CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-341

CHEMISTRY REVIEW(S)

MEMORANDUM

Date: 04-Aug-2009

From: Joseph Leginus, Review Chemist, Branch II/DPA I/ONDQA

To: NDA 22-341 Victoza® (liraglutide (rDNA origin) injection)

Subject: Single, multi-dose (1.2 mg/1.8 mg) injector pen

Background:

- On December 19, 2009, Novo Nordisk submitted an amendment to NDA 22-341 describing an alternate pen configuration that would allow patients to use a single pen to inject each of the recommended doses (0.6, 1.2, 1.8 mg) of Victoza (liraglutide rDNA) injection). [redacted]
- [redacted] b(4)

Reviewer's Comments:

- [redacted] b(4)
- [redacted]. The draft labeling is the same as the previously submitted labeling with the additional pen configuration included.
- Dose accuracy study data was provided showing acceptable performance of the new pen at the three dose levels (0.6, 1.2, 1.8 mg).
- [redacted] b(4)

Conclusion:

There are no CMC issues related to Novo Nordisk's alternate pen configuration for Victoza, a single, multi-dose (1.2 mg/1.8 mg) pen.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22341	ORIG 1		VICTOZA (LIRAGLUTIDE)

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/s/

JOSEPH M LEGINUS
08/04/2009

ALI H AL HAKIM
08/04/2009

Victoza®
Liraglutide Injection
NDA 22-341

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: Novo Nordisk, Inc.
100 College Road West,
Princeton, NJ 08540

Indication: Liraglutide is indicated as an adjunct to diet and exercise to achieve glycemic control in patients with type 2 diabetes mellitus

Presentation: Liraglutide injection is a parenteral drug product for once daily subcutaneous self-administration. It is supplied in multiple-dose pre-filled pen-injectors containing 3 mL of drug product at a concentration of 6 mg/mL. [redacted] :

b(4)

EER Status: Acceptable, 23-Mar-2009

Consults: EA – Categorical exclusion granted
CDRH - Completed, S. Syad, 13-Feb-2009
Methods Validation – Revalidation by Agency was not requested
Microbiology – Acceptable, B. Riley, 4-Mar-2009

Original Submission: 23-May-2008

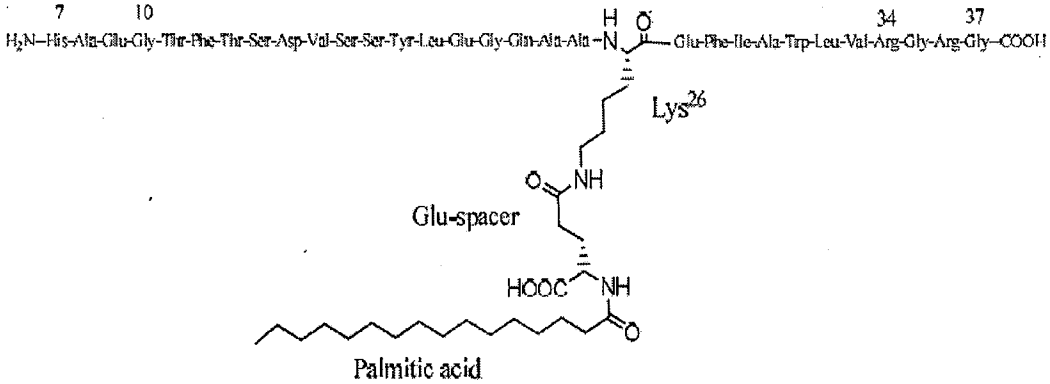
Re-submissions: N/A

Post-Approval CMC Agreements: None beyond the typical stability commitments.

Drug Substance:

Liraglutide is a fragment of the naturally occurring human GLP-1 (Glucagon-like peptide-1) sequence position 7-37 having two modifications: 1) substitution of the naturally occurring lysine amino acid residue in position 34 by arginine, and 2) addition of a glutamic acid-spaced palmitic acid to the ε-amino group of lysine in position 26. Liraglutide precursor is produced using recombinant DNA technology in yeast (*Saccharomyces cerevisiae*). The chemical name of liraglutide is

glycine, L-histidyl-L-alanyl-L-α-glutamylglycyl-Lthreonyl-L-phenylalanyl-L-threonyl-L-seryl-L-α-aspartyl-L-valyl-L-seryl-L-seryl-L-tyrosyl-L-leucyl-L-α-glutamylglycyl-Lglutaminyl-L-alanyl-L-alanyl-N6-[N-(1-oxohexadecyl)-L-γ-glutamyl]-L-lysyl-L-α-glutamyl-Lphenylalanyl-L-isoleucyl-L-alanyl-L-tryptophyl-L-leucyl-L-valyl-L-arginylglycyl-L-arginyl-. The chemical structure, molecular formula and molecular weight are provided below:



The molecular formula of liraglutide is $C_{172}H_{265}N_{43}O_{51}$ with a molecular weight of 3751.20.

Liraglutide precursor is produced by recombinant DNA technology form yeast *Saccharomyces cerevisiae.* The manufacturing process is a step process divided into three sections, fermentation, recovery, and purification. The purification process consists of purification of the liraglutide precursor, acylation of this precursor and finally purification of liraglutide. b(4)

The structure of liraglutide was elucidated by a variety of analytical and spectrophotometric techniques, including amino acid analysis (AAA), amino acid sequencing, mass spectrometry (MALDI-TOF MS), circular dichroism (CD) and peptide mapping.

The proposed release specifications include appearance, identification (peptide mapping and HPLC), content (HPLC), specific bioactivity (cAMP assay), individual peptide related impurities and total peptide related impurities (HPLC), bacterial endotoxin, total viable count and host cell protein (ELISA). The proposed regulatory methods have been validated. b(4)

Reference standards for the API have been developed and characterized. Product related impurities structurally related to liraglutide generated during the fermentation, recovery, purification or storage of the drug substance have classified based on their RP-HPLC elution position relative to the drug substance. Process derived impurities originating from the liraglutide manufacturing process were not detected in the drug substance. A shelf life of 24 months will be granted for the drug substance when stored at -18°C ±2°C/ambient RH or lower temperatures based on real-time studies obtained from primary stability data.

