CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206321Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM

Date: 21-Oct-2014
From: Joseph Leginus, Review Chemist, Branch VII/DNDQA III/ONDQA
To: NDA 206321, Saxenda™ (Liraglutide [rDNA origin] Injection)
Subject: CMC Approval Recommendation

Background:

- In Chemistry Review #1 (14-May-2014), the recommendation from the standpoint of chemistry, manufacturing and controls was Approval for NDA 206321. However, at that time, a recommendation from the Office of Compliance was pending.
- On 16-Jan-2014, a recommendation for Approval was provided by the Microbiology Reviewer, B. Riley.

Update:

- On 10-Oct-2014, a recommendation of Acceptable was provided by the Office of Compliance for NDA 206321.

Conclusion:

- NDA 206321 is recommended for Approval from the standpoint of chemistry, manufacturing and controls. A recommendation for Approval has been provided from Microbiology and an overall Office of Compliance recommendation of Acceptable has been provided.

Joseph Leginus, PhD
Review Chemist

joseph.leginus@fda.hhs.gov

Digitally signed by joseph.leginus@fda.hhs.gov
DN: cn=joseph.leginus@fda.hhs.gov
Date: 2014.10.21 07:25:44 -04'00'

NDA 206321
Saxenda™
(Liraglutide [rDNA origin] Injection)

Novo Nordisk Inc.

Joseph Leginus, PhD
Division of Pre-Marketing Assessment III, Branch VII, ONDQA

For the Division of
Metabolism and Endocrinology Products

CHEMISTRY REVIEW #1

Table of Contents

Chemistry Review Data Sheet

1. NDA 206321

2. REVIEW #: 1

3. REVIEW DATE: 14-May-2014

4. REVIEWER: Joseph Leginus, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA	20-Dec-2013

7. NAME & ADDRESS OF APPLICANT:

Name:	Novo Nordisk Inc.
Address:	PO Box 846, Plainsboro NJ, 08536
Representative:	Robert B. Clark, VP, Regulatory Affairs
Telephone:	609-786-4690

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Saxenda™
b) Non-Proprietary Name (USAN): Liraglutide
c) Code Name/# (ONDC only): Liraglutide 3 mg
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: Type 1
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: This NDA is submitted as a 505(b)(1) application.

10. PHARMACOL. CATEGORY: Chronic weight management

11. DOSAGE FORM: Injectable solution

12. STRENGTH/POTENCY: 6 mg/mL

13. ROUTE OF ADMINISTRATION: Subcutaneous injection

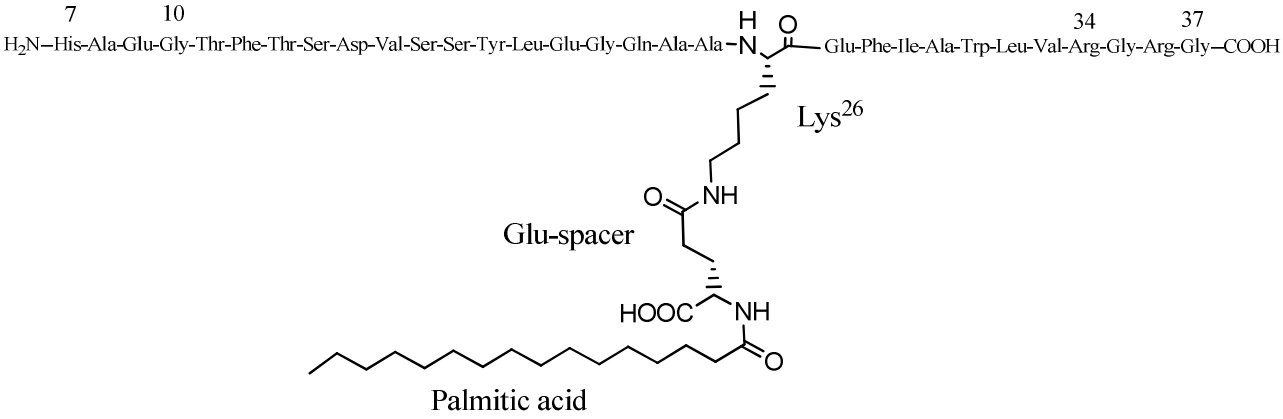
14. Rx/OTC DISPENSED: _X_Rx ___OTC

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

__X___Not a SPOTS product

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

Chemical Name (USAN): Liraglutide
Structural Formula:



