

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204977Orig1s000**

**CHEMISTRY REVIEW(S)**

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

**Application:** NDA 204977/000  
**Submission Date:** 31-JAN-2013  
**Regulatory:** 30-NOV-2013

**Action Goal:**  
**District Goal:** 01-OCT-2013

**Applicant:** TRYGG  
7400 WEST 110TH ST STE 300  
OVERLAND PARK, KS 66210

**Brand Name:** OMEGA-3 ACID ETHYL ESTERS  
**Estab. Name:**  
**Generic Name:** OMEGA-3 ACID ETHYL ESTERS

**Priority:** 5  
**Org. Code:** 510

**Product Number; Dosage Form; Ingredient; Strengths**  
001; CAPSULE; TOCOPHEROL; 4.6MG  
001; CAPSULE; (b) (4); 375MG  
001; CAPSULE; (b) (4); 465MG

**Application Comment:**

<b>FDA Contacts:</b>	M. HABER	Prod Qual Reviewer		3017961675
	B. RILEY	Micro Reviewer	(HFD-805)	3017961595
	R. MCKNIGHT	Product Quality PM		3017961765
	K. JOHNSON	Regulatory Project Mgr	(HFD-510)	3017961234
	S. TRAN	Team Leader		3017961764

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**Overall Recommendation:** ACCEPTABLE on 26-NOV-2013 by J. WILLIAMS ( ) 3017964196

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**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

Establishment:



(b) (4)

DMF No:

AADA:

Responsibilities: FINISHED DOSAGE PACKAGER

Establishment Comment: PACKAGING OF THE CAPSULES INTO BOTTLES (on 12-FEB-2013 by R. MCKNIGHT () 3017961765)

Profile: CAPSULES, PROMPT RELEASE OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	27-FEB-2013				MCKNIGHTR
SUBMITTED TO DO PROFILE STILL INITIAL. PDUFA	27-FEB-2013	10-Day Letter	GOAL DATE:30-NOV-2013		PRABHAKARAR
DO RECOMMENDATION	27-FEB-2013			ACCEPTABLE BASED ON FILE REVIEW	PHILPYE
OC RECOMMENDATION	04-MAR-2013			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

Establishment:



DMF No:

**Responsibilities:** DRUG SUBSTANCE MANUFACTURER

**Establishment Comment:** MANUFACTURE OF DRUG SUBSTANCE FROM 36/27 EE US PH INTERMEDIATE.

**Profile:** TESTING FOR APPEARANCE TOCOPHEROL, (b) (4), on 12-FEB-2013 by R. MCKNIGHT ( ) 3017961765  
NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	27-FEB-2013				MCKNIGHTR
SUBMITTED TO DO	(b) (4)	Product Specific and GMP Inspection	FIRST FDA EVAL OF ESTB. PDUFA GOAL DATE: 30-NOV-2013		PRABHAKARAR
ASSIGNED INSPECTION TO IB	(b) (4)	Product Specific and GMP Inspection			PHILPYE
INSPECTION SCHEDULED	(b) (4)				IRIVERA
INSPECTION PERFORMED					Michele.Forster
<p>This was a PAI and GMP inspection of an API manufacturer that specializes in production of concentrated omega-3 fatty acids. The inspection was conducted in accordance with CP7346.836 PAI and CP7356.002F API Process Inspections. The PAI was issued to cover the manufacturing and testing of (b) (4) and omega-3 ethyl esters (NDA 204977/000).</p> <p>This was the first FDA inspection of the firm. The firm does not currently manufacture any products for the U.S. market. The quality, laboratory, production, facilities and equipment systems were covered as well as material supplier qualification. PAI CP objectives 1, 2, and 3 were also covered.</p> <p>A one-point FDA 483 was issued for failure to follow procedures applicable to the quality unit including failure to complete deviation investigations within 30 days, failure to complete complaint records, failure to close OOS investigations, and failure to review a batch record. A corrective action plan was provided and a written response was submitted after the inspection. No refusals were encountered, and no samples were collected.</p> <p>Current drug establishment registration was verified.</p>					
DO RECOMMENDATION	19-AUG-2013			ACCEPTABLE INSPECTION	PHILPYE
OC RECOMMENDATION	20-AUG-2013			ACCEPTABLE DISTRICT RECOMMENDATION	CAPACCIDANIC

