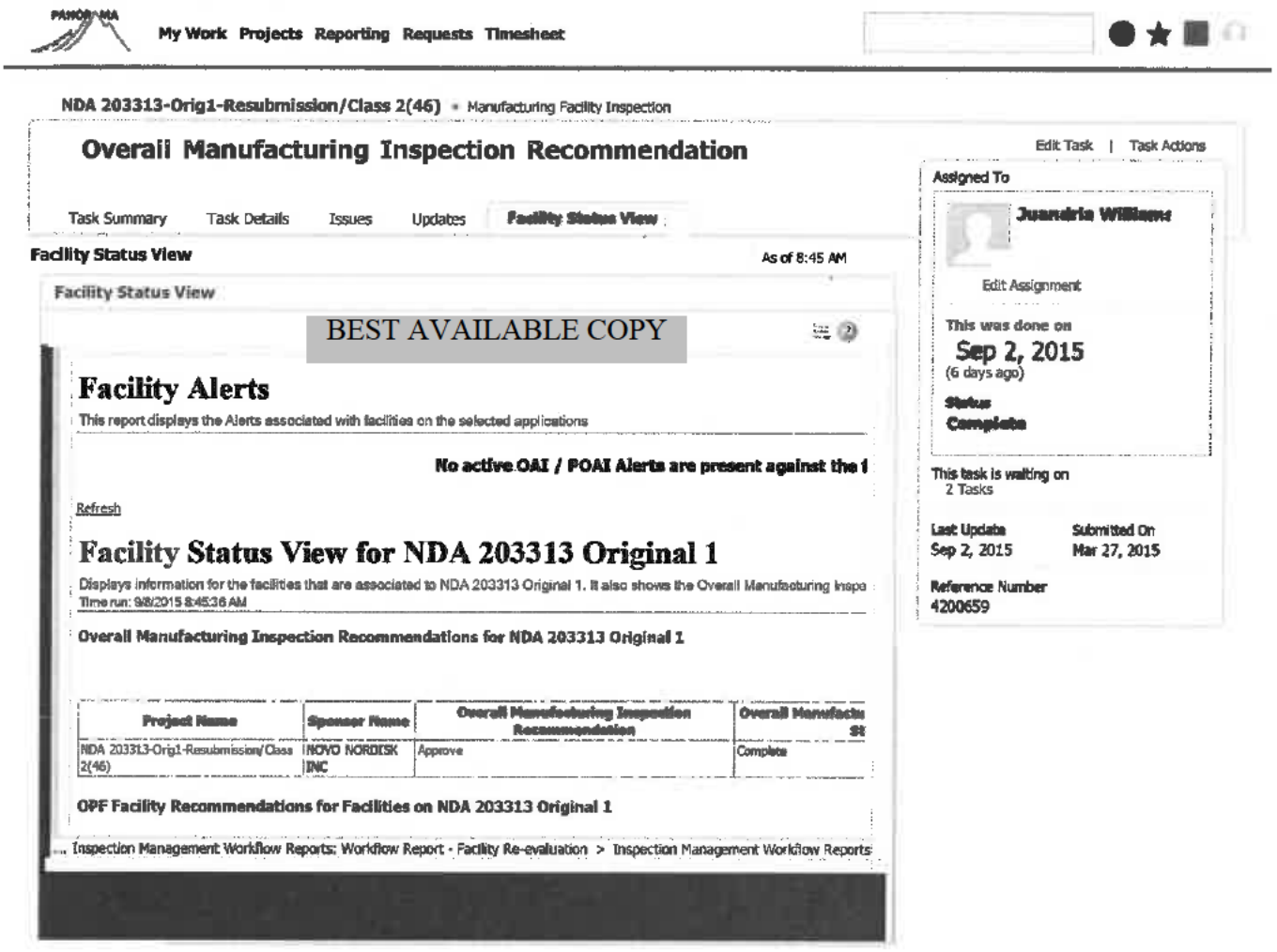
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203313Orig1s000
203314Orig1s000

CHEMISTRY REVIEW(S)



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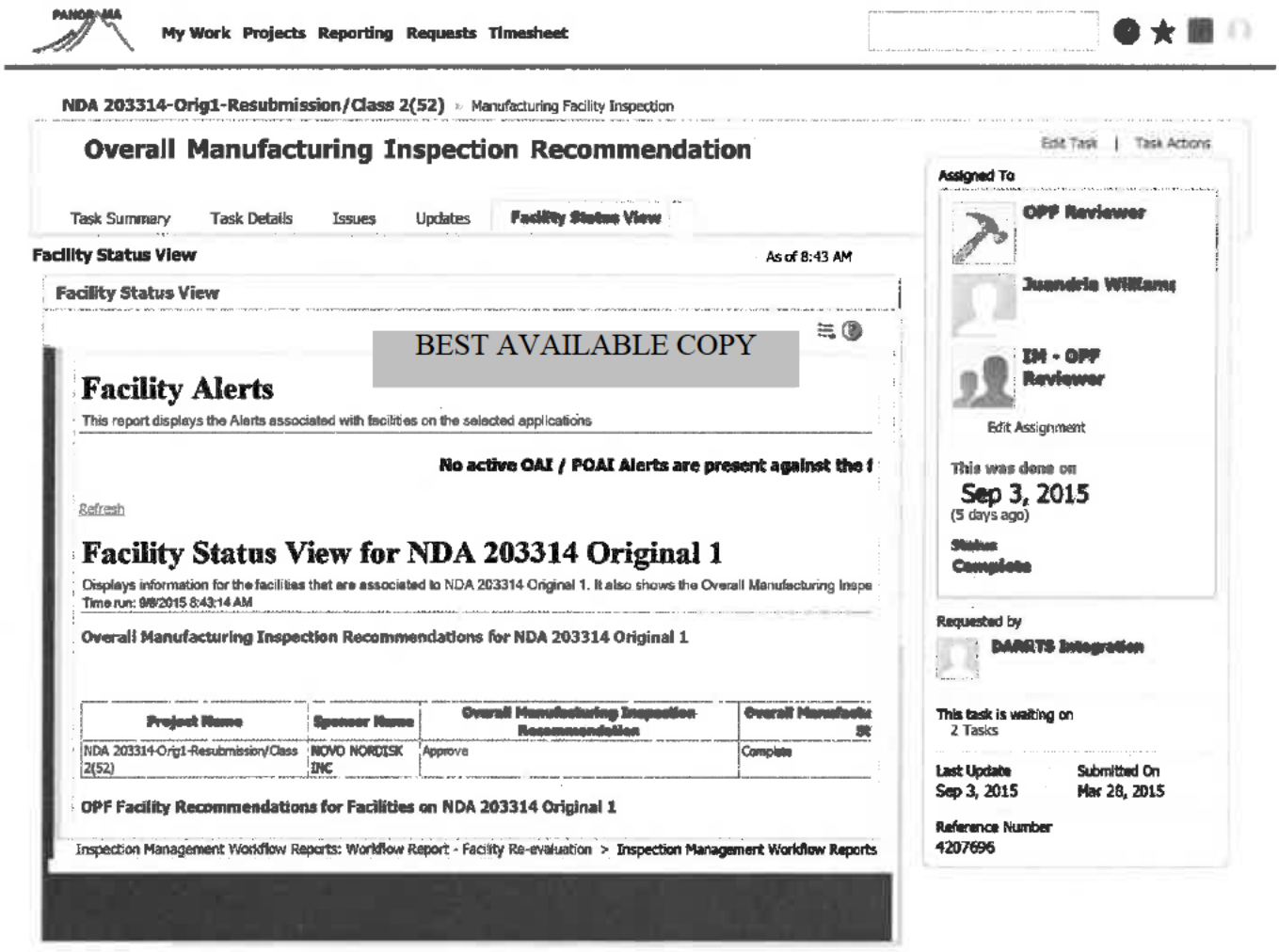


PANORAMA My Work Projects Reporting Requests Timesheet

NDA 203314-Orig1-Resubmission/Class 2(52) » Manufacturing Facility Inspection

Overall Manufacturing Inspection Recommendation

Edit Task | Task Actions

Task Summary | Task Details | Issues | Updates | Facility Status View

Facility Status View As of 8:43 AM

Facility Status View

BEST AVAILABLE COPY

Facility Alerts

This report displays the Alerts associated with facilities on the selected applications

No active OAI / POAI Alerts are present against the f

Refresh

Facility Status View for NDA 203314 Original 1

Displays information for the facilities that are associated to NDA 203314 Original 1. It also shows the Overall Manufacturing Inspe
Time run: 9/8/2015 8:43:14 AM

Overall Manufacturing Inspection Recommendations for NDA 203314 Original 1

Project Name	Sponsor Name	Overall Manufacturing Inspection Recommendation	Overall Manufactu St
NDA 203314-Orig1-Resubmission/Class 2(52)	NOVO NORDISK INC	Approve	Complete

OPF Facility Recommendations for Facilities on NDA 203314 Original 1

Inspection Management Workflow Reports: Workflow Report - Facility Re-evaluation > Inspection Management Workflow Reports

Assigned To

OPF Reviewer

Juandria Williams

IM - OPF Reviewer

Edit Assignment

This was done on
Sep 3, 2015
(5 days ago)

Status
Complete

Requested by
DARRTS Integration

This task is waiting on
2 Tasks

Last Update
Sep 3, 2015

Submitted On
Mar 28, 2015

Reference Number
4207696

QUALITY ASSESSMENT

Recommendation:
NDA: Approval

NDA 203313
Review # 1 (Resubmission)
September 3, 2015

Drug Name	**Insulin Degludec and Insulin Aspart**
Dosage Form	Solution for Injection
Strength	100 Units/mL
Route of Administration	Subcutaneous Administration
Rx Dispensed	Rx
Applicant	Novo Nordisk Inc.
US agent, if applicable	Not Applicable

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Resubmission/Class 2	March 26, 2015

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Joseph Leginus (Original Submission dated Sep. 29, 2011)	Branch II, Division I, ONDP
Drug Product	Muthukumar Ramaswamy (Original and Resubmission)	Branch VI, Division III, ONDP
Process	Muthukumar Ramaswamy (Original Submission)	Branch VI, Division III, ONDP
Microbiology	Vinayak Pawar (Original Submission)	OPF
Facility	Juandria Williams (Resubmission)	OPF
Biopharmaceutics	NA	NA
Project/Business Process Manager	Anika Lalmansingh (Resubmission)	ONDP/OPRO
Application Technical Lead	Muthukumar Ramaswamy (Resubmission) Su Tran (IQA for Original submission Sep. 29, 2011)	Branch VI, Division III, ONDP
Laboratory (OTR)	NA	NA
ORA Lead	NA	NA
Environmental Assessment (EA)	Joseph Leginus (Original Submission)	Branch II, Division I, ONDP

Table of Contents

Quality Review Data Sheet

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

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	V	Novo Nordisk, Inc.	(b) (4)	Adequate	Reviewed during original Submission review	none

[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	73198	[Insulin degludec/Insulin aspart] (rDNA origin) Injection
NDA	203314	Insulin degludec (rDNA origin) Injection
NDA	20986	Insulin aspart (rDNA origin) Injection

3. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
CDRH	Complete	Acceptable	9/02/15	Lana Shiu
Microbiology	Complete	Acceptable (Original Submission dated Sep. 29, 2011)	6/07/12	Vinayak Pawar
EA	Complete	Acceptable (Original Submission dated Sep. 29, 2011)	2/8/12	J. Leginus
EES	Complete	Acceptable	9/ 3/15	Juandria Williams

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 203313 *(Ryzodeg® (70% insulin degludec and 30% insulin aspart [rDNA origin] injection))* is recommended for approval from a CMC perspective. There are no outstanding deficiencies related to chemistry, microbiology, and manufacturing facilities. Office of Process and facilities has provided an approval recommendation for NDA 203313.

Labeling comments will be negotiated through the clinical project manager.

Based on available stability data, the following shelf-life recommendation is granted for the drug substance (insulin degludec) and drug product (provided as FlexTouch® pen device):

a) A shelf life of (b) (4) months is granted for drug substance insulin degludec when stored at (b) (4) (b) (4)

b) A shelf life of 24 months is granted for drug product (b) (4) provided as prefilled pen device (FlexTouch® Pen), when stored at (b) (4) An in-use period of 28 days at up to 30°C is granted for drug product (provided as FlexTouch® Pen).