Molecular Formula: $C_{172}H_{265}N_{43}O_{51}$
Molecular Weight: 3751.2 Da

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	V	(b) (4)		1	Adequate	8/12/2011	Reviewed by S. Langille
	V			1	Adequate	5/30/2012	Reviewed by V. Pawar

[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
NDA	22341	Victoza® (liraglutide [rDNA] injection)
IND	73206	Liraglutide Injection

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending.		N/A
Pharm/Tox	N/A. (b) (4) .		
Biopharmaceutics	"No Biopharm review/er is needed for this NDA." (12/24/2013 email from T. Ghosh, Biopharm Team Leader).		
Methods Validation	Not required. No novel methods.		
EA	Categorical Exclusion Granted under 21 CFR §25.31(b).	14-May-2014	J. Leginus
Microbiology	Approval	1/16/2014	B. Riley

19. ORDER OF REVIEW: N/A

The Chemistry Review for NDA 206537

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The recommendation from a CMC perspective is Approval.

At this time, a recommendation from the Office of Compliance is pending.

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

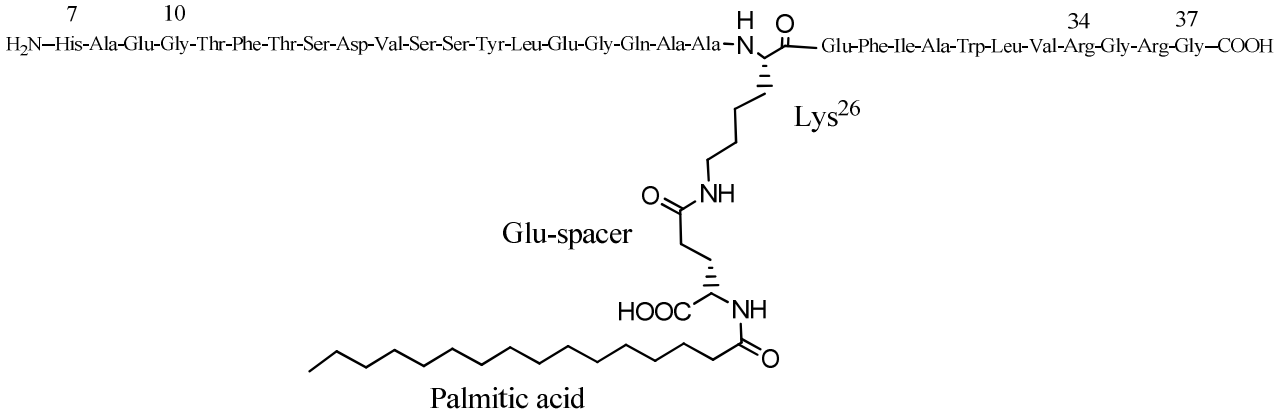
Not applicable.

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-N6-[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 white to almost white powder. It is freely soluble in aqueous base solutions (> 270 mg/mL), but its water solubility decreases below pH 7 and reaches its lowest level at pH 4-5 (approximately 0.05 mg/mL). Solubility increases marginally at pH 2.5 where it is very slightly soluble (≤ 0.8 mg/mL). Liraglutide is soluble in methanol (68 mg/mL) and very slightly soluble in ethanol (1.1 mg/mL). The isoelectric point of liraglutide is approximately 4.9. The pH of a 1 mg/mL aqueous solution of drug substance is approximately 9.3.

DRUG PRODUCT

Liraglutide 3 mg consists of an aqueous formulation at pH 8.15 of (b) (4) liraglutide with (b) (4) disodium phosphate dihydrate (b) (4) propylene glycol (b) (4) and (b) (4) phenol (b) (4)

Liraglutide 3 mg is a parenteral drug product for subcutaneous administration. The drug product is (b) (4) filled in a 3 mL 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, 1.8 mg, 2.4 mg or 3.0 mg depending on the setting of the multi-dose pen-injector.