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

**Establishment:** [REDACTED] (b) (4)

**DMF No:** [REDACTED] **AADA:** [REDACTED]

**Responsibilities:** DRUG SUBSTANCE MANUFACTURER

**Establishment Comment:** MANUFACTURE OF 36/27 EE US PH INTERMEDIATE. (on 27-FEB-2013 by R. MCKNIGHT () 3017961765)

**Profile:** [REDACTED] (b) (4) **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	27-FEB-2013				MCKNIGHTR
SUBMITTED TO DO	27-FEB-2013	Product Specific and GMP Inspection			PRABHAKARAR
FIRST FDA EVAL OF ESTB. PDUFA GOAL DATE:30-NOV-2013					
ASSIGNED INSPECTION TO IB	27-FEB-2013	Product Specific and GMP Inspection			PHILPYE
INSPECTION PERFORMED	[REDACTED] (b) (4)				IRIVERA
INSPECTION SCHEDULED	[REDACTED] (b) (4)				IRIVERA
DO RECOMMENDATION	25-NOV-2013			ACCEPTABLE	MROSE
ADDITIONAL REVIEW OF THE FDA 483 AND T-CON WITH INVESTIGATOR DETERMINED THE SITE IS ACCEPTABLE				INSPECTION	
OC RECOMMENDATION	25-NOV-2013			ACCEPTABLE	WILLIAMSJU
				DISTRICT RECOMMENDATION	

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

**Establishment:** [REDACTED] (b) (4)

**DMF No:** [REDACTED] **AADA:** [REDACTED]

**Responsibilities:** DRUG SUBSTANCE RELEASE TESTER  
FINISHED DOSAGE RELEASE TESTER

**Establishment Comment:** [REDACTED] (b) (4)  
[REDACTED] (b) (4) OVERSIGHT FOR  
RELEASE OF DRUG SUBSTANCE AND DRUG PRODUCT AND STABILITY STORAGE.  
(on 26-FEB-2013 by R. MCKNIGHT ( ) 3017961765)

**Profile:** CONTROL TESTING LABORATORY **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	27-FEB-2013				MCKNIGHTR
SUBMITTED TO DO	27-FEB-2013	Product Specific and GMP Inspection			PRABHAKARAR
FIRST FDA EVAL OF ESTB. PFUDA GOAL; DATE: 30-NOV-2013					
ASSIGNED INSPECTION TO IB	27-FEB-2013	Product Specific and GMP Inspection			PHILPYE
IN ON PERFORMED	[REDACTED] (b) (4)				IRIVERA
INSPECTION SCHEDULED	[REDACTED] (b) (4)				IRIVERA
DO RECOMMENDATION	25-NOV-2013			ACCEPTABLE INSPECTION	MROSE
EXPEDITED REVEIW INCLUDED REVIEW OF FDA 483 AND T-CON WITH INVESTIGATOR. DIDQ DETERMINED THE SITE IS ACCEPTABLE FOR THIS APPLICATION.					
OC RECOMMENDATION	26-NOV-2013			ACCEPTABLE DISTRICT RECOMMENDATION	WILLIAMSJU

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

Establishment:



(b) (4)

DMF No:

AADA:

Responsibilities:

FINISHED DOSAGE OTHER TESTER  
FINISHED DOSAGE STABILITY TESTER

Establishment

STORAGE OF STABILITY SAMPLES FOR ONGOING STABILITY STUDIES, TESTING FOR MICROBIAL LIMITS. (on 12-FEB-2013 by R. MCKNIGHT ( ) 3017961765)

Comment:

Profile:

CONTROL TESTING LABORATORY

OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	27-FEB-2013				MCKNIGHTR
SUBMITTED TO DO PENDING REG ACTION. PDUFA GOAL DATE: 30-NOV-2013	27-FEB-2013	10-Day Letter			PRABHAKARAR
DO RECOMMENDATION	27-FEB-2013			WITHHOLD REGULATORY ACTION TAKEN AND/OR	PHILPYE
DO RECOMMENDATION	23-MAY-2013			ACCEPTABLE BASED ON FILE REVIEW	PHILPYE
OC RECOMMENDATION STABILITY AND OTHER TESTER (TESTING FOR MICROBIAL LIMITS).	23-MAY-2013			ACCEPTABLE DISTRICT RECOMMENDATION	PRABHAKARAR

