

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204977Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 204977

SUPPL #

HFD #

Trade Name Omtryg

Generic Name Omega-3-Acid Ethyl Esters Type A

Applicant Name Trygg Pharma Inc.

Approval Date, If Known: April 23, 2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES X

NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES

NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES X NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

d) Has pediatric exclusivity been granted for this Active Moiety?

YES NO X

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO X

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference

to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2

YES

NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND #

YES

!

! NO

! Explain:

Investigation #2

IND #

YES

!

! NO

! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Kati Johnson
Title: Senior Regulatory Project Manager
Date: 6/20/2016

Name of Office/Division Director signing form: James P. Smith, MD, MS
Title: Deputy Director, Division of Metabolism and Endocrinology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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
06/21/2016

JAMES P SMITH
06/22/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 204977 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Omtryg Established/Proper Name: omega-3 acid ethyl esters A Dosage Form: Capsules		Applicant: Trygg Pharma Agent for Applicant (if applicable): Beckloff Associates (Beth Minter)
RPM: Kati Johnson		Division: Division of Metabolism and Endocrinology Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p>X No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: 4/16/2014</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is _____ 		X AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		X None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: Standard Priority
 Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action and date AP 4/23/2014
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> Most-recent draft labeling 	<input type="checkbox"/> Included
❖ Proprietary Name	
<ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) Review(s) (<i>indicate date(s)</i>) 	Acceptable 6/5/2013 6/3/2013
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: None 4/25/2013 DMEPA: <input type="checkbox"/> None 9/18/2013 DMPP/PLT (DRISK): <input type="checkbox"/> None 11/4/2013 OPDP: <input type="checkbox"/> None 10/29/2013 SEALD: <input type="checkbox"/> None 11/7/2013 CSS: X None Other: X None
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	4/8/2013
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2) 10/22/2013, 4/16/2014
❖ NDAs only: Exclusivity Summary ***to be done at a future date per lawyers	<input type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes X No

⁴ Filing reviews for scientific disciplines should be filed with the respective discipline.

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>5/21/2014 (when the application was first submitted, it was thought that it did NOT trigger PREA. Later, it was determine that it contained a different active ingredient. But we could not get to Perc prior to taking an action, so we will discuss after approval).</u> If PeRC review not necessary, explain: _____ 	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	X
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	X
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	X N/A or no mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 1/17/2013, 11/15/2012 (CMC)
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	X No mtg
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	X N/A
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	X N/A
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	N/A
❖ Advisory Committee Meeting(s)	X No AC meeting
<ul style="list-style-type: none"> • Date(s) of Meeting(s) 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	X None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4/23/2014
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	X None
PMR/PMC Development Templates (<i>indicate total number</i>)	X None
Clinical	
❖ Clinical Reviews	
<ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	X No separate review
<ul style="list-style-type: none"> • Clinical review(s) (<i>indicate date for each review</i>) 	11/26/2013, 3/28/2013
<ul style="list-style-type: none"> • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Page 21 of 11/26/2013 clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	X None

❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	X N/A
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	N/A <input type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested 10/28/2013
Clinical Microbiology X None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	X No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	X No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 10/15/2013, 4/5/2013
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	X No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	X No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 11/14/2013, 3/22/2013
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	None requested 10/8/2013
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	X No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	X No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8/5/2013, 3/13/2013
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	X None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	X No carc
❖ ECAC/CAC report/memo of meeting	X None
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	X None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	X No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	X No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 11/26/2013, 10/17/2013, 3/4/2013, 10/16/2013, 3/15/2013
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	Not needed 3/14/2013
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	X None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	Page 68 of 10/17/2013 CMC review
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i>	Date completed: 11/26/2013 X Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) <i>(original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	X Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁵ i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input checked="" type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done N/A
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input type="checkbox"/> Done To be done post-approval
❖ Send approval email within one business day to CDER-APPROVALS	<input type="checkbox"/> Done

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
04/30/2014

Johnson, Kati

Jm: Yao, Lynne P
Sent: Wednesday, April 23, 2014 12:41 PM
To: Smith, James P. (FDA/CDER); Colman, Eric C; Johnson, Kati
Cc: Greeley, George; Addy, Rosemary; Inglese, Jane
Subject: RE: PERC plans for an overdue 505B2 application planned for AP action on 4/23/2014

Hi Jim,

I just reviewed the case with my project management staff. I, as PeRC Chair, am granting the division's recommendation for full waiver of studies for this product based on the previous precedent established with [REDACTED] (b) (4). Please note, that we'll still need to review this formally at PeRC at a later date, and there is a very small possibility that we might need to amend the pediatric plan if the PeRC does not agree. However, given the detailed information you have provided, I feel confident that you can proceed with granting the waiver so that you may take an action today.

Regards,
Lynne

Minter, Beth

From: Johnson, Kati [Kati.Johnson@fda.hhs.gov]
Sent: Wednesday, August 07, 2013 1:32 PM
To: Minter, Beth
Cc: Chowdhury, Iffat; Johnson, Kati
Subject: NDA 204977, AKR-963, request for info re: drug administration

Beth,
Please respond to the following request for information;

1. Please clarify the timing of daily treatment administration with respect to meals in your Phase 3 trial. Did subjects take the treatments at a consistent time relative to the time of breakfast (e.g. consistently with breakfast, prior to breakfast, or after breakfast)? If treatments were to be taken either before or after breakfast, how much time was there between the meal and treatment administration?
2. Specify the composition of diet recommended for the patients during the trial (for breakfast, lunch, and dinner)?