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

The proposed indication for Liraglutide 3 mg is as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients. Liraglutide 3 mg is administered once daily at any time, independent of meals, and can be injected subcutaneously in the abdomen, in the thigh or in the upper arm. The starting dose is 0.6 mg and is intended to be increased with 0.6 mg weekly increments until the maintenance dose of 3 mg is achieved. The 0.6, 1.2, 1.8 and 2.4 mg doses are intended to reduce gastrointestinal symptoms during initial dose escalation.

C. Basis for Approvability or Not-Approval Recommendation

The recommendation from a CMC perspective is Approval.

This is a 505(b)(1) application for a new indication (chronic weight management) for the same approved drug product Victoza® (liraglutide [rDNA] injection) of NDA 22341 (glycemic control in patients with type 2 diabetes). The applicant is the same for both NDAs.

The drug products of the two NDAs have the same a) drug substance, (b) (4) Both NDAs use the identical 3 mL glass cartridge as the primary container closure system. The 3 mL glass cartridge for liraglutide 3 mg will be provided in a different pen-injector referred to as the PDS290 pen-injector for liraglutide (PDS290). The PDS20 is capable of delivering 5 different doses of Liraglutide: 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg and 3.0 mg.

Data provided from the stressed stability and photostability studies for Liraglutide 3 mg do not show evidence of any changes to the stability compared to the approved Victoza® (NDA 22341). The applicant's proposal that the long-term and in-use shelf lives of the approved product should apply to the new product as bridged by 3-month data under stressed conditions of 37°C for the product in cartridges alone and product in cartridges assembled in the new pen injector is acceptable. Therefore, the shelf life and the in-use conditions for Liraglutide 3 mg using the PDS290 pen-injector (b) (4) i.e., an expiry of (b) (4) months at 2°C – 8°C plus (b) (4) days at 28°C – 32°C is granted for the drug product.

Biopharmaceutics concluded that "No Biopharm review/er is needed for this NDA." (12/24/2013 email from T. Ghosh, Biopharm Team Leader).

Microbiology has provided an Acceptable recommendation.

A recommendation from the Office of Compliance for manufacturing facilities associated with this application is pending.

The risk associated with Saxenda® is low. With the exception of the pen-injector, Saxenda is the same drug product as the Applicant's approved Victoza® (liraglutide [rDNA] injection; NDA 22341) intended for the treatment of diabetes. The pen injector is under review by CDRH.

III. Administrative

A. Reviewer's Signature: in DAARTS
B. Endorsement Block: in DAARTS
C. CC Block: in DAARTS

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

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

/s/

JOSEPH LEGINUS
05/14/2014

DANAE D CHRISTODOULOU
05/14/2014

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: 206321
2. DATES AND GOALS:

Letter Date: 20-DEC-2013	Submission Received Date : 20-DEC-2013

PDUFA Goal Date: 20-OCT-2014 (NDA is NOT in "The Program")

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Proposed: Saxenda
Established Name (USAN):	Liraglutide
Dosage Form:	Injectable solution
Route of Administration	Subcutaneous injection
Strength/Potency	6 mg/mL
Rx/OTC Dispensed:	Rx

4. INDICATION: Chronic weight management
5. DRUG SUBSTANCE STRUCTURAL FORMULA:

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

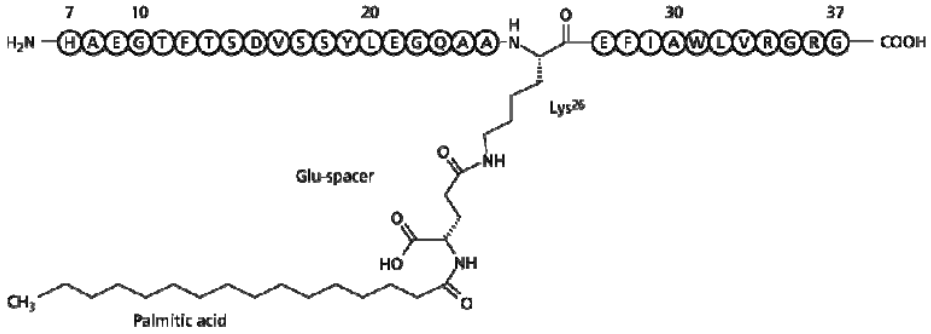

Figure 1 Structure of liraglutide

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.