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

**Establishment:** (b) (4)

**DMF No:** (b) (4) **AADA:** (b) (4)

**Responsibilities:** DRUG SUBSTANCE RELEASE TESTER  
FINISHED DOSAGE RELEASE TESTER

**Establishment Comment:** FACILITY TESTS DRUG SUBSTANCE AND DRUG PRODUCT FOR IDENTIFICATION, FATTY ACID COMPOSITION,  
(b) (4)  
(on 26-FEB-2013 by R. MCKNIGHT () 3017961765)

**Profile:** CONTROL TESTING LABORATORY **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	27-FEB-2013				MCKNIGHTR
SUBMITTED TO DO	27-FEB-2013	Product Specific and GMP Inspection			PRABHAKARAR
FIRST FDA EVAL FOR ESTB. PDUFA GOAL DATE: 30-NOV-2013					
ASSIGNED INSPECTION TO IB	27-FEB-2013	Product Specific and GMP Inspection			PHILPYE
INSPECTION SCHEDULED	<span style="background-color: #cccccc; padding: 2px;">(b) (4)</span>				IRIVERA
INSPECTION PERFORMED	<span style="background-color: #cccccc; padding: 2px;">(b) (4)</span>				Bill.Tackett
DO RECOMMENDATION	22-NOV-2013			ACCEPTABLE	MROSE
6/2013 INSPECTION FOUND CTL ACCEPTABLE				INSPECTION	
OC RECOMMENDATION	22-NOV-2013			ACCEPTABLE	SAFAAIJAZIR
				DISTRICT RECOMMENDATION	

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

Establishment:



(b) (4)

DMF No:

AAUA:

Responsibilities:

FINISHED DOSAGE MANUFACTURER

Establishment  
Comment:

ENCAPSULATION OF AKR-963  
TESTING FOR UNIFORMITY OF DOSAGE UNITS, APPEARANCE, AND DISINTEGRATION TIME (on 12-FEB-2013 by R.  
MCKNIGHT () 3017961765)

Profile:

CAPSULES, SOFT GELATIN

OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	27-FEB-2013				MCKNIGHTR
SUBMITTED TO DO FINISHED DOSAGE MANUFACTURER	01-MAR-2013	10-Day Letter			SAFAAIJAZIR
DO RECOMMENDATION	12-MAR-2013			ACCEPTABLE BASED ON FILE REVIEW	PHILPYE
OC RECOMMENDATION	20-MAR-2013			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

**Establishment:** (b) (4)

**DMF No:** [REDACTED] **AADA:** [REDACTED]

**Responsibilities:** FINISHED DOSAGE OTHER TESTER

**Establishment Comment:** TESTING FOR MICROBIAL LIMITS (on 12-FEB-2013 by R. MCKNIGHT () 3017961765)

**Profile:** CONTROL TESTING LABORATORY **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	27-FEB-2013				MCKNIGHTR
OC RECOMMENDATION	27-FEB-2013			ACCEPTABLE BASED ON PROFILE	PRABHAKARAR

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SHANNON J CREWS  
05/07/2014

**NDA 204-977**

**Omtryg (AKR-963, omega-3-acid ethyl esters) Capsules**

**Trygg Pharma, Inc.**

**Martin Haber, Ph.D.  
Division of New Drug Quality Assessment III**

**For  
Division of Metabolism and Endocrinology Products**

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# Chemistry Review Data Sheet

1. NDA 204-977
2. REVIEW #1
3. REVIEW DATE: October 17, 2013
4. REVIEWER: Martin Haber, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

NA

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original

Amendment

Document Date

January 13, 2013

August 5, 2013

7. NAME & ADDRESS OF APPLICANT:

Name: Trygg Pharma, Inc. (US Agent: Beckloff Associates, Inc.)

Address: 7400 W 110<sup>th</sup> Street, Overland Park, KS 66210

Representative: Beth Minter

Telephone: 913-451-3955

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Omtryg

b) Non-Proprietary Name (USAN): Omega-3 acid ethyl esters

c) Code Name/# (ONDC only): AKR-963

## Executive Summary Section

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 5 (New formulation, manufacturer)
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Lipid Altering

11. DOSAGE FORM: Soft Gelatin Capsules

12. STRENGTH/POTENCY: 1200 mg fish oil (Label states “at least 900 mg omega-3 acid ethyl esters”)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

The major polyunsaturated fatty acid ethyl esters present in purified fish oil are EPAee and DHAee:

## Executive Summary Section

**Chemical Names**

The chemical names for the main constituents in AKR-963 are given below.