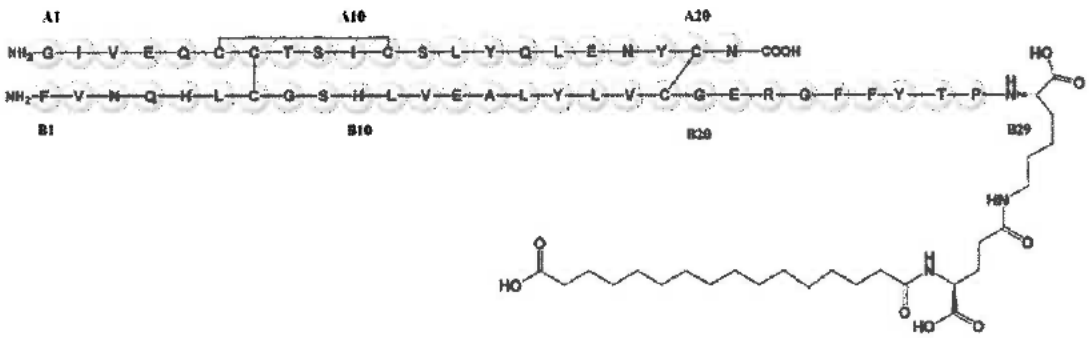
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Quality Assessments

A. Drug Substance [Insulin degludec/Insulin aspart] Quality Summary

The drug product, Ryzodeg™ contains two active ingredients (insulin degludec and insulin aspart). Insulin degludec is a new molecular entity responsible for providing long acting profile. Insulin aspart is the rapid acting form and was an approved under NDA 20906. Insulin aspart is produced by recombinant technology from yeast (*Saccharomyces cerevisiae) strain.*

Insulin degludec is produced from desB30-insulin (a human insulin analog) by chemical modification. The amino acid sequence of desB30-insulin is the same as human insulin except that it is missing a threonine at B30 position. DesB30-insulin is produced by recombinant DNA technology from yeast (*Saccharomyces cerevisiae*) (b) (4) Insulin degludec contains a C-16 fatty acid (hexadecanedioic acid) chain and a glutamic acid spacer at B29 lysine (b) (4) desB30-insulin (Refer to structure shown below; Structure reproduced from the NDA).



The chemical name of insulin degludec is N6, 29B-[N-(15-carboxypentadecanoyl)-L-γ-glutamyl]-des-30B-L-threonine-human insulin. The molecular formula of insulin degludec is $C_{274}H_{411}N_{65}O_{81}S_6$ with a molecular weight of (b) (4) The isoelectric point of insulin degludec is approximately (b) (4) Insulin degludec is a (b) (4) It is freely soluble in water at neutral pH.

The structure and biological properties of insulin degludec were elucidated by suitable chemical, biophysical, and biological methods such as (b) (4) (b) (4)

Insulin degludec is manufactured (b) (4) (b) (4) (b) (4) (b) (4)

The proposed manufacturing process is adequately designed to assure the purity of final drug substance by (b) (4) (b) (4)

The proposed drug substance specifications include appearance (visual), identification ((b) (4) (b) (4) and HPLC), assay of content (HPLC), bioactivity (cell-based assay), individual and total (b) (4) related impurities (HPLC) and high molecular weight proteins, loss on drying, bioburden, and bacterial endotoxin. The proposed regulatory methods have been validated. Reference standards for the API have been developed and characterized.

The recommended shelf-life for drug substance is (b) (4) months for insulin degludec when stored at -(b) (4) For additional information, please refer to Dr. Leginus's CMC review dated Feb. 8, 2012 in DARRTS under NDA 203314

The drug substance (insulin degludec) will be manufactured at Novo Nordisk A/S located in Bagsvaerd Denmark ((b) (4) and at Kalundborg Denmark (b) (4) quality control of drug substance). The Office of Process and Facilities has provided approve recommendation for the drug substance facilities associated with this application.

B. Drug Product [70% Insulin Degludec and 30% Insulin Aspart Injection] Quality Summary

The proposed drug product is a 70/30 mixture of insulin degludec and insulin aspart provided for mimicking the combined action profiles of long acting and rapid acting insulins. The drug product is a sterile, clear, colorless aqueous solution provided in a 3mL Type I glass cartridge preassembled in a disposable pen delivery device (FlexTouch ® pen). The cartridge contains a rubber plunger on one end and a (b) (4) rubber disc on the other end.

The potency of the proposed formulation is 100 Units/mL (U-100). A total of 300 Units of insulin degludec/aspart is provided per device. The device is capable delivering a maximum dose of 80 U per injection. The proposed product is intended for once daily use as meal time insulin by subcutaneous administration.

Initially, the Applicant (b) (4) FlexTouch ® pen (prefilled pen). (b) (4) (b) (4) The finished product will be available as 5 x 3 mL prefilled pens in cartons. The proposed product is light sensitive and therefore (b) (4) packaging is critical to assure the stability of the product.

Each mL of the drug product contains 420 nmol of insulin degludec and 180 nmol of insulin aspart, 19.0 mg glycerol (b) (4) 1.50 mg phenol (b) (4) 1.72 mg metacresol (b) (4), sodium chloride (0.58 mg, (b) (4)), and 27.4 µg zinc (b) (4) and water for injection. Hydrochloric acid or sodium hydroxide is added to adjust pH to approximately 7.4.

(b) (4)

attribute that defines the long-acting profile of insulin degludec. The proposed commercial formulation is based on screening various drug product formulations containing different ratios of insulin degludec/insulin aspart and different levels of excipients for stability and action profile in clinical studies. The final formulation contains monograph grade materials, which is acceptable. The proposed final formulation is the same as the one used in Phase 3 clinical studies.

During development, the Applicant has defined Quality Target Product Profile (QTPP) and critical quality attributes (CQAs). The Applicant used design of experiments (DOE) and risk assessment techniques to define critical process parameters. The proposed CQAs for the drug products include insulin content of each active ingredient, extractable volume, plunger friction (for measuring device performance), *purity factors (individual impurities related to each active ingredients, high molecular weight proteins, product identity,* (b) (4) *content)*, closure integrity (sterility), (b) (4) efficacy, endotoxin levels, appearance (particulate load), and other physical tests such pH and isotonicity.

The drug product (Ryzodeg™ 100 U/mL) is manufactured by (b) (4)
(b) (4)

The NDA states that all equipment that comes into contact with the product (tubing, tanks, sterile filters, etc.) are inert material and the product contact surfaces are sterilized (b) (4) (b) (4) Dr. Vinayak Pawar reviewed the sterilization validation information provided in DMF (b) (4) and concluded that the DMF is adequate to support NDA 20313. Please refer to his DMF review in DARRTS dated 5/30/12.

The NDA contains batch formula and a description of the proposed commercial process. Together with the information provided in the master batch record, the available information in the NDA is adequate to support the proposed commercial process. The NDA contains adequate process control information for manufacturing the proposed product. The proposed critical process parameters (in-process tests) include (b) (4)
(b) (4)

The NDA contains batch analysis data from development through commercial scale to support the manufacturability of the proposed product. The NDA contains adequate information on the release specification used for controlling for quality of the drug product. The Applicant has proposed general tests typically expected for a parenteral product, and product-specific tests. The proposed general tests include pH, endotoxin limit, and sterility, and particulate matter.

The product-specific tests include identity, insulin content, zinc content, product related impurities (b) (4) and (b) (4) content. In addition, the applicant is proposing to monitor the dose accuracy of the pen-filled syringe. The proposed limits for monitoring the individual insulin degludec and insulin aspart related substances and impurities are acceptable. The test methods proposed for the product are adequately described and are validated per applicable ICH guidelines.

The Applicant is proposing a separate release and shelf-life specification (i.e., wider than the release specification) for controlling and monitoring the quality of the drug product. Per FDA request, the Applicant has tightened the shelf-life specification limits for (b) (4) related substances and (b) (4) impurities. Considering the manufacturer's limited experience with the product, the proposed shelf-life specifications for the product related substances and impurities are acceptable.

Dr. Vinayak Pawar has reviewed information pertaining to microbiological product quality control of the product provided in the NDA. Specifically his review evaluated information pertaining to (b) (4) effectiveness, container closure integrity, (b) (4) processing, and microbiological test methods (Sterility and endotoxin. Dr. Pawar's review concluded that the microbiology information provided in NDA 203313 and DMF (b) (4) is adequate to support the proposed product.

The applicant has provided 18-24 month real time and 6 month accelerated stability data for several batches of the drug product manufactured at (b) (4) scale. This Application also contains limited stability information for product manufactured at commercial scale ((b) (4) scale). In addition, the NDA contains in-use stability and photo stability data for the proposed product packaged in (b) (4) packaging configurations. The stability studies were performed on the drug product packaged in (b) (4) Photo stability data show that the (b) (4) packaging (the PDS290 pen injector (b) (4) and carton) provides adequate protection against light.

Based on available long-term and accelerated stability data and in-use stability data, the CMC reviewer provided the following recommendation:

i. *a shelf life of 24 months for the drug product when stored at 5°C ± 3°C.*
ii. *An in-use period of 28 days is recommended for storage at up to 30°C*

The NDA contains a post-approval stability protocol and commitment to place 3 full scale batches on stability. The Applicant will update their stability protocol with limits for individual product related substances and impurities.

The Formulation, filling and release of bulk drug product will be performed by Novo Nordisk A/S located in Bagsvaerd Denmark (Formulation, filling and release of bulk drug product). The assembly, labelling, packaging and release of finished drug product will be performed by Novo Nordisk A/S facility located at Hillerod, Denmark. Labelling and packaging of finished drug product may be performed at Novo Nordisk A/S located in Kalundborg, Denmark. In consultation with CDRH Compliance group, the Office of Process and Facilities, has provided an approve recommendation for the facilities associated with the drug product.

The Applicant has adequately resolved issues identified during Chemistry Review #1. There are no pending CMC issues to be resolved at this stage.

A. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Ryzodeg
Non Proprietary Name of the Drug Product	70% Insulin Degludec and 30% Insulin Aspart Injection
Non Proprietary Name of the Drug Substance	Insulin degludec/insulin aspart
Proposed Indication(s) including Intended Patient Population	Type 1 and Type 2 diabetic patients
Duration of Treatment	Long-term
Maximum Daily Dose	Once daily
Alternative Methods of Administration	-

B. Life Cycle Knowledge Information (see Attachment A)

Primary Quality Review

ASSESSMENT OF THE DRUG SUBSTANCE/ DRUG PRODUCT /MANUFACTURING PROCESS/ MICROBIOLOGICAL CONTROL OF PRODUCT

Ryzodeg® 70/30 insulin degludec /insulin aspart injection is **a drug device combination product**. CMC **information for** drug substance, drug product and **maintenance of** microbiological controls in the manufacturing process was completed during first review cycle. Product quality Review of NDA 203313 was conducted as a Team Review with Joseph Leginus reviewing the Drug Substance and Muthukumar Ramaswamy reviewing the Drug Product. Dr. V. Pawar reviewed product quality microbiology information (microbiology tests and (b) (4) processing procedures provided in the NDA) and sterilization validation information provided under DMF (b) (4) Please refer to CMC reviews dated Feb. 8, 2012, March 6, 2012, May 25, 2012, and June 13, 2012 in DARRTS.

Performance aspects of the pen delivery device (including human factors study and biocompatibility aspects) was reviewed by CDRH (Refer to CDRH inter consult review dated 9/2/15 in DARRTs).

An assessment of the drug substance and drug product manufacturing facilities was completed by Juandria Williams in consultation with CDRH reviewer, Crystal Lewis and an Approve recommendation was recorded in Panorama on 9/3/15.

There are no pending CMC issues to be resolved.

R.2 Comparability Protocols

Under a comparability protocol, Novo Nordisk is proposing to add additional manufacturing sites for the manufacturing (b) (4) FlexTouch pen (prefilled pen device). The Applicant is proposing to CBE-30 submission with 3 mo. long-term/accelerated stability data support the change. Applicant's proposal to submit the proposed changes in a CBE-30 submission is acceptable. Refer CMC review dated 2/08/12 in DARRTS for additional details.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

The manufacturing process for (b) (4)

Labeling & Package Insert

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

Relevant proprietary name and established name Information from Highlights section: Ryzodeg (70% [redacted] 30% [redacted] injection for subcutaneous use.

Conclusion: Adequate with comment

Comment: Delete [redacted] established name to be consistent with other recently approved labeling for insulin products.

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: Ryzodeg® Established Name: 70% Insulin degludec/30% insulin aspart [redacted] injection	Acceptable with comment. Delete [redacted] established name to be consistent with other recently approved labeling for insulin products.
Dosage form, route of administration	Dosage: Injection Route: Subcutaneous administration	Acceptable
Controlled drug substance symbol (if applicable)	NA	NA
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	[redacted]	Acceptable

(b) "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

RYZODEG 100U/mL (U-100) available as 3 mL FlexTouch® (3) **Conclusion: Adequate**

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Injection	Acceptable
Strengths: in metric system	100 [redacted] units/mL	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	3 mL FlexTouch pen	

#11: Description (21CFR 201.57(c)(12))

RYZODEG (70% insulin degludec and 30% insulin aspart [redacted] injection) [redacted] is a human insulin analog solution containing 70% insulin degludec and 30% insulin aspart. It consists of insulin degludec, a [redacted] long-acting insulin, and insulin aspart, a rapid-acting

insulin both of which function as parenteral blood-glucose-lowering agents [*see Clinical Pharmacology (12)*].

Insulin degludec differs from human insulin in that the amino acid threonine in position B30 has been omitted and a side-chain consisting of glutamic acid and a C16 fatty acid has been attached (chemical name: LysB29(Nε-hexadecandioyl-γ-Glu) des(B30) human insulin) and is produced by recombinant DNA technology utilizing *Saccharomyces cerevisiae*. Insulin degludec has a molecular formula of $C_{274}H_{411}N_{65}O_{81}S_6$ and a molecular weight of 6103.97.