I have cc'd the clinical reviewer on this e-mail.
If you have a question re: this request, please respond "to all".
We can chat next week, if necessary.
Please provide a timeline for responding when you can.
Thanks,
Kati

Kati Johnson
Senior Regulatory Project Manager
Food and Drug Administration
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
301-796-1234



NDA 204977

GENERAL ADVICE

Beckloff Associates, Inc.
US Agent for Trygg Pharma, Inc.
Attention: Beth Minter
Director, Managing Consultant, Scientific Consulting
Commerce Plaza II, Suite 300
7400 West 110th Street
Overland Park, KS 66210

Dear Ms. Minter:

Please refer to your New Drug Application (NDA) submitted January 31, 2013 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AKR-963 Capsules.

We also refer to your May 3, 2013, submission, containing a response to our April 8, 2013, filing letter.

We have completed our review of the Biopharmaceutics portion of your submission. The April 8, 2013 comments are in regular text, your May 3, 2013 response is in *italics*, and our responses are in **bold** text.

FDA's April 8, 2013 Comment #1:

The terminology of (b) (4) test for a soft gelatin capsule is not appropriate. It is requested that you change the terminology to rupture test, as it reflects the terminology used by USP for soft gelatin capsules.

Applicant's May 3, 2013 Response:

The terminology of (b) (4) test for a soft gelatin capsule is used by USP in (b) (4) (b) (4) which includes a procedure for soft gelatin capsules.

(u) (4) . The time that the capsule first opens (rupture), or a hole forms, is not recorded. (b) (4)

(u) (4) test.

FDA's Response to Applicant Response:

AKR-963 Capsule is a soft gelatin that (b) (4) ruptures and becomes a soft mass having no palpably firm core. Although (b) (4)

Furthermore, even if USP uses (u) (4) for soft gelatin capsule, it does not reflect the correct mechanism by which a soft gelatin capsule releases the API.

Additionally, ICH Q6A guidance outlines that (b) (4) may be used in lieu of dissolution if the following conditions are met:

(b) (4)

Since your product cannot meet the above four criteria, the terminology should be change to a rupture test. Therefore, please correct all appropriate sections in the NDA to reflect rupture test and record the time taken for each capsule shell to rupture.

FDA's April 8, 2013 Comment #2:

Provide the specified liquid medium, the experimental conditions (volume, temperature, time, etc.), and the procedure to assess the (b) (4) of your dosage form. Also, provide your testing plan if 1 or 2 capsules fail to (b) (4) completely and how many times you plan to repeat the test and the number of capsules you plan to test to meet the proposed specification.

Applicant's May 3, 2013 Response:

(b) (4)

FDA's Response to Applicant Response:

It is not clear how you determined that the selected volume, apparatus, and speed are appropriate test conditions for your dosage form, as you did not provide the test method development report. Refer to USP<2040> Rupture Test for Soft Shell Capsules for test conditions (medium, apparatus, time, procedure, and tolerances) used for soft gelatin capsule and use these test conditions to assess the rupture time for your dosage form.

FDA's April 8, 2013 Comment #3:

Your proposed (b) (4) specification (b) (4) is not justified. Provide the (b) (4) data (individual, mean, SD, in tabulated and graphical form) from the pivotal clinical batches and primary (registration) stability batches.

Applicant's May 3, 2013 Response:

The (b) (4) time results are the maximum time (b) (4) and no individual results are reported. Therefore, the individual, mean, and standard deviation data are not available. The release data for all lots, which include the pivotal clinical batches and the primary (registration) stability batches, included in NDA section 3.2.P.5.4 (SN 0000) are tabulated in Table 1.11.3-2 and graphed in Figure 1.11.3-1 and Figure 1.11.3-2 as the initial test interval. Data from stability studies are also included.

1 Page has been Withheld in Full as b4 (CCI/TS)
immediately following this page

(b) (4)



FDA Response to Applicant Response:

You are requested to submit in tabulated and graphical form the individual, mean, and standard deviation data from the pivotal clinical batches and primary (registration) stability batches. This is accomplished by recording the time taken for each capsule shell to rupture (Refer to USP <2040>). It is not acceptable to record the maximum time for (b) (4) capsules to rupture. Also, FDA sets tolerances based on the long-term stability data and not the accelerated conditions. Therefore, your proposal to revise the tolerances based on release and stability data need to take that into consideration. Based on the data provided at release and long-term stability, all the capsules tested rupture in NMT (b) (4) minutes.

If you have any questions, call Kati Johnson, Regulatory Project Manager, at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Danae Christodoulou, Ph.D.
Acting Branch Chief, Branch VII, Division III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

DANAE D CHRISTODOULOU
07/22/2013



NDA 204977

GENERAL ADVICE

Beckloff Associates, Inc.
US Agent for Trygg Pharma, Inc.
Attention: Beth Minter
Director, Managing Consultant, Scientific Consulting
Commerce Plaza II, Suite 300
7400 West 110th Street
Overland Park, KS 66210

Dear Ms. Minter:

Please refer to your New Drug Application (NDA) submitted January 31, 2013 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AKR-963 Capsules.