EPAee:

5,8,11,14,17-eicosapentaenoic acid, ethyl ester, (all-Z)-

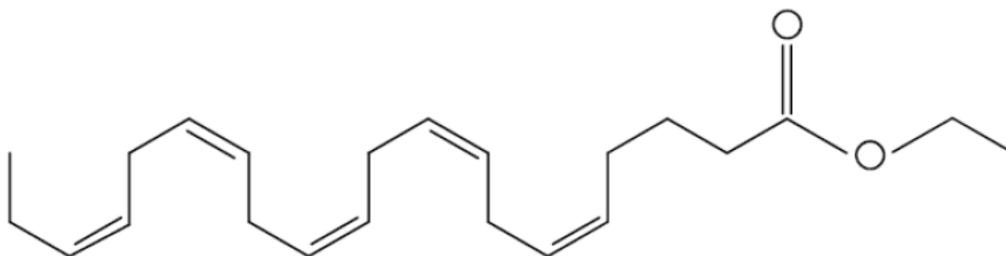
Ethyl (5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenoate

DHAee:

4,7,10,13,16,19-docosahexaenoic acid, ethyl ester, (all-Z)-

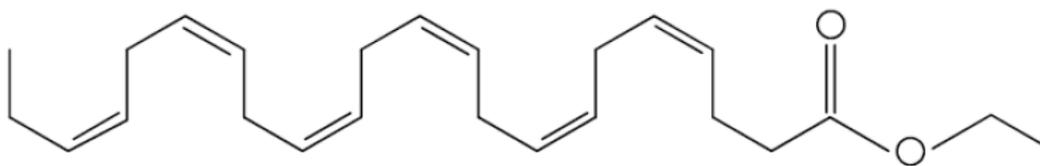
Ethyl (4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoate

The structure, molecular formula, and molecular weight for the main constituents in AKR-963 are provided below.

**EPAee**

Molecular Formula:  $C_{22}H_{34}O_2$

Molecular Weight: 330.51

**DHAee**

Molecular Formula:  $C_{24}H_{36}O_2$

Molecular Weight: 356.55

**17. RELATED/SUPPORTING DOCUMENTS:****A. DMFs:**

DMF	TYPE	HOLDER	ITEM	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE	COMMENTS
-----	------	--------	------	-------------------	---------------------	------	----------

Executive Summary Section

#			REFERENCED			REVIEW COMPLETED	
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	10/16/2013 by Dr. Martin Haber	Drug substance (purified fish oil)
	III			4	Adequate	N/A	
	III			4	Adequate	N/A	
	III			4	Adequate	N/A	
	III			4	Adequate	N/A	
	III			4	Adequate	N/A	
	III			4	Adequate	N/A	

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	107259	Clinical trials

18. STATUS:

## Executive Summary Section

**ONDC:**

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
EES	Pending		
Pharm/Tox	Approval	7/2013	I. Antonipillai
Quality Biopharm	Approval	10/16/2013	H. Mahayni
Methods Validation	Not required	8/30/2013	M. Haber
DMEPA (labeling)	Pending		
EA	Acceptable	8/30/2013	M. Haber
Microbiology	Approval	3/14/2013	B. Riley

# The Chemistry Review for NDA 204-977

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

Recommend approval, pending acceptable cGMP recommendation and acceptability of the established name and strength as will be determined by ORP.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

NA

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance, AKR-963, is a mixture of polyunsaturated fatty acid ethyl esters obtained by esterification of the body oil from several species of oily fish. The sponsor has proposed the name (b) (4). However, there is a USP drug substance monograph for that name and the amounts of fatty acid ethyl esters in this product do not meet the monograph requirements (the listed fatty acid ester concentrations are higher in the monograph). Therefore, the currently proposed established name cannot be used. An acceptable established name for the drug substance is needed for approval. This issue has been consulted to the Office of Regulatory Policy.

In the drug substance, the (b) (4) major omega-3 fatty acid ethyl esters are (b) (4) eicosapentaenoic acid (EPA), (b) (4) and docosahexaenoic acid (DHA). The main components are EPA (about (b) (4)%) and DHA (about (b) (4)%).