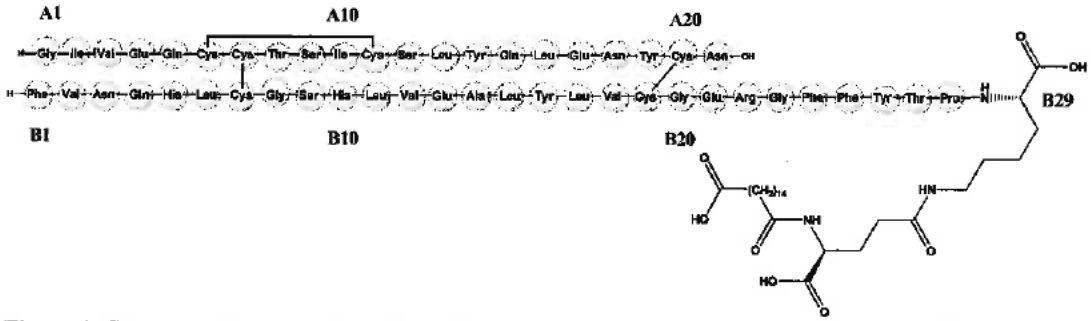


Figure 1: Structural formula of insulin degludec Insulin aspart is homologous with regular human insulin with the exception of a single substitution of the amino acid proline by aspartic acid in position B28, and is produced by recombinant DNA technology utilizing *Saccharomyces cerevisiae*. Insulin aspart has a molecular formula of $C_{256}H_{381}N_{65}O_{79}S_6$ and a molecular weight of 5825.8.

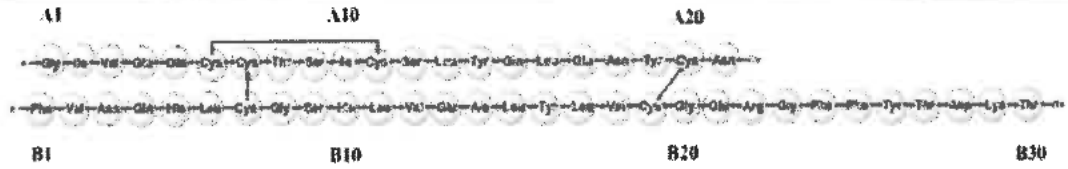


Figure 2: Structural formula of insulin aspart

RYZODEG is a sterile, aqueous, clear, and colorless solution and contains a total of 100 Units of insulin degludec and insulin aspart mixture per mL, glycerol 19 mg/mL, metacresol 1.72 mg/mL, phenol 1.50 mg/mL, sodium chloride 0.58 mg/mL, zinc 27.4 mcg/mL and water for injection. RYZODEG has a pH of approximately 7.4. Hydrochloric acid or sodium hydroxide may be added to adjust pH.

RYZODEG is a sterile, aqueous, clear, and colorless solution and contains a total of 100 Units of insulin degludec and insulin aspart mixture per mL, glycerol 19 mg/mL, metacresol 1.72 mg/mL, phenol 1.50 mg/mL, sodium chloride 0.58 mg/mL, zinc 27.4 mcg/mL and water for injection. RYZODEG has a pH of approximately 7.4. Hydrochloric acid or sodium hydroxide may be added to adjust pH.

Conclusion: Adequate

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Ryzodeg/ 70% insulin degludec and 30% insulin aspart injection	Adequate
Dosage form and route of administration	Solution for injection and subcutaneous administration	
Active moiety expression of strength with equivalence statement for salt (if applicable)	*Each mL of the drug product contains a total of 100 Units of insulin degludec and insulin aspart (70/30 ratio) per mL (U-100).*	
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Inactive ingredients per mL are: 19 mg glycerol, 1.50 mg phenol, 1.72 mg metacresol, 0.58 mg sodium chloride, 27.4 mcg zinc and water for injection. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH. Ryzodeg has a pH of approximately 7.4	
Statement of being sterile (if applicable)	Ryzodeg is a sterile solution	
Pharmacological/ therapeutic class	Hormone/ Treatment of diabetes	
Chemical name, structural formula, molecular weight	The chemical name of insulin degludec is N6, 29B-[N-(15-carboxypentadecanoyl)-L-γ-glutamyl]-des-30B-L-threonine-human insulin. The molecular formula of insulin degludec is $C_{274}H_{411}N_{65}O_{81}S_6$ with a molecular weight of (b) (4)	
If radioactive, statement of important nuclear characteristics.	Not applicable	
Other important chemical or physical properties (such as pKa, solubility, or pH)	API is a (b) (4) Freely soluble in water. Isoelectric point is (b) (4)	

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

RYZODEG is available as 3mL FlexTouch pen (see Table 11). Each prefilled pen contains a total of 100 Units of insulin degludec and insulin aspart mixture per mL (U-100).

Table 11 Presentations of RYZODEG

RYZODEG	Total volume	Concentration	Total units available in presentation	NDC number	Max dose per injection*	Dose increment*
U-100 FlexTouch	3 mL	100 U/mL	300 U	0169-2770-15	80 U	1 U

Recommended Storage
Unused (b) (4) RYZODEG should be stored between 2° and 8°C (36° to 46°F). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze. Do not use RYZODEG if it has been frozen. (b) (4)

Open (In-Use) FlexTouch disposable prefilled pen:
The in-use RYZODEG FlexTouch pen should NOT be refrigerated but should be kept at room temperature, below 30°C (86°F) away from direct heat and light. The opened (in-use) RYZODEG FlexTouch pen may be used for up to 28 days (4 weeks) after being opened, if it is kept at room temperature.

Table 12: Storage Conditions for RYZODEG FlexTouch®

	Not in-use (unopened) **Refrigerated (2°C - 8°C [36°F - 46°F])**	**Not in-use (unopened)** **Room Temperature (below 30°C [86°F])**	**In-use (opened)** **Room Temperature (below 30°C[86°F])**
3 mL RYZODEG U100 FlexTouch	Until expiration date	28 days (4 weeks)	28 days (4 weeks) **(Do not refrigerate)**

Item	**Information Provided in NDA**	**Reviewer's Assessment**
Strength of dosage form	100 units per mL	Adequate
Available units (e.g., bottles of 100 tablets)	5 x 3mL FlexTouch Pen in carton	
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	NDC Number: 0169-2770-15	
Special handling (e.g., protect from light, do not freeze)	Stored in the carton away from light.	
Storage conditions	Store unused FlexTouch® pen between 2° and 8°C (36° to 46°F). *After initial use,* Ryzodeg *may be used for up to 28 days (4 weeks) at room temperature, below 30°C (86°F)*	

Manufacturer/distributor name listed at the end of PI, following Section #17
Manufactured by: Novo Nordisk A/S, DK-2880 Bagsvaerd, Denmark

For information about RYZODEG contact: Novo Nordisk Inc., 800 Scudders Mill Road, Plainsboro, NJ 08536

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Manufactured by: Novo Nordisk A/S, DK-2880 Bagsvaerd, Denmark Distributed by : Novo Nordisk, Plainsboro, NJ	Adequate

Conclusion: Adequate

2. **Labels**

Immediate Container Label **Carton Label**

(b) (4)

[redacted]

1) Reviewer's Assessment for Immediate Container Label:

QUALITY ASSESSMENT
NDA # 203313

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Ryzodeg/ (b) (4) (b) (4)	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	100 Units/mL	
Net contents (21 CFR 201.51(a))	Yes. 3mL prefilled Pen	
Lot number per 21 CFR 201.18	Yes	
Expiration date per 21 CFR 201.17	Yes	
"Rx only" statement per 21 CFR 201.100(b)(1)	Yes.	
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	NDC No.: 0169-2770-90	
Bar Code per 21 CFR 201.25(c)(2)**	yes	
Name of manufacturer/distributor	Novo Nordisk, Plainsboro, NJ 08536	
Others		

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: Adequate

1) Carton Label

QUALITY ASSESSMENT
NDA # 203313

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Ryzodeg/ (b) (4) (b) (4)	
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Yes. 100 units/mL	
Net contents (21 CFR 201.51(a))	3mL (b) (4)	
Lot number per 21 CFR 201.18	yes	
Expiration date per 21 CFR 201.17	yes	
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]	(b) (4)	
Sterility Information (if applicable)	No. Sterile solution	**Declaration in the package insert**
"Rx only" statement per 21 CFR 201.100(b)(1)	Yes.	
Storage Conditions	(b) (4)	
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	NDC No.: 0169-2770-90	
Bar Code per 21 CFR 201.25(c)(2)**	Yes	
Name of manufacturer/distributor	Novo Nordisk, Plainsboro, NJ 08536	
"Keep out of reach of children" (optional for Rx, required for OTC)	NA	
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	Yes.	

Conclusion: Adequate

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

II. Administrative

Muthukumar Ramaswamy -S

Digitally signed by Muthukumar Ramaswamy -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000341660, cn=Muthukumar Ramaswamy -S
Date: 2015.09.03 14:45:53 -04'00'

Muthukumar Ramaswamy,
Application Technical Lead
ONDP, OPQ, CDER

10/30/12

MEMO

From: Muthukumar Ramaswamy, Ph.D.,
CMC Reviewer, Office of New Drug Quality Assessment (ONDQA), CDER

To: File

Date: Oct 29, 2012

Subject: CMC Recommendation for NDA 203313 - Ryzodeg® ([Insulin degludec/Insulin aspart] (rDNA origin) Injection

This memo documents the overall CMC recommendation for NDA 203313 - Ryzodeg® ([Insulin degludec/Insulin aspart] (rDNA origin) Injection application. From Chemistry, Manufacturing, and Controls (CMC) perspective, the NDA is not recommended for approval due to a withhold recommendation for this application from the Office of Compliance (Refer to Establishment Evaluation Request Summary Report for additional details).

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 203314/000	**Sponsor:**	NOVO NORDISK INC
Org. Code:	510		800
Priority:	14		PLAINSBORO, NJ 08536
Stamp Date:	29-SEP-2011	**Brand Name:**	Ryzodeg
PDUFA Date:	29-OCT-2012	**Estab. Name:**	[insulin degludec/insulin aspart] (rDNA origin) injection
Action Goal:		**Generic Name:**	
District Goal:	30-MAY-2012	**Product Number; Dosage Form; Ingredient; Strengths**	001; SOLUTION, INJECTION; INSULIN DEGLUDEC; 100UNT

FDA Contacts:	K. SHARMA	Project Manager		3017961270
	J. LEGINUS	Review Chemist	(HFD-810)	3017964102
	S. TRAN	Team Leader		3017961764

Overall Recommendation:	WITHHOLD	on 29-OCT-2012	by F. GODWIN	(HFD-320)	3017965362
	PENDING	on 19-JUL-2012	by EES_PROD		
	PENDING	on 24-JAN-2012	by EES_PROD		
	PENDING	on 13-OCT-2011	by EES_PROD		

Establishment:	CFN: 9610699	FEI: 3002807751	
	NOVO NORDISK A S HALLAS ALLE		
	KALUNDBORG, , DENMARK		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
	FINISHED DOSAGE LABELER		
	FINISHED DOSAGE PACKAGER		
Profile:	(b) (4)	**OAI Status:**	NONE
Last Milestone:	DC RECOMMENDATION		
Milestone Date:	24-JAN-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		
Profile:	(b) (4)	**OAI Status:**	NONE
Last Milestone:	DC RECOMMENDATION		
Milestone Date:	15-OCT-2012		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:** 9613244 **FEI:** 3002807752		
	NOVO NORDISK A S BERNNUM PARK, DK-3400		
	HILLEROED, , DENMARK		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE LABELER		
	FINISHED DOSAGE PACKAGER		
	FINISHED DOSAGE STABILITY TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	24-SEP-2012		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		
Profile:	(b) (4)	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	24-SEP-2012		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:** 9616213 **FEI:** 3000151919		
	NOVO NORDISK A S NOVO ALLE		
	BAGSVAERD, , DENMARK		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
	FINISHED DOSAGE MANUFACTURER		
Profile:	(b) (4)	**OAI Status:**	POTENTIAL OAI
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	26-OCT-2012		
Decision:	WITHHOLD		
Reason:	DISTRICT RECOMMENDATION		

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/s/

MUTHUKUMAR RAMASWAMY
10/30/2012

ALI H AL HAKIM
10/30/2012

QUALITY ASSESSMENT

Recommendation:
NDA: Approval

NDA 203314
Review # 1 (Resubmission)
September 3, 2015

Drug Name	**Insulin Degludec**
Dosage Form	Solution for Injection
Strength	100 and 200 Units/mL
Route of Administration	Subcutaneous Administration
Rx Dispensed	Rx
Applicant	Novo Nordisk Inc., Princeton, NJ 08540
US agent, if applicable	Not Applicable

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Resubmission/Class 2	March 26, 2015

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Joseph Leginus (Original Submission dated Sep. 29, 2011)	Branch II, Division I, ONDP
Drug Product	Muthukumar Ramaswamy (Original and Resubmission)	Branch VI, Division III, ONDP
Process	Muthukumar Ramaswamy (Original Submission)	Branch VI, Division III, ONDP
Microbiology	Vinayak Pawar (Original Submission)	OPF
Facility	Juandria Williams (Resubmission)	OPF
Biopharmaceutics	NA	NA
Project/Business Process Manager	Anika Lalmansingh (Resubmission)	ONDP/OPRO
Application Technical Lead	Muthukumar Ramaswamy (Resubmission) Su Tran (IQA for Original submission Sep. 29, 2011)	Branch VI, Division III, ONDP
Laboratory (OTR)	NA	NA
ORA Lead	NA	NA
Environmental Assessment (EA)	Joseph Leginus (Original Submission)	Branch II, Division I, ONDP

Table of Contents

Quality Review Data Sheet

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

2. **RELATED/SUPPORTING DOCUMENTS:**

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	V	Novo Nordisk, Inc.	(b) (4)	Adequate	Reviewed during original Submission review	none
(b) (4)	III		(b) (4)	1	Adequate	Reviewed by O. Stephens 9/6/2011
	III			1	Adequate	Reviewed by O. Stephens 8/24/2011

[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	76,496	Insulin degludec (rDNA origin) Injection
IND	73198	Insulin degludec/Insulin aspart (rDNA origin) Injection
NDA	203313	Insulin degludec/Insulin aspart (rDNA origin) Injection

3. **CONSULTS:**

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
CDRH	Complete	Acceptable	9/02/15	Lana Shiu
Microbiology	Complete	Acceptable (Original Submission dated Sep. 29, 2011)	6/07/12	Vinayak Pawar
EA	Complete	Acceptable (Original Submission dated Sep. 29, 2011)	2/8/12	J. Leginus
EES	Complete	Acceptable	9/ 3/15	Juandria Williams

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 203314 is recommended for approval from a CMC perspective. There are no outstanding deficiencies related to chemistry, microbiology, and manufacturing facilities. Office of Process and facilities has provided an approval recommendation for NDA 203314.

