CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203313Orig1s000
203314Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

Product Quality Microbiology Review

JUNE 11, 2012

NDA: 203314

Drug Product Name
Proprietary: Tresiba™
Non-proprietary: Insulin degludec [rDNA origin] injection.

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
September 29, 2011	September 29, 2011	October 7, 2011	October 13, 2011

Submission History (for amendments only) – N/A

Applicant/Sponsor
Name: Novo Nordisk Inc.
Address: 100 College Road West,
Princeton, NJ 08540
Representative: Anne Phillips, Corp. Vice President, CMR
Telephone: Nina Liang, Mgr. R A, 609-987-5803

Name of Reviewer: Vinayak B. Pawar, Ph.D.

Conclusion: Recommend approval.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original NDA

2. SUBMISSION PROVIDES FOR: TresibaTM (insulin degludec [rDNA origin] injection) solution for subcutaneous injection.

3. MANUFACTURING SITE: Novo Nordisk, Bagsvaerd, Denmark

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

100 Units of insulin degludec per mL (U-100)

- 3 mL FlexTouch® pen injector

(b) (4)

200 Units of insulin degludec per mL (U-200)

- 3 mL FlexTouch® pen injector

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Treatment of patients with Diabetes mellitus.

B. SUPPORTING/RELATED DOCUMENTS: DMF 21494

C. REMARKS: Novo Nordisk submits an original New Drug Application for TresibaTM (insulin degludec [rDNA origin] injection) solution for subcutaneous injection. While some Microbiology Product Quality information was provided in the NDA submission, reference was made to DMF 21494 for sterilization validation information. The information reviewed in the DMF will not be included or discussed in this NDA review. IQA was filed by ONDQA (Suong Tran) on November 22, 2011. The drug product manufacturing site was scheduled for inspection on March 23, 2012.

filename: N203314R1

Executive Summary

I. Recommendations

A. Recommendation on Approvability – Recommend approval.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology - The bulk containing a [redacted (b) (4)].

B. Brief Description of Microbiology Deficiencies – N/A

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

III. Administrative

A. Reviewer's Signature _____
Vinayak B. Pawar, Ph.D., NDMS, OPS, CDER

B. Endorsement Block _____
John W. Metcalfe, Ph.D., NDMS, OPS, CDER

C. CC Block
N/A

Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

S DRUG SUBSTANCE – N/A

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- Description of drug product – The drug product, Tresiba™ (Insulin Degludec [rDNA Origin] Injection) will be available in two strengths (100 Units or 200 Units of insulin degludec/mL) as a sterile, clear, colorless aqueous solution for injection.
- Drug product composition – The quantitative composition of insulin degludec 100 units/mL is provided in Table 1 (copied from Table 1, Section 2.3.P.1 Description and Composition of the drug product). The other formulation is insulin degludec 200 units/mL.

Table 1. Quantitative Composition of Insulin Degludec 100 U/mL

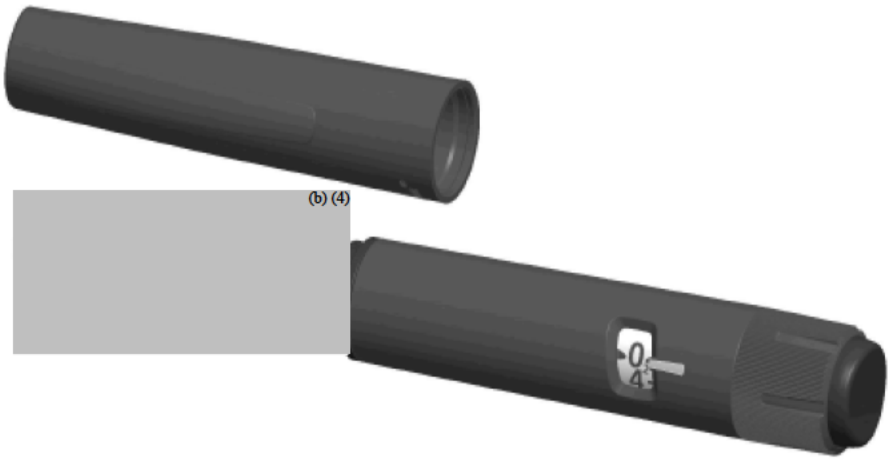
Name of components	Quantity per ml	Function	Reference to standards
Active substance			
Insulin degludec	600 nmol	Drug substance	Novo Nordisk
Excipients			
Phenol[1]	1.50 mg	(b) (4)	Ph Eur ,USP, JP
Metacresol[1]	1.72 mg		Ph Eur, USP
Glycerol	19.6 mg		Ph Eur ,USP, JP
Zinc	32.7 µg		Ph Eur ,USP, JPE[2]
Hydrochloric acid[3]	(b) (4)	pH adjustment	Ph Eur ,USP, JP
Sodium hydroxide[3]		pH adjustment	Ph Eur ,USP, JP
Water for injections		(b) (4)	Ph Eur ,USP, JP
			(b) (4)

[3] To reach pH 7.6

- Description of container closure system – The 100 and 200 U/mL strengths will be filled in (b) (4) cartridges with a nominal fill volume of (b) (4) mL, which includes an overage of (b) (4) mL. The 100 U/mL strength is intended for the market in two presentations: (b) (4) a pre-filled disposable PDS290 pen-injector. The 200 U/mL strength is intended for the market in a pre-filled disposable PDS290 pen-injector. A schematic drawing of the cartridge container closure system is provided in Figure 1 (copied from Appendix A, Section 3.2.P.7). A design of the PDS290 pen-injector is provided in Figure 2 (copied from Figure 1, Section 2.3.P.7 Container closure system).

Figure 1. Schematic Drawing of the Container Closure System

Figure 2. PDS290 U200 2U pen-injector with the cap



P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

Container-Closure and Package integrity – The container closure integrity test for 3 mL cartridges has been reviewed in DMF 21494 and was found adequate. In the subject NDA submission, the container closure integrity was correlated with Residual Seal Force (RSF) testing of the sealing

integrity [redacted]. RSF is a measure of the force the [redacted] cap is compressed with after the [redacted] process. [redacted] Primary Stability Batch results for reported time of 24 months (VCQ0014, VCQ0015 & XCQ0001) were provided and the batches were free of microbial growth. The sponsor assures that the [redacted] rubber disc complies with the test described in Ph Eur regarding Test for Penetrability, Fragmentation and Self sealing.