The drug substance is purified from crude fish oil, the starting material, by (b) (4) Subsequent manufacturing steps at (b) (4) are described in DMF# (b) (4)

## Executive Summary Section

(b) (4)

The drug product is a liquid oil filled, soft gelatin capsule. The fill weight is 1.16 g (rounding up to 1200 mg) of drug substance fish oil per capsule. There is roughly (b) (4) of total omega-3 fatty acid ethyl esters per capsule (the exact composition varies from batch to batch). The sponsor has proposed a labeled strength of 900 mg based on the total omega-3 fatty acid ester content. The capsule shell contains gelatin and glycerin. There are no added excipients. An identifying mark is printed on the capsules in white ink. Encapsulation of drug substance is carried out by (b) (4)

Drug product specifications include appearance, EPA and DHA identification, EPA EE composition (b) (4) mg/capsule, target 465 mg), DHA EE composition ((b) (4) mg/capsule, target 375 mg), total omega-3-acid EE's ( $\geq 900$  mg), uniformity of dosage units, (b) (4) tocopherol content and microbiology tests (total aerobic microbial count (total yeasts and molds and E. coli)).

**B. Description of How the Drug Product is Intended to be Used**

The drug product is intended for oral administration as an immediate release soft gelatin capsule. There is one strength, namely 1200 mg (1.16 g) of fish oil per capsule. The sponsor has proposed a labeled strength of 900 mg, based on the content of total omega-3 fatty acid ethyl esters per capsule. The statement of the strength depends on how the drug substance is defined and is pending a decision by ORP. The recommended dosage is 4 capsules per day. The container/closure system is a 400 mL HDPE bottle containing 120 capsules capped with a (b) (4) closure. An expiry of 24 months is granted with storage at controlled room temperature and is supported by adequate stability data.

**C. Basis for Approvability or Not-Approval Recommendation**

NA

**III. Administrative****A. Reviewer's Signature**

## Executive Summary Section

See DARRTS

**B. Endorsement Block**

See DARRTS

**C. CC Block**

See DARRTS

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/s/  
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MARTIN T HABER  
10/17/2013

DANAE D CHRISTODOULOU  
10/17/2013

I concur with the reviewer's conclusions and recommendation

ONDQA  
 IQA (Initial Quality/CMC Assessment)

**Division of Metabolism and Endocrinology Products**

**NDA: 204977**

**Applicant:** Trygg Pharma, Inc.

**Stamp Date:** 31-JAN-2013

**PDUFA Date:** 30-NOV-2013

**Proposed Proprietary Name:** [None indicated]

**Established Name:** Omega-3-acid-ethyl esters

**Dosage form and strength:** Soft capsule: immediate release  
 900 mg

**Route of Administration:** oral

**Indications:** Reduction of triglycerides

**Submission type:** 505(b)(2) NDA (listed drug: Lovaza)

**CMC Lead:** Su (Suong) Tran, ONDQA

Is the Product Quality Section of the application fileable from a CMC perspective?		
Yes	No	
<input checked="" type="checkbox"/>	<input type="checkbox"/>	

Are there potential CMC review issues to be forward to the Applicant with the 74 day letter?		
Yes	No	
<input type="checkbox"/>	<input checked="" type="checkbox"/>	

QUALITY PARTNERS	COMMENT
Biopharmaceutics	The ONDQA Biopharmaceutics Reviewer (H. Mahayni) will review all dissolution, (b) (4)-related information.
EA	The categorical exclusion claim will be assessed by Primary Reviewer.
EES	EER to be sent to Compliance by ONDQA PM.
Methods Validation	Validation may be requested of FDA labs after test methods are finalized.
Microbiology	Review of Microbial Limits.
Pharm/Tox	Review of qualification studies of impurities.

Reference is made to IND 107259 (same sponsor).

ONDQA  
 IQA (Initial Quality/CMC Assessment)

Reference is made to the following DMFs:

Copies of the letters of authorization to the following DMFs are provided:

Company	Material	DMF
(b) (4)	AKR-963 drug substance	(b) (4)
	Drug product ink	
	Drug product bottle	
	Drug product bottle (b) (4)	
	Drug product bottle (b) (4)	
	Drug product bottle closure	
	Drug product cap liner	
	Drug product cap (b) (4)	

Has all information requested during the IND phases and at the pre-NDA meetings been included? Yes.  
 See the discussion in the review.

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.

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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?

