

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202057Orig1s000

CHEMISTRY REVIEW(S)

Addendum to CMC Review #2

From: Su (Suong) Tran, CMC Lead, ONDQA
To: NDA 202057 (icosapent ethyl)
Through: Ali Al Hakim, Branch Chief, ONDQA
Subject: Final ONDQA recommendation for NDA 202057

This addendum finalizes the CMC Review #2 dated 23-MAY-2012 which included two pending items: the Biopharmaceuticals review and the Compliance/OMPQ/EES overall recommendation. (Please note that the PharmTox review is not a pending consult necessary for finalizing the CMC review.) There is no pending CMC issue.

- The ONDQA Biopharmaceuticals review dated 30-MAY-2012 recommends APPROVAL.
- The Compliance/OMPQ/EES overall recommendation dated 25-JUL-2012 is ACCEPTABLE.

Conclusion: The final CMC recommendation for NDA 202057 is APPROVAL with no pending issue.

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/s/

SUONG T TRAN
07/26/2012

ALI H AL HAKIM
07/26/2012

NDA 202-057

Vascepa (icosapent ethyl) Capsules

Amarin Pharmaceuticals

Martin Haber, Ph.D.

Division of New Drug Quality Assessment III

For

Division of Metabolism and Endocrinology Products

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	7
I. Recommendations.....	7
A. Recommendation and Conclusion on Approvability.....	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s)	7
B. Description of How the Drug Product is Intended to be Used.....	9
C. Basis for Approvability or Not-Approval Recommendation.....	9
III. Administrative.....	9
A. Reviewer's Signature.....	9
B. Endorsement Block.....	9
C. CC Block	9
Chemistry Assessment	10
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	10
S DRUG SUBSTANCE [Icosapent ethyl, Nisshin Pharma].....	10
P DRUG PRODUCT [Vascepa, Capsules].....	14
A APPENDICES	16
R REGIONAL INFORMATION	16
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	17
A. Labeling & Package Insert	17
B. Environmental Assessment Or Claim Of Categorical Exclusion	17

Chemistry Review Data Sheet

1. NDA 202-057
2. REVIEW #2
3. REVIEW DATE: May 23, 2012
4. REVIEWER: Martin Haber, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original NDA	9/23/2011
IQA	11/10/2011
Amendment (Response to 74-day letter)	1/30/2012
Amendment (Microbial limit testing)	2/6/2012
Chemistry Review #1	3/19/2012
Discipline Review Letter (Chemistry)	3/26/2012

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment (Response to DR letter)	4/10/2012

7. NAME & ADDRESS OF APPLICANT:

Name: Amarin Pharma Inc. (US Agent for Amarin Pharmaceuticals Ireland Limited)

Address: 1430 Route 206, Suite 200, Bedminster, NJ 07921

Representative: Peggy J. Berry

Telephone: 302-563-4575

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Vascepa
- b) Non-Proprietary Name (USAN): Icosapent ethyl

Executive Summary Section

- c) Code Name/# (ONDC only): EPA-E
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 1
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505b(1)

10. PHARMACOL. CATEGORY: Triglyceride Reduction

11. DOSAGE FORM: Soft Gelatin Capsules

12. STRENGTH/POTENCY: 1 g

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

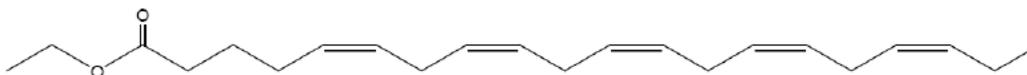
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):
 SPOTS product – Form Completed
 Not a SPOTS product

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

Chemical Name:

Ethyl (5Z,8Z,11Z,14Z,17Z)-5,8,11,14,17-icosapentaenoate

Structural Formula:



Molecular Formula: C₂₂H₃₄O₂

Molecular Weight: 330.51

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Executive Summary Section

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
15062	II	Nisshin Pharma	EPA-E (Drug Substance)	1	Adequate Inadequate	5/22/2012 3/8/2012	Reviewed by this reviewer
(b) (4)				1	Adequate	3/7/2012	""
				1	Adequate	3/7/2012	""
				1	Adequate	3/7/2012	""
25289	II	Catalent Pharma	AMR101 1 g Capsules (Drug Product)	1	Adequate	3/7/2012	""
(b) (4)				3			
				3			
				3			
				3			
				3			
				3			

¹ 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")

² 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
Original	IND 102457	Clinical trials

Executive Summary Section

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
Pharm/Tox	Pending		
Biopharm	Pending		
Methods Validation	Not Required	3/5/2012	M. Haber
EA	Exclusion Acceptable	3/5/2012	M. Haber
Microbiology	Approval	5/23/2012	J. Metcalfe

The Chemistry Review for NDA 202-057

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a CMC perspective, the Applicant has resolved satisfactorily all deficiencies identified in Review #1. There is no pending issue specific to the CMC review. At this time, OMPQ has not issued an overall recommendation for the commercial manufacturing and testing facilities listed in the NDA.