In your application, it appears that you propose the established name [REDACTED] (b) (4) capsules” for this product.

A United States Pharmacopeia (USP) drug product monograph for Omega-3-Acid Ethyl Esters Capsules became official on May 1, 2013 in the USP 36 - NF 31. Please explain how your proposed Omega-3-Acid Ethyl Esters product complies with this new monograph, and with the drug substance monograph for Omega-3-Acid Ethyl Esters, the standards for which are incorporated by reference in the drug product monograph.

Also, your counsel [REDACTED] (b) (4) contacted FDA to indicate that citizen petition FDA docket no. 2013-P-0148 was filed on your behalf. If you would like to address FDA's request for information regarding compliance with the new monograph standards in that public docket, you may supplement your petition to do so. If you intend to supplement your petition, please notify the Agency.

If you have any questions, call Kati Johnson, Regulatory Project Manager, at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Eric P. Duffy, Ph.D.
Director
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

ERIC P DUFFY
06/18/2013



DEPARTMENT OF HEALTH AND HUMAN
SERVICES

Food and Drug
Administration Silver
Spring MD 20993

NDA 204977

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Trygg Pharma, Inc.
c/o Beckloff Associates, Inc.
Commerce Plaza II, Suite 300
7400 West 110th Street
Overland Park, KS 66210

Attention: Beth Minter
Director, Managing Consultant
U.S. Agent for Trygg Pharma, Inc.

Dear Ms. Minter:

Please refer to your New Drug Application (NDA) dated and received January 31, 2013, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Omega-3-acid ethyl esters Capsules, 0.9 grams.

We also refer to your March 8, 2013, correspondence, received March 11, 2013, requesting review of your proposed proprietary name, Omtryg. We have completed our review of the proposed proprietary name, Omtryg, and have concluded that it is acceptable. However, we note that your proposed name incorporates part of the company name *Trygg Pharma*. Although acceptable for this product, the continued use of 'tryg' in future proposed proprietary names may create similar names. Thus, we recommend you refrain from incorporating the company name in future proposed proprietary name submissions for other products.

The proposed proprietary name, Omtryg, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your March 11, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Kati Johnson, at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

CAROL A HOLQUIST
06/05/2013



NDA 204977

GENERAL ADVICE

Beckloff Associates, Inc.
US Agent for Trygg Pharma, Inc.
Attention: Beth Minter
Director, Managing Consultant, Scientific Consulting
Commerce Plaza II, Suite 300
7400 West 110th Street
Overland Park, KS 66210

Dear Ms. Minter:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AKR-963 Capsules.

We wish to bring your attention to concerns that have arisen during the preliminary efficacy review of TRGG-963-002, titled *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*.

First, when considering whether to accept a single study to support an efficacy claim, we typically expect a statistically persuasive, robust result. In study TRGG-963-002, the pairwise comparison of AKR-963 vs. placebo yielded a median % difference in TG of -12.2% (95% CI, -23.9% to -0.4%), with $p=0.041$ using the Wilcoxon test. This met the prespecified criterion of $p<0.05$. However, we have performed multiple sensitivity analyses and each has resulted in a less convincing finding: (1) a log-transformed analysis yielded $p=0.046$; (2) the Kruskal-Wallis test yielded $p=0.049$; and (3) a completers analysis yielded $p=0.051$.

Second, if one accepts the AKR-963 vs. placebo comparison as demonstrating superiority, the interpretation of the non-inferiority comparison raises additional concerns. Specifically, establishing non-inferiority of a test drug to an active control by means of a pre-specified non-inferiority margin relies on the "constancy assumption," i.e., that the effect of the active control in the non-inferiority trial is similar to the historical effect of the active control established through placebo-controlled data. The non-inferiority margin is calculated using this historical data and is typically constructed as a conservative estimate of previous differences between the active control (Lovaza, in this case) and placebo. In TRGG-963-002, the inclusion of a placebo group allows an assessment of the constancy assumption because the effect of Lovaza is directly evaluated. In this case, the absolute value of the median difference between Lovaza and placebo was 14%, which is smaller - not larger than - the margin. In fact, the 95% CI of the median % difference in TG between Lovaza and placebo does not even overlap with the historical 95% CI of this comparison that was used to calculate the margin. Additionally, if one were to use this trial's data (Lovaza vs. placebo) to calculate a non-inferiority margin for a future trial, we note

that 50% of the absolute value of the upper bound of the 95% CI would be extremely close to zero (i.e., 0.55%). Taken together, these data suggest that the margin of 15% should not be used to evaluate non-inferiority in this trial.

We would like to offer you the opportunity to opine on why the treatment effects of AKR-963 and Lovaza were far less than expected when compared with placebo in this trial.

