints and Labeling Development (SEALD) Director sign-off review of the end-of-cycle, prescribing information (PI) for important format items reveals **outstanding format deficiencies** that should be corrected before taking an approval action. After these outstanding format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The Selected Requirements of Prescribing Information (SRPI) is a checklist of 42 important format PI items based on labeling regulations [21 CFR 201.56(d) and 201.57] and guidances. The word “must” denotes that the item is a regulatory requirement, while the word “should” denotes that the item is based on guidance. Each SRPI item is assigned with one of the following three responses:

- **NO:** The PI does not meet the requirement for this item (**deficiency**).
- **YES:** The PI meets the requirement for this item (**not a deficiency**).
- **N/A:** This item does not apply to the specific PI under review (**not applicable**).

Selected Requirements of Prescribing Information

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment:

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- NO** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment: *The horizontal line to the right of each heading does not extend over the entire width of the column.*

- NO** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: *There should be white space between the Highlights Limitation Statement and the Product Title in HL. Also, there is no white space before Drug Interactions heading in HL. Insert.*

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- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S.**

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Approval:” followed by the 4-digit year.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

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- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- NO** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment: *Must insert (name of manufacturer) instead of "contact TBD" and (manufacturer's U.S. phone number) instead of "1-xxx-xxx-xxxx."*

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- NO** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: In TOC, subsection heading "6.2 Postmarketing Experience" is the correct subsection heading to use. However, the FPI reads: "Skin: Pruritus and rash. 6.2 Postmarketing Experience." Correct FPI subsection 6.2 heading to match TOC subsection 6.2 heading .

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "[see *Warnings and Precautions (5.2)*]" or "[see *Warnings and Precautions (5.2)*]".

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Comment:

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- YES** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

NO

Selected Requirements of Prescribing Information

41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment: *The statement should read: See FDA-approved Patient Labeling (Patient Information), not: [REDACTED]^{(b) (4)}. The reference should include the "type" of FDA-approved patient labeling (i.e., Patient Information).*

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

- [text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEANNE M DELASKO
11/07/2013

ERIC R BRODSKY
11/07/2013

I agree. Eric Brodsky, labeling team leader, signing for Sandra Kweder, Acting SEALD Director.

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: November 03, 2013

To: Mary Parks, MD
Director
Division of Metabolism and Endocrinology Products (DMEP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Melissa Hulett, MSBA, BSN, RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Shawna Hutchins, MPH, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Ankur Kalola, Pharm.D.
Consumer Safety Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): OMTRYG (omega-3-acid ethyl esters)

Dosage Form and Route: Capsules, for Oral Use

Application Type/Number: NDA 204-977

Applicant: Trygg Pharma Inc.

1 INTRODUCTION

On January 31, 2013, Trygg Pharma Inc., submitted for the Agency's review a New Drug Application (NDA 204-977) for Omtryg (omega-3-acid ethyl esters) indicated as an adjunct to diet to reduce triglyceride levels in adults with severe hypertriglyceridemia.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) on February 26, 2013 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for Omtryg (omega-3-acid ethyl esters) Capsules for Oral Use.

2 MATERIAL REVIEWED

- Draft Omtryg (omega-3-acid ethyl esters) PPI received on January 31, 2013 and received by DMPP on October 29, 2013.
- Draft Omtryg (omega-3-acid ethyl esters) received on January 31, 2013 and received by OPDP on October 29, 2013.
- Draft Omtryg (omega-3-acid ethyl esters) Prescribing Information (PI) received on January 31, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on October 29, 2013.
- Draft Omtryg (omega-3-acid ethyl esters) Prescribing Information (PI) received on January 31, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on October 29, 2013.
- Approved Lovaza (omega-3-acid ethyl esters) comparator labeling dated June 26, 2013.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved Lovaza comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

6 Page(s) of Draft Labeling have been
Withheld in Full as b4 (CCI/TS) immediately
following this page

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: October 29, 2013

To: Kati Johnson, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Ankur Kalola, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Consult Request

NDA 204977 OMTRYG (omega-3-acid ethyl esters) Capsules, for oral use

On February 26, 2013, OPDP received a consult request from DMEP to review the proposed draft Prescribing Information (PI) and Patient Information (PPI) for Omtryg. OPDP's comments on the proposed draft PI for Omtryg are based on the version sent via email from Kati Johnson on October 29, 2013.

General Comments:

We note that the drug is referred to by the established name in some sections of the PI, and by the proprietary name in other sections. We have highlighted specific occurrences where the PI uses the established name in a manner that may not clearly communicate that the information stated is specific to Omtryg. For example, we are concerned that the statement, "Omega-3-acid ethyl esters are not indicated for the treatment of AF or flutter," from Warning and Precaution 5.3, may minimize this risk because it does not clearly communicate that this risk is associated with Omtryg. Therefore, we recommend using the proprietary instead of the established name in these highlighted occurrences. In addition, this will provide consistency with the Lovaza PI.

We also note that the established name for the drug is not yet finalized. Once finalized, please reflect the changes, if any, throughout the PI.

The remainder of OPDP's comments on the PI are provided directly on the marked version below.

