CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-654

Chemistry Review(s)

DRAFT

NDA 21-654

Omacor (omega-3-acid ethyl esters) Capsules

CHEMISTRY DIVISION DIRECTOR REVIEW

Applicant: Ross Products Division Abbott Laboratories,Inc.
Columbus, OH

Indication: Treatment of Hypertriglyceridemia

Presentations: 3 oz. — Physicians Sample/28 count
375 mL — bottes/120 count

EER Status: Acceptable 2-MAR-2004

Consults: DMETS – Omacor tradename is unacceptable 11-NOV-2004
[Note that the Division finds it acceptable]
Statistics – none
EA – no consult - waiver requested - granted

Omacor NDA 21-654 — submitted 01-SEP-2004. NDA 21-654 is considered for approval from a clinical perspective. A CMC IR letter was sent 17-AUG-2004.

[

]

The **drug substance** is manufactured by: Pronova Biocare a.s., Norway, in [ ] process involving [ ] triglycerides from fish body oil. The oil is extracted from ocean fish families such as *Engaulidae, Carangidae, Clupeidae, Osmeridae, Salmonidae* and *Scrombroidae*. [ ]

Omega-3 acid ethyl esters is a fish-oil fatty acid ester concentrate containing about — all-cis-(Z) 5,8,11,14,17-eicosapentaenoic acid ethyl ester (EPA-EE, C20:5n-3) and about all-cis 4,7,10,13,16,19-docosahexaenoic acid ethyl ester (DHA-EE, C22:6n-3). Another approximately consists of the ethyl esters of the following [ ] alpha-linolenic acid (C18:3n-3),

Also present at about — of the total mixture are the ethyl esters [ ] About 4 mg/g of α-tocopherol in partially hydrogenated vegetable oils is added to the drug substance — — . Adequate characterization was performed for the major components — EPA and EE-DHA.

Stability data support a re-test period of — stored at 25° C. (The drug substance is stable for up to — when stored under — at room temperature.) Note that no protocol for extension of the re-test period has been provided.

Drug substance specifications are condidered adequate. They cover a range of impurities which may be present [ ] A meeting was held 11/10/2004 with the CMC reviewer and TL Martin Haber and Mamta Gautam Basak and the Pharm/Tox supervisor Karen Davis Bruno to consider the specifications for these impurities. — are well within the acceptable EPA drinking water limits. — — are below CFSAN limits for food intake. — limits were also considered acceptable. Conclusion re. impurities specifications – acceptable.

Conclusion
Drug substance information is acceptable.

The **drug product** manufacturer is Cardinal Health, St Petersburg FL. Manufacturing information is provided in DMF[redacted] which was found acceptable for manufacture and controls. The product is a soft gelatin capsule filled with the purified fish oils and α-tocopherol in partially hydrogenated vegetable oils added to the drug substance . Release testing is done by Pronova Biocare, Norway by the same methods used for the drug substance – this is acceptable because the product formulation does not differ from the drug substance formulation (an added test for disintegration is performed on the gelatin capsules).

Submitted stability data support the proposed 18 month expiry. The stability protocol is in accord with ICH recommendations. Stability testing commitments are acceptable.

Labeling is acceptable. The established name has finally been agreed to be Omega-3-acid ethyl esters.

All associated DMFs are acceptable.

Conclusion
Drug product information is acceptable.

Overall Conclusion
From a CMC perspective an approval action is recommended.

Eric P Duffy, PhD

Director, DNDC II/ONDC

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/s/

Eric Duffy
11/10/04 02:10:11 PM
CHEMIST
Revised review - corrected recommendation from DMETS to refect the recommendation that Omacor is unacceptable.

11/1/04

CHEMISTRY REVIEW

NDA 21-654

Omacor (omega-3-acid ethyl esters) Capsule

Ross Products Division – Abbott Laboratories, Inc.

Martin Haber, Ph.D.
Division of Metabolism and Endocrine Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-654

2. REVIEW #: 2

3. REVIEW DATE: November 1, 2004

4. REVIEWER: Martin Haber, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA	1/9/04
Initial Filing Memorandum	3/24/04
Amendment	5/10/04
Amendment	7/1/04
Amendment	7/20/04
IR Letter	8/17/04
Amendment	9/3/04
Amendment	9/8/04
Amendment	9/10/04
Amendment	9/24/04
Amendment	9/29/04
Amendment	10/5/04
Chemistry Review #1	10/20/04