6. NAME OF APPLICANT (as indicated on Form 356h): Novo Nordisk Inc.
7. SUBMISSION PROPERTIES:

Review Priority (select one)	Standard
Submission Classification (Chemical Classification Code)	10

ONDQA Initial Quality Assessment (IQA) and Filing Review
For new NDAs

Application Type	505(b)(1)
Breakthrough Therapy	No
Responsible Organization (Clinical Division)	Division of Metabolism and Endocrinology Products CMC Lead: Suong (Su) Tran

8. CONSULTS:

CONSULT	YES	NO	COMMENTS:
Biometrics		x	
Clinical Pharmacology		x	
Establishment Evaluation Request (EER)	x		To be sent by ONDQA-PM
Pharmacology/Toxicology		x	
Methods Validation			To be determined by Primary Reviewer
Environmental Assessment			Categorical exclusion request to be reviewed by Primary Reviewer
CDRH	x		Review of pen injectors

Does the submission contain any of the following elements? No			
Nanotechnology	QbD Elements	PET	Other, please explain

Is a team review recommended?	No - Reference is made to the approved NDA 22341 for all CMC information on the drug substance and drug product, with the exception of information on the new pen injector of the new NDA and stability data of the product assembled in the new pen. One CMC reviewer will review the new stability data and labeling.

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective? Yes
Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter? No

Biopharmaceutics:n/a

From: Ghosh, Tapash
To: Tran, Suong T; Christodoulou, Danae D; Kumar, Priyanka; CDER OPS IO MICRO
Cc: Duan, John Z.; Ghosh, Tapash
Subject: RE: please send assignments for new NDA FW: NDA 206321 from NOVO NORDISK INC product name Liraglutide 3.0 mg
Date: Tuesday, December 24, 2013 1:59:52 PM

No biopharm review/er is needed for this NDA. Thanks,

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective?

ONDQA Initial Quality Assessment (IQA) and Filing Review
For new NDAs

See Microbiology Filing Review in DARRTS for details and for any potential Microbiology review issues.

Previous quality-related meeting between ONDQA and the sponsor: None.

Summary of Critical Issues and Complexities

This new NDA is for a new indication (weight management) for the same approved product Victoza of NDA 22341 (diabetes). Both NDAs have the same applicant.
The applicant states that the drug products of the two NDAs (b) (4) are packaged in the same primary container closure system (glass cartridges). The pre-filled cartridges will be assembled in two different pen injectors (each pen injector is specific to the one NDA). A technical comparison of the pen injectors is included in the NDA. A CDRH consult request will be sent by the Clinical Division and will cover CDRH Compliance, human factors and technical reviews. CDRH and the Office of Combination Products had several communications with the sponsor during the IND development.

Reference is made to the approved NDA 22341 for all CMC information on the drug substance liraglutide.
The new NDA includes drug product information that is not the same between the two NDA: manufacturing process and stability data.

- The reviewer will note the manufacturing process information that is the same in the two NDAs and evaluate the new information.
- The drug product specifications are the same between the two NDAs with the exception of the device-specific attribute of Dose Accuracy, which will be part of the CDRH technical review (as was done in other NDA reviews).
- Stability data are provided in the NDA in support of the new pen injector, including a photostability study report. The three primary stability batches were manufactured at the commercial site, commercial scale, and packaged with the commercial cartridges. The applicant's proposal that the long-term and in-use shelf lives of the approved product should apply to the new product as bridged by 3-month data under stress conditions of 37°C for the product in cartridges alone and product in cartridges assembled in the new pen injector. The reviewer will compare the new data to all available stability data in NDA 22341 in evaluating the applicant's proposal.