Additionally, OPDP will work collaboratively with DMPP to provide comments on the PPI under separate cover.

Thank you for the opportunity to comment on these materials. If you have any questions, please contact Ankur Kalola at 301-796-4530 or Ankur.Kalola@fda.hhs.gov.

12 Page(s) of Draft Labeling have been
Withheld in Full as b4 (CCI/TS)
immediately following this page

CLINICAL INSPECTION SUMMARY

DATE: October 7, 2013

TO: Iffat Chowdhury, M.D., Clinical Reviewer
Eric Colman, M.D., Deputy Director
Kati Johnson, Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

FROM: Cynthia F. Kleppinger, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 204977

APPLICANT: Trygg Pharma

DRUG: AKR-963/OMTRYG

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: As an adjunct to diet to reduce triglyceride (TG) levels in adult patients

with severe (≥ 500 mg/dL) hypertriglyceridemia.

CONSULTATION REQUEST DATE: April 29, 2013

CLINICAL INSPECTION SUMMARY GOAL DATE: October 4, 2013

DIVISION ACTION GOAL DATE: November 22, 2013

PDUFA DATE: November 22, 2013

I. BACKGROUND

Trygg Pharma is seeking approval of AKR-963 (OMTRYG), a combination of ethyl esters of omega-3 fatty acids derived from fish oil, principally eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), as an adjunct to diet to reduce triglyceride levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia. The application is based on the results of a multicenter, randomized, double-blind, placebo-controlled Phase 3 trial TRGG-963-002 entitled, "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Phase III Study to Assess Efficacy and Safety of AKR-963 Therapy in Subjects with Severe Hypertriglyceridemia".

This 82-week Phase 3 study consisted of a 6-week diet-only lead-in period, a 12-week double-blind treatment period (Period A), a 40-week double-blind treatment period (Period B), and an up to 24-week double-blind safety extension period (Period C). Qualifying subjects were randomly assigned at Visit 4 (Week 0) to one of three double-blind treatment groups for Period A: AKR-963 (3600 mg/day), Lovaza[®] (3600 mg/day), or matching placebo. During Period B, subjects assigned to placebo were re-assigned equally to double-blind treatment with either Lovaza[®] or AKR-963.

This multicenter study included 68 U.S. sites. The first subject was screened October 5, 2010, and the last subject completed the study July 20, 2012.

These inspections were conducted as part of the routine PDUFA pre-approval clinical investigation data validation in support of NDA 204977 in accordance with Compliance Program 7348.811 and 7348.810. General instructions were also provided with this assignment.

II. RESULTS (by Site)

Name of CI/ Site #	Protocol # and # of Subjects Randomized	Inspection Date	Pending Classification
Wayne Harper, MD Site 105	TRGG-963-002 11 subjects	July 31- August 2, 2013	NAI
Craig Thompson, MD Site 113	TRGG-963-002 6 subjects	June 24-28, 2013	NAI

Dario Altamirano, DO Site 114	TRGG-963-002 6 subjects	June 25-28, 2013	NAI
Roger Miller, Jr., MD Site 139	TRGG-963-002 13 subjects	July 8-10, 2013	VAI
Michael Dao, MD Site 124	TRGG-963-002 12 subjects	July 8-12, 2013	OAI
(b) (4) CRO	TRGG-963-002	July 10-11, 2013	NAI

Key to Classifications

NAI = No deviation from regulations

VAI = Deviation(s) from regulations

OAI = Significant deviations from regulations; data unreliable.

Pending = Preliminary classification based on information in Form FDA 483, preliminary communication with the field, and review of EIR; final classification is pending.

1. Wayne Harper, MD

Wake Research Associates, LLC
3100 Duraleigh Road, Suite 304
Raleigh, NC 27612

- a. **What was inspected:** There were 29 subjects screened at the site, 11 subjects enrolled, and eight subjects completed the study. One subject (105-024) continued into Period C of the trial. The informed consent forms for all 29 screened subjects were reviewed and all 11 enrolled subjects' charts were reviewed. Inclusion/exclusion criteria, test article accountability, source documents, case report forms, dietary questionnaires, lab reports, ECGs, monitoring logs, curriculum vitas, financial disclosures, Form FDA 1572, Institutional Review Board correspondences, training documents, and administrative files were reviewed.
- b. **General observations/commentary:** Values recorded in the source documents matched the listings provided with the assignment. The study site was blinded to the laboratory results for the Lipid Panel. The site was only given this blinded information if the levels were cause for concern for subject safety; the reference laboratory was responsible for reporting the source data to the study sponsor. There were no significant protocol deviations or inadequate recordkeeping. No evidence of under-reporting of adverse events was observed. Minor issues such as not taking a third blood pressure for two subjects, time of last meal missing for one subject, and diabetes status missing for one subject were discussed verbally at close-out.