Conclusion: The drug substance is acceptable.

Drug Product:

The drug product consists of an aqueous formulation at pH 8.15 of [redacted] liraglutide with 0.14% disodium phosphate dihydrate [redacted], 1.4% propylene glycol [redacted] and [redacted] phenol [redacted]. It is supplied in multiple-dose pre-filled pen-injectors [redacted]. b(4)

[redacted] b(4)

The release specifications include appearance, identification (HPLC), content (HPLC), pH, [redacted] related impurities and [redacted] related impurities (HPLC), bacterial endotoxin, sterility, phenol content, particulate matter, freezing point depression (osmolality) and dose accuracy. A close correlation has been demonstrated between biological activity of liraglutide and content by HPLC under both normal and stressed conditions for the drug product. As a result, it has been determined that the HPLC assay is able to offer a reliable indication of the biological activity of liraglutide in the drug product. Therefore, bioactivity is not included in the proposed drug product specification. b(4)

No new impurities were found in the drug product compared to the drug substance. The secondary packaging (pen-injector) adequately protects the drug product from degradation due to light. Review of the data for the primary stability batches through 24 months of real time stability at 2 - 8°C show that the liraglutide 6.0 mg/mL drug product remains within the shelf life specification limits during this time. Satisfactory in-use stability evaluation was performed for 32 days at 28 - 32°C using drug product batches. As a result, an expiry of 24 months at 2 – 8 °C plus 32 days at 28 – 32 °C is granted for the drug product.

Conclusion: The drug product is satisfactory.

Overall Conclusion: From a CMC perspective, the application is recommended for approval.

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/s/

Christine Moore
7/15/2009 11:19:42 AM
CHEMIST

NDA 22-341

Victoza®
Liraglutide Injection

Novo Nordisk Inc.

Joseph Leginus, PhD
Division of Pre-Marketing Assessment 1
Office of New Drug Quality Assessment

Division of Metabolism and Endocrinology Products
HFD-510

CHEMISTRY REVIEW #2

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-341

2. REVIEW #: 2

3. REVIEW DATE: 14-Apr-2009

4. REVIEWER: Joseph Leginus

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA	23-May-2008
Amendment	25-Aug-2008
Amendment	19-Dec-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA Amendment	11-Feb-2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Novo Nordisk Inc.
Address:	100 College Road West, Princeton, NJ 08540
Representative:	Mary Ann McElligott, PhD, Assoc. Vice President Regulatory Affairs
Telephone:	(609) 987-5831

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Victoza®
b) Non-Proprietary Name (USAN): Liraglutide
c) Code Name/# (ONDC only): NNC 90-1170, NN2211
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 1
- Submission Priority: Standard

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

10. PHARMACOL. CATEGORY:
    Glycemic control in patients with type 2 diabetes

11. DOSAGE FORM: Solution for injection

12. STRENGTH/POTENCY: 6 mg/mL

13. ROUTE OF ADMINISTRATION: Subcutaneous injection

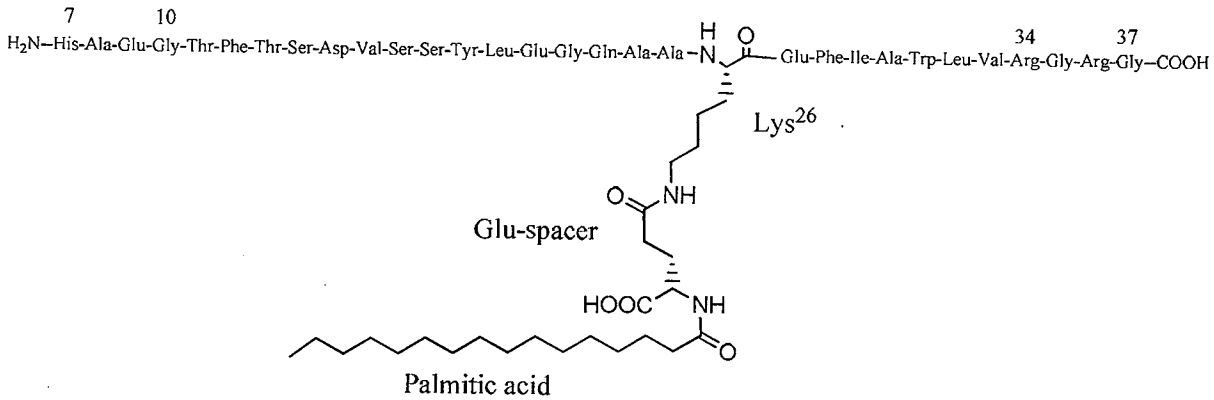
14. Rx/OTC DISPENSED: __X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

    __X__SPOTS product - Form Completed (9/11/2008)
    _____ Not a SPOTS product

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

    USAN: Liraglutide
    $C_{172}H_{265}N_{43}O_{51}$ (MW = 3751.20 Da)



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	III	[redacted]	[redacted]	1	Adequate	Reviewed by Yvonne Yang 9/15/2001	Letter of Authorization 9/26/2007
[redacted]	III	[redacted]	[redacted]	1	Adequate	Reviewed by Yvonne Yang 9/16/2001	Letter of Authorization 9/26/2007

b(4)

[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	61,040	NNC 90-1170 GLP-1 Analog

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Overall Acceptable recommendation.	23-Mar-2009	Compliance
Pharm/Tox	Qualification of impurities conducted according to ICH Q6B for Biotech/Biological Products		
Biopharm/ClinPharm	Not applicable. This is an injectable product, and the commercial formulation was used in Phase 3 studies.		
Methods Validation	Not applicable. Standard analytical test methods employed.		
CDRH	Clarification of certain clinical issues required before conclusion can be made that the device can be safely and effectively used with the proposed drug.	13-Feb-2009	Sajjad H. Syed. See Review In Appendix 1.
OSE	Labeling consult requested as part OND's labeling review.		
EA	Categorical exclusion granted as per 21 CFR 25.31.	12-Dec-2008	Joseph Leginus
Microbiology	This submission is recommended for approval on the basis of product quality microbiology.	4-Mar-2009	Bryan S. Riley, Ph.D.