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 product, **Vascepa™ Capsules**, is an (b) (4) soft gelatin capsule containing 1 g of the drug substance, icosapent ethyl. (b) (4)

The drug substance also contains (b) (4) tocopherol, (b) (4). There are no other excipients added to the capsule (b) (4). The capsule (b) (4) contains compendial gelatin, (b) (4) sorbitol, glycerin, maltitol and water (b) (4)

The drug product is manufactured by Banner Pharmacaps Europe in the Netherlands and Catalent Pharma Solutions in St. Petersburg, Florida. However, because of a lack of stability data, the Catalent manufacturing site was withdrawn. The Banner facility inspection is pending. The manufacturing process consists of (b) (4)

The drug product specifications include identification and assay of icosapent ethyl by gas chromatography, identification and assay of tocopherol by HPLC, uniformity of dosage units, related substance impurities, disintegration, (b) (4) and microbiological examination with acceptance limits for

Executive Summary Section

release and shelf-life. No new degradants are observed in the drug product. Stability tests included all release tests except identity and uniformity of dosage units. Stability studies showed no significant change in any test result for up to 24 months at room temperature. A small increasing trend (b) (4) with time was observed but results remained within the proposed acceptance limits. The comparability protocol submitted for post-approval changes was modified as requested.

The drug substance, **icosapent ethyl**, is a long chain, poly-unsaturated omega-3 fatty acid ester derived from fish oil. Icosapent ethyl is the US Accepted Name for eicosapentaenoic acid ethyl ester (EPA-E). It is a clear, pale yellow liquid with very low water solubility. In general, all other related (b) (4) normally found in fish oil (b) (4) have been reduced to low levels, individually not more than (u) (4) or less.

The drug substance is manufactured by Nisshin Pharma Inc. in Japan, holder of DMF 15062. Little information regarding the drug substance was provided in the NDA. Manufacturing of icosapent ethyl involves (b) (4)

Drug substance specifications include identification, assay, related substances, residue on ignition, heavy metals, (b) (4), refractive index, specific gravity and (b) (4). Assay values averaged 98%. Total related substances are limited to NMT (b) (4). There are (b) (4) specified related substances for the drug substance (and the same for the drug product) with acceptance limits ranging from NMT (b) (4) to NMT (b) (4). (b) (4) the specified impurities include (b) (4)

Executive Summary Section

DMF 15062 was reviewed on 3/8/2012 and found inadequate. DMF deficiencies involved related substance standards and specifications. The DMF was amended on 5/8/2012 with the holder's response. It was reviewed on 5/22/2012 and the response was found adequate.

Since the maximum daily dose is > 2 g, according to the ICH Q3A(R2) Guidance for Impurities, the identification and qualification threshold for related substances for impurities in drug substances should be 0.05% (b) (4) as for most drugs. Therefore, the DMF holder tightened the proposed limit for "Related Substances, Each Other Individual Impurity" (b) (4) in the drug substance specifications and provided identification and qualification data for four new impurities present (b) (4). In addition, data was provided to justify the lack of a specification for oligomers and an additional reference standard was prepared for related substances. The related substances standard was used to validate the test methods.

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

The drug product is intended for oral administration. There is one strength, 1 gram of icosapent ethyl per capsule. The recommended dosage is 4 g per day. The commercial container/closure system is a (b) (4) HDPE bottle containing 120 capsules and capped (b) (4). (u) (4) An expiry of 36 months is requested with storage at controlled room temperature.

C. Basis for Approvability or Not-Approval Recommendation

N/A

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

See DFS

B. Endorsement Block

See DFS

C. CC Block

See DFS

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/s/

MARTIN T HABER
05/23/2012

ALI H AL HAKIM
05/23/2012

I concur with the reviewer's recommendation.

NDA 202-057

Vascepa (icosapent ethyl) Capsules

Amarin Pharmaceuticals

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

For
Division of Metabolism and Endocrinology Products

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	7
I. Recommendations.....	7
A. Recommendation and Conclusion on Approvability.....	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s)	7
B. Description of How the Drug Product is Intended to be Used.....	9
C. Basis for Approvability or Not-Approval Recommendation.....	9
III. Administrative.....	9
A. Reviewer's Signature.....	10
B. Endorsement Block.....	10
C. CC Block	10
Chemistry Assessment	11
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	11
S DRUG SUBSTANCE [Icosapent ethyl, Nisshin Pharma].....	11
P DRUG PRODUCT [Vascepa, Capsules].....	23
A APPENDICES	66
R REGIONAL INFORMATION	67
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	73
A. Labeling & Package Insert	73
B. Environmental Assessment Or Claim Of Categorical Exclusion	74

Chemistry Review Data Sheet

1. NDA 202-057
2. REVIEW #1
3. REVIEW DATE: March 19, 2012
4. REVIEWER: Martin Haber, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
IQA	11/10/2011

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	9/23/2011
Amendment (Response to 74-day letter)	1/30/2012
Amendment (Microbial limit testing)	2/6/2012

7. NAME & ADDRESS OF APPLICANT:

Name: Amarin Pharma Inc. (US Agent for Amarin Pharmaceuticals
Ireland Limited)

Address: 1430 Route 206, Suite 200, Bedminster, NJ 07921

Representative: Peggy J. Berry

Telephone: 302-563-4575

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Vascepa
- b) Non-Proprietary Name (USAN): Icosapent ethyl
- c) Code Name/# (ONDC only): EPA-E
- d) Chem. Type/Submission Priority (ONDC only):

Executive Summary Section

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505b(1)

10. PHARMACOL. CATEGORY: Triglyceride Reduction

11. DOSAGE FORM: Soft Gelatin Capsules

12. STRENGTH/POTENCY: 1 g

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

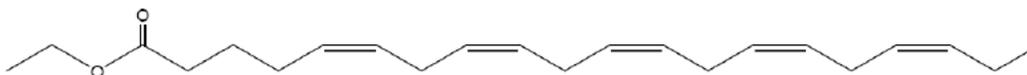
Not a SPOTS product

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

Chemical Name:

Ethyl (5Z,8Z,11Z,14Z,17Z)-5,8,11,14,17-icosapentaenoate

Structural Formula:



Molecular Formula: C₂₂H₃₄O₂

Molecular Weight: 330.51

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF	TYPE	HOLDER	ITEM	CODE ¹	STATUS ²	DATE	COMMENTS
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Executive Summary Section

#			REFERENCED			REVIEW COMPLETED	
15062	II	Nisshin Pharma	EPA-E	1	Inadequate	3/8/2012	Reviewed by this reviewer
(b) (4)				1	Adequate	3/7/2012	""
				1	Adequate	3/7/2012	""
				1	Adequate	3/7/2012	""
25289	II	Catalent Pharma	AMR101 1 g Capsules	1	Adequate	3/7/2012	""
(b) (4)				3			
				3			
				3			
				3			
				3			
				3			
				3			

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7 – Other (explain under "Comments")

² 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
Original	IND 102457	Clinical trials

18. STATUS:

Executive Summary Section

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
Pharm/Tox	Pending		
Biopharm	Pending		
Methods Validation	Not Required	3/5/2012	M. Haber
EA	Exclusion Acceptable	3/5/2012	M. Haber
Microbiology	Pending		

The Chemistry Review for NDA 202-057

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Additional information required, see Section II.C.

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 product, **Vascepa™ Capsules**, is an (b) (4) soft gelatin capsule containing 1 g of the drug substance, icosapent ethyl. (b) (4)

The drug substance also contains (b) (4) tocopherol, (b) (4). There are no other excipients added to the capsule (b) (4). The capsule (b) (4) contains compendial gelatin, (b) (4) sorbitol, glycerin, maltitol and water (b) (4) (u) (4)

The drug product is manufactured by Banner Pharmacaps Europe in the Netherlands and Catalent Pharma Solutions in St. Petersburg, Florida. The Banner inspection is pending. The manufacturing process consists of (b) (4) (u) (4)

The drug product specifications include identification and assay of icosapent ethyl by gas chromatography, identification and assay of tocopherol by HPLC, uniformity of dosage units, related substance impurities, disintegration, (b) (4) and microbiological examination with acceptance limits for release and shelf-life. No new degradants are observed in the drug product. Stability tests included all release tests except identity and uniformity of dosage units. Stability studies showed no significant change in any test result for up to 24 months at room temperature. A small increasing trend (b) (4) with time was observed but results remained within the proposed acceptance limits.

Executive Summary Section

Because the expiration period can not be determined due to a lack of stability data for capsules manufactured by Catalent, this manufacturing site is recommended to be withdrawn. In addition, the comparability protocol submitted for post-approval changes does not follow normal Agency post-approval procedures in some cases and therefore it must be modified.

The drug substance, **icosapent ethyl**, is a long chain, poly-unsaturated omega-3 fatty acid ester derived from fish oil. Icosapent ethyl is the US Accepted Name for eicosapentaenoic acid ethyl ester (EPA-E). It is a clear, pale yellow liquid with very low water solubility. In general, all other related (b) (4) normally found in fish oil (b) (4) have been reduced to low levels, individually not more than (u) (4) or less.

The drug substance is manufactured by Nisshin Pharma Inc. in Japan, holder of DMF 15062. Very little information regarding the drug substance was provided in the NDA and had to be obtained from the DMF. DMF 15062 has been reviewed and found inadequate. (b) (4)

(b) (4) Additional information on environmental contaminant testing, reference standards and batch data has been requested.

Drug substance specifications include identification, assay, related substances, residue on ignition, heavy metals, (b) (4), refractive index, specific gravity and (b) (4). Assay values averaged 98%. Total related substances are limited to NMT (b) (4). There are 11 specified related substances for the drug substance (and the same for the drug product) with acceptance limits ranging from (b) (4)

Executive Summary Section

(b) (4)

DMF 15062 deficiencies are for related substance standards and specifications. Since the maximum daily dose is > 2 g, according to the ICH Q3A(R2) Guidance for Impurities, the identification and qualification threshold for related substances for impurities in drug substances should be 0.05% (b) (4) as for most drugs. However, the sponsor decided that this limit is too rigorous for a fish oil product. Because of the harsh manufacturing process and the resulting impurity profile of this drug substance, a tighter threshold for qualification of impurities is required. Therefore, the DMF holder was requested to tighten the proposed limit for 'related substances, others' (b) (4) in the drug substance specifications and to provide identification and qualification data for impurities greater than (b) (4). In addition, data on oligomers to justify the lack of a specification for oligomers and reference standards for related substances has been requested. Adequate reference standards for related substances need to be established and used to validate the test methods.

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

The drug product is intended for oral administration. There is one strength, 1 gram of icosapent ethyl per capsule. The recommended dosage is 4 g per day. The commercial container/closure system is a (b) (4) HDPE bottle containing 120 capsules and capped (b) (4). (b) (4). An expiry of 36 months is requested with storage at controlled room temperature.

C. Basis for Approvability or Not-Approval Recommendation

The drug substance DMF 15062 is inadequate because of inadequate specifications regarding unidentified related substance impurities, lack of data on oligomers and the lack of reference standards for specified impurities.

The NDA can not be approved presently due to the drug substance deficiencies given above and lack of data from the Catalent manufacturing site. In addition, facility inspections are pending.