(

The inspectional findings indicate adequate adherence to good clinical practice regulations and the study protocol. No Form FDA-483, Inspectional Observations, was issued.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

2. Craig Thompson, MD
Frederick C Smith Clinic Inc.
1040 Delaware Avenue
Marion, OH 43302

- a. **What was inspected:** A total of 23 subjects were screened and six subjects were randomized. All informed consents for the 23 subjects were reviewed and all six randomized subjects' records were reviewed. All subjects were patients at the local clinic where the PI practices medicine. The current inspection included a review of IRB correspondences, monitor and sponsor correspondences, drug accountability, adverse events, protocol adherence, subject records, financial disclosure, safety reports, signature logs, monitor logs, FDA 1572s, curriculum vitas, laboratory credentials and other supply records, source documents, and case report forms. All electronic records requested were able to be generated by the study site upon request.
- b. **General observations/commentary:** The study site was blinded to the laboratory results for the Lipid Panel. The site was only given this blinded information if the levels were cause for concern for subject safety; the reference laboratory was responsible for reporting the source data to the study sponsor. No discrepancies between the case report forms and available data line listings were noted. All adverse events appeared to have been captured. There were a few instances where the subjects received the wrong week of their own bottle of medication but did not receive the wrong test article. All deviations were reported to the sponsor.

The inspectional findings indicate adequate adherence to good clinical practice regulations and the study protocol. No Form FDA-483, Inspectional Observations, was issued.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

3. Dario Altamirano, DO
900 West 49th Street, Suite 430
Hialeah, FL 33012

- a. **What was inspected:** There were 41 subjects screened, 6 subjects enrolled, and 4 subjects completed. All 41 informed consents were reviewed and all 6 enrolled subjects' records were reviewed. Inclusion/exclusion criteria, source documents, case report forms, dosing/procedure logs, IRB correspondences, adverse event reports, investigator agreements and certification, financial disclosure statement, and monitoring activities were reviewed.
- b. **General observations/commentary:** The study site was blinded to the laboratory results for the Lipid Panel. The site was only given this blinded information if the levels were cause for concern for subject safety; the reference laboratory was responsible for reporting the source data to the study sponsor. It was confirmed that blood was drawn from each subject for each test at the appropriate visit. Subject 114-009 was a duplicate subject from another Miami site; upon notification by the sponsor, Dr. Altamirano removed her from the study. There was no under-reporting of adverse events. There were no repeat violations from the previous inspection done October 2011, which was classified as VAI.

The inspectional findings indicate adequate adherence to good clinical practice regulations and the study protocol. No Form FDA-483, Inspectional Observations, was issued.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.
4. Roger Miller, Jr., MD
2950 Halcyon Lane, Suite 706
Jacksonville, FL 32223
 - a. **What was inspected:** There were 30 subjects screened, 13 subjects enrolled, and eight subjects who completed the study. One subject continued into the Period C safety extension. Of the 13 subjects, all were reviewed for informed consent, adverse events, and concomitant medications. Nine charts were reviewed in full and four had random checks of study activities and data points. The inspection included review of source documents, protocol adherence, FDA-1572, financial disclosure, adverse events, IRB correspondences, sponsor correspondences, drug accountability, training, and site reporting.
 - b. **General observations/commentary:** The subject source documentation was readily available and well organized. Electronic case report forms were used and the data was made available by disk for review during the course of the inspection. The study site was blinded to the laboratory results for the Lipid Panel. The site was only given this blinded information if the levels were cause

for concern for subject safety; the reference laboratory was responsible for reporting the source data to the study sponsor. Therefore, the primary efficacy endpoint and many of the secondary efficacy endpoints could not be verified. Data that could be compared were found to be as reported and no discrepancies were noted. There was no under-reporting of adverse events.

The inspection resulted in the issuance of a Form FDA-483 citing one observation. Two subjects were randomized and received study medication although they did not meet the study eligibility criteria of the protocol by taking prohibited medications (androgens). Subject 139-003 took Testosterone Cypionate every two weeks since 7/2/10. This subject was randomized on 1/4/11. Subject 139-019 took Androgel from 7/3/07 and Vytorin, a combination daily lipid altering medication, since 6/28/05. This subject was randomized on 4/5/11. Both subjects were long time patients of Dr. Miller. The deviation was discovered up to three months later for one of the subjects and the site received approval by the sponsor and IRB for both of the subjects to continue in the study. Ultimately, one of the two subjects was discontinued from the study (Subject 139-019 was discontinued by the sponsor in May 2011 due to the continued use of the Vytorin). The site has already taken acceptable corrective action to prevent the observation from occurring during the conduct of any other study.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. Although the inspection resulted in one observation, the audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

5. Michael Dao, MD
Arlington Premier Health Clinic (APHC), P.A.
501 Rita Lane, #109
Arlington, TX 76014

- a. **What was inspected:** At the site, 38 subjects were screened, 12 subjects were enrolled, and nine subjects completed the study. Most of the subjects (i.e. eight of the 12 enrolled in the study) were patients who were already under the collaborative care of Dr. Michael Dao or (b) (4) (the sub-investigator). All informed consents for the 38 screened subjects were reviewed and the charts of all 12 randomized subjects were reviewed. No subjects at the site participated in the study safety extension period (Period C). The inspection covered financial disclosure, the study's inclusion/exclusion (I/E) criteria, safety and data monitoring, investigational drug accountability, Institutional Review Board (IRB) correspondences, sponsor correspondences, informed consent forms (ICFs), CI's compliance with the protocol, human subject files, concomitant medications (con meds), adverse event reports (AERs)/serious AER (SAERs), and the site's adherence with applicable regulations for the investigational product (IP) as well as the investigational plan. The inspection

focused on verifying the accuracy of the safety and efficacy endpoints of the study by auditing the original source documents (SDs) and comparing them with the electronic case report forms (eCRFs) plus data line listings (DLs).