**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 (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.*

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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)

**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.

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**Drug substance**

**USAN Nonproprietary Name**

Omega-3-acid ethyl esters

**Chemical Description**

AKR-963 is obtained by esterification of the body oil of fish species primarily from the families (b) (4)

(b) (4) The active ingredient is total omega-3-acid ethyl esters, which is defined as the (b) (4)  
(b) (4)

(b) (4) The main constituents are ethyl esters of eicosapentaenoic acid (EPA, (b) (4)  
and docosahexaenoic acid (DHA, (b) (4) AKR-963 contains about (b) (4) mg/g  
eicosapentaenoic acid ethyl ester (EPAee) about (b) (4) mg/g docosahexaenoic acid ethyl ester  
(DHAee), (b) (4) total omega-3-acid ethyl  
esters. AKR-963 is (b) (4) with 4 mg/g of *d* $\alpha$ -tocopherol.

**Chemical Names**

The chemical names for the main constituents in AKR-963 are given below.

EPAee:

5,8,11,14,17-eicosapentaenoic acid, ethyl ester, (all-Z)-

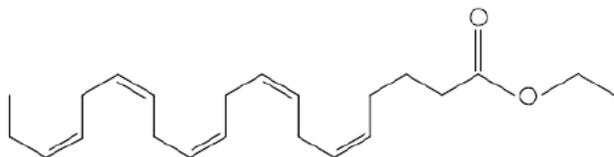
Ethyl (5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenoate

DHAee:

4,7,10,13,16,19-docosahexaenoic acid, ethyl ester, (all-Z)-

Ethyl (4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoate

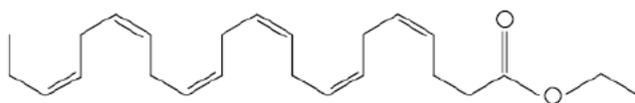
EPAee



Molecular Formula: C<sub>22</sub>H<sub>34</sub>O<sub>2</sub>

Molecular Weight: 330.51

DHAee



Molecular Formula: C<sub>32</sub>H<sub>54</sub>O<sub>2</sub>

Molecular Weight: 356.55

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Property	Value
(b) (4)	

**2.3.S.3.1 Elucidation of Structure and Other Characteristics**

AKR-963 is characterized using the results of UV/Visible, FTIR, <sup>1</sup>H and <sup>13</sup>C NMR, physiochemical properties, and fatty acid ethyl ester composition by gas chromatography (GC). The results support the composition of AKR-963 as proposed.

**Comments:**

- **Starting materials.** (b) (4)  
[Redacted]

(b) (4)  
[Redacted]

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<b>Process Step</b>	<b>Purpose</b>	<b>Manufactured Intermediate</b>
(b) (4)		

(b) (4)

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(b) (4)

Table 2.3.S-17. Release Specification for AKR-963			
Test	Acceptance Criteria		Analytical Procedure
Appearance	Clear, colorless to faint yellow liquid		Visual inspection
EPA ethyl ester identification	Retention time in conformance with reference standard		<i>Ph Eur 2.4.29</i>
DHA ethyl ester identification	Retention time in conformance with reference standard		
Composition (mg/g):	Minimum	Maximum	<i>Ph Eur 2.4.29</i>
EPA ethyl ester	365	435	
DHA ethyl ester	290	360	
(b) (4)			GC, (b) (4)
			USP <401>, <i>Ph Eur 2.5.1</i>
			USP <401>, <i>Ph Eur 2.5.5, Method A</i>
			USP <401>, <i>Ph Eur 2.5.36</i>
			HPLC, (b) (4)
			AAS ( <i>Section 3.2.S.4.2</i> )
			GC, Refer to <i>DMF</i> (b) (4)
(b) (4)			(b) (4)
			(b) (4)
			(b) (4)
AAS = Atomic absorption spectroscopy. GC = Gas chromatography. HPLC = High performance liquid chromatography.			

**Drug product**

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The drug product is a soft gelatin capsule, liquid filled, containing at least 900-mg omega-3-acid ethyl esters, for oral administration. The major components are eicosapentaenoic acid ethyl ester (EPAee) and docosahexaenoic acid ethyl ester (DHAee). An identifying mark is printed on the capsules. The components, their function, and quality are provided in *Table 2.3.P-1*.

The drug product is packaged with 120 capsules in a white opaque high-density polyethylene 400-mL bottle with a (b) (4) white opaque (b) (4) screw cap.