If you have any questions, call Kati Johnson, Regulatory Project Manager, at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Eric Colman, MD
Deputy Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

ERIC C COLMAN
05/21/2013



4/8/2013

Food and Drug Administration
Silver Spring MD 20993

NDA 204977

FILING COMMUNICATION

Beckloff Associates, Inc.
US Agent for Trygg Pharma, Inc.
Attention: Beth Minter
Director, Managing Consultant, Scientific Consulting
Commerce Plaza II, Suite 300
7400 West 110th Street
Overland Park, KS 66210

Dear Ms. Minter:

Please refer to your New Drug Application (NDA) dated January 31, 2013, received January 31, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for AKR-963 Capsules.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application was filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is November 30, 2013.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by October 25, 2013.

We request that you submit the following information:

Clinical

1. Please submit a rationale for assuming the applicability of foreign data in the submission (bioequivalence trials) to the U.S. population.

2. Please submit data from your excluded site, #124 (Dr. Michael Dao), in a similar format to the Site-Level Dataset submitted to the Agency on March 19, 2013.

Biopharmaceutics

1. The terminology of [REDACTED] (b) (4) test for a soft gelatin capsule is not appropriate. It is requested that you change the terminology to rupture test, as it reflects the terminology used by USP for soft gelatin capsules.
2. Provide the specified liquid medium, the experimental conditions (volume, temperature, time, etc.), and the procedure to assess the [REDACTED] (b) (4) of your dosage form. Also, provide your testing plan if 1 or 2 capsules fail to [REDACTED] (b) (4) completely and how many times you plan to repeat the test and the number of capsules you plan to test to meet the proposed specification.
3. Your proposed [REDACTED] (b) (4) specification [REDACTED] (b) (4) minutes is not justified. Provide the [REDACTED] (b) (4) data (individual, mean, SD, in tabulated and graphical form) from the pivotal clinical batches and primary (registration) stability batches.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application.

If you have any questions, call Kati Johnson, Regulatory Project Manager, at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, MD
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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
signing for Mary H. Parks, MD



NDA 204977

NDA ACKNOWLEDGMENT

Beckloff Associates, Inc.
US Agent for Trygg Pharma, Inc.
Attention: Beth Minter
Director, Managing Consultant, Scientific Consulting
Commerce Plaza II, Suite 300
7400 West 110th Street
Overland Park, KS 66210

Dear Ms. Minter:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

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

Date of Application: January 31, 2013

Date of Receipt: January 31, 2013

Our Reference Number: NDA 204977

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on **April 1, 2013**, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at 301-796-1234.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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
02/07/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

1/17/2013

Food and Drug Administration
Silver Spring MD 20993

IND 107259

MEETING MINUTES

Trygg Pharma, Inc.
Attention: Aaron Kramer, President
107 S. West Street
Alexandria, VA 22314

Dear Mr. Kramer:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AKR-963 (omega-3-acid ethyl esters) Capsules.

We also refer to the meeting between representatives of your firm and the FDA on December 10, 2012. The purpose of the meeting was to discuss your to-be-submitted NDA for the treatment of severe (≥ 500 mg/dL) hypertriglyceridemia.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

IND 107259
Meeting Minutes
Pre-NDA Meeting

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA (clinical)
Meeting Date and Time: Monday, December 10, 2012, noon
Meeting Location: FDA White Oak Campus
Building 22, Conference Room 1419

Application Number: IND 107259
Product Name: AKR-963 (omega-3-acid ethyl esters), 900 mg.
Indication: Severe Hypertriglyceridemia
Sponsor/Applicant Name: Trygg Pharma Inc.

Meeting Chair: Eric Colman
Meeting Recorder: Kati Johnson

FDA ATTENDEES

<i>Division of Metabolism and Endocrinology Products</i>	
Eric Colman, MD	Deputy Director
Iffat Chowdhury, MD	Clinical Reviewer
James P. Smith, MD	Clinical Reviewer
Karen Davis Bruno, PhD	Supervisory Pharmacologist
Indra Antonipillai, PhD	Nonclinical Reviewer
Kati Johnson	Project Manager
<i>Office of Biometrics II, Division of Biometrics II</i>	
Japobatra Choudhury, PhD	Statistical Reviewer
<i>Office of Clinical Pharmacology, Division of Clinical Pharmacology II</i>	
Immo Zadezensky, PhD	Clinical Pharmacology Team Leader
Zhihong Li, PhD	Clinical Pharmacology Reviewer
<i>Office of Surveillance and Epidemiology</i>	
Margarita Tossa, MS	Safety Regulatory Project Manager
Reasol Agustin, PharmD	Division of Medication Errors and Prevention Analysis
<i>Office of Scientific Investigations, Division of Good Clinical Practice, Good Clinical Practice Assessment Branch</i>	
Cynthia Kleppinger	Senior Medical Officer

SPONSOR ATTENDEES

Aaron Kramer	Trygg Pharma, Inc., President
Egil Bodd, MD, PhD	Trygg Pharma, Inc., Executive Chairman

IND 107259

Page 2

Atle Skattebøl, MD, PhD	Trygg Pharma, Inc., Vice President Clinical Development
	(b) (4) Regulatory Advisor
	(b) (4) Regulatory Advisor
	(b) (4) Clinical Consultant
	Nonclinical Consultant (teleconference participant)
	(b) (4) Executive Vice President and Sr. Toxicologist (teleconference participant)
(b) (4)	(b) (4) Regulatory Consultant (teleconference participant)
	(b) (4) Sr. Medical Consultant
	(b) (4) Sr. VP. Scientific Affairs

1.0 BACKGROUND

This IND was submitted June 29, 2010, proposing to develop AKR-963 for the treatment of hypertriglyceridemia with the goal of submitting a 505(b)(2) application, referencing LOVAZA (omega-3-acid ethyl ester) Capsules.