III. Administrative

Executive Summary Section

A. Reviewer's Signature

See DFS

B. Endorsement Block

See DFS

C. CC Block

See DFS

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/s/

MARTIN T HABER
03/19/2012

ALI H AL HAKIM
03/19/2012

ONDQA
IQA (Initial Quality/CMC Assessment)

Division of Metabolism and Endocrinology Products

NDA: 202057
Applicant: Amarin Pharmaceuticals
Stamp Date: 26-SEP-2011
PDUFA Date: 26-JUL-2012
Proposed Proprietary Name: Vascepa
Established Name: Icosapent ethyl
Dosage form and strength: Soft capsule: immediate release
1 g
Route of Administration: oral
Indications: Reduction of triglycerides

CMC Lead: Su (Suong) Tran, ONDQA

ONDQA Fileability: Yes

Are there comments for the 74-day letter? Yes.

- In the NDA, you include the drug substance specifications from the drug substance manufacturer and from the drug product manufacturer Banner. Reference is made to DMF 25289 for the drug substance specification from the drug product manufacturer Catalent. Provide a copy of the Catalent drug substance specification in the NDA. In addition, clarify which drug substance specification will serve as the regulatory specification (i.e., for FDA's method validation and GMP enforcement purposes).
- A comparability protocol cannot be located in the NDA even though you proposed one at the Pre-NDA meeting. As stated in FDA's 2003 draft guidance "Comparability Protocols – CMC Information", the protocol should be submitted either in the original NDA or in a post-approval supplement (prior-approval) for FDA's approval prior to the applicant's initiation of the protocol studies. Clarify whether you still intend to use a comparability protocol for qualifying a new drug substance manufacturer.
- Justify the lack of Microbial Limits in the drug substance specifications. The drug substance is naturally derived and such an attribute should be included in the specification.
- Include in the drug substance specifications tests and acceptance criteria for contaminants commonly found in fish oil [REDACTED] (b) (4)
[REDACTED] Provide safety information to support the proposed acceptance criteria.
- Submit the Catalent product composition to the NDA.

ONDQA
 IQA (Initial Quality/CMC Assessment)

- The NDA includes only 1-month stability data (long-term and accelerated) for one product batch manufactured by Catalent. An expiration dating period cannot be determined based on such limited data. We strongly recommend that Catalent be submitted in a post-approval supplement (i.e., withdrawn from the current NDA submission) with all the necessary supporting data (comparative in-vitro testing, at minimum 3-month long-term and accelerated stability data for three product batches at no less than (b) (4) commercial scale).

[End of comments for the 74-day letter]

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharmaceutics	The ONDQA Biopharmaceutics Review Staff will review all dissolution-related information.
CDRH or CBER	<i>Not Applicable</i>
EA	The categorical exclusion claim will be assessed by Primary Reviewer.
EES	EER was sent to Compliance on 10-OCT-2011 by ONDQA PM.
OSE	<i>Labeling consult request will be sent as part of DMEP's request.</i>
Methods Validation	<i>Validation may be requested of FDA labs after test methods are finalized.</i>
Microbiology	Review of Microbial Limits (the product is derived from fish oil and a soft gel capsule).
Pharm/Tox	Review of qualification studies of impurities.
Quality by Design	<i>Not Applicable</i>

This is an electronic NDA. The supporting IND is IND 102457. It was initially filed as a 505(b)(1) application but changed by the applicant to a 505(b)(2) based on published toxicology studies for a non-U.S. product called Epadel (marketed in Japan). There is no mention of this Japanese product in the CMC section of the NDA.

The drug substance icosapent ethyl, an ethyl ester of the omega-3 fatty acid eicosapentaenoic acid (E-EPA). E-EPA is one of the two major components of the approved Lovaza, omega-3-acid ethyl esters, (Lovaza has a different applicant).

The drug product is a soft-gelatin capsule containing 1 g of icosapent ethyl and these excipients: tocopherol, gelatin, glycerin, maltitol, sorbitol, and purified water.

The product will be packaged in 120-count bottles for commercial distribution and 4-count bottles as physician samples, and will be stored at room temperature.

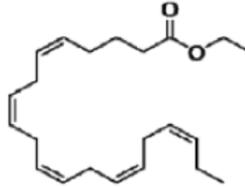
Maximum daily dose is 4 g (4 capsules).

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

ONDQA
IQA (Initial Quality/CMC Assessment)

Drug substance

Each VASCEPA capsule contains 1 gram of icosapent ethyl. Icosapent ethyl is an ethyl ester of the omega-3 fatty acid eicosapentaenoic acid (EPA). The empirical formula of icosapent ethyl is $C_{22}H_{34}O_2$ and the molecular weight is 330.51. The chemical name for icosapent ethyl is ethyl all-cis-5,8,11,14,17-icosapentaenoate with the following chemical structure:



Appearance

Icosapent ethyl is a clear, colorless to pale yellow liquid.

(b) (4)

ONDQA
IQA (Initial Quality/CMC Assessment)

(b) (4)

Review comments:

Reference is made to the DMF 15062 for all CMC information on the drug substance. The primary reviewer will review any new information in the DMF submitted after the most recent review.

- (b) (4) Icosapent ethyl is a liquid oil at room temperature, BCS 2, and readily oxidized. (b) (4) tocopherol is used (b) (4) and this excipient does appear in the drug product composition as well as the proposed labeling.

ONDQA
IQA (Initial Quality/CMC Assessment)

(b) (4)

Question 1B. Does the Agency agree that the API starting material for the manufacture of the Nisshin ethyl-EPA (b) (4) and that the ethyl-EPA manufacturing process should be conducted under GMP (b) (4) (b) (4)

FDA Response: No. The initial processing (b) (4) involves many steps (b) (4) (b) (4) “specified in ICH Q7 as not being subject to CGMPs.