- b. **General observations/commentary:** Inspection of this site was done to confirm the persistent and systemic issues with GCP non-compliance raised during routine monitoring and follow-up audits by the sponsor and to evaluate for sufficient oversight by the CRO and sponsor. The site was both a private practice (Arlington Premier Health Clinic (APHC) and a (b) (4) [REDACTED]. The site utilizes both paper charts as well as electronic medical records to document subjects' study data. Both systems exist as the PI likes paper records and his brother likes electronic records.

During the inspection, it was discovered that on or around April/May 2012, the Chief Medical Officer (CMO) of Trygg Pharma initially requested Dr. Michael Dao to obtain affidavits from his patients to clear the confusion from discrepancies between the site's medical records versus the site's study subject files and from the study coordinator's mistakes. In response to the request, Dr. Michael Dao decided against the affidavits. The sponsor then requested the site to obtain patient declarations, which were not required to be notarized, in lieu of the affidavits. In the end, Dr. Dao declined the request for patient declarations and felt the statements were not necessary as most of his subjects were his own patients under his care at his private practice.

During the inspection, significant deficiencies were observed such as enrolling subjects who did not meet the inclusion/exclusion criteria, repeated protocol violations on safety assessments, insufficient training of study staff (e.g. no documented attendance of the sub-investigator at the web-based investigators' meeting), inadequate supervision by the clinical investigator (CI) of study personnel (e.g. staff erasing source data), administration of the wrong test article to subjects, and using advertisements prior to IRB approval. This inspection resulted in the issuance of a four-item Form FDA 483, Inspectional Observations (FDA 483), to the CI:

- 1) An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.
 - The protocol states "Inclusion and exclusion criteria... will be assessed during the diet lead-in screening visits (Visits 1-4) using medical history information, physical examination and electrocardiogram findings, measurements of fasting lipid profiles, safety labs, HbA1c, pregnancy tests, and MEDFACTS dietary assessment questionnaires." Several of the enrolled subjects did not meet the eligibility criteria and two had multiple exclusions (Subject 020/(b) (6) was not qualified for entering the study due to two exclusion criteria and Subject 022/(b) (6) was not qualified for joining the study due to three exclusion criteria). For example, Subject 020/(b) (6) was prescribed Niaspan on Visit 4 although protocol exclusion criterion #2 prohibited such medication. *Written response to the 483 by the CI acknowledged that the subject did not meet criteria for entrance into the*

study. Subject 022/ (b) (6) was on statin therapy that was not discontinued for four weeks prior to Visit 2, as per the protocol. *Written response to the 483 by the CI acknowledged that the subject did not meet criteria for entrance into the study.* Subject 003/ (b) (6) was not on a stable dose of antihypertensive medication ≥ 2 months prior to Visit 1 as per protocol exclusion criterion #13. *Written response to the 483 by the CI acknowledged that the subject did not meet criteria for entrance into the study.* Subject 020/ (b) (6) and Subject 034 (b) (6) were not on a stable dose of a hypoglycemic agent ≥ 2 months prior to Visit 1 per protocol exclusion criterion #18. *Written response to the 483 by the CI acknowledged that the subjects did not meet criteria for entrance into the study.*

- Per the protocol, if a subject had a triglyceride (TG) level >1500 mg/dL at any point during the treatment period, the Investigator was to repeat the test within 10 days. Subject 023/ (b) (6) exhibited an elevated TG level of 1595 mg/dL at Visit 12 dated 12/5/2011 but was not scheduled for the repeat test until 1/5/2012. . *Written response to the 483 by the CI acknowledged this protocol deviation.*
 - Per the protocol, an increase in alkaline phosphatase to $> 2x$ the upper limits of normal plus an increase in one or more of the following: ALT, AST, or bilirubin, was to be investigated by contacting the subject immediately for repeat lab tests using the central laboratory, interviewing the subject regarding other factors relating to risk of hepatotoxicity and examining the subject for physical signs/symptoms of hepatotoxicity. Subject 003/ (b) (6) had abnormal lab results on Visit 11 (9/8/2011) but the PI did not follow-up with the subject concerning the liver function test abnormalities until 10/10/2011. *Written response to the 483 by the CI acknowledged this protocol deviation.*
- 2) Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.
- Of the 12 randomized subjects' source documents reviewed, six subjects took prohibited/exclusionary medications. Medications in the electronic medical record did not match the study trial medications. More so, several medications on the concomitant medication log were inconsistent with the electronic records in terms of start and stop dates. *Written response to the 483 by the CI acknowledged this protocol deviation.*
 - Former staff erased source data. Patients were given a MEDFICTS form at Visits 1, 4, 8, and 13 to complete to see if they qualified for the study at Visit 4. Protocol exclusion criterion # 23 states "Total MEDFICTS final score ≥ 70 at Week 0 (Visit 4)". The subject was required to sign and date the questionnaire, acknowledging completion of the questionnaire on their own accord. However, Subject 034/ (b) (6)'s MEDFICTS form at Visit 4 had a note written by a former study staff person that stated "Subject completed with coersion [sic]." The final score for Subject 034/ (b) (6)'s Visit 4 MEDFICTS questionnaire would have summed up to 81 before the MEDFICTS score modifications (i.e. single line cross-outs), which would