Labeling comments will be negotiated through the clinical project manager.

Based on available stability data, the following shelf-life recommendation is granted for the drug substance (insulin degludec) and drug product (provided as FlexTouch® pen device):

a) A shelf life of (b) (4) months is granted for drug substance insulin degludec when stored at (b) (4)

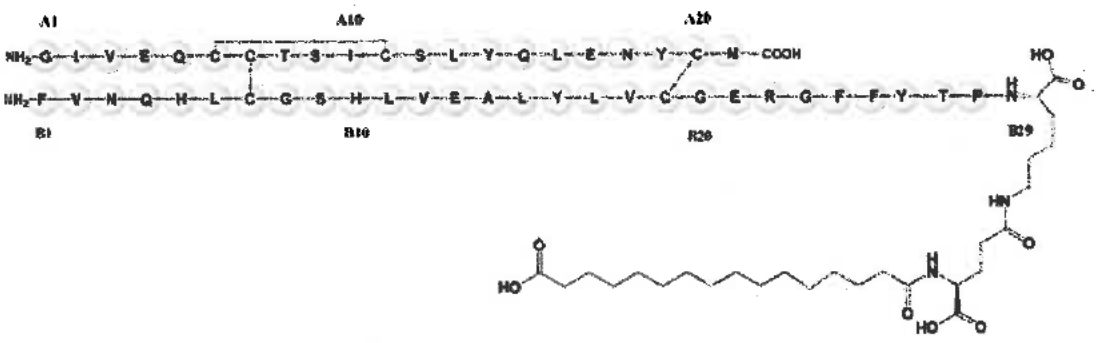
b) A shelf life of 30 months is granted for drug product (Tresiba FlexTouch® (insulin degludec [rDNA origin]) injection) 100U/mL and 200U/mL, when stored at 5°C ± 3°C. An in-use period of 56 days at up to 30°C is granted for Tresiba, 100Units/mL and 200 Units/mL.

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

II. Summary of Quality Assessments

A. Drug Substance [Insulin degludec] Quality Summary

Insulin degludec is a new molecular entity. Insulin degludec is a long acting form of insulin. Insulin degludec is produced from desB30-insulin (a human insulin analog) by chemical modification. The amino acid sequence of desB30-insulin is the same as human insulin except that it is missing a threonine at B30 position. DesB30-insulin is produced by recombinant DNA technology from yeast (*Saccharomyces cerevisiae*) (b) (4)
Insulin degludec contains a C-16 fatty acid (hexadecanedioic acid) chain and a glutamic acid spacer at B29 lysine residue of desB30-insulin (Refer to structure shown below; Structure reproduced from the NDA).



The chemical name of insulin degludec is N6, 29B-[N-(15-carboxypentadecanoyl)-L-γ-glutamyl]-des-30B-L-threonine-human insulin. The molecular formula of insulin degludec is $C_{274}H_{411}N_{65}O_{81}S_6$ with a molecular weight of (b) (4) The isoelectric point of insulin degludec is approximately (b) (4) Insulin degludec is a (b) (4) It is freely soluble in water at neutral pH.

The structure and biological properties of insulin degludec were elucidated by suitable chemical, biophysical, and biological methods such as (b) (4) (b) (4)

Insulin degludec is manufactured (b) (4) (b) (4) (b) (4)

The proposed manufacturing process is adequately designed to assure the purity of final drug substance by (b) (4) (b) (4)

The proposed drug substance specifications include appearance (visual), identification ((b) (4) (b) (4) and HPLC), assay of content (HPLC), bioactivity (cell-based assay), individual and total (b) (4) related impurities (HPLC) and high molecular weight proteins, loss on drying, bioburden, and bacterial endotoxin. The proposed regulatory methods have been validated. Reference standards for the API have been developed and characterized.

The recommended shelf-life for drug substance is (b) (4) months for insulin degludec when stored at -(b) (4) and is granted. For additional information, please **refer to Dr. Leginus's CMC review dated Feb. 8, 2012 in DARRTS under NDA 203314**

The drug substance (insulin degludec) will be manufactured at Novo Nordisk A/S located in Bagsvaerd Denmark (b) (4) and at Kalundborg Denmark (b) (4). The Office of Process and Facilities has provided approve recommendation for the drug substance facilities associated with this application.

B. Drug Product (Insulin degludec [rDNA origin] injection) Quality Summary

The drug product, Tresiba™ (Insulin Degludec [rDNA Origin] Injection) is a sterile, aqueous, clear, colorless solution and will be available in two strengths(100 Units/mL (U-100) or 200 Units/mL (U-200) as product filled glass cartridges preassembled in a pen delivery device. The proposed product is a long-acting basal insulin formulation intended for once daily use by subcutaneous administration.

The 100 Units/mL presentation contains 600 nmol of insulin degludec, 19.6 mg glycerol (b) (4) (b) (4) 1.50 mg phenol (b) (4) 1.72 mg metacresol (b) (4) 32.7 µg zinc (b) (4) (b) (4) and water for injection. The 200 Units/mL presentations contains 1200 nmol of insulin degludec, 19.6 mg glycerol, 1.50 mg phenol, 1.72 mg metacresol, 71.9 µg zinc and water for injection. Hydrochloric acid or sodium hydroxide is added to adjust pH. The pH of the proposed product is approximately 7.6.

During Phase 1 and 2 studies, the Applicant has screened several insulin formulations containing 600-1200 nmol/mL of insulin degludec and excipients such as phenol/metacresol, glycerol, zinc, (b) (4) (b) (4) for action profile and stability. The two strength products differ mainly in (b) (4) The NDA states that the formulation was optimized to maximize (b) (4) form. The Applicant has defined (b) (4) form as a critical

quality attribute that defines the long-acting profile of insulin degludec. The Applicant is proposing to use monograph grade excipients in the final formulation and this is acceptable.

The Applicant is proposing to market the 100 and 200 units/mL strength products as pre-filled pen (cartridge pre-assembled in a PDS290 pen-injector). The finished product will be marketed as 5 x 3 mL prefilled pens in cartons. The proposed product is light sensitive (b) (4) packaging is critical to assure the stability of the product.

The drug products, insulin degludec 100 and 200 U/mL are manufactured by (b) (4) (b) (4)

During development, the Applicant has defined Quality Target Product Profile (QTPP) and critical quality attributes. The proposed critical quality attributes (CQAs) for the drug product include content of each active, extractable volume, plunger friction (for measuring device performance), purity factors (individual impurities related to each active ingredients), high molecular weight proteins, product identity, (b) (4) content, closure integrity (sterility), (b) (4) efficacy, endotoxin levels, appearance (particulate load), and other physical tests such pH and isotonicity.

The Applicant also used design of experiments risk assessment techniques and process evaluation studies to define critical process parameters. The proposed process parameters are adequate to ensure complete dissolution of excipients and active ingredient. Developmental stability on in-process solutions and bulk formulation assured whether the proposed pH ranges for these solutions are adequate with respect chemical and physical attributes.

The NDA contains batch formula and a description of the proposed commercial process. Together with the information provided in the master batch record, the available information in the NDA is adequate to support the proposed commercial process. The NDA contains in-process control information for the manufacturing and filling of the proposed products (100 U/mL and 200 U/mL insulin degludec solution for injection). The proposed critical process parameters include (b) (4) (b) (4) content, and inspection for visible particle control. The Applicant has provided batch analysis data from development through commercial scale to support the manufacturability of the proposed products.

The NDA contains adequate information on the release specification used for controlling for quality of the drug product. The proposed general and product-specific tests are what is expected for other approved insulin analogs. The proposed general tests include pH, endotoxin limit, sterility, and particulate matter. The product-specific tests include identity, insulin content, zinc content, product related impurities (b) (4) (b) (4) and (b) (4) content. In addition, the applicant is proposing to monitor the dose accuracy of the product filled in the delivery device. The Applicant is also performing in-process control tests such as closure integrity, the extractable volume test, and air content requirement in the cartridge.

Due to method limitation, the Applicant has proposed collective limits for individual groups of product related substances and impurities (b) (4) (b) (4) **impurities). Considering the complexity of the product and Firm's** characterization data on impurities, the proposed approach is acceptable. The test methods proposed for the product are adequately described and are validated per applicable ICH guidelines.

The Applicant is proposing a separate release and shelf-life specification (i.e., wider than the release specification) for controlling and monitoring the quality of the drug product. *Per FDA request, the Applicant has tightened the shelf-life specification limits for* (b) (4) *related substances and* (b) (4) *impurities. Considering the manufacturer's limited experience with the product, the proposed shelf-life specifications for the product related substances and impurities are acceptable.*

The applicant has provided 24-30 month real time and 6 month accelerated stability data for several batches of the drug product (100 and 200 U/mL) manufactured at (b) (4) scale. This Application also contains stability information for commercial scale batches ((b) (4) scale) as well as in-use stability and photo stability data for the product packaged in (b) (4) packaging configuration.

In general, the stability studies were performed on the drug product packaged in (b) (4) (b) (4) Since the drug product is only in contact with the (b) (4) the stability data of the drug product in the (b) (4) (in darkness) are considered to be representative for the stability of the drug product in the PDS290 pen-injector.

- *Based on the long term and accelerated stability data evaluated in this document, a shelf life of 30 months at* (b) (4) *is recommended for insulin degludec 100 and 200U/mL.*
- *Based on the in-use stability data evaluated in this document, an in-use period of 56 days at up to 30°C is recommended for insulin degludec 100 and 200U/mL.*
- *Photo stability data show that the* (b) (4) *packaging (the PDS290 pen-injector* (b) (4) (b) (4) *and carton) provides adequate protection against light.*

The NDA contains post-approval stability protocol and commitment to place 3 full scale batches on stability and continue to update information on existing stability studies. The Applicant should update their stability protocol and post-approval stability protocol to include limits for individual product related substances and impurities.

The Formulation, filling and release of bulk drug product will be performed by Novo Nordisk A/S located in Bagsvaerd Denmark (Formulation, filling and release of bulk drug product). The assembly, labelling, packaging and release of finished drug product will be performed by Novo Nordisk A/S facility located at Hillerod, Denmark. Labelling and packaging of finished drug product may be performed at Novo Nordisk A/S located in Kalundborg, Denmark. In consultation with CDRH Compliance group, the Office of Process and Facilities, has provided an approve recommendation for the facilities associated with the drug product.

The Applicant has adequately resolved issues identified during Chemistry Review #1. There are no pending CMC issues to be resolved at this stage.

A. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Tresiba
Non Proprietary Name of the Drug Product	Insulin Degludec [rDNA origin] injection
Non Proprietary Name of the Drug Substance	Insulin degludec
Proposed Indication(s) including Intended Patient Population	Type 1 and Type 2 diabetic patients
Duration of Treatment	Long-term
Maximum Daily Dose	Once daily
Alternative Methods of Administration	-

B. Life Cycle Knowledge Information (see Attachment A)

Primary Quality Review

ASSESSMENT OF THE DRUG SUBSTANCE/ DRUG PRODUCT /MANUFACTURING PROCESS/ MICROBIOLOGICAL CONTROL OF PRODUCT/ASSESSMENT OF THE FACILITIES

Tresiba insulin degludec injection is a drug device combination product. CMC review for drug substance, drug product, and microbiological controls in the manufacturing process was completed during first review cycle.

Product quality Review of NDA 203314 was conducted as a Team Review with Joseph Leginus reviewing the Drug Substance and Muthukumar Ramaswamy reviewing the Drug Product. Dr. V. Pawar reviewed product quality microbiology information (provided in the NDA) and sterilization validation information provided under DMF (b) (4) Please refer to CMC reviews dated Feb. 8, 2012, March 6, 2012, May 25, 2012 and June 13, 2012 in DARRTS.

Performance aspects of the pen delivery device were reviewed by CDRH reviewer Lana Shiu. Refer to her review in DARRTS dated 9/2/15.