- **Drug substance specification.** In addition to release testing by the drug substance manufacturer Nisshin (DMF 15062), the 2 drug product manufacturers also conduct release testing of drug substance upon receipt. The NDA includes the drug substance specification from the drug substance manufacturer Nisshin (DMF 15062) and the drug substance specification from the drug product manufacturer Banner (copied on pages 18-19 of this review). Reference is made to DMF 25289 for the drug substance specification from the drug product manufacturer Catalent, which is not acceptable because all drug substance specifications should be included in the NDA. In addition, the applicant should clarify which drug substance specification will serve as the regulatory specification ([see the 74-day letter comment](#)).

The drug substance specification should include Microbial Limits because the drug substance is naturally derived, unless the applicant has an acceptable justification for the omission (e.g., providing data to show that the drug substance is not capable of supporting microbial growth or that the manufacturing process can effectively reduce/remove microorganisms) ([see the 74-day letter comment](#)).

The drug substance specification should include tests and acceptance criteria for contaminants commonly found in fish oil (b) (4)

ONDQA
 IQA (Initial Quality/CMC Assessment)

(b) (4)

- Comparability protocol.** At the Pre-NDA meeting, the sponsor presented a draft of a comparability protocol for qualifying an additional drug substance manufacturer. FDA conveyed comments to the sponsor regarding this draft protocol. The final protocol cannot be located in the NDA. The applicant should clarify whether the applicant still intends to use a comparability protocol for qualifying a new drug substance manufacturer, and if so, the final protocol should be submitted to the NDA for approval by FDA. As stated in FDA’s 2003 draft guidance “Comparability Protocols – CMC Information”, the protocol should be submitted either in the original NDA or in a post-approval supplement (prior-approval) for FDA’s approval prior to the applicant’s initiation of the protocol studies ([see the 74-day letter comment](#)).
- Impurities.** Reference is made to DMF 15062 for information on impurities. In addition, the NDA includes information on the qualification of specified impurities as tabulated below. With consult from the PharmTox team, the reviewer will consider this information and all other available data from the stability and characterization reports in finalizing the drug substance specification.

Table 2.3.S.3-1 Summary of Drug Substance Batches Used in Non-Clinical Toxicology Studies

Related Substances ^a (all data reported as %w/w)	Drug Substance Batch Number					
	EE171GQ	EE050JR (LAX101-20050) ^b	U-99A-D4-K (b) (4)	EE070IX	EE141IS	EE030HU (b) (4)
Type of Study (Study or Report No.)	Genotox: Ames (01-0680-G1) Genotox: Chrom abb (01-0680-G2) Genotox: micronucleus (01-0690-G3)	Genotox: CHO cells (21548 and 21549)	Genotox: CHO cells (21882 and 21883)	4-wk mouse (459549) 4-wk rat (ZOC0001) 14-d DRF dog (515147) 39-wk dog (515194) Developmental tox rat (494981) 26-wk care in transgenic mouse (8222196)	104-wk care in rat (23040)	104-wk care in rat (23040)

^a All data reported as %w/w. Data are from Nisshin Certificate of Analysis, unless otherwise noted.
^b Test Article was provided in relative amounts.
^c Listed as (b) (4) on CoA.
 n.d. = Not detected
 - Not determined. Test was not part of the specification at the time of testing. See DMF 015062 for more information.

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Table 2.3.S.3-2 Summary of Related Substances Qualification Data Used in Non-Clinical Studies

(b) (4)



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Drug product

Amarin uses two drug product manufacturers to produce AMR101 Capsules, 1 g: Banner Pharmacaps Europe BV [Banner] and Catalent Pharma Solutions [Catalent]. Please refer to [Section 2.3.P.3.1](#) for additional information on the drug product manufacturers. Both firms produce AMR101 Capsules, 1 g, using the same components and composition, (b) (4)



Table 2.3.P.1-1 Composition of Drug Product Manufactured by Banner

Component	Unit Quantity (mg/capsule)	Function	Reference to Standard
(b) (4)			
Icosapent Ethyl ^a	1000	Active	In-House
(b) (4)			
Gelatin	(b) (4)		USP/NF, Ph.Eur.
(b) (4) Sorbitol (b) (4)			USP/NF, Ph.Eur.
Glycerin			USP/NF, Ph.Eur.
Purified Water			USP/NF, Ph.Eur.
Maltitol (b) (4)			USP/NF, Ph.Eur.

- **Product composition.** The NDA includes the product formulation from the drug product manufacturer Banner and references DMF 25289 for the formulation from the second manufacturer Catalent, which is not acceptable. The applicant should submit the Catalent

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formulation to the NDA ([see the 74-day letter comment](#)). The Banner and Catalent formulations

(b) (4)

- **Gelatin.** The applicant states that BSE/TSE certifications for gelatin are included in the NDA and DMF 25289; they will be checked by the primary reviewer. The applicant manufactures the capsule (b) (4) as part of the drug product manufacturing process.
- **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 (b) (4)

Manufacturing process of the drug product

(b) (4)

Review comments:

- **Comparability of the product used in the clinical studies, stability studies, and commercial product.** The applicant states that Banner manufactured the pilot-scale (b) (4) commercial scale) batches for the pivotal clinical studies and primary stability studies, using the commercial formulation, manufacturing process and equipment. The process was transferred to an additional manufacturer, Catalent. The reviewer will evaluate Catalent's DMF 25289 to determine whether Catalent's process will produce the same drug product as Banner's. Stability data are included in the NDA for one batch manufactured by Catalent (see comments in the Stability section of this review). [The Biopharm team will handle any biowaiver issue in bridging the 2 manufacturers.](#)
- **Critical process controls.** There are 2 critical aspects in the drug product manufacturing process:

(b) (4) The

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reviewer will evaluate the adequacy of the controls. The same critical controls should apply to both manufacturers Banner and Catalent.