have met the exclusion criterion, but the adjusted total score of 68 fell short of the 70 exclusionary score threshold. Subject 026/ (b) (6) inappropriately scored his own MEDFICTS questionnaire at Visit 13. The MEDFICTS questionnaire at Visit 13 for Subject 029/ (b) (6) was not attributable due to the lack of the signatures/initials from the study subject/staff who filled out the form. *Written response to the 483 by the CI acknowledged this protocol deviation.*

- The research coordinator determined causality and relationship of an adverse event to the study article, and would sign off on the reports. *Written response to the 483 by the CI acknowledged this protocol deviation.*
 - Subject records for the study did not match the subject's medical records for normal visits to the private practice in terms of patient height, weight, blood pressure, respiration rates, and other vitals. *Written response to the 483 by the CI acknowledged this protocol deviation.*
- 3) Investigational drug disposition records are not adequate with respect to quantity and use by subjects.
- The IP Kit 179 bottles one, two and three were not returned by the site nor accounted for, and drug accountability for Subject 034/ (b) (6)'s Visits 11 and 12 was not known. Wrong bottles of IP were dispensed for two subjects (Subject 026 (b) (6) and Subject 034/ (b) (6)). *Written response to the 483 by the CI acknowledged this protocol deviation.*
- 4) Not all changes in research activity were approved by an IRB prior to implementation.
- The IRB responsible for governing the protection of rights, safety, health, and welfare of human subjects for the study at the site was (b) (4). The unanticipated problem (UP) submission form to the IRB dated 11/9/2011 stated "Sites are instructed to submit advertising prior to using it" and "Site have been reminded to submit advertising for IRB approval prior to use". The study advertisements revealed Internet postings on San Antonio and Dallas craigslist web pages for recruitment of interested participants. These were never submitted to the IRB for approval. *Written response to the 483 by the CI acknowledged this protocol deviation.*

Source data was inputted with a thicker ballpoint pen that appeared to be pre-filled in sections with a thinner ballpoint pen. The previous staff person who generated these records had been fired earlier. Verbal items were also discussed with the CI regarding invariability of blood pressure (BP) measurements as well as physical examination (PE) results. The FDA inspector observed a plethora of illogical BP measurements for a number of subjects where the five minute resting (first) measurement, two minute sit (second) measurement, and/or additional readings were 100% congruent at each study visit. All 12 subjects at the site treated with study drug had normal PEs for all body systems and there were several examples of contradicting information based on differing sources (e.g. electronic medical records, paper charts) for the results of the PEs.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site are not acceptable. The audit indicated serious deviations/findings that would impact the validity or reliability of the submitted data. Prior to database lock, the sponsor determined that all data collected from the 12 subjects randomized at the site would be excluded from the efficacy and safety analyses. The lack of quality of the data has been confirmed.

6.

(b) (4)

- a. **What was inspected:** As noted above, the study sites were blinded to the laboratory results for the Lipid Panel and other efficacy data. The sites were only given this blinded information if the levels were cause for concern for subject safety. This was a limited inspection of a contract research organization. The efficacy data for the five assigned study sites and one additional randomly selected site for all subjects who completed the full 13 visits were reviewed. This included triglyceride, non-high-density lipoprotein cholesterol (non-HDL-C), very low-density lipoprotein cholesterol (VLDL-C), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol, HbA1c, high sensitivity C-reactive protein (hsCRP), Apolipoprotein A-I, Apolipoprotein B and Fasting Insulin levels for 30 subjects across 5 study sites: 101, 105, 113, 114, and 139. Site 101 was the randomly chosen site. All primary and secondary efficacy endpoints were verified. The homeostatic model assessment for insulin resistance (HOMA-IR) values present in the sponsor-provided data line listings were not reviewed because it is a calculated value and (b) (4) did not have those values tabulated.
- b. **General observations/commentary:** There were no discrepancies between the source data from the laboratory and the sponsor-submitted data. The safety laboratory results reported by the sponsor were also verifiable in the data observed. The sponsor, Trygg, received monthly updates on metrics (but not unblinded study data) such as randomization, recruitment rates, query rates, SAEs, SAE rates, subject dropout rates, and other metrics but was blinded to the data until the study was over and the database was locked.