Adequate

[redacted] *Effectiveness* – The sponsor claims that their insulin products have been used for decades with the same [redacted] system which has been proposed for insulin degludec 100 U/ml drug products to be marketed. Based on Novo Nordisk experience with other subcutaneous insulin products, the same [redacted] system consisting of [redacted] was also chosen for insulin degludec formulation. The Ph Eur and USP acceptance criteria for evaluation of antimicrobial activity is provided in Table 2 (copied from Table 1 Section 3.2.P.2.5 Microbiological Attributes) which indicates log reduction in terms of the number of viable micro-organisms against the value obtained in the inoculum. A full confirmatory test of efficacy of antimicrobial [redacted] has been performed according to Ph Eur, USP and JP for the insulin degludec 100 U/ml drug product at target concentrations of [redacted] The Primary Stability Batches for degludec 100 U/ml when tested at start [XCQ0036, XCQ0037 and XCQ0044] and after 24 months [VCQ0014, VCQ0015 and XCQ0001] comply with criteria B in Ph Eur, USP and JP. Only 3 month (initial stability time point) results were available for degludec 200 U/ml and the results were in compliance. An example of the results from Batch VCQ0014 is summarized in Table 3 (copied from Table 4, Section 3.2.P.2.5 Microbiological Attributes).

Adequate

Table 2. The Ph Eur and USP acceptance criteria for evaluation of antimicrobial activity in terms of log reduction

Pharmacopoeia	Ph Eur		Ph Eur		USP	
Log reduction	Log reduction Criteria A		Log reduction Criteria B		Log reduction	
Hours/days	Bacteria	Fungi	Bacteria	Fungi	Bacteria	Fungi
6 hours	2					
24 hours	3		1			
7 days		2	3		1.0	NI[2]
14 days				1	3.0	NI[2]
28 days	NR[1]	NI[2]	NI[2]	NI[2]	NI[2]	NI[2]

[1] NR: No recover

[2] NI: No increase

Table 3. Batch VCQ0014 -Log reductions after 24 months at 5°C

Hours/days	Result (cfu/ml)	Log reduction	Criteria A log red.	Criteria B log red.
Aspergillus niger				
Control	3.9E+04			
7 days	1.0E+02	2.59	2	
14 days	1.0E+02	2.59		1
28 days	1.0E+02	2.59	No increase	No increase
Candida albicans				
Control	1.0E+06			
7 days	1.0E+00	6.02	2	
14 days	1.0E+00	6.02		1
28 days	1.0E+00	6.02	No increase	No increase
Pseudomonas aeruginosa				
Control	2.2E+05			
6 hours	1.0E+00	5.34	2	
24 hours	1.0E+00	5.34	3	1
7 days	1.0E+00	5.34		3
28 days	1.0E+00	5.34	No recovery	No increase
Staphylococcus aureus				
Control	1.4E+06			
6 hours	8.8E+05	0.20	2	
24 hours	8.6E+02	3.21	3	1
7 days	1.0E+00	6.14		3
28 days	1.0E+00	6.14	No recovery	No increase

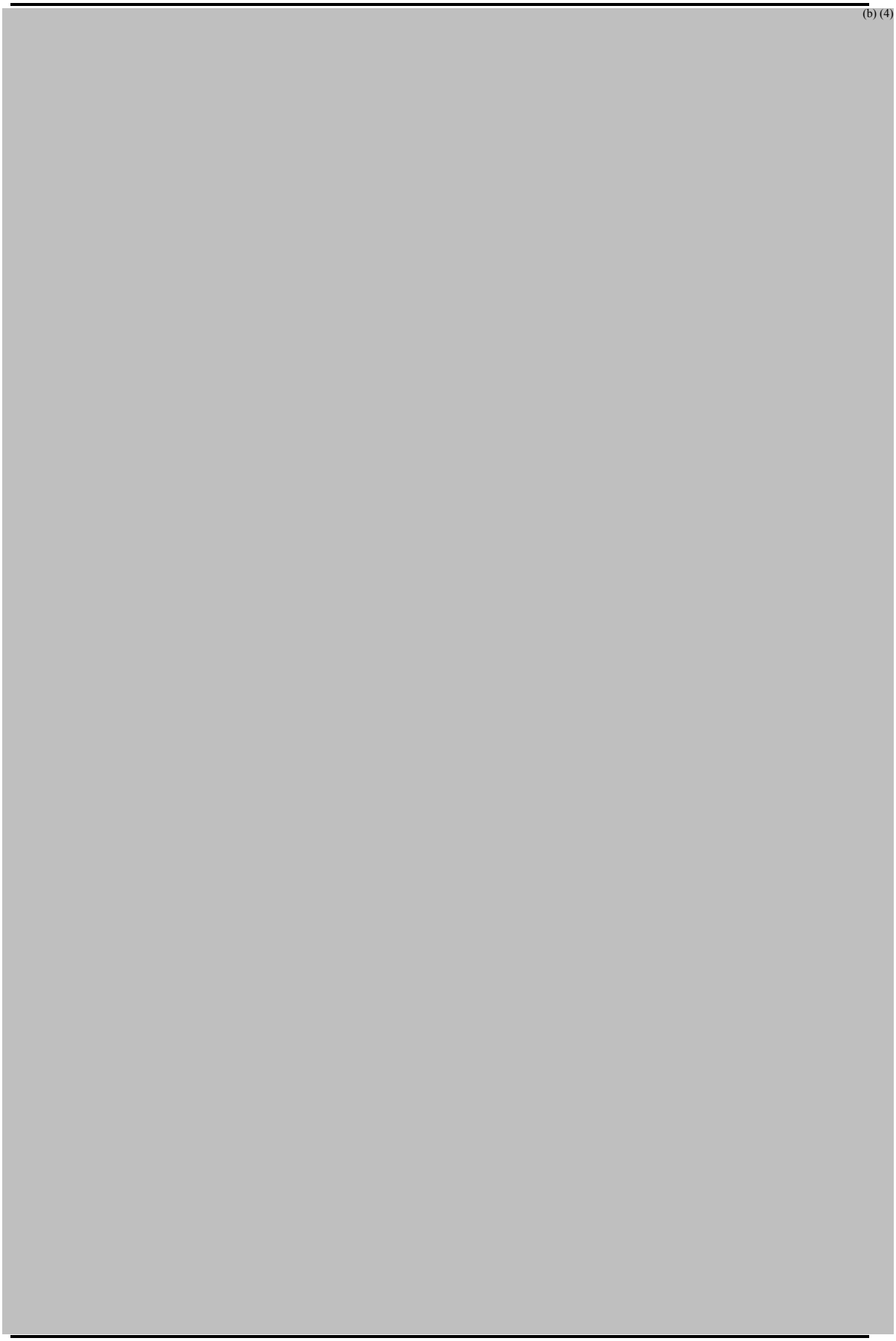
- Justification for not having a microbial limit specification for a non-sterile drug product -