Drug product specification

The drug product specification is copied on pages 20-21 of this review.

Review comments:

- **Limits on degradation products.** The applicant states that there is no degradant in the drug product that differs from the drug substance-related impurities. The drug product specification has the same specified impurities/degradants and limits as those in the drug substance specification. The proposed limit on the unspecified impurity/degradant is (b) (4), which is within the ICH identification and qualification thresholds for the maximum drug exposure of 4 g.
- **Disintegration.** The proposed use of Disintegration in lieu of Dissolution will be evaluated by the ONDQA Biopharm team. This issue was discussed at the Pre-NDA meeting (see copied comments below).

Question 4. Amarin proposes that, since the drug substance is an oil and therefore insoluble in water, the dissolution test is not necessary and that the disintegration test is adequate for quality control testing. Does the Agency agree with this approach?

FDA Response: Yes. Provide a justification in the NDA for the choice of disintegration medium and the proposed disintegration time (NMT (b) (4) specification. Also, for a soft gelatin capsule, "disintegration test" should be more appropriately termed as "rupture test" and the specification should indicate "rupture time".

- **Omitted tests.** The reviewer will evaluate the justification for the following tests not being included in the drug product specification: residual solvents (historical data show insignificant levels of residual (b) (4)), hardness (in-process test), mean gross weight (in-process test), and dimensions (in-process test).

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Container closure systems for product distribution

- Commercial Market Presentation

The primary packaging for AMR101 Capsules, 1 g, for commercial marketing is in (b) (4) high density polyethylene (HDPE) bottles. Each HDPE bottle contains 120 capsules and is capped (b) (4).

- Physician Sample Presentation

The primary packaging for AMR101 Capsules, 1 g, for physician samples is in (b) (4) high density polyethylene (HDPE) bottles. Each HDPE bottle contains 4 capsules and is capped (b) (4).

Review comment: The primary 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

Table 2.3.P.8-1 Summary of Primary and Supportive Stability Studies for AMR101 Capsules

Description	Packaging Configuration	Manufacturer	Stability Study Number	Number of Batches	Data Presented in NDA			
					25°C/	15-30°C / NMT	30°C/	40°C/ (b) (4)
Primary Stability	Commercial ^b	Banner	BD10-028	3	12 mo	---	---	6 mo
		Catalent	TTP-ANN-M0004	1	1 mo	---	1 mo	1 mo
	Physician Sample ^c	Catalent	TTP-ANN-M0005	3	1 mo	---	---	1 mo
Supportive Stability ^a	Commercial ^b	Banner	BD09-033	2	24 mo	---	24 mo	6 mo
		(b) (4)						

^a AMR101 Capsules used for Supportive stability studies are not printed. All other components and composition are the same as capsules used for the Primary stability studies.

^b Commercial packaging configuration is 120-ct in a (b) (4) bottle with (b) (4) cap.

^c Physician Sample packaging configuration is 4-ct in a (b) (4) bottle with (b) (4) cap.

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Table 2.3.P.8-3 Details of Batches for AMR101 Capsules, 1 g – Commercial Market Presentation

Designation	Primary Stability				Supportive Stability		
Protocol No.	BD10-028			TTP-ANN-M0004	BD09-033		
Drug Product Batch No.	256188A	256189A	256190A	1204849	249353A	249356A	249356A
Drug Product Batch Size	(b) (4)						
Capsule Printing	"EPA1000"	"EPA1000"	"EPA1000"	"AMR101"	Not printed	Not printed	Not printed
Drug Substance Batch No.	EE020AX	EE130FW	EE050LY	EE020BB	EE020AX	EE020AX	EE020AX
Drug Substance Manufacturer	(b) (4)						
Drug Product Manufacturer	Banner	Banner	Banner	Catalent	Banner	Banner	Banner
Date of Manufacture of Finished Product	March 2010	March 2010	March 2010	June 2011	October 2008	October 2008	October 2008
Packaging Batch No.	XI07D5	XI07D4	XI07D6	CLR-16441-001	XI07D1	XI07D2	XI07C1
Type of Packaging	(b) (4)						
Number of Capsules/ Bottle	120	120	120	120	120	120	60
Date Study Initiated	June 2010	June 2010	June 2010	July 2011	July 2009	July 2009	July 2009

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Table 2.3.P.5-2 Summary of AMR101 Capsule, 1 g Batches

Bulk Drug Product Lot Number	Batch Size (capsules)	Place of Manufacture	Date of Manufacture	Drug Substance Batch Number ^a	Use
249353A	(b) (4)	Banner	October 2008	EE020AX	Clinical study 0016 (open label) Supportive stability
249354A		Banner	October 2008	EE070IX	Clinical study 0016 (double blind) Clinical study 0017 (double blind) Supportive stability
249355A		Banner	October 2008	EE100LX	Clinical study 0016 (open label) Clinical study 0017 (double blind) Supportive stability
249356A		Banner	October 2008	EE020AX	Supportive stability
256188A		Banner	March 2010	EE020AX	Primary stability
256189A		Banner	March 2010	EE130FW	Clinical study 0016 (open label) Clinical study 0018 Clinical study 0020 Clinical study 0021 Clinical study 0023 Primary stability
256190A		Banner	March 2010	EE050LY	Primary stability
263672A		Banner	June 2011	EE100LX, EE130FW EE070IX	Process verification (development study)
1204849		Catalent	June 2011	EE020BB	Primary stability

^a All drug substance batches of icosapent ethyl were supplied by Nisshin Pharma, Inc.