FILING REVIEW CHECKLIST

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*				
*	**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.**			
	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		

	Parameter	**Yes**	**No**	**Comment**
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • 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)	x		

8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • 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)	x		

	Parameter	Yes	No	Comment
9.	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: • 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)	x		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment or claim of categorical exclusion been provided?	x		

D.	DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)			
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	x		Reference is made to the approved NDA 22341.
13.	Does the section contain identification and controls of critical steps and intermediates of the DS	x		
14.	Does the section contain information regarding the characterization of the DS?	x		
15.	Does the section contain controls for the DS?	x		
16.	Has stability data and analysis been provided for the drug substance?	x		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		x	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		x	

E.	DRUG PRODUCT (DP)			
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
21.	Is there a batch production record and a proposed master batch record?	x		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		

23.	Has any biowaiver been requested?		x	
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	x		
25.	Does the section contain controls of the final drug product?	x		
26.	Has stability data and analysis been provided to support the requested expiration date?	x		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		x	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	

F.	**METHODS VALIDATION (MV)**			
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	x		

G.	**MICROBIOLOGY**			
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product	x		

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		Reference is made to the approved NDA 22341.

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		

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
01/23/2014

DANAE D CHRISTODOULOU
01/23/2014

Application	Level 1	Level 2	Level 3	Subtype	Pepfar	Sponsor	Status	Status Date	FEI	CFN	Establishment	Address
NDA 206321/000				N/A	N	NOVO NORDISK INC	PN	12/20/2013	3002807751	9610699	NOVO NORDISK A S	HALLAS ALLE KALUNDBORG / DNK HALLAS ALLI
NDA 206321/000				N/A	N	NOVO NORDISK INC	PN	12/20/2013	1000158576	1058438	NOVO NORDISK PHARMACEUTICAL INDUSTRIES INC	3612 POWHATAN RD CLAYTON NC/275279217 U
NDA 206321/000				N/A	N	NOVO NORDISK INC	PN	12/20/2013	3000151819	9616213	NOVO NORDISK A S	NOVO ALLE BAGSVAERD / DNK NOVO ALLE
NDA 206321/000				N/A	N	NOVO NORDISK INC	PN	12/20/2013	3000151819	9616213	NOVO NORDISK A S	NOVO ALLE BAGSVAERD / DNK NOVO ALLE
NDA 206321/000				N/A	N	NOVO NORDISK INC	PN	12/20/2013	3003131673	9613244	NOVO NORDISK A S	HILLEROD /DK3400 DNK BERNNUM PARK, DK-34
NDA 206321/000				N/A	N	NOVO NORDISK INC	PN	12/20/2013	3003131673	9613244	NOVO NORDISK A S	HILLEROD /DK3400 DNK BERNNUM PARK, DK-34

Overall Recommendation - Acceptable
Overall Re-eval Date - October 20, 2016

Country	Profile	Stage	Process	Last Milestone	Compliance Status	Milestone Date	OAI Alert Status	EER Re-eval Date
DNK	CTL	DRUG SUBSTANCE	OTHER TESTER	OC RECOMMENDATION	AC	2/17/2014	**NONE**	5/10/2016
USA	(b) (4)	FINISHED DOSAGE	MANUFACTURER	OC RECOMMENDATION	AC	9/4/2014	**NONE**	8/16/2016
DNK	CTL	DRUG SUBSTANCE,FINISHED DOSAGE	MANUFACTURER,OTHER TESTER	OC RECOMMENDATION	AC	2/25/2014	**NONE**	9/3/2016
DNK	(b) (4)	DRUG SUBSTANCE,FINISHED DOSAGE	MANUFACTURER,OTHER TESTER	OC RECOMMENDATION	AC	2/21/2014	**NONE**	9/3/2015
DNK	DKA	FINISHED DOSAGE	LABELER,MANUFACTURER,PACKAGER	OC RECOMMENDATION	AC	7/30/2014	**NONE**	10/10/2016
DNK	(b) (4)	FINISHED DOSAGE	LABELER,MANUFACTURER,PACKAGER	OC RECOMMENDATION	AC	7/30/2014	**NONE**	10/10/2016