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	10/25/04
Amendment	11/1/04

7. NAME & ADDRESS OF APPLICANT:

Name:	Ross Products Division Abbott Labs, Inc.
Address:	625 Cleveland Avenue, Columbus, OH 43215-1724
Representative:	Elizabeth M. Zola, Associate Director, Regulatory Affairs
Telephone:	614 624-3316

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: **Omacor**
b) Non-Proprietary Name (USAN): omega-3-acid ethyl esters
c) Code Name/# (ONDC only): K85EE
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1 (21-654)
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: NA

10. PHARMACOL. CATEGORY: Treatment of hypertriglyceridemia

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 1 gram

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

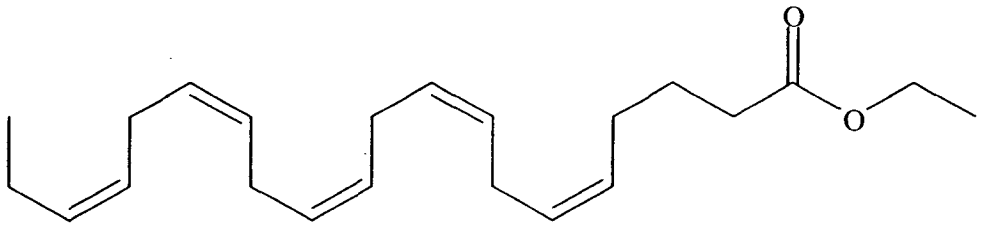
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
___x__SPOTS product – Form Completed

_____Not a SPOTS product

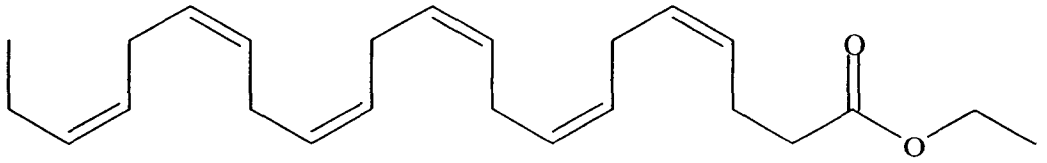
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Omega-3 acid ethyl esters is a fish-oil fatty acid ester concentrate containing about [redacted] all-cis (Z),5,8,11,14,17-eicosapentaenoic acid ethyl ester (EPA-EE, C20:5n-3) and about [redacted] all-cis 4,7,10,13,16,19-docosahexaenoic acid ethyl ester (DHA-EE, C22:6n-3). Another approximately [redacted] consists of the ethyl esters of the following [redacted] alpha-linolenic acid [redacted]. Also present at about [redacted] of the total mixture are the ethyl esters of [redacted]. About 4 mg/g of α-tocopherol in partially hydrogenated vegetable oils is added to the drug substance as an antioxidant.

EPA ethyl ester: Formula: $C_{22}H_{34}O_2$ Molecular Weight: 330.51 CAS # 86227-47-6



DHA ethyl ester: Formula $C_{24}H_{36}O_2$ Molecular Weight: 356.55 CAS # 81926-94-5



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	Soft Gelatin Capsule – Drug Product	1	Adequate	8/11/04	M. Haber
[redacted]	III	[redacted]	[redacted]	3	Adequate	7/27/04	S. Pope
[redacted]	III	[redacted]	[redacted]	3	Adequate	3/5/04	D.Chiapperino
[redacted]	III	[redacted]	[redacted]	3	Adequate	7/27/04	S. Pope

[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
IND	45,998	Fish Oils

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	AC	2/18/04	Dr. M. Haber
Pharm/Tox	NA		
Biopharm	AC	10/20/04	Dr. Wei Qiu
Methods Validation	Adequate, pending lab verification	10/20/04	Dr. M. Haber
DMETS	Tradename is acceptable	3/20/04	
EA	Categorical exclusion is acceptable	10/20/04	Dr. M. Haber
Microbiology	NA		

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-654

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend approval from a CMC standpoint.

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)

Omacor (omega-3-acid ethyl esters) is a soft clear gelatin capsule containing 1 gram of fish oil. There is only one strength marketed in 120-count plastic bottles. Omacor capsules also contain the following inactive ingredients: 4 mg α-tocopherol (antioxidant), gelatin, [redacted] Omacor is indicated for treatment of hypertriglyceridemia. The drug product capsules are manufactured by Cardinal Health, St. Petersburg, FL. Polyunsaturated fatty acids are susceptible to oxidation but the capsules are processed [redacted] and the gelatin shell protects against [redacted]. The capsules are stored in [redacted] bottles with plastic caps. The drug product capsules are stable at controlled room temperature for at least 18 months.