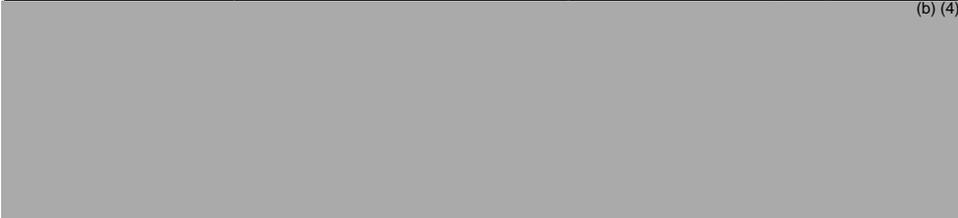
Review comments:

- As shown by the tables above, 12-month long-term stability data and 6-month accelerated data are submitted for 3 batches of drug product manufactured by Banner, at (b) (4) commercial scale. The primary reviewer will determine the final expiry based on all available data and per ICH Q1E Evaluation of Stability Data.
- The primary stability data package was previously discussed at the Pre-NDA phase. However, no mention of a second drug product manufacturer (Catalent) was made by the sponsor prior to the NDA submission. The NDA includes only 1-month stability data (long-term and accelerated) for one product batch manufactured by Catalent. The one Catalent batch has (b) (4) capsules and it is not known how this batch size compares to the commercial scale. There is no information regarding the Catalent product in the NDA because reference is made to DMF 25289. It would be

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extremely difficult to determine an expiration dating period based on only one product batch and one-month stability data ([see the 74-day letter comment](#)).

Supporting DMFs:

DMF number	DMF Holder		Letter of authorization
15062	Nisshin	EPA-E	X
25289	Catalent Pharma	AMR101 1 g Capsules	X
 (b) (4)			X
			X
			X
			X
			X

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GMP facilities: EER was sent to Compliance on 10-OCT-2011 by ONDQA PM.

Icosapent ethyl is manufactured, packaged, labeled, tested, and released, under GMP conditions, at:

Nisshin Pharma Inc.
Ueda Plant
751 Kamishiojiri
Uedashi, Nagano
386-0042 Japan

The drug product, AMR101 Capsules, 1 g, is manufactured according to current Good Manufacturing Practices (cGMP) and controlled at the following manufacturers.

AMR101 Capsules are manufactured and bulk packaged by:

Banner Pharmacaps Europe BV
De Posthoornstraat 7
5048 AS Tilburg
The Netherlands
FEI Number: 1000384811
DUNS Number: 417524097
Contact Person: Sandor Noordermeer, Director of Operations
snoordermeer@banpharm.com
+31-13-4624196

Catalent Pharma Solutions, LLC
2725 Scherer Drive
St. Petersburg, FL 33716
FEI Number: 1811396
DUNS Number: 051762268
Contact Person: Terese A. Dixon, Quality and Regulatory Affairs Director
terry.dixon@catalent.com
727-803-2247

AMR101 Capsules are primary packaged by:



Catalent Pharma Solutions, LLC
3001 Red Lion Road
Philadelphia, PA 19114
FEI Number: 1000522077
DUNS Number: 806746405
Contact: Josette Miceli, Director, Quality Systems
josette.miceli@catalent.com
215-501-1221

ONDQA
IQA (Initial Quality/CMC Assessment)

AMR101 Capsules are tested by:

Banner Pharmacaps Europe BV
De Posthoornstraat 7
5048 AS Tilburg
The Netherlands
FEI Number: 1000384811
DUNS Number: 417524097
Contact Person: Sandor Noordermeer, Director of Operations
snoordermeer@banpharm.com
+31-13-4624196

Catalent Pharma Solutions, LLC
2725 Scherer Drive
St. Petersburg, FL 33716
FEI Number: 1811396
DUNS Number: 051762268
Contact Person: Terese A. Dixon, Quality and Regulatory Affairs Director
terry.dixon@catalent.com
727-803-2247

Catalent Pharma Solutions, LLC
160N Pharma Drive
Morrisville, NC 27560
FEI Number: 1000110912
DUNS Number: 945090236
Contact Person: Trevor Lewis, Ph.D., Director, Quality
trevor.lewis@catalent.com
919-465-8199

(b) (4)

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IQA (Initial Quality/CMC Assessment)

AMR101 Capsules are tested for microbial attributes by:

Banner Pharmacaps Europe BV
De Posthoornstraat 7
5048 AS Tilburg
The Netherlands
FEI Number: 1000384811
DUNS Number: 417524097
Contact Person: Sandor Noordermeer, Director of Operations
snoordermeer@banpharm.com
+31-13-4624196

Catalent Pharma Solutions, LLC
2725 Scherer Drive
St. Petersburg, FL 33716
FEI Number: 1811396
DUNS Number: 051762268
Contact Person: Terese A. Dixon, Quality and Regulatory Affairs Director
terry.dixon@catalent.com
727-803-2247

Catalent Pharma Solutions, LLC
160N Pharma Drive
Morrisville, NC 27560
FEI Number: 1000110912
DUNS Number: 945090236
Contact Person: Trevor Lewis, Ph.D., Director, Quality
trevor.lewis@catalent.com
919.465.8199