19. ORDER OF REVIEW: N/A

The application submission(s) covered by this review was taken in the date order of receipt.
__X__ Yes ____ No. If no, explain reason(s) below:

The Chemistry Review for NDA 22-341

The Executive Summary

I. Recommendations

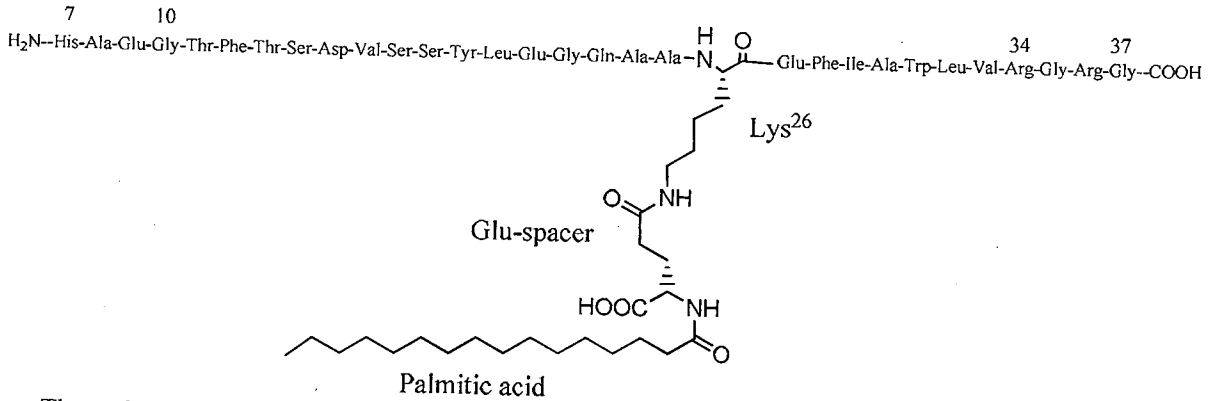
A. Recommendation and Conclusion on Approvability

NDA 22-341 is recommended for Approval from the standpoint of chemistry, manufacturing and controls.

II. Summary of Chemistry Assessments

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

DRUG SUBSTANCE: Liraglutide is a fragment of the naturally occurring human GLP-1 (Glucagon-like peptide-1) sequence position 7-37 having two modifications: 1) substitution of the naturally occurring lysine amino acid residue in position 34 by arginine, and 2) addition of a glutamic acid-spaced palmitic acid to the ε-amino group of lysine in position 26. Liraglutide precursor is produced using recombinant DNA technology in yeast (*Saccharomyces cerevisiae*). The chemical name of liraglutide is glycine, L-histidyl-L-alanyl-L-α-glutamylglycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-α-aspartyl-L-valyl-L-seryl-L-seryl-L-tyrosyl-L-leucyl-L-α-glutamylglycyl-Lglutaminyl-L-alanyl-L-alanyl-N^6-[N-(1-oxohexadecyl)-L-γ-glutamyl]-L-lysyl-L-α-glutamyl-L-phenylalanyl-L-isoleucyl-L-alanyl-L-tryptophyl-L-leucyl-L-valyl-L-arginylglycyl-L-arginyl-, and its structure is presented below:



The molecular formula of liraglutide is $C_{172}H_{265}N_{43}O_{51}$ with a molecular weight of 3751.20.

Liraglutide is characterized as a [redacted]

b(4)

Liraglutide precursor is produced by recombinant DNA technology form yeast *Saccharomyces cerevisiae*. The manufacturing process is a [redacted]), b(4)

b(4)

A shelf life of 24 months will be granted for the drug substance when stored at -18°C ±2°C/ambient RH or lower temperatures. This is based on real-time studies obtained from primary stability data conducted on pilot scale production batches (Batch Numbers G1K4S009, G1K4S010 and G1K4S011 from Campaign 6) of the drug substance.

DRUG PRODUCT: Liraglutide injection is a parenteral drug product for subcutaneous administration. It is supplied in multiple-dose pre-filled pen-injectors . The drug product is filled in a glass cartridge and assembled at the manufacturing facility into a disposable multi-dose pen injector. Each pen-injector contains 3 mL of drug product at a concentration of 6 mg/mL. The delivered dose of each injection is 0.6 mg, 1.2 mg or 1.8 mg depending on the setting of the multi-dose injector.

b(4)

The drug product consists of an aqueous formulation at pH 8.15 of liraglutide with disodium phosphate dihydrate propylene glycol and phenol .

The three pilot drug product batches (SQ50423, SQ50447, SQ50549) are regarded to be the primary stability batches, found acceptable by FDA at the pre-NDA stage, and were considered for assessing real time stability. Review of the data for these batches through 30 months of real time stability at 2 - 8°C show that the liraglutide 6.0 mg/mL drug product remains within the shelf life specification limits during this time. The in-use stability evaluation was performed for 32 days at 28 - 32°C using drug product batches a) newly produced, and b) after 24 months of storage at the recommended storage conditions of 2 - 8°C. In-use stability was evidenced when tested under all configurations (newly produced filled, newly produced half-filled, 24 month stored filled). As a result, an expiry of 24 months at 2 – 8°C plus 32 days at 28 – 32°C is granted for the drug product.