Omega-3 acid ethyl esters is a fish-oil fatty acid ester concentrate containing [redacted] eicosapentaenoic acid ethyl ester (EPA-EE) and [redacted] docosahexaenoic acid ethyl ester (DHA-EE). Another [redacted] of the drug substance consists of [redacted] Also present at [redacted] of the total are the ethyl esters [redacted] The drug substance is produced by Pronova Biocare a.s., Norway, in a [redacted] process involving [redacted] from fish body oil. The oil is extracted from ocean fish families such as *Engaulidae, Carangidae, Clupeidae, Osmeridae, Salmonidae* and *Scrombroidae*. The purification process [redacted] The drug substance is stable for up to [redacted] when stored under [redacted] at room temperature.

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

The recommended dose is 4 grams per day taken orally as a single dose (4 capsules) or as two 2-g doses. Patients should be on a lipid-lowering diet. The drug product consists of soft gelatin capsules containing 1 gram of omega-3-acid ethyl esters. The soft gelatin capsules are stored at controlled room temperature for up to 18 months in 120-count plastic bottles and caps.

C. Basis for Approvability or Not-Approval Recommendation

The quality of the drug substance, omega-3 acid ethyl esters, is adequate. The structures of the principle components, eicosapentaenoic acid ethyl ester and docosahexaenoic acid ethyl ester, were determined by . [redacted] The reference standards are appropriate and adequate. The manufacturing process is adequate and well-controlled. The drug substance is prepared by [redacted] by [redacted] The specifications for identity, assay, purity and consistency are adequate to assure the quality of the drug substance. Impurity testing includes tests for [redacted] Additional information regarding the fatty acid distribution was added to the specifications. The drug substance is susceptible to oxidation and 0.4% α-tocopherol is added to the bulk as an antioxidant. The drug substance is stored in [redacted] The stability of the drug substance has been demonstrated to be adequate at room temperature for up to without significant degradation in the absence of oxygen.

The quality of the drug product, Omacor Capsules, is adequate. The soft gelatin capsule drug product contains no excipients other than the antioxidant α-tocopherol and components of the capsule shell, gelatin and glycerin. The manufacturing process involves [redacted] The specifications are similar to those used for the drug substance and are adequate to assure the quality of the drug product. The drug product capsules are packaged in 28-count physician sample [redacted] bottles and 120-count market [redacted] bottles with plastic caps. Stability data submitted for the drug product capsules in bottles supports an expiration date of 18 months stored at room temperature. The cGMP status of all manufacturing facilities is satisfactory as per EER on 2/18/04. The firm has responded adequately to all CMC information requests and comments. There are no pending CMC deficiencies.

III. Administrative

A. Reviewer's Signature	See DFS.
B. Endorsement Block	See DFS
C. CC Block	See DFS.

Chemistry Assessment

[redacted] contains the exact same CMC information as NDA 21-654.

The 10/25/04 Amendment provides for an updated table of specifications for the drug product without dissolution testing and for 18 months of drug product stability data. The 11/1/04 Amendment provides for color copies of the bottle labels. For all other information, see Chemistry Review #1.

I. DRUG PRODUCT

1. Regulatory Specifications And Methods For Drug Product

An updated specification without dissolution has been submitted, see attachment.

APPEARS THIS WAY
ON ORIGINAL

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page(s) of trade secret and/or confidential commercial information (b4)

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/s/

Martin Haber
11/1/04 03:20:52 PM
CHEMIST

Mamta Gautam-Basak
11/1/04 04:09:42 PM
CHEMIST
Concur, AP recommendation with 18 months of expiry

10/21/04

CHEMISTRY REVIEW

NDA 21-654

Omacor (omega-3-acid ethyl esters) Capsule

Ross Products Division – Abbott Laboratories, Inc.

Martin Haber, Ph.D.
Division of Metabolism and Endocrine Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-654

2. REVIEW #: 1

3. REVIEW DATE: October 20, 2004

4. REVIEWER: Martin Haber, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Initial Filing Memorandum	3/24/04
IR Letter	8/17/04