P.3 Manufacture

P.3.1 Manufacturers

P.3.3 Description of the Manufacturing Process and Process Controls

(b) (4)



P.5 Control of Drug Product

P.5.1 Specifications

P.5.2 Analytical Procedures

Endotoxin – The test method is equivalent to Ph. Eur. Bacterial endotoxins method D (Chromogenic peptide kinetic LAL method) and the Kinetic Chromogenic bacterial endotoxin methods in the USP and JP. Product endotoxins detection limit of (b) (4) EU/mL was calculated based on lysate sensitivity at (b) (4) EU/mL CSE, the MVD established at (b) (4) [Validation Reports 001041559 (degludec 100 U) & 001027610 (degludec 200 U), dated June 16, 2011 per Section 3.2.R). For insulin injection, according to Ph. Eur, there is a limit of (b) (4) EU/100 units of insulin and therefore the acceptance criteria for the 100 unit degludec insulin product is set at NMT (b) (4) EU/mL and NMT (b) (4) EU/ml for the 200 unit degludec insulin product.

Validation Batches 412-N08493, 412-N08494 & 412-N08495 for degludec 100 U and 412-N09174, 412-N09175 & XLDF003 for degludec

200 U all tested at (b) (4) EU/mL. Endotoxin levels from Primary Stability Batches (see Review Section P.8.1) tested at (b) (4) EU/mL.

Adequate

- Sterility – Acceptable from DMF 21494 review.
- Microbial Limits – N/A

P.7 Container Closure System – See Review Section P.1

P.8 Stability

P.8.1 Stability Summary and Conclusion

The studies were performed according to the current ICH guidelines. The batches included in the stability studies, the protocols (time points and storage conditions) and the data available at submission are listed in Tables 4 & 5 (copied from Tables 2, Stability Summary Section 3.2.P.8.1 for each degludec 100U and Section 3.2.P.8.1 for degludec 200U). The (b) (4) is used as the primary container closure system for the drug product in the stability studies and is identical to the one intended for the market. Stability studies have been performed on supportive and primary batches (pilot scale) in order to establish and support the proposed shelf life of 30 months at 5°C. Stability studies have also been initiated on production scale batches (b) (4) units of process validation batches and (b) (4) units of process challenge batches) in order to confirm the proposed shelf life of 30 months at 5°C. In-use stability studies have been performed on primary batches to establish and support the proposed in-use period of 8 weeks at a maximum temperature of 30°C. Sterility test at stability time points is performed using (b) (4) method according to USP, Ph Eur. & JP. Bacterial endotoxins test at stability time points is performed using Chromogenic kinetic method according to USP, Ph Eur. & JP. Sterility and Bacterial Endotoxins test results were provided for the Primary Stability Batches YQ50516, YQ50517 and YQ50518 (degludec 100 U at initial stability time point only) and Primary Stability Batches YQ50519, YQ50520 and YQ50521 (degludec 200 U at initial stability time point only) and all were within the required specifications. An example of the results from Primary degludec 200U Batches YQ50519, YQ50520 and YQ50521 is provided in Table 6 (copied from Appendix A, Section 3.2.P.8.3).

Adequate

P.8.2 Post-Approval Stability Protocol and Stability Commitment

Novo Nordisk A/S commits to continue the following stability studies according to the study design described in the interim stability reports (Section 3.2.P.8.3): (1) Stability Data for Process Validation Batches ((b) (4) units), Two Process Challenge Batches (b) (4) units), and Primary

Stability Batches ((b) (4) units) for Insulin Degludec 100 U/ml product. (2) Stability Data for Process Validation Batches ((b) (4) units), one Process Challenge Batch ((b) (4) units), and Primary Stability Batches ((b) (4) units) for Insulin Degludec 200 U/mL product. In addition, Novo Nordisk A/S commits to initiate a new stability study with three ((b) (4) units) Process Validation Batches, according to the study set up described in Section 3.2.P.8.3.

Specifications and testing schedule for post-approval stability program.

- Container Closure Integrity – performed at expiration.
- Sterility – Performed according to review section P.5.2 at zero and at 24, 30 and 36 month stability time points.
- Endotoxin – performed according to review section P.5.2 at zero, and at 12, 24, 30 and 36 month stability time points
- Microbial Limits – N/A

P.8.3 Stability Data - See Review Section P.8.1 above.