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

Liraglutide is intended as an adjunct to diet and exercise to achieve glycemic control in patients with type 2 diabetes mellitus. Liraglutide is developed for once-daily administration as:

- Monotherapy
- Combination therapy with one or more oral antidiabetic drugs (metformin, sulphonylureas or a thiazolidinedione) when previous therapy does not achieve adequate glycemic control.

Liraglutide is designed for multidose use and is administered once daily at any time, independent of meals. It can be injected subcutaneously in the abdomen, in the thigh or in the upper arm. The injection site and timing can be changed without dose adjustment. For all patients, liraglutide should be initiated with a dose of 0.6 mg for at least one week, after which the dose should be increased to 1.2 mg. Based on clinical response and after at least one week, the dose can be increased to 1.8 mg to achieve maximum efficacy.

C. Basis for Approvability or Not-Approval Recommendation

The application is **approval** from a CMC perspective. This recommendation is based upon the evaluation of the relevant drug product manufacturing, characterization and stability data provided in this 505(b)(1) application. These data are substantial, detailed and acceptable. The applicant has demonstrated lot-to-lot consistency in the manufacture and quality of the drug product. Labeling revisions will be finalized as part of the multidisciplinary review of the labeling. The CDRH consult review of the device has pending clinical issues only and no pending issue for CMC.

III. Administrative

A. Reviewer's Signature

See electronic signature page

B. Endorsement Block

Chemist Name/Date: J. Leginus/Date
Chemistry Team Leader: S. Tran/Date
Project Manager: J. Bishai/Date

C. CC Block

Chemistry Assessment

On Feb 11, 2009, Novo Nordisk submitted a complete response to the CMC request for information dated Jan 8, 2009. The deficiencies, Novo Nordisk responses and review comments are provided as follows:

Drug Substance

b(4)

29 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 1

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/s/

Joseph Leginus
4/17/2009 12:23:10 PM
CHEMIST

Ali Al-Hakim
4/17/2009 03:07:25 PM
CHEMIST

NDA 22-341

Victoza®
Liraglutide Injection

Novo Nordisk Inc.

Joseph Leginus, PhD
Division of Metabolism and Endocrinology Products
HFD-510

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-341

2. REVIEW #: 1

3. REVIEW DATE: 19-Dec-2008

4. REVIEWER: Joseph Leginus

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA	23-May-2008
Amendment	25-Aug-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA	23-May-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Novo Nordisk Inc.
Address:	100 College Road West, Princeton, NJ 08540
Representative:	Mary Ann McElligott, PhD, Assoc. Vice President Regulatory Affairs
Telephone:	(609) 987-5831

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Victoza®
b) Non-Proprietary Name (USAN): Liraglutide
c) Code Name/# (ONDC only): NNC 90-1170, NN2211
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: Standard

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

10. PHARMACOL. CATEGORY:
    Glycemic control in patients with type 2 diabetes

11. DOSAGE FORM: Solution for injection

12. STRENGTH/POTENCY: 6 mg/mL

13. ROUTE OF ADMINISTRATION: Subcutaneous injection

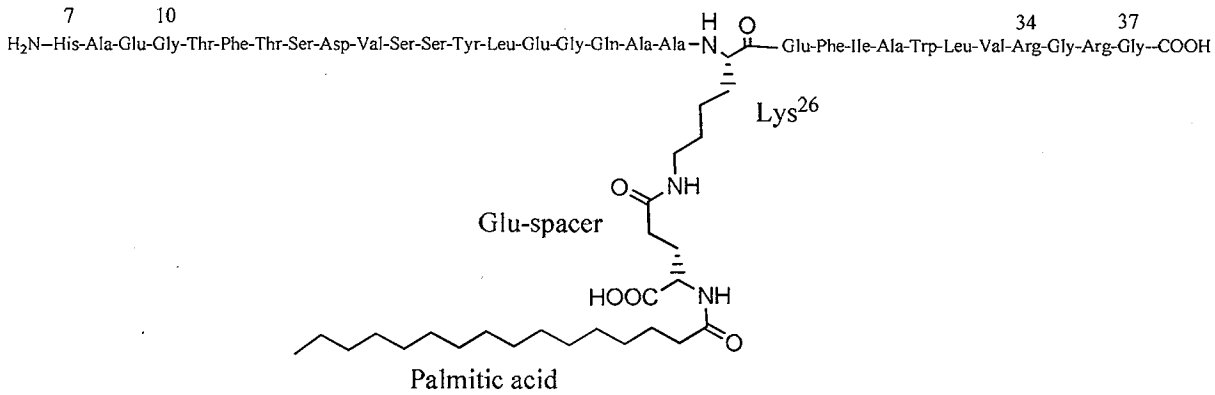
14. Rx/OTC DISPENSED: __X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

    __X__SPOTS product - Form Completed (9/11/2008)
    _____ Not a SPOTS product

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

    USAN: Liraglutide
    $C_{172}H_{265}N_{43}O_{51}$ (MW = 3751.20 Da)



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
—	III			1	Adequate	9/15/2001	Reviewed by Yvonne Yang
—	III			1	Adequate	9/16/2001	Reviewed by Yvonne Yang

b(4)

[1] Action codes for DMF Table:
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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	61,040	NNC 90-1170 GLP-1 Analog

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending. EER was sent to Office of Compliance on 12-Jun-2008.		
Pharm/Tox	To be determined by CMC reviewer. A consult review may be needed for the safety evaluation of leachables and impurities.		
Biopharm/ClinPharm	May not be applicable. This is an injectable		

	product, and the commercial formulation was used in Phase 3 studies.		
Methods Validation	Validation may be requested of FDA labs after test methods are finalized.		
CDRH	Review of the disposable multi-dose pen injector.		
ODS/DMETS	Labeling consult request will be sent as part of DMEP's request.		
EA	To be done by CMC reviewer.	12-Dec-2008	Joseph Leginus
Microbiology	Review of 1) microbiology controls proposed for the drug substance and drug product, and 2) sterilization and (b) (4) processing validation for the drug product.		