An assessment of the drug substance and drug product manufacturing facilities was completed by Juandria Williams in consultation with CDRH reviewer, Crystal Lewis and an Approve recommendation was provided by the facility reviewer in Panorama.

There are no pending issues to be resolved.

R.2 Comparability Protocols

The Applicant has provided comparability protocol for adding manufacturing site (a cGMP compliant site) for the assembly, packaging, labeling, and quality control of the prefilled PDS290 pen-injector containing **insulin degludec 100 U/mL and insulin degludec 200 U/mL. Applicant's proposal to submit the proposed** changes in a CBE-30 submission is acceptable. Refer CMC review dated 2/08/12 in DARRTS for additional details.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

The manufacturing process for (b) (4)

(b) (4)

Labeling & Package Insert

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

Proprietary name and established name Information: Tresiba® (insulin degludec [redacted] injection) for subcutaneous use.

Conclusion: Adequate with comment

Comment: Delete [redacted] from established name to be consistent with other recently approved labeling for insulin products.

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: Tresiba® Established Name: Insulin degludec [redacted] injection	Acceptable with comment. Delete [redacted] from established name to be consistent with the label for other recently approved insulin products.
Dosage form, route of administration	Dosage: Injection Route: Subcutaneous administration	Acceptable
Controlled drug substance symbol (if applicable)	NA	NA
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Tresiba [redacted] 100 or 200 [redacted]	Acceptable

(b) "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Tresiba 100 and 200 Units/mL (U-100 and U-200) [redacted] 3 mL FlexTouch® (3)

Conclusion: Adequate

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Injection	Acceptable
Strengths: in metric system	100 and 200 units/mL	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	3 mL FlexTouch pen	

#11; Description (21CFR 201.57(c)(12))

TRESIBA (insulin degludec injection) is long-acting basal human insulin analog . Insulin degludec is produced by a process that includes expression of recombinant DNA in *Saccharomyces cerevisiae* followed by chemical modification.

Insulin degludec differs from human insulin in that the amino acid threonine in position B30 has been omitted and a side-chain consisting of glutamic acid and a C16 fatty acid has been attached (chemical name: LysB29(Nε-hexadecandioyl-γ-Glu) des(B30) human insulin) (b) (4) (b) (4) Insulin degludec has a molecular formula of $C_{274}H_{411}N_{65}O_{81}S_6$ and a molecular weight of 6103.97.

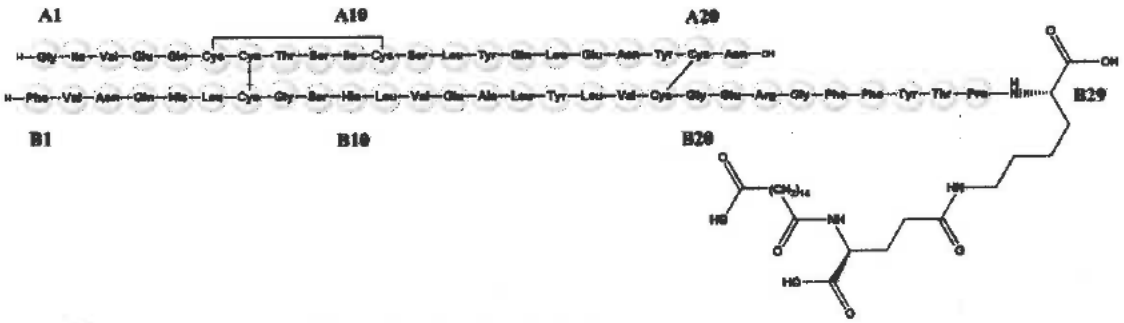


Figure 1: Structural formula of insulin degludec

TRESIBA is a sterile, aqueous, clear, and colorless solution that contains insulin degludec 100 Units/mL (U-100) or 200 Units/mL (U-200). (b) (4) (b) (4)

Inactive ingredients for the 100 Units/mL are: glycerol 19.6 mg/mL, phenol 1.50 mg/mL, metacresol 1.72 mg/mL, zinc 32.7 mcg/mL and water for injection.

Inactive ingredients for the 200 Units/mL are glycerol 19.6 mg/mL, phenol 1.50 mg/mL, metacresol 1.72 mg/mL, zinc 71.9 mcg/mL and water for injection.

Tresiba has a pH of approximately 7.4. Hydrochloric acid or sodium hydroxide may be added to adjust pH.

Conclusion: Adequate

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	TRESIBA insulin degludec injection	Adequate
Dosage form and route of administration	Solution for injection and subcutaneous administration	
Active moiety expression of strength with equivalence statement for salt (if applicable)	*Each mL of the drug product contains a 100 Units of insulin degludec per mL (U-100) or 200 Units of insulin degludec per mL (U-200).*	
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Inactive ingredients for the 100 units/mL are: 19 mg glycerol, 1.50 mg phenol, 1.72 mg metacresol, 27.4 mcg zinc and water for injection. Inactive ingredients for the 200 units/mL are 19 mg glycerol, 1.50 mg phenol, 1.72 mg metacresol, 71.9 mcg zinc and water for injection. Tresiba has a pH of approximately 7.6. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH.	
Statement of being sterile (if applicable)	Tresiba is a sterile solution	
Pharmacological/ therapeutic class	Hormone/ Treatment of diabetes	
Chemical name, structural formula, molecular weight	The chemical name of insulin degludec is N6, 29B-[N-(15-carboxypentadecanoyl)-L-γ-glutamyl]-des-30B-L-threonine-human insulin. The molecular formula of insulin degludec is $C_{274}H_{411}N_{65}O_{81}S_6$ with a molecular weight of (b) (4)	
If radioactive, statement of important nuclear characteristics.	Not applicable	
Other important chemical or physical properties (such as pKa, solubility, or pH)	API is a (b) (4). Freely soluble in water. Isoelectric point is (b) (4)	

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

TRESIBA is available as (b) (4) (b) (4)

Table 11 Presentations of Tresiba

Tresiba	Total volume	Concentration	Total units available in presentation	NDC number	Max dose per injection*	Dose increment*
U-100 FlexTouch	3 mL	100 U/mL	300 U	0169-2660-15	80 U	1 U
U-200 FlexTouch	3 mL	200 U/mL	600 U	0169-2550-13	160U	2U

Recommended Storage
Unused (b) (4) TRESIBA should be stored between 2° and 8°C (36° to 46°F). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze. Do not use TRESIBA if it has been frozen. (b) (4)

Open (In-Use) FlexTouch disposable prefilled pen:
The in-use TRESIBA FlexTouch pen should NOT be refrigerated but should be kept at room temperature, below 30°C (86°F) away from direct heat and light. The opened (in-use) TRESIBA FlexTouch pen may be used for up to 56 days (8 weeks) after being opened, if it is kept at room temperature.

Table 12: Storage Conditions for TRESIBA FlexTouch®

	Not in-use (unopened) **Refrigerated (2°C - 8°C [36°F - 46°F])**	**Not in-use (unopened)** **Room Temperature (below 30°C [86°F])**	**In-use (opened)** **Room Temperature (below 30°C[86°F])**
3 mL TRESIBA U100 FlexTouch	Until expiration date	56 days (8 weeks)	56 days (8 weeks) **(Do not refrigerate)**
3 mL TRESIBA U100 FlexTouch	Until expiration date	56 days (8 weeks)	56 days (8 weeks) **(Do not refrigerate)**

Item	**Information Provided in NDA**	**Reviewer's Assessment**
Strength of dosage form	100 units or 200 Units per mL	Adequate
Available units (e.g., bottles of 100 tablets)	5 x 3mL FlexTouch Pen in carton	
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	NDC Number: 0169-2660-15 (U-100) 0169-2550-13 (U-200)	
Special handling (e.g., protect from light, do not freeze)	Stored in the carton away from light.	
Storage conditions	Store unused FlexTouch® pen between 2° and 8°C (36° to 46°F). *After initial use,* TRESIBA *may be used for up to 56 days (8 weeks) at room temperature, below 30°C (86°F)*	

Manufacturer/distributor name listed at the end of PI, following Section #17
Manufactured by: Novo Nordisk A/S, DK-2880 Bagsvaerd, Denmark

For information about TRESIBA contact: Novo Nordisk Inc., 800 Scudders Mill Road, Plainsboro, NJ 08536

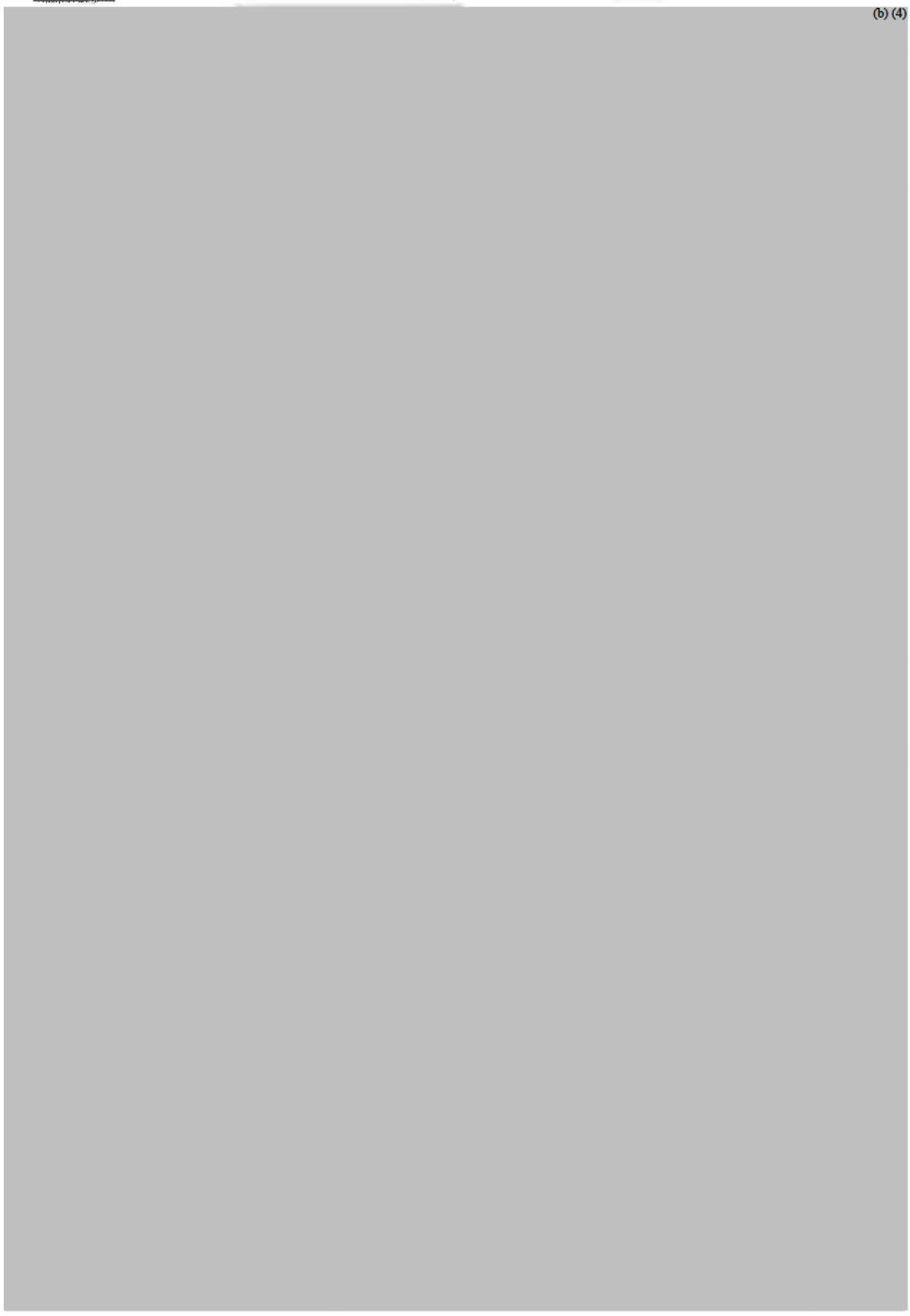
Item	**Information Provided in NDA**	**Reviewer's Assessment**
Manufacturer/distributor name (21 CFR 201.1)	Manufactured by: Novo Nordisk A/S, DK-2880 Bagsvaerd, Denmark Distributed by : Novo Nordisk, Plainsboro, NJ	Adequate

Conclusion: Adequate

2. Labels

Immediate Container Label ____

(b) (4)



1) Reviewer's Assessment for Immediate Container Label:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	TRESIBA insulin degludec (b) (4) injection	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	100 or 200 Units/mL	
Net contents (21 CFR 201.51(a))	Yes. 3mL	
Lot number per 21 CFR 201.18	Yes	
Expiration date per 21 CFR 201.17	Yes	
"Rx only" statement per 21 CFR 201.100(b)(1)	Yes.	
Storage (not required)		
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	NDC No.: 0169-2660-15 and 0169-2550-13	
Bar Code per 21 CFR 201.25(c)(2)**	yes	
Name of manufacturer/distributor	Novo Nordisk, Plainsboro, NJ 08536	
Others		

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an **ointment labeled "sample", "physician's sample", or a substantially similar** statement and the contents of the package do not exceed 8 grams.