Table 4. Summary of Stability protocols degludec 100U

Batch no.	Batch size and type	Storage conditions	Protocol time points	Reported time points
ACQ0019 ACQ0020	(b) (4) (process challenge)	5°C ± 3°C/ambient humidity/darkness 25°C ± 2°C/ambient humidity/darkness	0, 1, 2, 3, 6, 9, 12, 18, 24, 30, 36 months 0, 1, 2, 3, 6 months	0, 1, 2 months 0, 1, 2 months
YQ50516 YQ50517 YQ50518	(b) (4) (process validation batches)	5°C ± 3°C/ambient humidity/darkness 25°C ± 2°C/ambient humidity/darkness	0, 3, 6, 9, 12, 18, 24, 30, 36 months 0, 1, 2, 3, 6 months	0, 3 months 0, 1, 2, 3 months
VCQ0014 VCQ0015 XCQ0001	(b) (4) (primary batches, study 1)	5°C ± 3°C/ambient humidity/darkness 25°C ± 2°C/ambient humidity/darkness	0, 3, 6, 9, 12, 18, 24, 30, 36 months 0, 1, 2, 3, 6 months	0, 3, 6, 9, 12, 18, 24, 30 months 0, 1, 2, 3, 6 months
XCQ0036 XCQ0037 XCQ0044	(b) (4) (primary batches, study 2)	5°C ± 3°C/ambient humidity/darkness 25°C ± 2°C/ambient humidity/darkness	0, 3, 6, 9, 12, 18, 24, 30, 36 months 0, 1, 2, 3, 6 months	0, 3, 6, 9, 12, 18 months 0, 1, 2, 3, 6 months
TQ50434	(b) (4) (supportive batch)	5°C ± 3°C/ambient humidity/darkness 25°C ± 2°C/ambient humidity/darkness	0, 3, 6, 9, 12, 18, 24, 30 months 0, 3, 6 months	0, 3, 6, 9, 12, 18, 24, 30 months 0, 3, 6 months
VCQ0014 XCQ0036 XCQ0037 XCQ0044	(b) (4) (primary batches)	30°C ± 2°C/ambient humidity/darkness Simulating patient usage including movement and penetrations of the rubber closure.	0, 4, 6, 8 weeks at 30°C after storage at 5°C ± 3°C for: - 15 months (2 batches) - 24 months (1 batch) - 30 months (1 batch) - 36 months (1 batch) During the in-use study the physical, chemical and microbial stability is investigated.	0, 4, 6, 8 weeks at 30°C after storage at 5°C ± 3°C for: - 15 months (2 batches) - 24 months (1 batch)
VCQ0014 XCQ0037	(b) (4) (primary batches)	Photostability study on primary batches in primary and secondary packaging (b) (4) (b) (4) (b) (4) (b) (4) pen-injector and according to ICH guideline Q1B (1.43 million lux hours, 585 Wh/m²).	26 hours (in light incubator)	26 hours (in light incubator)

Table 5. Summary of Stability protocols degludec 200U

Batch no.	Batch size and type	Storage conditions	Protocol time points	Reported time points
ACQ0021	(b) (4) (production scale batch)	5°C ± 3°C/ambient humidity/darkness 25°C ± 2°C/ambient humidity/darkness	0, 1, 2, 3, 6, 9, 12, 18, 24, 30, 36 months 0, 1, 2, 3, 6 months	0, 1 month 0, 1 month
YQ50519 YQ50520 YQ50521	(b) (4) (process validation batches)	5°C ± 3°C/ambient humidity/darkness 25°C ± 2°C/ambient humidity/darkness	0, 3, 6, 9, 12, 18, 24, 30, 36 months 0, 1, 2, 3, 6 months	0, 3 months 0, 1, 2, 3 months
XCQ0016 XCQ0017 XCQ0018	(b) (4) (primary batches, study 1)	5°C ± 3°C/ambient humidity/darkness 25°C ± 2°C/ambient humidity/darkness	0, 3, 6, 9, 12, 18, 24, 30, 36 months 0, 1, 2, 3, 6 months	0, 3, 6, 9, 12, 18 months 0, 1, 2, 3, 6 months
XCQ0041 XCQ0042 XCQ0043	(b) (4) (primary batches, study 2)	5°C ± 3°C/ambient humidity/darkness 25°C ± 2°C/ambient humidity/darkness	0, 3, 6, 9, 12, 18, 24, 30, 36 months 0, 1, 2, 3, 6 months	0, 3, 6, 9, 12, 18 months 0, 1, 2, 3, 6 months
412_N08620	(b) (4) (supportive batch, study 1)	5°C ± 3°C/ambient humidity/darkness 25°C ± 2°C/ambient humidity/darkness	0, 3, 6, 9, 12, 24, 30 months 0, 3, 6 months	0, 3, 6, 9, 12, 18, 24, 30 months 0, 3, 6 months
XLDP012	(b) (4) (supportive batch, study 2)	5°C ± 3°C/ambient humidity/darkness 25°C ± 2°C/ambient humidity/darkness	0, 3, 6, 9, 12, 18, 24 months 0, 3, 6 months	0, 3, 6, 9, 12, 18, 24 months 0, 3, 6 months
XCQ0016 XCQ0017 XCQ0018 XCQ0041 XCQ0042 XCQ0043	(b) (4) (primary batches)	30°C ± 2°C/ambient humidity/darkness Simulating patient usage including movement and penetrations of the rubber closure.	0, 4, 6, 8 weeks at 30°C - shortly after production (four batches) and after storage at 5°C ± 3°C for: - 24 months (one batch) - 30 months (one batch) - 36 months (one batch) During the in-use study the physical, chemical and microbial stability is investigated.	0, 4, 6, 8 weeks at 30°C - shortly after production (four batches)
XCQ0017 XCQ0042	(b) (4) (primary batches)	Photostability study on primary batches in primary and secondary packaging (b) (4) pen-injector) according to ICH guideline Q1B (1.43 million lux hours, 585 Wh/m^2).	26 hours (in light incubator)	26 hours (in light incubator)

Table 6. Results, 3 Month Stability Data at 5°C.

Test item	Proposed specification	Batch no.	Storage time (Months)	
			0	3
Macroscopy	(b) (4)	YQ50519	Complies	-
		YQ50520	Complies	-
		YQ50521	Complies	-
Content of insulin degludec (nmol/ml)		YQ50519	1207	1197
		YQ50520	1216	1216
		YQ50521	1210	1215
pH		YQ50519	7.55	-
		YQ50520	7.58	-
		YQ50521	7.56	-
HMWP (%)		YQ50519	≤0.2	≤0.2
		YQ50520	≤0.2	≤0.2
		YQ50521	≤0.2	≤0.2
Hydrophilic impurities (%)		YQ50519	0.2	0.3
		YQ50520	0.3	0.4
		YQ50521	0.3	0.3
Hydrophobic related substances (%)		YQ50519	0.6	1.0
		YQ50520	0.7	1.0
		YQ50521	0.6	1.0
Hydrophobic impurities (%)		YQ50519	≤0.2	≤0.2
		YQ50520	≤0.2	≤0.2
		YQ50521	≤0.2	≤0.2
Zinc total (µg/ml)		YQ50519	70.1	-
		YQ50520	69.7	-
		YQ50521	70.4	-
Bacterial endotoxins (IU/ml)		YQ50519	≤5	-
		YQ50520	≤5	-
		YQ50521	≤5	-
Sterility		YQ50519	Complies	-
		YQ50520	Complies	-
		YQ50521	Complies	-
Metacresol (mg/ml)		YQ50519	1.76	1.74
		YQ50520	1.76	1.75
		YQ50521	1.77	1.76
Phenol (mg/ml)		YQ50519	1.55	1.53
		YQ50520	1.55	1.54
		YQ50521	1.55	1.54
Particulate matter (b) (4) (particles/container)		YQ50519	782	-
		YQ50520	853	-
		YQ50521	2013	-
Particulate matter (b) (4) (particles/container)		YQ50519	30	-
		YQ50520	30	-
		YQ50521	50	-

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

A. PACKAGE INSERT

This is a (b) (4) sterile product for subcutaneous injection. There are no microbiology product quality labeling issues identified with the product label.