19. ORDER OF REVIEW: N/A

The application submission(s) covered by this review was taken in the date order of receipt.
__X__ Yes ____ No. If no, explain reason(s) below:

The Chemistry Review for NDA 22-341

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

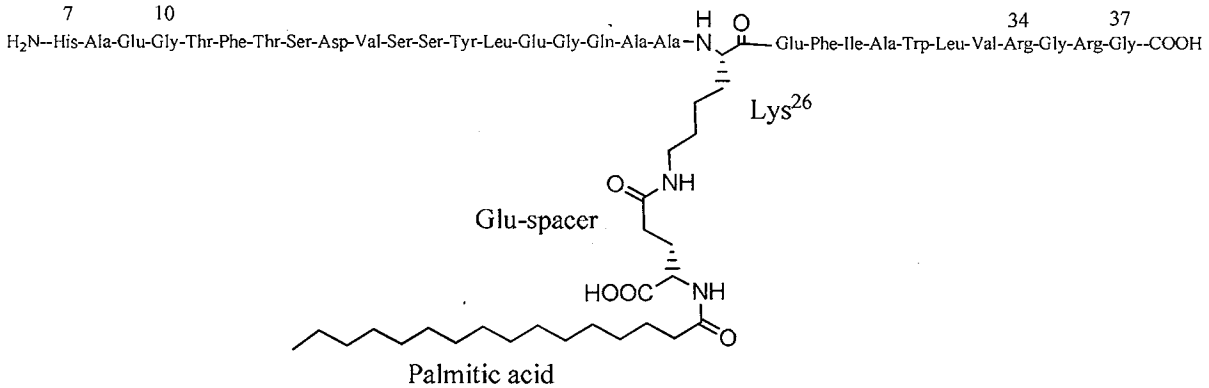
NDA 22-341 is recommended for Approvable from the standpoint of chemistry, manufacturing and controls pending 1) a satisfactory response to the deficiencies delineated in the Draft List of Deficiencies and Information Request (in the CMC reviews for NDA 22-341).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable – Not applicable

II. Summary of Chemistry Assessments

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

DRUG SUBSTANCE: Liraglutide is a fragment of the naturally occurring human GLP-1 (Glucagon-like peptide-1) sequence position 7-37 having two modifications: 1) substitution of the naturally occurring lysine amino acid residue in position 34 by arginine, and 2) addition of a glutamic acid-spaced palmitic acid to the ε-amino group of lysine in position 26. Liraglutide precursor is produced using recombinant DNA technology in yeast (*Saccharomyces cerevisiae*). The chemical name of liraglutide is glycine, L-histidyl-L-alanyl-L-α-glutamylglycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-α-aspartyl-L-valyl-L-seryl-L-seryl-L-tyrosyl-L-leucyl-L-α-glutamylglycyl-Lglutaminyl-L-alanyl-L-alanyl-N^6-[N-(1-oxohexadecyl)-L-γ-glutamyl]-L-lysyl-L-α-glutamyl-L-phenylalanyl-L-isoleucyl-L-alanyl-L-tryptophyl-L-leucyl-L-valyl-L-arginylglycyl-L-arginyl-, and its structure is presented below:



The molecular formula of liraglutide is $C_{172}H_{265}N_{43}O_{51}$ with a molecular weight of 3751.20.

Liraglutide is characterized as a

b(4)

Executive Summary Section

The structure of liraglutide was elucidated by a variety of analytical and spectrophotometric techniques, including amino acid analysis (AAA), amino acid sequencing, mass spectrometry (MALDI-TOF MS), circular dichroism (CD) and peptide mapping.

Liraglutide precursor is produced by recombinant DNA technology form yeast *Saccharomyces cerevisiae.* The manufacturing process is a [redacted] and purification (steps [redacted]). The purification process consists of purification of the liraglutide precursor (steps [redacted]). b(4)

The proposed release specifications include appearance, identification (peptide mapping and HPLC), content (HPLC), specific bioactivity (cAMP assay), [redacted] related impurities and [redacted] related impurities (HPLC), [redacted], bacterial endotoxin, total viable count and host cell protein (ELISA). The proposed regulatory methods have been validated. Reference standards for the API have been developed and characterized. b(4)

Product related impurities structurally related to liraglutide generated during the fermentation, recovery, purification or storage of the drug substance have classified based on their RP-HPLC elution position relative to the drug substance. These have been characterized as " [redacted] liraglutide related impurities", "liraglutide related impurities A", "liraglutide related impurities B", "liraglutide related impurities C", and " [redacted] liraglutide related impurities." The sum of product related impurities during pilot and manufacturing scale ranged from [redacted] %. Process derived impurities originating from the liraglutide manufacturing process were not detected in the drug substance. b(4)

A shelf life of [redacted] will be granted for the drug substance when stored at [redacted] °C ±2°C/ambient RH or lower temperatures. This is based on real-time studies obtained from primary stability data conducted on pilot scale production batches (Campaign 6) of the drug substance.

DRUG PRODUCT: Liraglutide injection is a parenteral drug product for subcutaneous administration. It is supplied in multiple-dose pre-filled pen-injectors [redacted]. The drug product is [redacted] filled in a glass cartridge and assembled into a disposable multi-dose pen injector. Each pen-injector contains 3 mL of drug product at a concentration of 6 mg/mL. The delivered dose of each injection is 0.6 mg, 1.2 mg or 1.8 mg depending on the setting of the multi-dose injector. ([redacted] b(4)

The drug product consists of an aqueous formulation at pH 8.15 of [redacted] % liraglutide with [redacted] % disodium phosphate dihydrate [redacted] % propylene glycol [redacted] and [redacted] % phenol [redacted]. b(4)

A close correlation has been documented between biological activity of liraglutide and content by HPLC under both normal and stressed conditions for the drug product. As a result, it has been determined that the HPLC assay is able to offer a reliable indication of the biological activity of liraglutide in the drug product. Therefore, bioactivity is not included in the proposed drug product specification.