According to the sponsor AKR-963 is a 900 mg capsule containing at least (b) (4) individual omega-3 fatty acid ethyl esters, principally EPA (b) (4) and DHA (b) (4). The proposed dosing regimen is 4 capsules daily.

The initial application contained the following protocols:

1. Bioequivalence Study: Long-Term Equivalence of EPA Plus DHA in Plasma for AKR-963 as Compared to Lovaza, Studied in Healthy Volunteers Over 28 days of Dosing. (Protocol TRGG-963-001)
2. Therapeutic Equivalence Study: Eight-Week Clinical Study, Starting From Baseline in Patients With Very High Triglycerides (> 500 mg/dL) and Assessing Mean Percent Reduction in TG From Baseline for AKR-963 as Compared to Placebo and For AKR-963 as Compared to Lovaza.(Protocol TRGG-963-002)

Comments were conveyed to the sponsor regarding both protocols. Regarding Protocol TRGG-963-001, we suggested that a conventional 2-way crossover study be conducted for the bioequivalence assessment between AKR-963 and Lovaza using a single dose, with the primary endpoint of Cmax and AUC of EPA, DHA, and their ethyl esters.

The firm has also conducted the following clinical studies:

1. TRGG-963-003: A Randomized, Double-Blind, Two Period Crossover, Bioequivalence Trial of Two Omega-3-Acid Ethyl Ester Products in Healthy Adult Volunteers.
2. TRGG-963-004: A Single-Dose, Comparative Bioavailability Study of Two Formulations of Omega-3-Acid Ethyl Esters Capsules under Fasting and Fed Conditions.
3. TRGG-963-005: A Replicate, Single-Dose, Comparative Bioavailability Study of Two Formulations of Omega-3-Acid Ethyl Esters Capsules under Fed Conditions.

IND 107259

Page 3

The sponsor never requested an End-of-Phase 2 meeting.

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

A Pre-NDA (Clinical) meeting was requested on September 14, 2012, and granted on September 20, 2012. The background package was submitted October 22, 2012.

2. DISCUSSION

The firm's background information and questions are in regular text. FDA preliminary responses are in **bolded** text. Any meeting discussion is in *italicized* text.

Clinical

1. An initial bioequivalence study (TRGG-963-003) where AKR-963 and Lovaza were administered following a low fat ($\leq 15\%$ of kcal) meal yielded inconclusive results. A subsequent bioavailability study (TRGG-963-004) evaluating bioavailability in fasted versus fed (FDA high fat [50% of kcal], high-caloric breakfast) conditions demonstrated that a high fat meal was required for adequate absorption of omega-3 fatty acid ethyl ester products. AKR-963 and Lovaza were measured by blood concentrations of both EPA ethyl esters and EPA total lipids (baseline adjusted) and DHA ethyl esters and DHA total lipids (baseline adjusted). Based on the aforementioned data, the definitive bioequivalence study (TRGG-963-005) was conducted in the fed state (administered after a high fat meal), upon which bioequivalence to Lovaza was demonstrated for all four endpoints (total EPA, total DHA, EPA ethyl ester, and DHA ethyl ester).

Subject to its review of the study data, does FDA agree that Trygg's definitive bioequivalence study (TRGG-963-005) is adequate to demonstrate the bioequivalence of AKR-963 to Lovaza?

FDA Response: Your approach to establish bioequivalence of AKR-963 to Lovaza seems reasonable. However, we note increasing concentrations at the last sampling time point for baseline adjusted total DHA in study TRGG-963-005. This may influence your estimate of $AUC_{0-\infty}$ and half-life.

In addition, submit bioequivalence analysis on AUC_{0-t} , $AUC_{0-\infty}$, baseline-adjusted AUC_{0-t} , baseline-adjusted $AUC_{0-\infty}$, C_{max} , and baseline-adjusted C_{max} for plasma EPA, plasma DHA, plasma EPA ethyl ester and plasma DHA ethyl ester individually for all the three bioequivalence studies (TRGG-963-003, TRGG-963-004, TRGG-963-005) in your NDA.

Meeting Discussion: By way of some background information, the Sponsor provided input into the design of study TRGG-963-003. In this study, AKR-963 and Lovaza were not shown to be bioequivalent. The sponsor designed a study after evaluating potential issues in study TRGG-963-003. In study TRGG-963-005 the diet was controlled. In addition, baseline sampling was done 24 hours pre-dosing and PK sampling was done 72 hours post-dosing. In this study, TRGG-963-005, AKR-963 was bioequivalent to Lovaza, according to the firm.