The inspectional findings indicate adequate adherence to good clinical practice regulations. No Form FDA-483, Inspectional Observations, was issued.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this CRO central laboratory appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this NDA consisted of five domestic sites as well as the central laboratory contract research organization (CRO). There were no regulatory violations noted at the sites of Drs. Harper, Thompson, and Altamirano and they have been classified as No Action Indicated (NAI). Dr. Miller's site was issued a Form FDA 483 citing inspectional observations, and the classification for this inspection is Voluntary Action Indicated (VAI). Although regulatory violations were noted as described above for this site, they do not significantly impact primary safety and efficacy data. Dr. Dao's site was issued a Form FDA 483 citing numerous inspectional observations, and the preliminary classification for this inspection is Official Action Indicated (OAI). The data from this site are not considered reliable and should be excluded, as has been done by the sponsor. In general, based on the inspection of the four remaining clinical study sites and the CRO, the inspectional findings support validity of data as reported by the sponsor under this NDA.

Observations noted above for all sites and the CRO are based on the review of the Establishment Inspection Reports and discussions with the ORA field inspectors. An inspection summary addendum will be generated if conclusions change upon final review of the EIR.

{See appended electronic signature page}

Cynthia F. Kleppinger, M.D.
Good Clinical Practice Assessment Branch
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/s/

CYNTHIA F KLEPPINGER
10/07/2013

JANICE K POHLMAN
10/08/2013

KASSA AYALEW
10/08/2013

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 204977

Application Type: New NDA

Name of Drug: TBD (AKR-963, omega-3-acid ethyl esters) Capsules, 900 mg

Applicant: Trygg Pharma

Submission Date: 3/8/2013

Receipt Date: 3/11/2013

1.0 Regulatory History and Applicant's Main Proposals

This product has been developed as a 505b2 application referencing LOVAZA (NDA 21654), as an adjunct to diet to reduce triglyceride (TG) levels in adults with severe (≥ 500 mg/dL) hypertriglyceridemia. The product consists of EPA (approx 465 mg) and DHA (approx 375 mg) for a dosage strength of 900 mg and a fill weight of 1.16 grams. For LOVAZA, the dosage strength is 1 gram based on the fill weight. AKR-963, although it contains the same amount of EPA and DHA, the drug substance of the new product does not meet the omega-3-acid-ethyl esters content requirements specified in the USP monograph. Therefore, it can not be submitted/reviewed as an ANDA. There is ongoing internal discussion as to whether it can be called "omega-3-acid ethyl esters" since it does not comply with the USP monograph.

The firm's drug development strategy has been to obtain an AB rating to LOVAZA. The firm has been told that determination of an AB rating is made after approval, and does not involve the review division.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix. These minor deficiencies will be conveyed to the sponsor during labeling negotiations once the application is otherwise approvable.

5.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment: *HL and TOC are in font 9.*

- NO** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

NOTE: Once the firm’s header is deleted and the font is revised to 8, the proposed PI will likely comply with the ½ page rule.

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- NO** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is

Selected Requirements of Prescribing Information (SRPI)

the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

YES

6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

YES

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment:

Product Title

YES

10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

YES

Selected Requirements of Prescribing Information (SRPI)

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning

N/A

12. All text must be **bolded**.

Comment:

N/A

13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

N/A

14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment:

N/A

15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

N/A

16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A

17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A

18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A

19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

N/A

20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES

Selected Requirements of Prescribing Information (SRPI)

21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment:

Dosage Forms and Strengths

- YES** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Selected Requirements of Prescribing Information (SRPI)

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: **“FULL PRESCRIBING INFORMATION: CONTENTS”**.

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

- YES** 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

- YES** 34. When a section or subsection is omitted, the numbering does not change.

Comment:

- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading **“FULL PRESCRIBING INFORMATION: CONTENTS”** must be followed by an asterisk and the following statement must appear at the end of TOC: **“*Sections or subsections omitted from the Full Prescribing Information are not listed.”**

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: **“FULL PRESCRIBING INFORMATION”**.

Comment:

- YES** 37. All section and subsection headings and numbers must be **bolded**.

Comment:

- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS

Selected Requirements of Prescribing Information (SRPI)

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

NO

39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment: *Contains 17.1 (Information for Patients) and 17.2 (FDA-Approved Patient Labeling) This will be revised to delete these sections.*

YES

40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

N/A

41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

N/A

42. All text is **bolded**.

Comment:

N/A

43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Selected Requirements of Prescribing Information (SRPI)

Comment:

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

- NO** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment: *The first sentence does not comply, however, the rest of the text does. The firm will be asked to revise the first sentence.*

Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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/s/

KATI JOHNSON
04/25/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 204977 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: TBD Established/Proper Name: omega-3-acid ethyl ester, AKR-963 Dosage Form: Capsules Strengths: 900 mg		
Applicant: Trygg Pharma, Inc. Agent for Applicant (if applicable): Beckloff Associates, Inc.		
Date of Application: 1/31/2013 Date of Receipt: 1/31/2013 Date clock started after UN:		
PDUFA Goal Date: 11/30/2013		Action Goal Date (if different): 11/22/2013
Filing Date: 4/1/2013		Date of Filing Meeting: 3/21/2013
Chemical Classification: (1,2,3 etc.) (original NDAs only) 5		
Proposed indication: adjunct to diet to reduce triglyceride levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: September 17, 2013

Reviewer: Reasol S. Agustin, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Yelena Maslov, Pharm D
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Omtryg (omega-3-acid ethyl esters) Capsules,
0.9 gram

Application Type/Number: NDA 204977

Applicant/sponsor: Trygg Pharma, Inc.