Component	Function	Quality Standard	Amount per Capsule (g)
<b>AKR-963 Drug Substance<sup>a</sup></b>		Trygg Pharma, Inc	1.16
Total omega-3-acid ethyl esters	Active ingredient		(b) (4)
<i>αα</i> -Tocopherol	(b) (4)		
<b>Capsule Shell</b>	(b) (4)		(b) (4)
Gelatin		NF, Ph Eur	
Glycerin		USP, Ph Eur	
Purified water		USP, Ph Eur	
<b>White Ink</b>	(b) (4)		Trace
		USP	
		NF	c
		USP	c
		USP	c
		NF	c
		USP	c
		NF	
		USP	

<sup>a</sup> = Each capsule contains 1.16 g of AKR-963 drug substance, which is composed of at least 900 mg of total omega-3-acid ethyl esters, approximately 465-mg EPAee, approximately 375-mg DHAee, and 4.6-mg *αα*-tocopherol (b) (4)

- **Product composition.** The drug product consists of the drug substance (with the (b) (4) tocopherol) filled in gelatin capsule shells. Other than the (b) (4) in the drug substance, there is no excipient added to the drug product.
- **Dosage strength.** The proposed dosage strength is 900 mg and is based on the specification that each capsule contains ≥ 900 mg of omega-3-acid-ethyl esters (see the copied drug product specification later in this review). The fill weight of each capsule is 1.16 g. For the approved Lovaza (listed drug relied upon), the dosage strength is 1 g based on the fill weight, with the

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prescribing information stating that “Each 1-gram capsule of Lovaza contains at least 900 mg of the ethyl esters of omega-3 fatty acids sourced from fish oil”. To avoid confusion, the dosage strength of the new product (subject of this review) should be labeled the same way as for Lovaza. The reviewer will evaluate this issue during the labeling review. At the Pre-NDA meeting on 10-DEC-2012, the sponsor indicated that they will be prepared to revise the dosage strength as deemed appropriate by FDA during the NDA review cycle.

- **NDA vs. ANDA.** This new product and Lovaza (listed drug relied upon) both contain  $\geq 900$  mg of omega-3-acid-ethyl esters per capsule. However, the new product cannot be an ANDA because the drug substance of the new product does not meet the omega-3-acid-ethyl esters content requirements specified in the USP monograph. Specifically, the USP monograph for this drug substance requires 430-495 mg/g EPA<sub>ee</sub>, 347-403 mg/g DHA<sub>ee</sub>, 800-880 mg/g EPA<sub>ee</sub>+DHA<sub>ee</sub>, and 90% w/w total Omega-3-acid-ethyl esters. The drug substance of the new product contains (b) (4) EPA<sub>ee</sub>, (b) (4) DHA<sub>ee</sub>, (b) (4) total Omega-3-acid-ethyl esters.
- **Established name.** The Office of the Chief Counsel will evaluate the established name of this new product (see attached emails at the end of this review).
- **Gelatin.** The applicant states that the BSE/TSE certification for gelatin is included in the NDA, which will be checked by the primary reviewer. (b) (4)
- **Comparability of the product used in the clinical studies, stability studies, and commercial product.** The applicant states that the formulation is the same for all clinical and stability batches and the commercial product.

**Manufacturing process of the drug product**

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**Capsule Shell Formation**



**Encapsulation**



- **Master batch records.** These records are included in the NDA, complying with the 505(b)(2) regulations.
- **Comparability of the product used in the clinical studies, stability studies, and commercial product.** The applicant states that the manufacturing process is the same for all clinical and stability batches and the commercial product.
- **Critical quality attributes and process parameters.** The proposed critical quality attributes are: content of omega-3-acid-ethyl esters, degradation ( (b) (4) value and (b) (4) value), and drug release ( (b) (4) time). The proposed critical process parameters for these attributes are fill weight, (b) (4) in the manufacturing process, and gelatin composition/processing. The reviewer will evaluate the adequacy of the proposed controls. It is noted that the fill weight is only a process control, it is not included in the drug product specification.

**Drug product specification**

The drug product specification is copied here.



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reviewer will determine whether the fill weight should be added to the drug product specification, especially if the dosage strength should reflect the fill weight instead of the total Omega-3-acid-ethyl esters (see earlier comment on the issue of dosage strength earlier in this review).