[redacted] b(4)

The proposed release specifications include appearance, identification (HPLC), content (HPLC), pH, individual [redacted] related impurities and total [redacted] related impurities (HPLC), bacterial endotoxin, sterility, phenol content, b(4)

particulate matter, freezing point depression (osmolality) and dose accuracy. The proposed regulatory methods have been validated.

No new impurities were found in the drug product compared to the drug substance. The liraglutide drug product is photo labile and the primary container does not provide adequate protection from exposure to light. However, the secondary packaging (pen-injector) adequately protects the drug product from degradation due to light.

The three pilot drug product batches (SQ50423, SQ50447, SQ50549) are regarded to be the primary stability batches, found acceptable by FDA at the pre-NDA stage, and were considered for assessing real time stability. Review of the data for these batches through months of real time stability at 2 - 8°C show that the liraglutide 6.0 mg/mL drug product remains within the shelf life specification limits during this time. The in-use stability evaluation was performed for 32 days at 28 - 32°C using drug product batches a) newly produced, and b) after months of storage at the recommended storage conditions of 2 - 8°C. In-use stability was evidenced when tested under all configurations (newly produced filled, newly produced half-filled, month stored filled). As a result, an expiry of months at 2 – 8°C plus 32 days at 28 – 32°C is granted for the drug product. (The applicant's proposal of a month shelf life period is not warranted). b(4)

Novo Nordisk requested a categorical exclusion from submitting an environmental assessment for the drug product liraglutide based on the regulations in 21 CFR, part 25, section 25.31(b). The request is granted.

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

Liraglutide is intended as an adjunct to diet and exercise to achieve glycemic control in patients with type 2 diabetes mellitus. Liraglutide is developed for once-daily administration as:

- Monotherapy
- Combination therapy with one or more oral antidiabetic drugs (metformin, sulphonylureas or a thiazolidinedione) when previous therapy does not achieve adequate glycemic control.

Liraglutide is designed for multidose use and is administered once daily at any time, independent of meals. It can be injected subcutaneously in the abdomen, in the thigh or in the upper arm. The injection site and timing can be changed without dose adjustment. For all patients, liraglutide should be initiated with a dose of 0.6 mg for at least one week, after which the dose should be increased to 1.2 mg. Based on clinical response and after at least one week, the dose can be increased to 1.8 mg to achieve maximum efficacy.

C. Basis for Approvability or Not-Approval Recommendation

The application is **approvable** for a CMC perspective pending satisfactory responses from the applicant. This recommendation is based upon several issues identified in the review. These issues include 1) identification and summation of all product related impurities that have bioactivity and inclusion of this as a parameter in the specifications for the drug substance and drug product, 2) revision of the release and shelf life limits of the product related impurities of the drug product specifications, and 3) submission of a Prior Approval Supplement (PAS) for the proposed addition of a new manufacturing site for the drug product.

III. Administrative

A. Reviewer's Signature

See electronic signature page

B. Endorsement Block

Chemist Name/Date: J. Leginus/Date
Chemistry Team Leader: S. Tran/Date
Project Manager: J. Bishai/Date

C. CC Block

111 Page(s) Withheld

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_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 2

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/s/

Joseph Leginus
12/29/2008 10:02:37 AM
CHEMIST

Revisions made as we discussed.

Ali Al-Hakim
12/29/2008 10:46:08 AM
CHEMIST

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

Division of Metabolism and Endocrinology Products

NDA:	**22-341**
Applicant:	Novo Nordisk Inc.
Stamp Date:	**23-MAY-2008**
PDUFA Date:	**23-MAR-2009**
Proposed Proprietary Name:	Victoza
Established Name:	Liraglutide
Dosage form and strength:	Injectable solution, 6 mg/mL
Route of Administration:	Subcutaneous injection
Indications:	Glycemic control in patients with type 2 diabetes.
PAL:	Su (Suong) Tran, Branch II/DPA I/ONDQA
ONDQA Fileability:	**Yes**
Filing date:	**22-JUL-2008**
Comments for 74-Day Letter:	**Yes, on the last page.**

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharm/ClinPharm	*May not be applicable. This is an injectable product, and the commercial formulation was used in Phase 3 studies.*
CDRH	Review of the disposable multi-dose pen injector.
EA	Categorical exclusion request will be assessed by Primary Reviewer.
EES	EER was sent to Office of Compliance on 12-JUN-2008.
DMETS	*Labeling consult request will be sent as part of DMEP's request.*
Methods Validation	*Validation may be requested of FDA labs after test methods are finalized.*
Microbiology	Review of 1) microbiology controls proposed for the drug substance and drug product, and 2) sterilization and [redacted] processing validation for the drug product.
Pharm/Tox	*To be determined by the primary reviewer. A consult review may be needed for the safety evaluation of leachables and impurities.*

b(4)

Summary:

[See the discussion in Critical Issues later in this review.]

This is an electronic NDA, filed as a 505(b)(1) application. The associated IND is IND 61040. This drug substance is a New Molecular Entity (NME) and is produced by recombinant DNA (rDNA) technology in *Saccharomyces cerevisiae*. The drug product is a sterile solution for subcutaneous injection, packaged in a cartridge which is assembled at the manufacturing facility into a disposable multi-dose pen injector. The pre-assembled pen injector is the product system to be distributed to the end users. The protein concentration of the product is 6 mg/mL, pH 8.15. Each cartridge contains 3 mL of the drug product. The delivered dose of each injection is 0.6 mg, 1.2 mg, or 1.8 mg, depending on the setting of the multi-dose pen injector. The proposed labeling states "1.2 mg" and "1.8 mg" as the dosage strengths.

Drug substance:

[See the discussion in Critical Issues later in this review.]