IND 107259

Page 4

Responding to the Agency's comment regarding increasing concentrations at the last sample time point for baseline adjusted total DHA, the firm proposes to substitute AUC 0 to 72 hours for AUC to infinity. The Agency said that bioequivalence depends on comparing rate and extent of absorption to the listed drug. The fact that the last timepoint increases may be an issue extrapolating to infinity, but that is a review issue. The Agency recognizes that the sponsor is not solely relying on bioequivalence for the demonstration of safety and efficacy; a clinical study was also conducted. Safety and efficacy will be determined on the totality of the data submitted. The Agency requested that individual data be provided in the NDA along with a full study report. The sponsor only has an abbreviated report for Study -003 and Study -004, but individual dataset and bioequivalence analysis will be submitted in the NDA; the Agency found this acceptable.

2. In its 505(b)(2) NDA (Module 2), Trygg will fully summarize in eCTD format the complete results of the studies conducted in support of its application. 21 CFR 314.50(d)(5) specifies inclusion of Integrated Summaries of Safety and Efficacy in the NDA. Considering the 505(b)(2) NDA is based upon a single Phase III safety and efficacy study (TRGG-963-002), no integration is possible.

Does FDA agree that an ISS and an ISE are not required for Trygg's 505(b)(2) NDA?

FDA Response: Yes, we agree that an ISS and an ISE are not required for your submission.

Please confirm that your nonclinical studies and your Phase III clinical trial have been conducted with the final to-be-marketed formulation of AKR-963.

Note: in a subsequent conversation with Dr. [REDACTED] (b)(4), it was confirmed that the formulation has been constant throughout drug development.

Please see the attached document entitled "Pre-NDA General Advice for Planned Marketing Applications" for a list of requests regarding electronic submissions. In addition, we request that laboratory data be presented in conventional units.

We request that you scan any paper review copies in a text readable format and include in the electronic submission.

Lastly, we request that you use the attached site selection tool from the Office of Scientific Investigations and include the requested items in your electronic submission.

Meeting Discussion: None

3. Clinical non-inferiority of AKR-963 to Lovaza was demonstrated in Study TRGG-963-002 in patients with severe hypertriglyceremia, and the study included a long-term safety evaluation per DMEP's feedback in response to its review of the draft study protocol and statistical analysis plan. These data support the clinical comparability between AKR-963 and Lovaza in terms of both products' safety and efficacy. Together with the clinical pharmacology data in healthy subjects demonstrating bioequivalence between AKR-963

IND 107259

Page 5

and Lovaza (see **Question 1**) and the nonclinical bridging data (see **Question 8**), as well as the data to be included in the CMC module, Trygg believes these data support the proposed 505(b)(2) NDA approach based upon bridging to FDA's prior determination of the safety and effectiveness of Lovaza.

Does FDA agree that the proposed bridging data package is adequate to support the filing, review, and subject to the Agency's review, approvability of a 505(b)(2) NDA for AKR-963?

FDA Response: We agree that the proposed bridging data package is adequate for submission of the NDA. Whether this bridging data is sufficient for approval is a review issue.

Meeting Discussion: None

4.

(b) (4)

FDA Response: We cannot comment on the current Lovaza listing in the Orange Book. In regards to the issue of the strength of AKR-963 in relation to Lovaza as a RLD, Trygg Pharma can perform batch testing on sufficient lots of Lovaza to establish the omega-3 acid ester content range. If your proposed product's omega-3 acid ester content is within the range for Lovaza, you would not be expected to conduct any additional studies to demonstrate safety and effectiveness.

Meeting Discussion: None

5. Based upon the results of Trygg's definitive bioequivalence study demonstrating the bioequivalence of AKR-963 and Lovaza, as further reinforced by the Phase III study results demonstrating (b) (4) of AKR-963 to Lovaza with equivalent clinical safety and efficacy profiles, and based upon the CMC module that demonstrates the pharmaceutical equivalence of AKR-963 and Lovaza, Trygg intends to request classification of AKR-963 as (b) (4) to Lovaza Capsules.

IND 107259
Page 6

(b) (4)

Meeting Discussion: None

Labeling

6. Based upon the results of its definitive bioequivalence study (TRGG-963-005) demonstrating, subject to the Agency's review, that AKR-963 Capsules are bioequivalent to the RLD, Lovaza Capsules, and further based upon the results of its Phase III safety and efficacy clinical trial (TRGG-963-002) demonstrating, subject to the Agency's review, that AKR-963 Capsules are non-inferior to the RLD, Trygg plans to propose in its forthcoming 505(b)(2) NDA submission that the prescribing information include a statement to the effect that AKR-963 Capsules are bioequivalent to Lovaza Capsules and patients currently on Lovaza Capsules (b) (4). Does FDA agree that, subject to its review of the data from Trygg's definitive bioequivalence study and Phase III clinical trial, the prescribing information for AKR-963 Capsules can include a statement that AKR-963 Capsules are bioequivalent to Lovaza Capsules and patients currently on Lovaza Capsules (b) (4). (b) (4),

FDA Response: See response to Question #5. We reserve discussion regarding the prescribing information until after submission of the NDA.

Meeting Discussion: The sponsor referred to slide #7 (in which Lovaza's strength is described in three different ways) and asked the Agency for guidance on which description to use in their to-be-submitted NDA. The Agency responded that the sponsor should decide on which strength description to use and justify that choice of strength description.