OSE RCM #: 2013-604

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed container label and insert labeling for Omtryg (omega-3-acid ethyl esters) NDA 204977 for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND

The Applicant, Trygg Pharma, Inc. submitted a request for review of the proposed label and labeling for Omtryg (omega-3-acid ethyl esters), on March 11, 2013 as part of NDA 204977.

1.2 PRODUCT INFORMATION

The following product information is provided in the March 11, 2013 proprietary name submission.

- Active Ingredient: Omega-3-acid ethyl esters
- Indication: Adjunct to diet to reduce (b)(4) triglyceride levels (≥ 500 mg/dL) in adult patients with severe hypertriglyceridemia.
- Route: Oral
- Dosage Form: Soft gel capsules
- Strengths: 0.9 gram (1 capsule contains a minimum of 900 mg of omega-3 acid ethyl esters)
- Dose and Frequency: 4 capsules daily; may be taken as 4 capsules once daily or as 2 capsules twice daily
- How Supplied: Bottles of 120
- Storage: Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Do not freeze. Keep out of reach of children.
- Container and Closure: White opaque high density polyethylene (HDPE) 400 mL bottle with a (b)(4) white opaque (b)(4) screw cap.

2 METHODS AND MATERIALS REVIEWED

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted March 11, 2013 (Appendix A)

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Insert Labeling submitted March 11, 2013

3 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed container label and insert labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product, to mitigate any confusion, and to clarify information.

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. Comments to the Division

a. Highlights of Prescribing Information and Full Prescribing Information:

- i. Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice's List of Error-Prone Abbreviations, Symbols, and Dose Designations appear throughout the package insert.² As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products. Thus, please revise the those abbreviations, symbols, and dose designations as follows:

1. Revise the “<, >, and ≥” symbols appearing throughout the insert labeling to read “less than, greater than, and greater than or equal to”.

- ii. Revise the strength presentation from “0.9 gram” to “900 mg” because the leading zero may be omitted during prescription writing and decimal points are easily overlooked, thus the strength or dose of Omtryg may be misinterpreted as 9 gram.

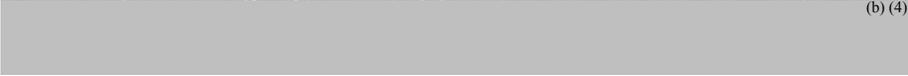
b. Highlights of Prescribing Information:

- i. *Indications and Usage*, define the abbreviations, EPA and DHA, prior to using the abbreviations alone (i.e. Icosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA)).
- ii. *Dosage and Administration*, delete the statements (b)(4) and (b)(4) in the first bullet point and revise the sentence to read “The daily dose of OMTRYG is 4 capsules per day taken as a single dose or as 2 capsules given twice daily.”

c. Full Prescribing Information,

- i. *Dosage and Administration, Section 2*: In the third paragraph, revise the statement to read “The daily dose on OMTRYG is 4 capsules per day taken as a single dose or as 2 capsules given twice daily.”

² <http://www.ismp.org/Tools/errorproneabbreviations.pdf>, Last accessed 10/28/2009.

- ii. *Dosage and Administration, Section 2:* Delete the phrase “Patients should be advised to” from the statement “Patients should be advised to swallow OMTRYG capsules whole. Do not break, open, crush, dissolve or chew OMTRYG” to read “Swallow OMTRYG capsules whole. Do not break, open, crush, dissolve or chew OMTRYG”
- iii. *Patient Counseling Information, Section 17:* Revise the third bullet (b) (4)

 to read “Patients should be advised to swallow OMTRYG capsules whole. Do not break, open, crush, dissolve or chew OMTRYG.”

B. Comments to the Applicant

a. Container Label

- i. Revise the strength presentation, 0.9 gram to “900 mg.” Leading zeros may be omitted during prescription writing and decimal points are easily overlooked, thus the strength or dose of Omtryg may be misinterpreted as 9 gram.
- ii. Reduce the size of the manufacturer logo and statement as it appears more prominent than established names and product strength. The proprietary and established names and strength should be the most prominent information on the labels.
- iii. Relocate the net quantity statement (i.e., 120 Capsules) away from the strength statement (i.e., 0.9 gram). As currently presented, this statement appears too close to the strength statement and may be misinterpreted as the strength of the product. The net quantity statement can be relocated to the lower right hand side of the principal display panel.
- iv. Add the statement “Swallow capsules whole. Do not break open, crush, dissolve or chew.” to the primary display panel. This statement will be advantageous to have on the principal display panel because the packaging allows for dispensing directly to the patient. This warning may minimize the opening of the capsules and will support the proper administration of these capsules, as stated in the insert labeling.

If you have further questions or need clarifications, please contact Margarita Tossa, project manager, at 301-796-4053.