Liraglutide is a human Glucagon-Like Peptide-1 (GLP-1) analog with 97% homology to human GLP-1 that binds to and activates the GLP-1 receptor. The GLP-1 receptor is the target for native GLP-1, an endogenous incretin hormone that potentiates glucose-dependent insulin secretion from the pancreatic beta cells. Unlike native GLP-1, liraglutide has PK and PD profiles in humans suitable for once daily administration. Following subcutaneous administration, the protracted action profile is based on three mechanisms: self-association, which results in a slow absorption, binding to albumin and enzymatic stability towards the DPP-IV and NEP enzymes resulting in a long plasma half-life.

Liraglutide is a fragment of the naturally occurring human glucagon-like peptide-1 sequence position 7-37 (GLP-1[7-37]) with substitution of the naturally occurring amino acid residue in position 34 (Lys) by Arg and with addition of a Glu-spaced hexadecanoic acid (palmitic acid) to the ε-amino group of Lys in position 26. The analogue is produced using the recombinant DNA technology in Yeast (*Saccharomyces cerevisiae*) and further chemically modified by an addition of a Glu-spaced hexadecanoic (palmitic) acid (Figure 1).

The structural formula $Arg^{34}Lys^{26}$-(N-ε-(γ-Glu (N-α-hexadecanoyl)))-GLP-1[7-37] is given in Figure 1.

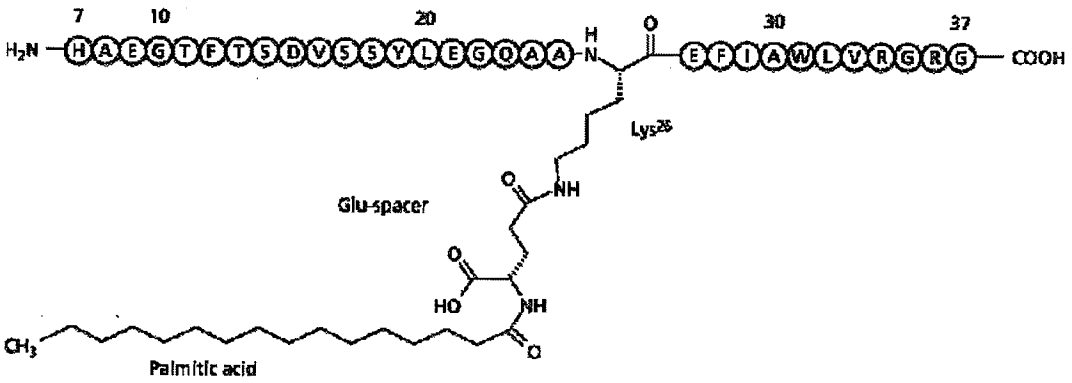

Figure 1 Structure of liraglutide

3.1 Molecular formula

The molecular formula of liraglutide is $C_{172}H_{265}N_{43}O_{51}$

3.2 Relative molecular mass

The theoretical molecular mass of liraglutide is 3751.20 Da.

United States Adopted Name (USAN)	Liraglutide
United States Adopted Name (USAN), Adopted 1. chemical name	Glycine, L-histidyl-L-alanyl-L-α-glutamylglycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-α-aspartyl-L-valyl-L-seryl-L-seryl-L-tyrosyl-L-leucyl-L-α-glutamylglycyl-L-glutaminyl-L-alanyl-L-alanyl-N^6-[N-(1-oxohexadecyl)-L-γ-glutamyl]-L-lysyl-L-α-glutamyl-L-phenylalanyl-L-isoleucyl-L-alanyl-L-tryptophyl-L-leucyl-L-valyl-L-arginylglycyl-L-arginyl-
USAN adopted 2. chemical name	$N^{\varepsilon 26}$-(N-hexadecanoyl-L-γ-glutamyl)-[34-L-arginine]glucagon-like peptide 1-(7-37)-peptide
USAN adopted 3. chemical name	$Arg^{34}Lys^{26}$-(N-ε-(γ-Glu (N-α-hexadecanoyl)))-GLP-1[7-37]

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_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 3

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/s/

Suong Tran
7/2/2008 02:06:31 PM
CHEMIST
as we discussed

Ali Al-Hakim
7/2/2008 02:30:34 PM
CHEMIST

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

ɔplication:	NDA 22341/000	**Action Goal:**	
am' 'e:	23-MAY-2008	**District Goal:**	22-JAN-2009
ɜgu .	23-MAR-2009		
ɔplicant:	NOVO NORDISK INC	**Brand Name:**	VICTOZA (LIRAGLUTIDE)
	100 COLLEGE RD WEST	**Estab. Name:**	
	PRINCETON, NJ 08540	**Generic Name:**	LIRAGLUTIDE
'iority:	1S	**Product Number; Dosage Form; Ingredient; Strengths**	
'g. Code:	510	001; SOLUTION, INJECTION; LIRAGLUTIDE; 6MG	

ɔplication Comment: DRUG SUBSTANCE: LIRAGLUTIDE [RDNA ORIGIN] IN SACCHAROMYCES CEREVISIAE
DRUG PRODUCT: 6 MG/ML PACKAGED IN PRE-FILLED CARTRIDGE INSIDE A DISPOSABLE INJECTOR PEN IN — b(4)
STRENGTHS: 1.2 MG AND 1.8 MG. (on 11-JUN-2008 by S. TRAN () 301-796-1764)

)A Contacts:	J. BISHAI	Project Manager		301-796-1311
	J. LEGINUS	Review Chemist	(HFD-810)	301-796-4102
	S. TRAN	Team Leader		301-796-1764

'erall Recommendation:	ACCEPTABLE	on 23-MAR-2009	by E. JOHNSON	(HFD-320)	301-796-3334

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

stablishment: **CFN:** 9610699 **FEI:** 3002807751

NOVO NORDISK A/S

HALLAS ALLE
KALUNDBORG, , DENMARK

MF No: **AADA:**

esponsibilities: DRUG SUBSTANCE MANUFACTURER

FINISHED DOSAGE PACKAGER

stab. Comment: LABELING AND PACKAGING OF PRODUCT (on 12-JUN-2008 by S. TRAN () 301-796-1764)