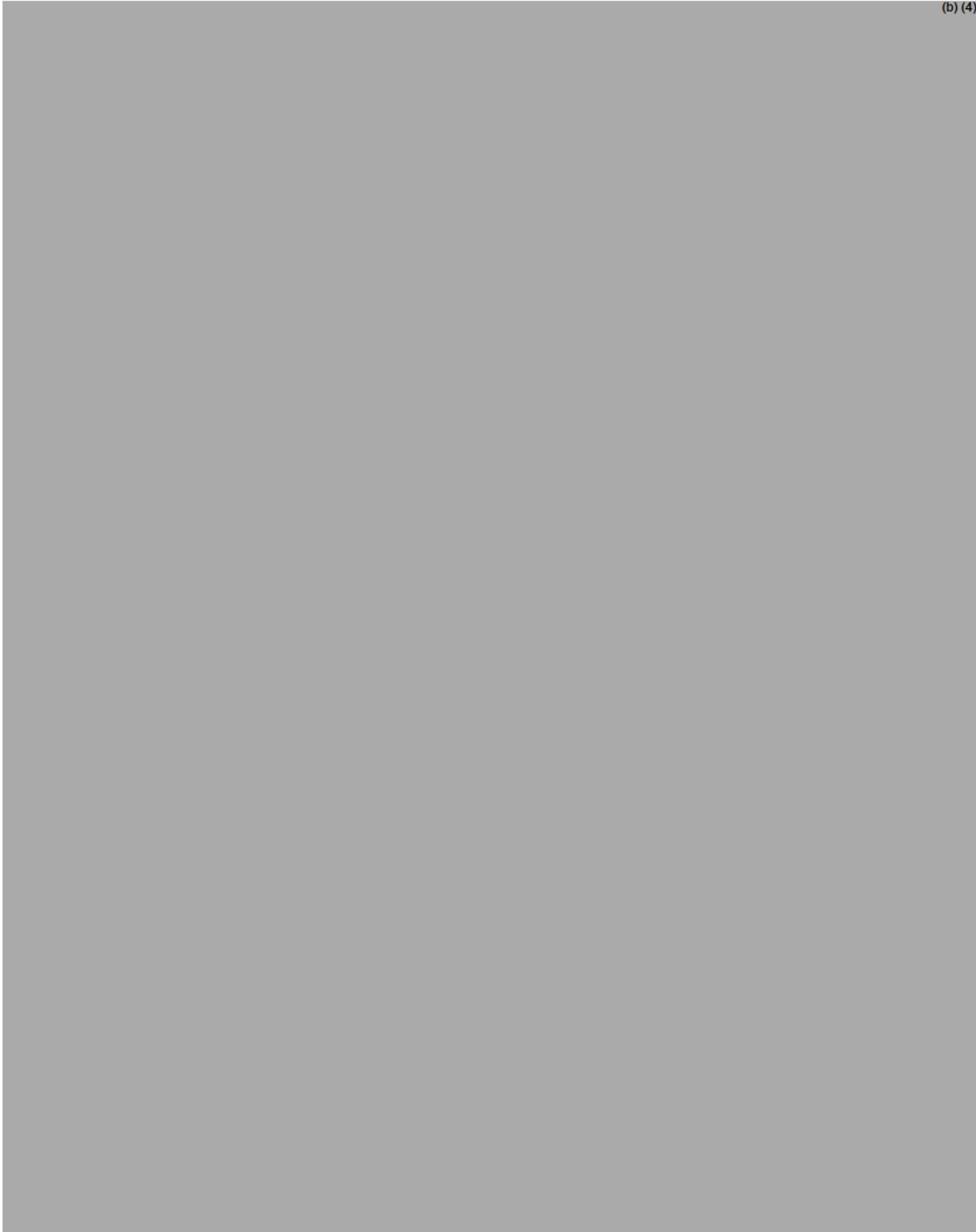
(b) (4)



ONDQA
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Drug substance specification

(b) (4)



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ONDQA
 IQA (Initial Quality/CMC Assessment)

PRODUCT QUALITY
FILING REVIEW FOR NDA (ONDQA)

NDA Number: 202057

Applicant: Amarin

Letter Date: 23-SEP-2011

Established/Proper Name:

Icosapent ethyl

Stamp Date: 26-SEP-2011

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? This question is not applicable for synthesized API.	x		Same facility (Nisshin Pharma, Japan) for the synthesis of the drug substance (b) (4)
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"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 			
8.	Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 			

ONDQA
 IQA (Initial Quality/CMC Assessment)

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"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 			
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		DMF 15062
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		DMF 15062
14.	Does the section contain information regarding the characterization of the DS?	X		DMF 15062
15.	Does the section contain controls for the DS?	X		DMF 15062
16.	Has stability data and analysis been provided for the drug substance?	X		DMF 15062
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		In addition, DMF 25289.
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		In addition, DMF 25289.
21.	Is there a batch production record and a proposed master batch record?	x		In addition, DMF 25289.
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?			See Biopharm filing memo
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		Review issue: whether data and analysis are adequate to support expiry
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?			Non-sterile oral dosage form.
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}

Su (Suong) Tran

CMC Lead, Office of New Drug Quality Assessment

{See appended electronic signature page}

Ali Al Hakim

Branch Chief, Office of New Drug Quality Assessment

Date *{see appended electronic signature page}*

Date *{see appended electronic signature page}*

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

/s/

SUONG T TRAN
11/10/2011

ALI H AL HAKIM
11/10/2011