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

None.

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

/s/

VINAYAK B PAWAR
06/13/2012

JOHN W METCALFE
06/13/2012
I concur.

Product Quality Microbiology Review

June 1, 2012

NDA: 203313

Drug Product Name
Proprietary: Ryzodeg™
Non-proprietary: 70% insulin degludec & 30% insulin aspart [rDNA origin] injection.

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
September 29, 2011	September 29, 2011	October 7, 2011	October 13, 2011

Submission History (for amendments only) – N/A

Applicant/Sponsor
Name: Novo Nordisk Inc.
Address: 100 College Road West
Princeton, NJ 08540
Representative: Anne Phillips, Corp. Vice President, CMR
Telephone: Nina Liang, Mgr. R A, 609-987-5803

Name of Reviewer: Vinayak B. Pawar, Ph.D.

Conclusion: Recommend approval.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original NDA

2. SUBMISSION PROVIDES FOR: Ryzodeg™ for subcutaneous injection.

3. MANUFACTURING SITE: Novo Nordisk, Bagsvaerd, Denmark

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: 100 Units of insulin degludec/insulin aspart per mL (U-100): • 3 mL FlexTouch® (b) (4)

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Treatment of patients with Diabetes mellitus.

B. SUPPORTING/RELATED DOCUMENTS: DMF 21494

C. REMARKS: Novo Nordisk submits an original New Drug Application (NDA) for Ryzodeg™ (70% insulin degludec and 30% insulin aspart [rDNA origin] injection) solution for subcutaneous injection. While some Microbiology Product Quality information was provided in the NDA submission, reference was made to DMF 21494 for sterilization validation information. The information reviewed in the DMF will not be included or discussed in this NDA review. IQA was filed by ONDQA (Suong Tran) on November 22, 2011. The drug product manufacturing site was scheduled for inspection on March 23, 2012.

filename: **N203313R1**

Executive Summary

I. Recommendations

A. Recommendation on Approvability – Recommend approval.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The bulk containing a [redacted] (b) (4)

B. Brief Description of Microbiology Deficiencies – N/A

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

III. Administrative

A. Reviewer's Signature _____
Vinayak B. Pawar, Ph.D., NDMS, OPS, CDER

B. Endorsement Block _____
John W. Metcalfe, Ph.D., NDMS, OPS, CDER

C. CC Block
N/A

Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

S DRUG SUBSTANCE – N/A

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- Description of drug product – The proposed drug product (70% Insulin Degludec and 30% Insulin Aspart [rDNA Origin] Injection; IDegAsp) is a mixture of insulin degludec (IDeg, a long acting insulin analog) and insulin aspart (IAsp, a rapid acting insulin analog) in 70/30 ratio to mimic the combined action profiles of long acting and rapid acting insulin. The drug product is a sterile, clear, colorless aqueous solution.

- Drug product composition – The quatitative composition of insulin degludec/insulin aspart 100 units/mL is provided in Table 1 (copied from Table 1, Section 2.3.P.1 Description and Composition of the drug product).

Table 1. Composition of insulin degludec/insulin aspart 100 units/mL

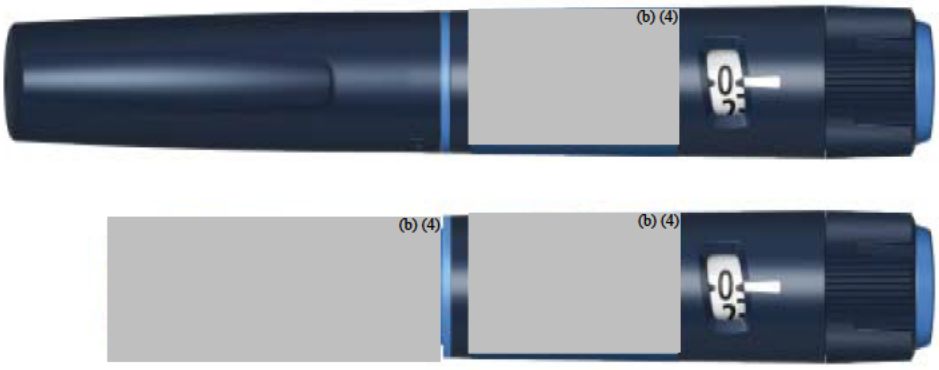
Name of components	Quantity per ml	Function	Reference to standards
Active substance			
Insulin degludec	420 nmol	Drug substance	Novo Nordisk
Insulin aspart	180 nmol	Drug substance	Novo Nordisk
Excipients			
Phenol[1]	1.50 mg	(b) (4)	Ph Eur, USP, JP
Metacresol[1]	1.72 mg		Ph Eur, USP
Glycerol	19.0 mg		Ph Eur, USP, JP
Sodium chloride	0.58 mg		Ph Eur, USP, JP
Zinc	27.4 µg		Ph Eur, USP, JPE[2]
Hydrochloric acid[3]	(b) (4)	pH adjustment	Ph Eur, USP, JP
Sodium hydroxide[3]		pH adjustment	Ph Eur, USP, JP
Water for injections		(b) (4)	Ph Eur, USP, JP

- Description of container closure system – The Applicant is proposing to market the product as (b) (4) FlexTouch® pre-filled pens (cartridge pre-assembled in a PDS290 pen-injector) with a nominal fill volume of (b) (4) mL, which includes an overage of (b) (4) mL. A schematic drawing of the cartridge container closure system is provided in Figure 1 (copied from Appendix A, Section 3.2.P.7). A design of the PDS290 pen-injector is provided in Figure 2 (copied from Figure 1, Section 2.3.P.7 Container closure system). The

assembled PDS290 pen-injector includes an approved (b) (4) cartridge containing insulin degludec 100 U/ml, insulin degludec 200 U/ml, or insulin degludec/insulin aspart 100 U/ml. Assembly processes and testing procedures for the PDS290 pen-injector are independent of the specific drug product formulation and no product contact occurs during the assembly.