MANUFACTURING RDNA DRUG SUBSTANCE (on 12-JUN-2008 by S. TRAN () 301-796-1764)

ofile: BIOTECHNOLOGY CRUDE DRUG **OAI Status:** NONE

STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS NONE

ilestone Name / Comment	Milestone Date	Request Type	Planned Completion	Decision / Reason	Creator
JBMITTED TO OC	12-JUN-2008				TRANS
C RECOMMENDATION	12-JUN-2008			ACCEPTABLE BASED ON PROFILE	ADAMSS
JBMITTED TO OC	12-JUN-2008				TRANS
JBMITTED TO DO	12-JUN-2008	GMP Inspection			ADAMSS
D RECOMMENDATION	28-JUL-2008			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
C RECOMMENDATION	29-JUL-2008			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

stablishment: **CFN:** 9613234 **FEI:** 3003234571

NOVO NORDISK A/S

SYDMARKEN 5
SOEBERG, , DENMARK

MF No: **AADA:**

esponsibilities: DRUG SUBSTANCE RELEASE TESTER

stab. Comment: QC OF RDNA DRUG SUBSTANCE (on 12-JUN-2008 by S. TRAN () 301-796-1764)

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

ilestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
JBMITTED TO OC	12-JUN-2008				TRANS
C RECOMMENDATION	12-JUN-2008			ACCEPTABLE BASED ON PROFILE	ADAMSS

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

stablishment: **CFN:** 9613244 **FEI:** 3002807752

NOVO NORDISK A/S

BERNNUM PARK, DK-3400
HILLEROED, , DENMARK

MF No: **AADA:**

esponsibilities: FINISHED DOSAGE PACKAGER

FINISHED DOSAGE RELEASE TESTER

stab. Comment: QC OF BULK AND FINISHED PRODUCT (on 12-JUN-2008 by S. TRAN () 301-796-1764)

LABELING AND PACKAGING OF PRODUCT (on 12-JUN-2008 by S. TRAN () 301-796-1764)

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

STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS NONE

ilestone Name / Comment	Milestone Date	Request Type	Planned Completion	Decision / Reason	Creator
JBMITTED TO OC	12-JUN-2008				TRANS
C RECOMMENDATION	12-JUN-2008			ACCEPTABLE BASED ON PROFILE	ADAMSS
JBMITTED TO OC	12-JUN-2008				TRANS
JBMITTED TO DO	12-JUN-2008	10-Day Letter			ADAMSS
D RECOMMENDATION	28-JUL-2008			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
C RECOMMENDATION	29-JUL-2008			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

stablishment: **CFN:** 9616213 **FEI:** 3000151819

NOVO NORDISK A/S

NOVO ALLE
BAGSVAERD, , DENMARK

MF No: **AADA:**

esponsibilities: DRUG SUBSTANCE MANUFACTURER

FINISHED DOSAGE MANUFACTURER

stab. Comment: MANUFACTURING OF PRODUCT (on 12-JUN-2008 by S. TRAN () 301-796-1764)

MANUFACTURING OF MASTER CELL BANK AND WORKING CELL BANK (on 12-JUN-2008 by S. TRAN () 301-796-1764)

ofile: BIOTECHNOLOGY CRUDE DRUG **OAI Status:** NONE

STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS NONE

ilestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
JBMITTED TO OC	12-JUN-2008				TRANS
JBMITTED TO DO	12-JUN-2008	GMP Inspection			ADAMSS
SSIGNED INSPECTION TO IB	28-JUL-2008	GMP Inspection			ADAMSS
SPECTION SCHEDULED	02-FEB-2009		06-MAR-2009		IRIVERA
SPECTION PERFORMED	06-MAR-2009		06-MAR-2009		GINGER.SYKES
ATIC WITHHOLD STATUS ISSUED BY FACTS, DUE TO FIRM BEING OUT OF BUSINESS RGED Please see the Endorsement Text.					
SPECTION PERFORMED	06-MAR-2009		06-MAR-2009		JOHNSONE
D RECOMMENDATION	23-MAR-2009			ACCEPTABLE INSPECTION	JOHNSONE
C RECOMMENDATION	23-MAR-2009			ACCEPTABLE DISTRICT RECOMMENDATION	JOHNSONE
JBMITTED TO OC	12-JUN-2008				TRANS
JBMITTED TO DO	12-JUN-2008	10-Day Letter			ADAMSS
D RECOMMENDATION	17-JUN-2008			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
C RECOMMENDATION	17-JUN-2008			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

stablishment: **CFN:** **FEI:** 3006036003

NOVO NORDISK A/S

NORDRE FASANVEJ 215 (FUGLEBAKKEN)
FREDERIKSVERG, , DENMARK

MF No: **AADA:**

esponsibilities: FINISHED DOSAGE RELEASE TESTER

stab. Comment: QC OF BULK PRODUCT (on 12-JUN-2008 by S. TRAN () 301-796-1764)

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

ilestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
JBMITTED TO OC	12-JUN-2008				TRANS
C RECOMMENDATION	12-JUN-2008			ACCEPTABLE BASED ON PROFILE	ADAMSS

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

stablishment: **CFN:** 1058438 **FEI:** 1000158576

NOVO NORDISK PHARMACEUTICAL INDUSTRIES INC

3612 POWHATAN RD
CLAYTON, NC 27520

MF No: **AADA:**

esponsibilities: FINISHED DOSAGE PACKAGER

tab. Comment: LABELING AND PACKAGING OF DRUG PRODUCT (on 12-JUN-2008 by S. TRAN () 301-796-1764)

ofile: STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS **OAI Status:** NONE

ilestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				**Reason**	
JBMITTED TO OC	12-JUN-2008				TRANS
C RECOMMENDATION	12-JUN-2008			ACCEPTABLE BASED ON PROFILE	KIEL