****Not required for Physician's samples.** The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: Adequate

1) Carton Label

QUALITY ASSESSMENT
NDA # 203314

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	TRESIBA insulin degludec (b) (4) injection	
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Yes. 100 and 200 units/mL	
Net contents (21 CFR 201.51(a))	3mL	
Lot number per 21 CFR 201.18	yes	
Expiration date per 21 CFR 201.17	yes	
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]	Inactive ingredients for the 100 Units per mL are: 19 mg glycerol, 1.50 mg phenol, 1.72 mg metacresol, 27.4 mcg zinc and water for injection. Inactive ingredients for the 200 Units per mL are: 19 mg glycerol, 1.50 mg phenol, 1.72 mg metacresol, 71.9 mcg zinc and water for injection.	
Sterility Information (if applicable)	No. Sterile solution	**Declaration in the package insert**
"Rx only" statement per 21 CFR 201.100(b)(1)	Yes.	
Storage Conditions	*Keep in cold place until first use. Store at 36°F (2-8°C). Do not freeze* (b) (4)	
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	NDC No.: 0169-2770-90	
Bar Code per 21 CFR 201.25(c)(2)**	Yes	
Name of manufacturer/distributor	Novo Nordisk, Plainsboro, NJ 08536	
"Keep out of reach of children" (optional for Rx, required for OTC)	NA	
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	Yes.	

Conclusion: Adequate

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II. Administrative

Muthukumar Ramaswamy -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000341660, cn=Muthukumar Ramaswamy -S
Date: 2015.09.03 14:49:25 -04'00'

Muthukumar Ramaswamy,
Application Technical Lead
ONDP, OPQ, CDER

11/02/12

MEMORANDUM

Date: 2 Nov 2012
From: Joseph Leginus, Review Chemist, Branch VII/DPA III/ONDQA
To: NDA 203314, Tresiba™ (Insulin Degludec [rDNA Origin] Injection)
Subject: CMC Recommendation

This memo documents the overall CMC recommendation for NDA 203314 - Tresiba™ (Insulin Degludec [rDNA Origin] Injection). The recommendation from CMC is Complete Response due to a Withhold recommendation for this application from the Office of Compliance on 26 Oct 2012. See Establishment Evaluation Request Detail Report below for details.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 203314/000	**Action Goal:**	
Stamp Date:	29-SEP-2011	**District Goal:**	30-MAY-2012
Regulatory:	29-OCT-2012		
Applicant:	NOVO NORDISK INC	**Brand Name:**	insulin degludec (rDNA origin) injection
	846	**Estab. Name:**	insulin degludec (rDNA origin) injection
	PLAINSBORO, NJ 08536	**Generic Name:**	
Priority:	3	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	510	001; SOLUTION, INJECTION; INSULIN DEGLUDEC; 100UNT 002; SOLUTION, INJECTION; INSULIN DEGLUDEC; 200UNT	
Application Comment:			

FDA Contacts:	K. SHARMA	Project Manager	3017961270
	M. RAMASWAMY	Review Chemist	3017961678
	S. TRAN	Team Leader	3017961764

Overall Recommendation:	WITHHOLD	on 26-OCT-2012	by F. GODWIN	(HFD-320)	3017965362
	PENDING	on 19-JUL-2012	by EES_PROD		
	PENDING	on 24-JAN-2012	by EES_PROD		
	PENDING	on 13-OCT-2011	by EES_PROD		
	PENDING	on 13-OCT-2011	by EES_PROD		

Joseph Leginus, PhD
Review Chemist

Ali Al-Hakim, Ph.D.
Branch VII, Chief, ONDQA

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/s/

JOSEPH LEGINUS
11/02/2012

ALI H AL HAKIM
11/02/2012

MEMORANDUM

Date: 2 Nov 2012
From: Joseph Leginus, Review Chemist, Branch VII/DPA III/ONDQA
To: NDA 203314, Tresiba™ (Insulin Degludec [rDNA Origin] Injection)
Subject: CMC Recommendation

This memo documents the overall CMC recommendation for NDA 203314 - Tresiba™ (Insulin Degludec [rDNA Origin] Injection). The recommendation from CMC is Complete Response due to a Withhold recommendation for this application from the Office of Compliance on 26 Oct 2012. See Establishment Evaluation Request Detail Report below for details.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 203314/000	**Action Goal:**	
Stamp Date:	29-SEP-2011	**District Goal:**	30-MAY-2012
Regulatory:	29-OCT-2012		
Applicant:	NOVO NORDISK INC	**Brand Name:**	insulin degludec (rDNA origin) Injection
	846	**Estab. Name:**	insulin degludec (rDNA origin) Injection
	PLAINSBORO, NJ 08536	**Generic Name:**	
Priority:	1	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	510	001; SOLUTION, INJECTION; INSULIN DEGLUDEC; 100UNT 002; SOLUTION, INJECTION; INSULIN DEGLUDEC; 200UNT	

Application Comment:

FDA Contacts:	K. SHARMA	Project Manager	3017961270
	M. RAMASWAMY	Review Chemist	3017961676
	S. TRAN	Team Leader	3017961764

Overall Recommendation:	WITHHOLD	on 26-OCT-2012	by F. GODWIN	(HFD-320)	3017965362
	PENDING	on 19-JUL-2012	by EES_PROD		
	PENDING	on 24-JAN-2012	by EES_PROD		
	PENDING	on 13-OCT-2011	by EES_PROD		
	PENDING	on 13-OCT-2011	by EES_PROD		

Joseph Leginus, PhD
Review Chemist

Ali Al-Hakim, Ph.D.
Branch VII, Chief, ONDQA

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/s/

JOSEPH LEGINUS
11/02/2012

ALI H AL HAKIM
11/02/2012

MEMO

From: Muthukumar Ramaswamy, Ph.D.,
CMC Reviewer, Office of New Drug Quality Assessment (ONDQA), CDER

To: File

Date: Oct 29, 2012

Subject: CMC Recommendation for NDA 203313 - Ryzodeg® ([Insulin degludec/Insulin aspart] (rDNA origin) Injection

This memo documents the overall CMC recommendation for NDA 203313 - Ryzodeg® ([Insulin degludec/Insulin aspart] (rDNA origin) Injection application. From Chemistry, Manufacturing, and Controls (CMC) perspective, the NDA is not recommended for approval due to a withhold recommendation for this application from the Office of Compliance (Refer to Establishment Evaluation Request Summary Report for additional details).

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 203313/000	**Sponsor:**	NOVO NORDISK INC
Org. Code:	510		846
Priority:	14		PLAINSBORO, NJ 08536
Stamp Date:	29-SEP-2011	**Brand Name:**	Ryzodeg
PDUFA Date:	29-OCT-2012	**Estab. Name:**	[Insulin degludec/Insulin aspart] (rDNA origin) injection
Action Goal:		**Generic Name:**	
District Goal:	30-MAY-2012	**Product Number; Dosage Form; Ingredient; Strengths**	001; SOLUTION, INJECTION; INSULIN DEGLUDEC; 100UNT

FDA Contacts:	K. SHARMA	Project Manager		3017961270
	J. LEGINUS	Review Chemist	(HFD-810)	3017964102
	S. TRAN	Team Leader		3017961764

Overall Recommendation:	WITHHOLD	on 26-OCT-2012	by F. GODWIN	(HFD-320)	3017965362
	PENDING	on 19-JUL-2012	by EES_PROD		
	PENDING	on 24-JAN-2012	by EES_PROD		
	PENDING	on 13-OCT-2011	by EES_PROD		

Establishment:	**CFN:** 9610699 **FEI:** 3002807751		
	NOVO NORDISK A S HALLAS ALLE		
	KALUNDBORG, , DENMARK		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
	FINISHED DOSAGE LABELER		
	FINISHED DOSAGE PACKAGER		
Profile:	(b) (4)	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	24-JAN-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		
Profile:	(b) (4)	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	15-OCT-2012		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:** 9613244 **FEI:** 3002807752		
	NOVO NORDISK A S BERNNUM PARK, DK-3400		
	HILLEROED, , DENMARK		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE LABELER		
	FINISHED DOSAGE PACKAGER		
	FINISHED DOSAGE STABILITY TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	24-SEP-2012		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		
Profile:	(b) (4)	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	24-SEP-2012		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:** 9616213 **FEI:** 3000151819		
	NOVO NORDISK A S NOVO ALLE		
	BAGSVAERD, , DENMARK		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
	FINISHED DOSAGE MANUFACTURER		
Profile:	(b) (4)	**OAI Status:**	POTENTIAL OAI
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	26-OCT-2012		
Decision:	WITHHOLD		
Reason:	DISTRICT RECOMMENDATION		

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/s/

MUTHUKUMAR RAMASWAMY
10/30/2012

ALI H AL HAKIM
10/30/2012

NDA 203313

Ryzodeg™
(70% Insulin Degludec and 30% Insulin Aspart [rDNA origin] Injection)

Novo Nordisk Inc.

Joseph Leginus, PhD (Drug Substance Reviewer)
Muthukumar Ramaswamy, PhD (Drug Product Reviewer)

Division of Pre-Marketing Assessment III, Branch VII, ONDQA

For the Division of
Metabolism and Endocrinology Products

CHEMISTRY REVIEW #2

Table of Contents

Chemistry Review Data Sheet

1. NDA 203313

2. REVIEW #: 2

3. REVIEW DATE: May 25, 2012

4. REVIEWER: Joseph Leginus, PhD and Muthukumar Ramaswamy, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	Sep 29, 2011
Amendment	Dec 22, 2011

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	Mar 16, 2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Novo Nordisk Inc.
Address:	100 College Road West, Princeton, NJ 08540
Representative:	Eddie Li, PhD, Vice President, Regulatory Affairs
Telephone:	609-786-4593

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Ryzodeg™
Non-Proprietary Name (USAN): Insulin Degludec/Insulin Aspart
b) Code Name/# (ONDC only): Insulin degludec: NNC [redacted] (b) (4), Insulin 454
c) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1 (NME) and Type 4 – new combination
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Treatment of diabetes mellitus

11. DOSAGE FORM: Solution for Injection

12. STRENGTH/POTENCY: 100 U/mL

13. ROUTE OF ADMINISTRATION: Subcutaneous Administration

14. Rx/OTC DISPENSED: __X__Rx ___OTC

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

_____Not a SPOTS product

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

Insulin Degludec

Chemical Name (WHO): $N^{6,B29}$-[N^{2}-(15-carboxypentadecanoyl)-L-γ-glutamyl]-des-B30-L-threonine-insulin human

USAN: Insulin degludec

Chemical Structure:

Molecular Formula: $C_{274}H_{411}N_{65}O_{81}S_6$

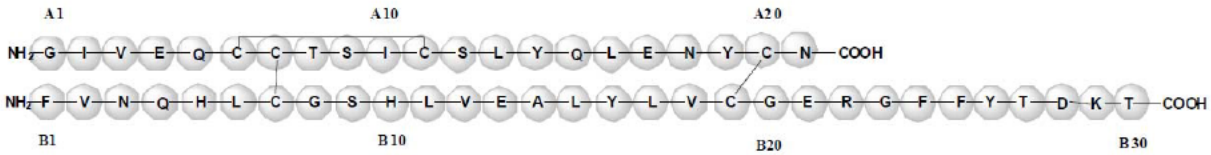
Molecular Weight: (b) (4) Da – monoisotopic; 6,103.97 Da - average

Insulin Aspart

Chemical Name (WHO): B28 insulin aspart

USAN: Insulin aspart

Chemical Structure:



Molecular Formula: $C_{256}H_{381}N_{65}O_{79}S_6$
Molecular Weight: 5825.8 Da

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	V	Novo Nordisk, Inc.	(b) (4)	1	Adequate	Reviewed by B. Riley 3/13/2009	Letter of Authorization 5/11/2011

[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	73198	[Insulin degludec/Insulin aspart] (rDNA origin) Injection
NDA	203314	Insulin degludec (rDNA origin) Injection
NDA	20986	Insulin aspart (rDNA origin) Injection

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending. EER was sent to Office of Compliance on 13-Oct-2011.	3/10/2012	OC recommendation is pending
Biopharm	May not be applicable. This is an injectable product, and the commercial formulation was used in Phase 3 studies.	N/A	
Methods Validation	Validation may be requested of FDA labs after test methods are finalized.	N/A	
CDRH	Review of the disposable multi-dose pen injector.	TBD	Jackie Ryan/Quynhnhu Nguyen
EA	Acceptable	2/7/2012	Joseph Leginus
Microbiology	Review of 1) microbiology controls proposed for the drug substance and drug product, and 2) sterilization (b) (4) processing validation for the drug product.	TBD	Vinayak Pawar

The Chemistry Review for NDA 203313

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a CMC perspective the Applicant has resolved satisfactorily the deficiencies identified in Review #1. There is no pending issue specific to the CMC review. At this time, the CMC final recommendation is pending the recommendations from CDRH and microbiology reviewers for the acceptability of the (b) (4) injector for the proposed use and acceptability of microbiology information, respectively. In addition, OMPQ has not issued an overall recommendation for the commercial manufacturing and testing facilities listed in the NDA.