Figure 1. Schematic Drawing of the Container Closure System

Figure 2. PDS290 pen-injector with and without cap



P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

Container-Closure and Package integrity – The container closure integrity test for 3 mL cartridges has been reviewed in DMF 21494 and was found adequate. In the subject NDA submission, the container closure integrity was correlated with Residual Seal Force (RSF) testing of the sealing integrity (b) (4). RSF is a measure of the force the (b) (4) cap is compressed with after the (b) (4) process. (b) (4) Primary Stability Batch results for reported time of 24 months (XCQ0004, XCQ0005 & XCQ0006) and 18 month (XCQ0038, XCQ0039 & XCQ0040) were provided and the batches were free of microbial growth. The sponsor assures that the (b) (4) rubber disc complies with the test described in Ph Eur regarding Test for Penetrability, Fragmentation and Self sealing.

Adequate

(b) (4) *Effectiveness* – The sponsor claims that their insulin products have been used for decades with the same (b) (4) system which has been proposed for insulin degludec/insulin aspart 100 U/ml drug products to be marketed. Based on Novo Nordisk experience with other subcutaneous insulin products, a (b) (4) system consisting of (b) (4) was also chosen for insulin degludec/insulin aspart formulation. The Ph Eur and USP acceptance criteria for evaluation of antimicrobial activity is provided in Table 2 (copied from Table 1 Section 3.2.P.2.5 Microbiological Attributes) which indicates log reduction in terms of the number of viable micro-organisms against the value obtained in the inoculum. A full confirmatory test of efficacy of antimicrobial (b) (4) has been performed according to Ph Eur, USP and JP for the insulin degludec/insulin aspart 100 U/ml drug product at target concentrations of (b) (4). The batches tested [XCQ0038, XCQ0039, XCQ0040, XCQ0004, XCQ0005 & XCQ0006] comply with criteria B in Ph Eur, USP and JP. An example of the results from Batch XCQ0038 is summarized in Table 3 (copied from Table 8, Section 3.2.P.2.5 Microbiological Attributes).

Adequate

Table 2. The Ph Eur and USP acceptance criteria for evaluation of antimicrobial activity in terms of log reduction

Pharmacopoeia	Ph Eur		Ph Eur		USP	
Log reduction	Log reduction Criteria A		Log reduction Criteria B		Log reduction	
Hours/days	Bacteria	Fungi	Bacteria	Fungi	Bacteria	Fungi
6 hours	2					
24 hours	3		1			
7 days		2	3		1.0	NI[2]
14 days				1	3.0	NI[2]
28 days	NR[1]	NI[2]	NI[2]	NI[2]	NI[2]	NI[2]

[1] NR: No recover

[2] NI: No increase

Table 3. Batch XCQ0006 -Log reductions after 24 months at 5°C

Hours/days	Result (cfu/ml)	Log reduction	Criteria A log red.	Criteria B (log red.)
Aspergillus niger				
Control	8.3E+04			
7 days	1.0E+02	2.92	2	
14 days	1.0E+02	2.92		1
28 days	1.0E+02	2.92	No increase	No increase
Candida albicans				
Control	9.2E+05			
7 days	1.0E+00	5.96	2	
14 days	1.0E+00	5.96		1
28 days	1.0E+00	5.96	No increase	No increase
Pseudomonas aeruginosa				
Control	1.2E+05			
6 hours	1.0E+00	5.08	2	
24 hours	1.0E+00	5.08	3	1
7 days	1.0E+00	5.08		3
28 days	1.0E+00	5.08	No recovery	No increase
Staphylococcus aureus				
Control	1.3E+06			
6 hours	1.1E+06	0.05	2	
24 hours	8.1E+03	2.19	3	1
7 days	1.0E+00	6.10		3
28 days	1.0E+00	6.10	No recovery	No increase

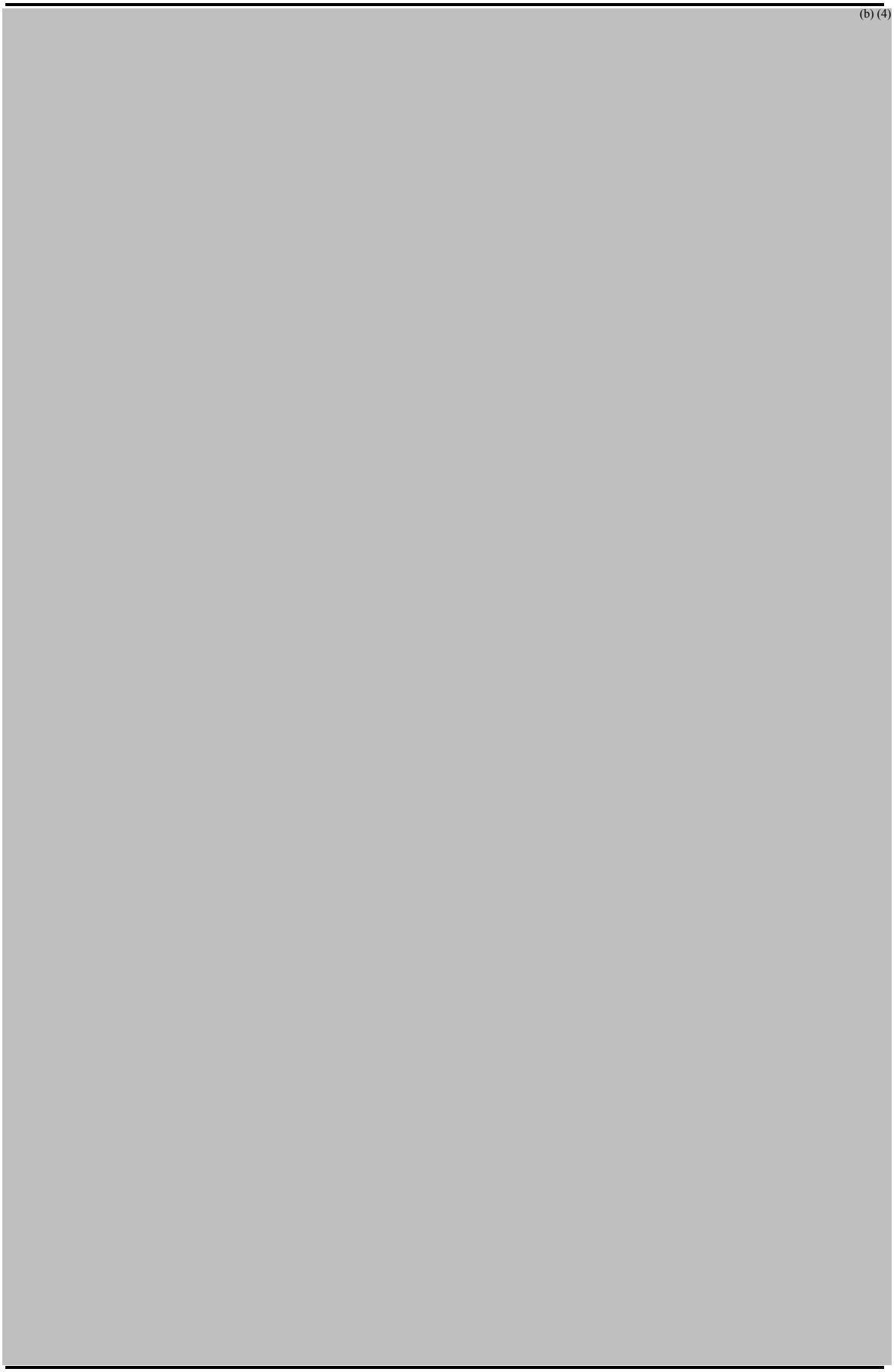
Justification for not having a microbial limit specification for a non-sterile drug product – N/A