7. Based upon the results of Trygg's Phase III safety and efficacy clinical trial (TRGG-963-002), Trygg plans to propose in its forthcoming 505(b)(2) NDA submission that the prescribing information include a statement to the effect that the comparative safety profile and efficacy of AKR-963 Capsules are (b) (4). (b) (4)

Does FDA agree that, subject to its review of the data from Trygg's Phase III clinical trial, the prescribing information for AKR-963 Capsules can include a statement that the

IND 107259
Page 7

safety and efficacy of AKR-963 Capsules are (b) (4)
(b) (4)

FDA Response: See responses to previous questions; we reserve discussion regarding the prescribing information until after submission of the NDA.

Meeting Discussion: None

Nonclinical

- 8. The nonclinical bridging toxicology program consisted of a comparative bridging toxicity study between AKR-963 and Lovaza in addition to two genotoxicity studies. Does the Agency agree that this program meets the objectives of demonstrating that reliance on the data for Lovaza® is justified and appropriate, and that the impurity profile of AKR-963 is well characterized?

FDA Response: The nonclinical development plan in support of a 505(b)(2) application seems reasonable. The adequacy of these data to support characterization of AKR-963 to support a marketing application is a review issue. The bridging toxicity study didn't use a control group and there's mortality noted in the high dose AKR-963 group, but not in the Lovaza comparator.

Meeting Discussion: The firm will provide, in the NDA, historical control data on the facility conducting the bridging toxicity study. The firm also stated that necropsy reports will be provided in the NDA. The Agency stated that the nonclinical reports could be submitted to the IND for review, as resources allow, if they are already finalized. In response to a question, the sponsor said that they are hoping to submit the NDA at the end of January 2013.

3.0 PREA PEDIATRIC STUDY PLAN

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at Pedsdrugs@fda.hhs.gov.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

[Insert any action items that were identify during the meeting. Include who is responsible to complete the action item and the due date. Responsible party should not be an individual, but either sponsor or FDA. Consider the use of a table to present the information]

Action Item/Description	Owner	Due Date
Meeting Minutes	FDA	January 9, 2013

IND 107259
Page 8

6.0 ATTACHMENTS AND HANDOUTS
Clinical and Non-Clinical Pre-NDA Meeting Slides

7 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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
01/17/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

11/15/2012

Food and Drug Administration
Silver Spring MD 20993

IND 107259

MEETING MINUTES

Trygg Pharma Inc.
Attention: Aaron Kramer
107 S. West St.
Alexandria, VA 22314

Dear Mr. Kramer:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AKR-963 (omega-3-acid ethyl esters) Capsules.

We also refer to the meeting between representatives of your firm and the FDA on September 13, 2012. The purpose of the meeting was to discuss CMC considerations for the forthcoming NDA in connection with development activities completed by Trygg.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Rebecca McKnight, Regulatory Project Manager, at (301) 796-1765.

Sincerely,

{See appended electronic signature page}

Eric P. Duffy, Ph.D.
Division Director
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
Slide Presentation from Trygg Pharma Inc.

Meeting Minutes
IND 107259
September 13, 2012

MEMORANDUM OF MEETING MINUTES

Meeting Date and Time: September 13, 2012
Meeting Location: White Oak

Application Number: IND 107259
Product Name: AKR-963 (omega-3-acid ethyl esters) Capsules
Indication: Treatment of hypertriglyceridemia
Sponsor/Applicant Name: Trygg Pharma Inc.

Meeting Chair: Eric Duffy, Ph.D.
Meeting Recorder: Rebecca McKnight

FDA ATTENDEES

Eric Duffy, PhD, Director
Ali Al-Hakim, PhD, Branch Chief
Norman Schmuff, PhD, Associate Director for Product Quality, ONDQA
Martin Haber, PhD, CMC Reviewer, ONDQA
Rebecca McKnight, Project Manager, ONDQA
Kati Johnson, Sr. Project Manager, DMEP
Erika Pfeiler, PhD, Microbiology Reviewer, OPS
Mustafa Unlu, JD, Attorney, OCC

SPONSOR ATTENDEES

Aaron Kramer, President
Egil Bodd, MD, PhD, Executive Chairman
Gitte Lyngø Nielsen, MscPharm, Vice President Quality Assurance
Atle Skattebøl, MD, PhD, Vice President Clinical Development
John Engel, JD, Engel & Novitt, Regulatory Advisor
(b) (4) Regulatory Advisor
(b) (4) CMC Consultant
(b) (4) CMC Consultant
(b) (4) CMC Consultant
Tone Madsen, DVM, Regulatory Manager (teleconference participant)
Vegard Vik, VP Commercial Development (teleconference participant)
(b) (4), CMC Consultant (teleconference participant)
(b) (4) Regulatory Consultant (teleconference participant)

Meeting Minutes
IND 107259
September 13, 2012

QUESTIONS (the Agency responses are in **bold text**):

1. Does FDA concur that there is not a need to test for oligomers, trans-isomers, and cholesterol as part of the release and stability testing of the drug substance?