6. SUBMISSION(S) BEING REVIEWED:

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Original NDA	1/9/04
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d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1 (21-654)
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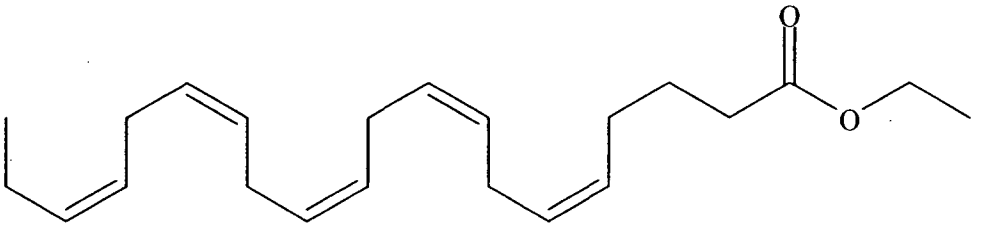

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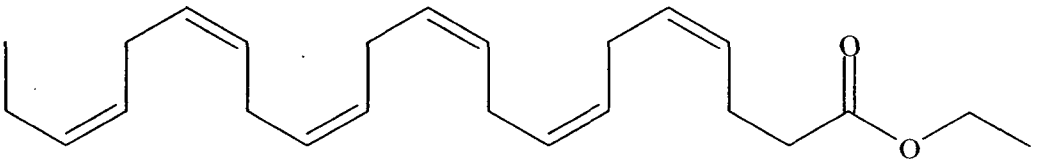

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Biopharm	AC	10/20/04	Dr. Wei Qiu
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DMETS	Tradename is acceptable	3/20/04	
EA	Categorical exclusion is acceptable	10/20/04	Dr. M. Haber
Microbiology	NA		

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-654

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

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

NA

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Omega-3 acid ethyl esters is a fish-oil fatty acid ester concentrate containing all-cis (Z) 5,8,11,14,17-eicosapentaenoic acid ethyl ester (EPA-EE) and [redacted] % all-cis 4,7,10,13,16,19-docosahexaenoic acid ethyl ester (DHA-EE). Another [redacted] of the drug substance consists of [redacted]

[redacted] Also present at [redacted] of the total are the ethyl esters of [redacted] The drug substance is produced by Pronova Biocare a.s., Norway, in [redacted] process involving [redacted] from fish body oil. The oil is extracted from ocean fish families such as *Engaulidae, Carangidae, Clupeidae, Osmeridae, Salmonidae* and *Scrombroidae*. The purification process [redacted]

[redacted] The drug substance is stable for up to [redacted] when stored under [redacted] at room temperature.

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

The recommended dose is 4 grams per day taken orally as a single dose (4 capsules) or as two 2-g doses. Patients should be on a lipid-lowering diet. The drug product consists of soft gelatin capsules containing 1 gram of omega-3-acid ethyl esters. The soft gelatin capsules are stored at controlled room temperature for up to 12 months in 120-count plastic bottles and caps.

C. Basis for Approvability or Not-Approval Recommendation

The quality of the drug substance, omega-3 acid ethyl esters, is adequate. The structures of the principle components, eicosapentaenoic acid ethyl ester and docosahexaenoic acid ethyl ester, were determined by [ ] The reference standards are appropriate and adequate. The manufacturing process is adequate and well-controlled. The drug substance is prepared by [

] The specifications for identity, assay, purity and consistency are adequate to assure the quality of the drug substance. Impurity testing includes tests for [ ] Additional information regarding the fatty acid distribution was added to the specifications. The drug substance is susceptible to oxidation and 0.4% α-tocopherol is added to the bulk as an antioxidant. The drug substance is stored [ ] The stability of the drug substance has been demonstrated to be adequate at room temperature for up to — — without significant degradation in the absence of oxygen.

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] The specifications are similar to those used for the drug substance and are adequate to assure the quality of the drug product. The drug product capsules are packaged in 28-count physician sample — bottles and 120-count market bottles with plastic caps. Stability data submitted for the drug product capsules in bottles supports an expiration date of — stored at room temperature. The cGMP status of all manufacturing facilities is satisfactory as per EER on 2/18/04. The firm has responded adequately to all CMC information requests and comments. There are no pending CMC deficiencies.

III. Administrative

A. Reviewer's Signature	See DFS.
B. Endorsement Block	See DFS
C. CC Block	See DFS.

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page(s) of trade secret and/or confidential commercial information (b4)

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/s/

Martin Haber
10/21/04 11:36:44 AM
CHEMIST

Mamta Gautam-Basak
10/21/04 11:55:23 AM
CHEMIST
Concur

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

) ation:	NDA 21654/000	Action Goal:	
Stamp:	12-JAN-2004	District Goal:	13-SEP-2004
Regulatory Due:	12-NOV-2004	Brand Name:	OMACOR (OMEGA-3-ACID
Applicant:	ROSS PRODS	Estab. Name:	ETHYL ESTERS) CAPS
	625 CLEVELAND AVE D103159	Generic Name:	OMEGA-3 ACID ETHYL
	COLUMBUS, OH 43215		ESTERS CAPS,1G.
Priority:	1S	Dosage Form:	(CAPSULE)
Org Code:	510	Strength:	1 GRAM