P.3 Manufacture

P.3.1 Manufacturers

P.3.3 Description of the Manufacturing Process and Process Controls

(b) (4)



(b) (4)

P.5 Control of Drug Product

P.5.1 Specifications

P.5.2 Analytical Procedures

- Endotoxin – The test method is equivalent to Ph. Eur. Bacterial endotoxins method D (Chromogenic peptide kinetic LAL method) and the Kinetic Chromogenic bacterial endotoxin methods in the USP and JP. Product endotoxins detection limit of (b) (4) EU/mL was calculated based on lysate sensitivity at (b) (4) EU/mL CSE, the MVD established at (b) (4) (Validation Report 001041877, dated June 16, 2011, Section 3.2.R). For insulin injection, according to Ph. Eur, there is a limit of (b) (4) EU/100 units of insulin and therefore the acceptance criteria for the 100 unit degludec/insulin product is set at NMT (b) (4) EU/mL. Validation Batch Numbers 412-N08485, 412-N08486 and 412-N08487 tested at (b) (4) (b) (4) EU/mL for endotoxin. Results of stability batches were also within acceptable limits (see Review Section P.8.1).

Adequate

- Sterility – Acceptable from DMF 21494 review.
- Microbial Limits – N/A

P.7 Container Closure System – See Review Section P.1**.**

P.8 Stability -

P.8.1 Stability Summary and Conclusion

The studies were performed according to the current ICH guidelines. The batches included in the stability studies, the protocols (time points and storage conditions) and the data available at submission are listed in Table 4 (copied from Table 2, Section 3.2.P.8.1). The (b) (4) is used as the primary container closure system for the drug product in the stability studies and is identical to the one intended for the market. Stability studies have been performed on supportive and primary batches (pilot scale) in order to establish and support the proposed shelf life of 30 months at 5°C. Stability studies have also been initiated on production scale batches in order to confirm the proposed shelf life of 30 months at 5°C. In-use stability studies have been performed on primary batches to establish and support the proposed in-use period of 4 weeks at a maximum temperature of 30°C. Sterility test at stability time points is performed using (b) (4) method according to USP, Ph Eur. & JP. Bacterial endotoxins test at stability time points is performed using Chromogenic kinetic method according to USP, Ph Eur. & JP. Sterility and Bacterial Endotoxins test results were provided for Batches XCQ0038, XCQ0039 and XCQ0040 (18 months time point) and Batches XCQ0004, XCQ0005 and XCQ0006 (24 month time point) and all were within the required specifications.

Adequate

Table 4. Summary of protocols

Batch no.	Batch size and type	Storage conditions	Protocol time points	Reported time points
ACQ0023	(b) (4) (production scale batch)	5°C ± 3°C/ambient humidity/darkness 25°C ± 2°C/ambient humidity/darkness	0, 1, 2, 3, 6, 9, 12, 18, 24, 30, 36 months 0, 1, 2, 3, 6 months	0, 1 months 0, 1 months
YQ50522 YQ50523 YQ50524	(b) (4) (process validation batches)	5°C ± 3°C/ambient humidity/darkness 25°C ± 2°C/ambient humidity/darkness	0, 3, 6, 9, 12, 18, 24, 30, 36 months 0, 1, 2, 3, 6 months	0, 3 months 0, 1, 2, 3 months
XCQ0004 XCQ0005 XCQ0006	(b) (4) (primary batches, study 1)	5°C ± 3°C/ambient humidity/darkness 25°C ± 2°C/ambient humidity/darkness	0, 3, 6, 9, 12, 18, 24, 30, 36 months 0, 1, 2, 3, 6 months	0, 3, 6, 9, 12, 18, 24 months 0, 1, 2, 3, 6 month
XCQ0038 XCQ0039 XCQ0040	(b) (4) (primary batches, study 2)	5°C ± 3°C/ambient humidity/darkness 25°C ± 2°C/ambient humidity/darkness	0, 3, 6, 9, 12, 18, 24, 30, 36 months 0, 1, 2, 3, 6 months	0, 3, 6, 9, 12, 18 months 0, 1, 2, 3, 6 month
TLDP010	(b) (4) supportive batch)	5°C ± 3°C/ambient humidity/darkness 25°C ± 2°C/ambient humidity/darkness	0, 3, 6, 9, 12, 18, 24, 30 months 0, 3, 6 months	0, 3, 6, 9, 12, 18, 24, 30 months 0, 3, 6 months
XCQ0004 XCQ0005 XCQ0006 XCQ0038 XCQ0039 XCQ0040	(b) (4) (primary batches)	30°C ± 2°C/ambient humidity/darkness Simulating patient usage including movement and penetrations of the rubber closure.	0, 3, 4 weeks at 30°C - shortly after production (four batches) and after storage at 5°C ± 3°C for: - 24 months (one batch) - 30 months (one batch) - 36 months (one batch)	0, 3, 4 weeks at 30°C - shortly after production (four batches) and after storage at 5°C ± 3°C for: - 24 months (one batch)
XCQ0004 XCQ0040	(b) (4) (primary batches)	Photostability study on primary batches in primary and secondary packaging (b) (4) (b) (4) according to ICH guideline Q1B (1.43 million lux hours, 585 Wh/m^2).	26 hours (in light incubator)	26 hours (in light incubator)

P.8.2 Post-Approval Stability Protocol and Stability Commitment

Novo Nordisk will document the drug product stability of insulin degludec/insulin aspart 100 U/ml from pilot scale to full production scale.