FDA's Response:

Adequate release and stability testing is a review issue to be determined during NDA review, not at this stage of the IND. Oligomers, trans-isomers and cholesterol test data for your product is currently limited. However, it appears that trans-isomers of EPA and DHA are elevated in your product. Also, note that for high daily dose drugs (> 2 g) the ICH Q3A(R2) threshold for identification and qualification is 0.05%. We refer you to *ICH Q3A(R2) Impurities in New Drug Substances*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073385.pdf>

Additional Meeting Discussion:

Trans-isomers for EPA and DHA are present at levels > (b)(4)%, therefore:

- *Trygg plans to add tests to the release specification*
- *Qualification of the acceptance criteria for the trans-isomers tests will be based on the nonclinical data provided in the NDA*
- *Trygg will provide data to support the justification of the proposed specification in the NDA*

For cholesterol and oligomers, Trygg will provide additional data in the NDA to support their exclusion from the specification.

FDA Response: *This approach seems reasonable provided that you can demonstrate the absence of cholesterol and oligomers.*

Trygg also noted that no additional fatty acids are present at levels above 0.05% that they are aware of.

2. Does FDA agree with the proposed testing to monitor stability of the drug substance?

FDA's Response:

Based on the data that you provided, the proposed testing appears reasonable.

Additional Meeting Discussion:

There was no additional discussion.

3. In light of the residual solvents data, does FDA concur with this proposal to delete residual solvents testing?

Meeting Minutes
IND 107259
September 13, 2012

FDA's Response:

No, we do not concur. Residual solvent testing is a safety issue and should continue. A proposal to delete this testing can be made post-approval.

Additional Meeting Discussion:

There was no additional discussion.

4. Given the drug substance microbial testing data and continued microbiological testing of the encapsulated drug product, does FDA concur that there is no need to test for microbial limits as part of the drug substance release and stability?

FDA's Response:

FDA's review of microbiological characteristics for products of this type focuses mainly on the finished drug product; however, microbiological monitoring of the drug substance is also considered. The appropriateness of removal of drug substance specifications would be assessed during the review of an NDA. FDA would be amenable to the removal of drug substance testing, with the appropriate justification. Justification in your NDA application may include a description of drug substance processing methods and a summary of stability studies performed to date.

Additional Meeting Discussion:

There was no additional discussion.

5. Does FDA agree with this approach to environmental pollutant testing?

FDA's Response:

Based on the data that you provided, this approach appears reasonable.

Additional Meeting Discussion:

There was no additional discussion.

6. Does FDA agree with this approach to supporting a ^{(b) (4)} month shelf life?

FDA's Response:

We do not determine a shelf life at this stage, the shelf life will be determined during our NDA review based on all available data.

Additional Meeting Discussion:

There was no additional discussion.

Meeting Minutes
IND 107259
September 13, 2012

7. Does FDA agree with the proposed use of a comparability protocol in the NDA for this type of post-approval change?

FDA's Response:

We do not review post-approval supplement proposals at this stage. We will evaluate the comparability protocol during our NDA review.

8. Does FDA agree that a waiver for bioequivalence studies would be acceptable based on the demonstration of equivalent quality of the drug substance manufactured by the two SMB chromatographic processes for Trygg's initial and future alternative supplier?

FDA's Response:

We do not review post-approval supplement proposals at this stage. We will evaluate the biowaiver request associated with your proposed post-approval supplement during our NDA review.

Additional Meeting Discussion for Questions 7 and 8:

Trygg has ongoing activities to support the change of drug substance manufacturing site and requests FDA's feedback that:

- *Chemical equivalence is the basis for an in vivo bioequivalence waiver*
- *Chemical equivalence is established by meeting protocol acceptance criteria for the post-change drug substance*
 - *Compliance with the approved drug substance specification*
 - *Demonstration that fatty acid ethyl ester profile, environmental pollutants, microbial limits, oligomers and cholesterol results from the three batches are consistent with the results from historical batches manufactured by BASF*

FDA Response: *The comparability protocol approach appears to be acceptable. Provide comparability for Q1 and Q2 of the drug substance – this assessment should address variability of the oil and what the limits will be over time. If comparability is demonstrated, bioequivalence studies would not be necessary. These are review issues and will be evaluated during the NDA review.*

9.



(b) (4)

Meeting Minutes
IND 107259
September 13, 2012

FDA's Response:

Unless you provide an authorization letter from the Lovaza applicant allowing FDA to discuss their Lovaza NDA with you, we cannot discuss this product with you.

Additional Meeting Discussion:

The Agency suggests that a pre-NDA meeting is not the place to discuss this issue. We can communicate that aspects of this matter are under consideration, but no decision will be made at this meeting. The information presented to us today is very helpful. We will take this information into consideration and work internally to try to determine ways to resolve this issue.

10. Does FDA agree that a categorical exclusion for an Environmental Assessment in accordance with 21 CFR 25.31© is appropriate for Trygg's forthcoming NDA?

FDA's Response:

We do not review the categorical exclusion for an environmental assessment at this stage. We will evaluate it during our NDA review.

Additional Meeting Discussion:

There was no additional discussion.

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

/s/

ERIC P DUFFY
11/15/2012