Application Comment: NDA PROVIDES FOR OMACOR SOFT GELATIN CAPSULES. THE DRUG SUBSTANCE IS [ ] FISH OILS, MAINLY EICOSAPENTAENOIC ACID (EPA) AND DOCOSAHEXAENOIC ACID (DHA) ETHYL ESTERS. THE MIXTURE CONTAINS OMEGA-3 FATTY ACID ETHYL ESTERS. [

] (on 09-FEB-2004 by M. HABER (HFD-510) 301-827-6420)

FDA Contacts:	V. JIMENEZ	(HFD-510)	301-827-9090	, Project Manager
	M. HABER	(HFD-510)	301-827-6420	, Review Chemist
	M. GAUTAM BASAK	(HFD-510)	301-827-9084	, Team Leader

Overall Recommendation: ACCEPTABLE on 02-MAR-2004by J. D AMBROGIO(HFD-322)301-827-9049

Establishment: CFN 1811396 FEI 1811396

CARDINAL HEALTH

2725 SCHERER DR

ST PETERSBURG, FL 337161016

MF No: 14685 AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE OTHER TESTER

Profile: CSG OAI Status: NONE

Estab. Comment: MANUFACTURER OF SOFT GELATIN CAPSULES CONTAINING FISH OILS. THIS SITE

ALSO DOES MICROBIOLOGICAL TESTING OF THE CAPSULES. (on 09-FEB-2004 by M. HABER (HFD-510) 301-827-6420)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
ITED TO OC	09-FEB-2004				HABERM
SUBMITTED TO DO	09-FEB-2004	PS			DAMBROGIOJ
DO RECOMMENDATION	18-FEB-2004			ACCEPTABLE BASED ON FILE REVIEW	PFIGAROL
OC RECOMMENDATION	18-FEB-2004			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

Establishment: CFN FEI

APPEARS THIS WAY
ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

)MF No: AADA:

:esponsibilities:

'rofile: CSG OAI Status: NONE

:stab. Comment:

(on 09-FEB-2004 by M. HABER (HFD-510) 301-827-6420)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-FEB-2004				HABERM
SUBMITTED TO DO	09-FEB-2004	GMP			DAMBROGIOJ
:TION PERFORMED	27-FEB-2004		27-FEB-2004		LJARRELL

GMP AND PAI INSPECTION L 1 FOUND NO OBJECTIONABLE CONDITIONS.

NO FDA-483 WAS ISSUED.

DO RECOMMENDATION	02-MAR-2004	ACCEPTABLE INSPECTION	LJARRELL

EI DONE 2/24--2/27-04. NO FDA-483 WAS ISSUED.

OC RECOMMENDATION	02-MAR-2004	ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

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stablishment: CFN 9616808 FEI 3000212124

PRONOVA BIOCARE A/S

SANDEFJORD, , NO

M : AADA:

e sibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE RELEASE TESTER

FINISHED DOSAGE RELEASE TESTER

rofile: CEX OAI Status: NONE

Estab. Comment: DRUG SUBSTANCE IS [ ] PRODUCT MIXTURE THAT IS EXTRACTED FROM FISH OILS, [ ] THEREFORE, THE PRODUCT PROFILE COULD BE CRU INSTEAD OF CEX. CRU WAS USED PREVIOUSLY FOR THIS ESTABLISHMENT. THIS SITE DOES RELEASE TESTING FOR DRUG SUBSTANCE AND FOR FINISHED DRUG PRODUCT, EXCEPT FOR MICROBIOLOGICAL TESTING. (on 09-FEB-2004 by M. HABER (HFD-510) 301-827-6420)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-FEB-2004				HABERM
SUBMITTED TO DO	09-FEB-2004	PS			DAMBROGIOJ
DO RECOMMENDATION	18-FEB-2004			ACCEPTABLE BASED ON FILE REVIEW	DAMBROGIOJ
OC RECOMMENDATION	18-FEB-2004			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Profile: CTL OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-FEB-2004				HABERM
SUBMITTED TO DO	09-FEB-2004	GMP			DAMBROGIOJ
DO RECOMMENDATION	18-FEB-2004			ACCEPTABLE BASED ON FILE REVIEW	DAMBROGIOJ
OC RECOMMENDATION	18-FEB-2004			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