APPENDICES

Appendix A. Container Labels



This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

REASOL AGUSTIN
09/17/2013

YELENA L MASLOV
09/18/2013

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): 107259				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>		X		NDA amended on 3/8/2013 with proposed name, OMTYGG. DARRTS will be kept as is until the evaluation of this name is complete.
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>				
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm		X		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid** <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required ** firm has submitted a request for a small business waiver, and if granted, will request a refund.</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>		<p>X</p>																		
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1499 1349 1640"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration														<p>X</p>		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>		<p>X</p>																		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: 3 years <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		X		
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:	X			

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			In a 3/27/2013 amendment, sponsor submitted a pediatric study plan (PSP)
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>				
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	X			
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
<u>Proprietary Name</u>	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>		X		Submitted in 3/8/2013 amendment
<u>REMS</u>	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>		X		
<u>Prescription Labeling</u>	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide)			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?				Waiting for TN
OTC Labeling	X Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	X			OCC-2/11/2013 Micro-2/7/2013
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):			X	Meeting not requested
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 12/10/2012	X			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):		X		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 21, 2013

BLA/NDA/Supp #: NDA 204977

PROPRIETARY NAME: TBD

ESTABLISHED/PROPER NAME: AKR-963

DOSAGE FORM/STRENGTH: Capsules, 900 mg

APPLICANT: Trygg Pharma Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): adjunct to diet to reduce triglyceride levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia.

BACKGROUND: The sponsor requested an End-of-Phase 2 meeting on November 20, 2009. They indicated in their request their plans to submit a 505(b)(2) application with LOVAZA (NDA 21654) as the reference product. LOVAZA is a mixture of omega-3-acid ethyl esters EPA and DHA, and other omega components sourced from fish oil. We responded that we would provide written responses following receipt of a background package. Due to internal discussion regarding the appropriateness/requirements for a 505(b)(2) application, we only provided written responses to the CMC questions contained in the background package.

The IND was submitted June 29, 2010. The firm has conducted a single clinical trial (TRGG-963-002) to evaluate the efficacy of AKR-963 as adjunctive therapy to diet for the treatment of severe hypertriglyceridemia. The study had the following treatment arms:

- LOVAZA 3600 mg (4 capsules) once daily
- AKR-963 3600 mg (4 capsules) once daily
- Placebo

The sponsor has also conducted 4 comparative BA and BE studies, comparing AKR-963 to LOVAZA.

A Pre-NDA (CMC) meeting was held on September 13, 2012.

A Pre-NDA (Clinical) meeting was held on December 10, 2012.

The firm's development plan from the beginning has been to obtain an AB rating to LOVAZA. In a December 16, 2009 letter from ENGEL & NOVITT, LLP (on behalf of TRYGG Pharma), and again on June 16, 2011, it was requested that the strength of LOVAZA in the Orange Book be revised. LOVAZA is currently described a "1 Gram contains at least 900 mg of the ethyl esters of omega-3 fatty acids". In a letter dated December 10, 2012, the firm was notified that they should submit this request pursuant to the procedures described in our regulations at 21 CFR 10.20. A Citizen's Petition was submitted February 6, 2013 and is currently pending.

While both products contain ≥ 900 mg of omega-3-acid ethyl esters per capsule, AKR-963 can not be reviewed as an ANDA because the drug substance of AKR-963 does not meet the omega-3-acid-ethyl esters content requirements specified in the USP monograph.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Kati Johnson	Y
	CPMS/TL:	N/A	N/A
Cross-Discipline Team Leader (CDTL)	Eric Colman		Y
Clinical	Reviewer:	Iffat Chowdhury	Y
	TL:	Eric Colman	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	N/A
	TL:	N/A	N/A

Clinical Pharmacology	Reviewer:	Manoj Khurana	Y
	TL:	Immo Zadezensky	Y
Biostatistics	Reviewer:	Lee-Ping Pian	Y
	TL:	Todd Sahlroot	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Intra Antonipillai	Y
	TL:	Karen Davis Bruno	Y
Statistics (carcinogenicity)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Product Quality (CMC)	Reviewer:	Martin Haber	Y
	TL:	Suong Tran	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Bryan Riley	N
	TL:	John Metcalfe	N
CMC Labeling Review	Reviewer:	Marin Haber	Y
	TL:	Suong Tran	Y
Facility Review/Inspection	Reviewer:	Steve Hertz	Y
	TL:	N/A	N/A
OSE/DMEPA (proprietary name)	Reviewer:	Reasol Agustin	Y
	TL:	Lubna Merchant	Y
OSE/DRISK (REMS)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	N/A
	TL:	N/A	N/A

Bioresearch Monitoring (OSI)	Reviewer:	Cynthia Kleppinger	Y
	TL:	Janice Pohlman	N
Controlled Substance Staff (CSS)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments: Biopharmaceutics has some comments to convey.</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments: Recommended approval in a review dated 3/14/2013.</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<p><input checked="" type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Eric Colman, MD	

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V):	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
X	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. X Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> X Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
X	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
X	Send review issues/no review issues by day 74
X	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and

	the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KATI JOHNSON
04/08/2013