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

Not Applicable

II. Summary of Chemistry Assessments

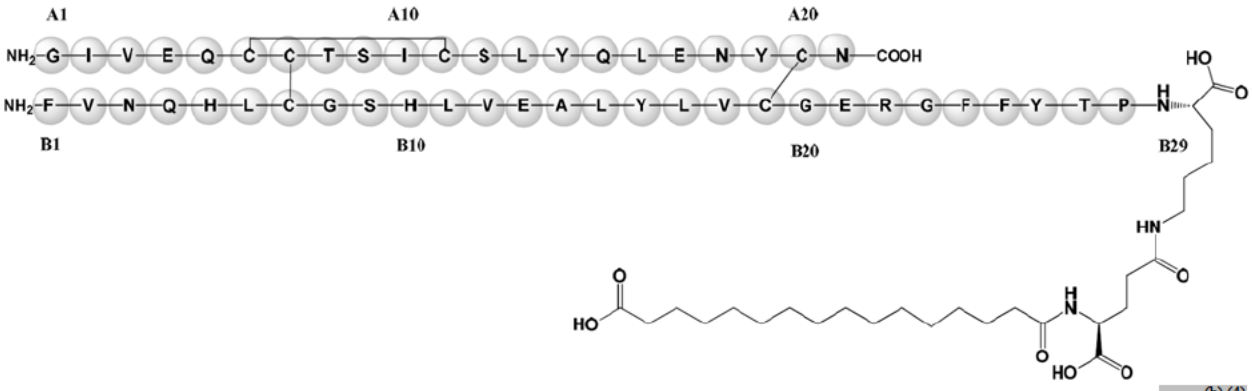
A. Description of the Drug Product(s) and Drug Substance(s)

Note: Review of NDA 203313 was conducted as a Team Review with Joseph Leginus reviewing the Drug Substance and Muthukumar Ramaswamy reviewing the Drug Product.

DRUG SUBSTANCE

Ryzodeg™ (70% Insulin Degludec and 30% Insulin Aspart [rDNA Origin] Injection) 100 U/mL solution for subcutaneous injection contains 420 nmol of insulin degludec and 180 nmol of insulin aspart per mL. Insulin aspart was approved previously for human use under NDA 20986.

One of the two drug substances, insulin degludec, is a new molecular entity and is an analog of human insulin. The chemical name of insulin degludec is $N^{6, 29B}$-[N-(15-carboxypentadecanoyl)-L-γ-glutamyl]-des-30B-L-threonine-human insulin, and its structure is presented below:



Insulin degludec is produced using recombinant DNA technology and chemical modification. The (b) (4) precursor of insulin degludec (desB30-insulin), produced by a process that includes expression of

recombinant DNA in yeast (*Saccharomyces cerevisiae*) differs from human insulin by the omission of threonine in position B30. Insulin degludec is made by chemically attaching a C-16 fatty acid (hexadecanedioic acid) with a glutamic acid spacer on the lysine (b) (4) at position B29 of the insulin precursor.

The molecular formula of insulin degludec is $C_{274}H_{411}N_{65}O_{81}S_6$ with a molecular weight of (b) (4)

Insulin degludec is a (b) (4). It is freely soluble in water at neutral pH (b) (4) The isoelectric point of insulin degludec is approximately (b) (4). The pH of a (b) (4) aqueous solution of drug substance is approximately 7.4.

The structure of insulin degludec was (b) (4)

Insulin degludec is produced by recombinant DNA technology from yeast (*Saccharomyces cerevisiae*) and chemical modification. The manufacturing process is (b) (4)

The proposed release specifications include appearance, identification (b) (4) and HPLC), content (HPLC), bioactivity (cell-based assay), individual (b) (4) related impurities (HPLC), loss on drying and bacterial endotoxin. The proposed regulatory methods have been validated. Reference standards for the API have been developed and characterized.

Product related impurities structurally related to insulin degludec (b) (4) (b) (4) impurities", (b) (4) related substances", (b) (4) impurities" and "high molecular weight proteins." (b) (4)

A shelf life of (b) (4) months will be granted for the drug substance when stored at (b) (4) This is based on acceptable long-term stability results from real-time studies obtained for the drug substance from Primary Stability batches at production scale.

DRUG PRODUCT

The proposed drug product (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. Each mL of the proposed contains 420 nmol of insulin degludec and 180 nmol of insulin aspart, 19.0 mg glycerol (b) (4) 1.50 mg phenol (b) (4), 1.72 mg metacresol (b) (4), sodium chloride (0.58 mg, (b) (4)), and 27.4 µg zinc (b) (4) and water for injection. Hydrochloric acid or sodium hydroxide is added to adjust pH to approximately 7.4. The potency of the proposed formulation is 100 Units/mL (U-100). The proposed product is intended for once or twice daily use as meal time insulin by subcutaneous administration.

During Phase 1 and 2 studies, the Applicant has screened formulations containing different ratios of insulin degludec/insulin aspart and different levels of excipients (e.g., phenol/metacresol, glycerol, zinc,

sodium chloride, [redacted] (b) (4)) for action profile and stability. Based on developmental data, the Applicant has chosen a formulation containing insulin degludec/insulin aspart at a ratio of 70:30 and phenol/metacresol, glycerol, sodium chloride, and zinc as excipients for use in Phase 2/3 studies. The proposed final formulation is the same as the one used in Phase 3 clinical studies.

Insulin degludec and insulin aspart together [redacted] (b) (4) promote self-association into di-hexamer and hexamer, respectively. The NDA states that drug product formulation has been optimized to maximize the di-hexamer and hexamer forms of insulin degludec and insulin aspart, respectively in the drug product. A concentration in total of [redacted] (b) (4) and a pH of 7.4 have been identified as optimal to confer [redacted] (b) (4) of the formulation. The Applicant is proposing to use monograph grade excipients in the final formulation and is acceptable.

The Applicant is proposing to market the proposed product as [redacted] (b) (4) pre-filled pen (cartridge pre-assembled in a PDS290 pen-injector). The finished product will be marketed as 5 x 3 mL [redacted] (b) (4) packaged in cartons or as 5 x 3 mL prefilled pens in cartons. The proposed product is light sensitive and [redacted] (b) (4) packaging is critical to assure the stability of the product.

The drug product, insulin degludec/insulin aspart 100 U/mL, is manufactured by [redacted] (b) (4)

The drug product is sterile [redacted] (b) (4)

During development, the Applicant has defined Quality Target Product Profile (QTPP) and critical quality attributes (CQAs). The proposed CQAs for the drug products include insulin content of each active ingredient, extractable volume, plunger friction (for measuring device performance), *purity factors (individual impurities related to each active ingredients, high molecular weight proteins, product identity,* [redacted] (b) (4) *content)*, closure integrity (sterility), [redacted] (b) (4) efficacy, endotoxin levels, appearance (particulate load), and other physical tests such pH and isotonicity.

The Applicant has defined [redacted] (b) (4)

The Applicant also used design of experiments and risk assessment techniques to define critical process parameters. The Applicant's developmental work and process evaluation studies were targeted to ensuring the proposed process parameters are adequate to ensure complete dissolution of excipients and active ingredients. Developmental stability on in-process solutions and bulk formulation assured whether the proposed pH ranges for these solutions are adequate with respect chemical and physical attributes.

The NDA contains batch formula and a description of the proposed commercial process. Together with the information provided in the master batch record, the available information in the NDA is adequate to support the proposed commercial process. The NDA contains process control information for manufacturing the proposed product. The proposed critical process parameters (in-process tests) include

(b) (4)

The NDA contains batch analysis data from development through commercial scale to support the manufacturability of the proposed product. The NDA contains adequate information on the release specification used for controlling for quality of the drug product. The Applicant has proposed general tests typically expected for a parenteral product, and product-specific tests. The proposed general tests include pH, endotoxin limit, and sterility, and particulate matter. The product-specific tests include identity, insulin content, zinc content, product related impurities (b) (4) (b) (4) impurities, (b) (4) product related substances and (b) (4) impurities) and (b) (4) content. In addition, the applicant is proposing to monitor the dose accuracy of the pen-filled syringe. The proposed limits for monitoring the individual insulin degludec and insulin aspart related substances and impurities are acceptable.

Due to method limitation, the Applicant has proposed collective limits for individual groups of product related substances and impurities (defined as (b) (4) impurities, (b) (4) product related substances and (b) (4) impurities). Considering the complexity of the product and the availability of characterization data for related substances and impurities, the proposed control strategy is acceptable. The test methods proposed for the product are adequately described and are validated per applicable ICH guidelines.

The Applicant is proposing a separate release and shelf-life specification (i.e., wider than the release specification) for controlling and monitoring the quality of the drug product. *Per FDA request, the Applicant has tightened the shelf-life specification limits for* (b) (4) *related substances and* (b) (4) *impurities. Considering the manufacturer's limited experience with the product, the proposed shelf-life specifications for the product related substances and impurities are acceptable.*

The applicant has provided 18-24 month real time and 6 month accelerated stability data for several batches of the drug product manufactured at (b) (4) scale. This Application also contains limited stability information for product manufactured at commercial scale (b) (4) scale). In addition, the NDA contains in-use stability and photo stability data for the proposed product (b) (4) packaging configurations. The stability studies were performed on the drug product packaged in (b) (4). *Photo stability data show that the* (b) (4) *packaging (the PDS290 pen-injector* (b) (4) *and carton) provides adequate protection against light.* Since the drug product is only in contact with the (b) (4) the stability data of the drug product in the (b) (4) (in darkness) in the PDS290 pen-injector is not needed.

- *Based on the long term and accelerated stability data evaluated in this document, a shelf life of 24 months at 5°C ± 3°C is recommended for Insulin degludec/Insulin aspart 100 U/mL.*
- *Based on the in-use stability data evaluated in this document, an in-use period of 28 days at up to 30°C is recommended for Insulin degludec/Insulin aspart 100 U/mL.*

The NDA contains a post-approval stability protocol and commitment to place 3 full scale batches on stability and continue to update information on existing stability studies. The Applicant should update

their stability protocol and post-approval stability protocol to include limits for individual product related substances and impurities.

The Applicant has adequately resolved issues identified during Chemistry Review #1.

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

Ryzodeg™ (70% Insulin Degludec and 30% Insulin Aspart [rDNA Origin] Injection) solution is intended for once or twice daily administration with any main meals in diabetic patients. When needed, the patient can change the time of administration as long as Ryzodeg is dosed with a main meal. The Ryzodeg drug can be administered either alone or in combination with oral anti-diabetic drugs (OADs).

The dosage of Ryzodeg should be individualized under the supervision of a health care provider in accordance with the needs of the patient with appropriate glucose monitoring. For patients with type 2 diabetes mellitus, the recommended total daily starting dose of IDegAsp is 10 Units with meal(s) followed by individual dosage adjustments. For patients with type 1 diabetes mellitus, IDegAsp is to be used once-daily at meal-time and with short-/rapid-acting insulin at the remaining meals followed by individual dosage adjustments.

Ryzodeg should be administered by subcutaneous injection into the abdominal wall, thigh, or upper arm. Ryzodeg should not be administered intravenously or intramuscularly or with insulin infusion pumps or mixed with any other insulin solutions. Ryzodeg should be inspected visually prior to administration and should only be used if the solution appears clear and colorless.

Drug product delivery system and appropriate storage are adequately described in both package insert and patient package insert. Drug product shelf-life is 24 months at 2° - 8°C, protected from light. In-use shelf-life period is 28 days at temperatures not exceeding 30°C

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective the NDA is satisfactory. There is no pending issue specific to the CMC review. At this time, the CMC final recommendation is pending the recommendations from CDRH and microbiology reviewers for the acceptability of the (b) (4) injector for the proposed use and acceptability of microbiology information, respectively. In addition, OMPQ has not issued an overall recommendation for the commercial manufacturing and testing facilities listed in the NDA.

III. Administrative

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

Chemistry Assessment

Chemistry assessment was completed by team review. Dr. J. Leginus completed the review of the drug substance section and Dr. M. Ramaswamy completed the review of the drug product section.

On Mar 16, 2012, Novo Nordisk, Inc. submitted a complete response to the CMC request for information dated Feb 8, 2011 resulting from Chemistry Review #1. Novo Nordisk's responses to FDA questions and review comments are provided below. For an evaluation of Novo Nordisk's response to drug substance related questions, please refer to NDA chemistry review #2 for NDA 203314.

FDA Question 1

Provide information on the following:

a. Levels of soluble di-hexameric forms of insulin degludec present in your drug product.

b. The stoichiometry of (b) (4)

c. Data to support the proposed levels of zinc and phenol for the proposed drug products.

Response to FDA Question 1a

During formulation development, the association pattern of insulin degludec has been investigated by (b) (4) High Performance Liquid Chromatography ((b) (4) HPLC) and Analytical (b) (4) (b) (4). The drug product formulation has been characterized to primarily consist of soluble, non-covalently bound di-hexamers to a level above 95%. In the chromatogram more than 95% of insulin degludec (b) (4) corresponding to the molecular mass of an insulin degludec di-hexamer.

Response to FDA Question 1b

(b) (4)

(b) (4)

Response to FDA Question 1c

(b) (4)

FDA Question 2

Your CMC section does not contain information on the levels of individual insulin degludec related substances and impurities present in the drug product. ICH Q6B guidance states that if impurities are known to be introduced or formed during the production and/or storage of the drug product, the levels of these impurities should be determined and acceptance criteria established. Therefore, provide the following:

a. Information on the levels of individual insulin degludec related substances and impurities present in batches used in phase 3 clinical studies and stability studies.