- (b) (4). The proposed use of (b) (4) in lieu of Dissolution will be evaluated by the [ONDQA Biopharmaceutics](#) team.
- **Microbial limits.** These limits will be evaluated by the [Microbiologist](#).

### Container closure systems for product distribution

The container closure system is a white opaque high density polyethylene bottle with a (b) (4) (b) (4) screw cap. Marketed product is packaged 120 capsules in a 400-mL bottle. Letters of authorization for the DMFs listed in *Table 2.3.P-15* are provided in *Section 1.4.2*. The specification is provided in *Section 3.2.P.7*.

The applicant states that the safety of the product-contact packaging components is shown by compliance to the indirect food additives regulations (21 CFR 177 and 170-189). Compatibility is shown by stability data. The reviewer will review information in the NDA and DMFs per internal policy on the review of container closure systems for solid oral drug products.

### Stability of the drug product

Data are available from 3 primary stability lots manufactured using the commercial process, at pilot scale, in the commercial facility, printed with black and white ink, packaged in the commercial container closure, and manufactured from a drug substance representative of the intended drug substance (DS) manufacturing process in the commercial DS facility.

Data are available from 5 supportive stability lots manufactured using the commercial process, at pilot scale, in the commercial facility, printed with either white ink or both black and white ink, packaged in the commercial container closure, and manufactured from clinical drug substance manufactured in the commercial DS facility.

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**Table 2.3.P-16. Primary Stability Lots**

Drug Product Lot	Batch Size (kg)	Manufacture Date	(b) (4)	Stability Start Date	Long-term Data Available (Month)
0003910400	(b) (4)	Jul 4, 2011	<i>d</i> $\alpha$ -tocopherol	Oct 20, 2011	12
0003910500	(b) (4)	Jul 4, 2011	<i>d</i> $\alpha$ -tocopherol	Oct 20, 2011	12
0003910600	(b) (4)	Jul 4, 2011	<i>d</i> $\alpha$ -tocopherol	Oct 20, 2011	12

**Table 2.3.P-17. Supportive Stability Lots**

Drug Product Lot	Batch Size (kg)	Manufacture Date	(b) (4)	Stability Start Date	Lot Age at Stability Start (Months)	Ink Color	Long-term Data Available (Months)
0003172900	(b) (4)	Feb 24, 2010	<i>d</i> $\alpha$ -tocopheryl acetate	Sep 15, 2010	7	White	24
0003170601	(b) (4)	May 3, 2010	<i>d</i> $\alpha$ -tocopheryl acetate	Jun 28, 2010	2	White	24
0003170602	(b) (4)	May 3, 2010	<i>d</i> $\alpha$ -tocopheryl acetate	Jun 28, 2010	2	White	24
0003550700	(b) (4)	Jan 17, 2011	<i>d</i> $\alpha$ -tocopheryl acetate	Mar 22, 2011	2	White and black	18
0003559500	(b) (4)	May 2, 2011	<i>d</i> $\alpha$ -tocopherols	Jul 20, 2011	3	White and black	12

**Comments:**

As shown above, 12-month long-term stability data and 6-month accelerated data are submitted for three primary stability batches of drug product. The primary reviewer will determine the final expiry based on all available data and per ICH Q1E Evaluation of Stability Data. Photostability data indicate that the product is light-sensitive, which should be stated on the labeling (i.e., “Store protected from light.”)

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**PRODUCT QUALITY**  
**FILING REVIEW FOR NDA (ONDQA)**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		
B. facilities*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b>			
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	x		
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	x		

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9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>			
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		

\* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
D. drug substance/active pharmaceutical ingredient (DS/api)				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	x		
12.	Does the section contain a description of the DS manufacturing process?	X		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		x	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		x	

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E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
21.	Is there a batch production record and a proposed master batch record?	x		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
23.	Have any biowaivers been requested?		x	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	x		
25.	Does the section contain controls of the final drug product?	x		
26.	Has stability data and analysis been provided to support the requested expiration date?	x		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		x	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	
F. methods validation (Mv)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?			
G. microbiology				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			
H. master files (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		
I. Labeling				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	x		
33.	Have the immediate container and carton labels been provided?	x		
J. filing conclusion				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	x		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	x		See the first page of the IQA.

*{See appended electronic signature page}*

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SUONG T TRAN  
03/04/2013

DANAE D CHRISTODOULOU  
03/04/2013