Stability studies at long term (5^{o} C $\pm$ 3^{o} C) and at accelerated storage conditions (25^{o} C $\pm$ 2^{o} C) have already been initiated on one production scale batch ((b) (4) units), three ((b) (4) units) process validation batches and six primary pilot scale batches. In addition, three ((b) (4) units) process validation batches will be produced and will be included in the stability program.

Specifications and testing schedule for post-approval stability program.

- Container Closure Integrity – performed at expiration.
- Sterility – Performed according to review section P.5.2 at zero and at 24, 30 and 36 month stability time points.
- Endotoxin – performed according to review section P.5.2 at zero, and at 12, 24, 30 and 36 month stability time points
- Microbial Limits – N/A

P.8.3 Stability Data – See Review Section P.8.1 above.

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

A. PACKAGE INSERT

This is a (b) (4) sterile product for subcutaneous injection. There are no microbiology product quality labeling issues identified with the product label. .

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

None

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/s/

VINAYAK B PAWAR
06/05/2012

JOHN W METCALFE
06/07/2012
I concur.

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 203313 **Applicant:** Novo Nordisk Inc. **Letter Date:** 09/29/2011

Drug Name: [Insulin Degludec/ Insulin Aspart 100 units/mL] **NDA Type:** Original **Stamp Date:** 09/29/2011

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	X		
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		Manufacturing Process/Controls, Section 3.2.P.3.3. Controls of Critical Steps & Intermediates, Section 3.2.P.3.4.
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	X		Process Validation, Section 3.2.P.3.5
4	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		X	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?	X		(b) (4) Effectiveness, Section 3.2.P.2.5. Container Closure Integrity, Section 2.3.P.2.6.
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		Drug Product Specifications, Section 3.2.P.5.6
7	Has the applicant submitted the results of analytical method verification studies?	X		Section 3.2.P.5.6, Bacterial Endotoxins Validation Report, Section 3.2.R.
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?			N/A
9	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: The two active substances in the drug product are: Insulin Aspart hexamers for rapid absorption into the capillaries & Insulin Degludec (b) (4)-hexamers for slow and continuous absorption into the circulation acting as a depot.

Reviewing Microbiologist: Vinayak B. Pawar, Ph.D. **Date**

Secondary Concurrence: Bryan S. Riley, Ph.D. **Date**

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/s/

VINAYAK B PAWAR
11/22/2011

BRYAN S RILEY
11/22/2011
I concur.

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 203314 **Applicant:** Novo Nordisk Inc. **Letter Date:** 09/29/2011

Drug Name: [Insulin degludec 100 Units/mL] **NDA Type:** Original **Stamp Date:** 09/29/2011

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	X		
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		Manufacturing Process/Controls, Section 3.2.P.3.3. Controls of Critical Steps & Intermediates, Section 3.2.P.3.4.
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	X		Process Validation, Section 3.2.P.3.5
4	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		X	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?	X		(b) (4) Effectiveness, Section 3.2.P.2.5. Container Closure Integrity, Section 2.3.P.2.6.
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		Drug Product Specifications, Section 3.2.P.5.6
7	Has the applicant submitted the results of analytical method verification studies?	X		Section 3.2.P.5.6, Bacterial Endotoxins Validation Report, Section 3.2.R..
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?			N/A
9	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: The active substance in the drug product is Insulin Degludec, a (b) (4) hexamers designed for slow and continuous absorption into the circulation, thus acting as a depot.

Reviewing Microbiologist: Vinayak B. Pawar, Ph.D. **Date**

Secondary Concurrence: Bryan S. Riley, Ph.D. **Date**

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/s/

VINAYAK B PAWAR
11/22/2011

BRYAN S RILEY
11/22/2011
I concur.

DEPARTMENT OF HEALTH AND HUMAN SERVICES Food and Drug Administration	REQUEST FOR CONSULTATION

TO *(Division/Office)*	FROM
OTS/OB/DB7	OTS/OB/DB2

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
11/22/2011		203-314	NDA submission	9/29/2011

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Tresiba (Insulin Degludec)	Standard	Type 1 and Type 2 Diabetes	6/1/2012

NAME OF FIRM
Novo Nordisk, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ PMANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY _____
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☑ OTHER *(Specify below)*

Meta-analyses of CV&hypoglycemia

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW	☐ CHEMISTRY
☐ END OF PHASE II MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☑ OTHER Safety
☑ OTHER New NDA (electronic)	

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILITY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE E.G. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS *(List below in comments)*
- ☐ COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☑ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS *(Attach additional sheets if necessary)*

As part of NDA 203314 submission for insulin degludec, Novo Nordisk has submitted reports of meta-analyses for cardiovascular events and hypoglycemia. These analyses were pre-planned. DB2 reviewed the SAPs pertaining to these meta-analyses. (Reviews in DARRTS.) (b) (4) The meta-analyses for CV events are important for assessing the cardiovascular safety of the drug.

The NDA arrived on 9/29/2011 with PDUFA goal date on 7/29/2012. Please have the review done with team leader's concurrence in DARRTS by June 1, 2012. There will be some meetings with clinicians to discuss the definitions and analyses for hypoglycemia.

The meta-analyses are available in Section 5.3.5.3.3. of Global Submit Review (9/29/11) and datasets in Sect 5.3.5.3.25.3.

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SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERY

FORM FDA 3291 (7/83)

PSC Media Arts (301) 443-1090 EF

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/s/

RACHEL E HARTFORD
11/22/2011