Response to FDA Question 2a

In accordance with the ICH Q6B guideline, the development of the RP-HPLC method A6020a to determine insulin degludec related substances and impurities has focused on the separation of the desired product (insulin degludec) from the different degradation products. The established analytical procedure A6020a has been shown to provide satisfactory selectivity and ability to detect the degradation of insulin degludec even for drug products subjected to extreme conditions (reference is made to 3.2.P.5.5 Biological Activity of Degradation Products in Insulin Degludec/Insulin Aspart Drug Product, where characterization by mass spectrometry of the main peak in method A6020a from the degraded samples showed more than (b) (4)% of the mass signals to comply with the theoretical monoisotopic mass for insulin degludec). A number of molecular variants of insulin degludec are formed during storage of the drug product at accelerated conditions (see 3.2.P.5.5 Characterization of Impurities). They elute well separated from the insulin degludec main peak, but not individually separated from each other, and collective acceptance criteria have therefore been established in accordance with ICH Q6B.

The separation of individual impurities may vary between analytical runs due to column-to-column variations, and integration of the product related substances and impurities in the three groups ((b) (4) impurities, (b) (4) related substances and (b) (4) impurities) therefore ensures the most robust method. At the same time, this approach ensures the most sensitive detection of all degradation products since all area segments eluting within the (b) (4) area segment would be less than the quantification limit. In addition, isomers and isolated degradation products of insulin degludec, representing all the major components of the three groups of insulin degludec related substances and impurities in degraded drug product, have been characterized with regard to biological activity. (b) (4) (see 3.2.S.3.1 Biological Activity of Insulin Degludec).

Based on the above, the use of collective acceptance criteria for insulin degludec related substances and impurities have been justified. Levels of insulin degludec related substances and impurities in drug product batches used in phase 3 clinical studies and stability studies, reported as (b) (4) impurities, (b) (4) related substances and (b) (4) impurities, have been provided in 3.2.P.5.4 Insulin Degludec/Insulin Aspart 100 U/mL, Batch Analysis and 3.2.P.8.1 Insulin Degludec/Insulin Aspart 100 U/mL, Stability Summary and Conclusion.

b. Explain which impurities are increasing during manufacturing, during long-term, accelerated and in-use stability studies.

Response to FDA Question 2b

For the insulin degludec/insulin aspart drug product and the insulin degludec drug substance used for drug

product manufacturing, comparable impurity profiles and levels of insulin degludec related substances and impurities have been documented in 3.2.P.5.5 Characterization of Impurities (see Figure 3 and Table 1 below, for convenience copied from the report).

Table 1 Content of insulin degludec related substances and impurities by RP-HPLC (A6020a) for insulin degludec drug substance and insulin degludec/insulin aspart drug product

Sample	Batch	(b) (4) impurities (%)	(b) (4) related substances (%)	(b) (4) impurities (%)
Insulin degludec/insulin aspart drug product	YQ50522	(b) (4)		
Insulin degludec drug substance	YK0SHP006			

It is therefore concluded that no new impurities of insulin degludec were found due to the manufacturing of the insulin degludec/insulin aspart drug product, and the drug product manufacturing process has only a very limited effect on the levels of insulin degludec related substances and impurities.

In the 3.2.P.5.5 Characterization of Impurities report, the impurity profile of insulin degludec/insulin aspart drug product, stored at accelerated conditions (25°C ± 2°C) for 6 months, was compared to the drug product kept at long term conditions (5°C ± 3°C), and the impurity profiles are provided in Figure 4 of the quality amendment dated 03/15/12. From the figure, it is seen that all the related substances and impurities separated by RP-HPLC method A6020a are increasing upon accelerated storage, except the (b) (4) (b) (4) insulin degludec, originating from the manufacturing of insulin degludec drug substance as described in 3.2.S.3.2 Overview of Potential Impurities in Drug Substance. Similarly, the potential (b) (4) insulin degludec (eluting in the group of (b) (4) impurities), the potential (b) (4) insulin degludec (eluting in the group of (b) (4) related substances), and the potential (b) (4) insulin degludec (eluting in the group of (b) (4) impurities) would not increase in level during storage as they also originate from the insulin degludec drug substance manufacturing. All the other insulin degludec related substances and impurities (b) (4) method A6020a are degradation products of insulin degludec and increase in level upon storage at long-term, accelerated, and in-use stability conditions.

c. Based on available data, propose a limit for each of the individual product related substances and impurities present in the product including limits for (b) (4) insulin degludec) and (b) (4) insulin degludec) in the drug product.

Response to FDA Question 2c

As described in our response to FDA Question 2a above, collective acceptance criteria have been established for insulin degludec related substances and impurities in accordance with ICH Q6B. The (b) (4) insulin degludec have been characterized as insulin degludec related

substances, and acceptance criteria for these compounds are covered by the acceptance criteria for [redacted] related substances.

d. Update your post-approval stability protocol to include limits for individual product related substances and impurities.

Response to FDA Question 2d

As described in our response to FDA Question 2a and 2c above, collective acceptance criteria have been established for insulin degludec related substances and impurities rather than individual limits. Thus, the post-approval stability protocol would remain unchanged from what was submitted in the original NDA.

e. Clarify whether glycerol used in the formulation [redacted] of the insulin degludec in your product.

FDA Question 2e

The insulin degludec drug product formulation includes glycerol as an excipient. Glycerol is an alcohol containing both [redacted] functional groups. The insulin degludec molecule includes [redacted]

[redacted]

This is supported by the experimental data of the degradation products of insulin degludec. None of the observed impurities possess relative molecular mass (M_r) values which could be assigned to the [redacted] products between glycerol and insulin degludec [redacted]

f. Provide intact and reduced mass data for each of the individual impurities separated by the analytical method, A6020a.

Response to FDA Question 2f

The insulin degludec related substances and impurities were comprehensively characterized using a combination of analytical methods including different mass spectrometric procedures. The impurities and related substances in the insulin degludec drug substance originating from the manufacturing process have been characterized as described in 3.2.S.3.2 Overview of Potential Impurities in Drug Substance, and all the major degradation products of insulin degludec have

been characterized as described in 3.2.P.5.5 Characterization of Impurities.

Table 2 Potential product related substances and impurities in insulin degludec determined by RP-HPLC

Classification	Identity/Content	Monoisotopic mass M_r		Experimental reduced	
		Theoretical	Experimental	A-chain	B-chain
(b) (4) impurities determined by RP-HPLC					(b) (4)
(b) (4) related substances determined by RP-HPLC					
(b) (4) impurities determined by RP-HPLC					

* Mass data reported as average mass using conventional (b) (4) MS ND: Not determined

A list of all the potential product related substances and impurities in insulin degludec, separated by the RP-HPLC method A6020a (and the equivalent drug substance specification method A7090a), is provided in Table 2, including the theoretical and experimental determined intact monoisotopic mass of each of the identified components determined using high-resolution MS. The analytical method A6020a uses mobile phases, which are not compatible with on-line MS detection, and therefore, the identification of the different components was primarily based on characterization of fractions isolated by the RP-HPLC method.

Determination of reduced masses for the isolated components in the insulin degludec product related substances and impurities was also included in the characterization for the majority of the components, and the experimentally determined reduced average mass using conventional (b) (4) MS have been provided in Table 2 for the (b) (4) insulin degludec. The theoretical average mass of insulin degludec (b) (4) respectively.

g. Clarify whether your proposed test method is capable of quantitating individual product-related substances and impurities with adequate specificity, accuracy and precision in the proposed product.

Response to FDA Question 2g

As described in the response to question 2a) above, the drug product specification test method A6020a, which has been established and optimized to determine all insulin degludec related substances and impurities, is not considered capable of providing quantitative information for all components on an individual basis (b) (4). By dividing the insulin degludec related substances and impurities into the three groups ((b) (4) impurities, (b) (4) related substances and (b) (4) impurities), a selective, accurate, and precise method has been obtained.

h. Explain your choice of RP HPLC over other applicable methods (e.g., ion exchange chromatography) for the quantitation of charged variants.

Response to FDA Question 2h

The RP-HPLC method A6020a developed to determine the insulin degludec related substances and impurities has focused on separating all changed molecular variants from the main peak of insulin degludec. By general experience with insulin products, RP-HPLC is a more selective principle in liquid chromatography when compared to ion exchange chromatography. By proper selection of the chromatographic conditions, charged variants of the parent substance may also be separated by RP-HPLC. This is the case for RP-HPLC method A6020a, where all the charged variants of insulin degludec are well separated from insulin degludec. The superiority of the selected RP-HPLC method over ion exchange chromatography in detecting product related impurities has been demonstrated in the comparability studies for different campaigns of insulin degludec drug substance (see 3.2.S.2.6 Demonstration of Comparability of Drug Substance Manufactured from Campaign 1 to Campaign 12).

Overall evaluation of the Applicant's response to questions 2a-h: Adequate.

a. The Applicant's response indicates that some of the peaks corresponding to insulin degludec related substances and impurities elute closely or co-elute partly in the chromatogram. As a result, the proposed analytical method (A6020a) is not capable of providing quantitative information on individual insulin degludec related substances and impurities. Therefore, the requested information on the levels of individual drug substance related substances and impurities in batches used in phase 3 clinical studies and stability studies was not available for review.

b. For the above reasons, the Applicant has grouped the impurities that elute in the RP-HPLC chromatogram into three groups ((b) (4) impurities, (b) (4) related substances and (b) (4) impurities) and established collective acceptance criteria for each group. Considering the complexity of the product, the proposed approach is acceptable. The proposed strategy ensures the detection of all degradation products below the proposed limit. This is further supported by the 18-24 months stability data available for primary stability batches. The stability data indicated that the product maintained a purity > (b) (4) % with respect to insulin degludec related substances and impurities during 18-24 months of real-time storage conditions.

c. The Applicant has characterized the identity of insulin degludec related substances and impurities formed during storage at long-term, accelerated, and in-use stability conditions (see Table 2, above). Due to method limitation, quantitative information on individual impurities is not available for review. Information provided within the CMC section indicated that [redacted] insulin degludec) and [redacted] insulin degludec) are the major impurities among them. The Applicant has also indicated that the levels of the following drug substance related substances do not increase during drug product storage:

a) [redacted] insulin degludec (eluting in the group of [redacted] impurities),
b) [redacted] insulin degludec (eluting in the group of [redacted] related substances),
c) [redacted] insulin degludec (eluting in the group of [redacted] impurities).

d. The Applicant's explanation that formation of [redacted] of the insulin degludec under neutral pH conditions is acceptable. If formed, this impurity could be identified during characterization studies by its unique mass.

e. The Applicant has provided satisfactory mass spec data information (intact and reduced mass data) for each of the individual impurities separated by the analytical method, A6020a Table 2). In addition, the applicant has characterized the biological activity of isomers and isolated degradation products of insulin degludec.

f. The Applicant's explanation for the choice of RP-HPLC over other applicable methods (e.g., ion exchange chromatography) to analyze charged variants is acceptable. In addition, the Applicant has used the same RP-HPLC method to demonstrate the comparability of various batches of drug substance manufactured during campaign runs.

FDA Question 3

Considering the expected purity of your drug product is ≥ [redacted]%, the combined limits for [redacted] related substances, [redacted] impurities and % HMWP would exceed the [redacted]% total impurity level. Therefore, revise your proposed limit for [redacted] related substances, [redacted] impurities and % HMWP to meet the purity expectations.

Novo Nordisk Response:

In the proposed specifications for the insulin degludec drug products, the acceptance criteria for content of insulin degludec are [redacted]% of label claim. The acceptance criteria for content of insulin degludec cannot be directly compared to the acceptance criteria for insulin degludec related substances and impurities and for HMWP, since quality attributes related to quantity and purity are controlled by three different methods:

- Determination of the insulin degludec related substances and impurities by RP-HPLC method A6020a
- Determination of the identity and content of insulin degludec by RP-HPLC method A6021a
- Determination of HMWP by GPC method A6022a

The methods and the acceptance criteria in the specifications are further explained below:

RP-HPLC method A6020a: This method determines the relative distribution of the insulin degludec and the insulin degludec related substances and impurities (divided into three groups: [redacted] impurities,

(b) (4) related substances and (b) (4) impurities). From the acceptance criteria proposed in the specifications for each of the three groups, a total level (relative amount) of insulin degludec related substances and impurities of ≤ (b) (4)% at release and ≤ (b) (4)% at end of shelf life may be calculated. The major part of the molecular variants of insulin degludec separated by RP-HPLC method A6020a and included in the limits described above have been characterized to possess full or high relative bioactivity compared to insulin degludec (reference is made to 3.2.S.3.1 Biological Activity of Insulin Degludec).

RP-HPLC method A6021a: The analytical method determines the combined content (b) (4) of insulin degludec and molecular variants of insulin degludec (impurities and related substances), which elute together in one main peak of insulin degludec. As documented in 3.2.S.3.1 Biological Activity of Insulin Degludec, (b) (4) degraded samples. It has therefore been concluded that the RP- HPLC method for the determination of the (b) (4) content offers a reliable indication of the biological activity of insulin degludec in the drug product. The acceptance criteria in the specifications ensure that the content of insulin degludec in the drug product is consistently within (b) (4)% of label claim throughout the shelf-life of the product.

GPC method A6022a: This method determines the total relative amount of high molecular weight proteins (HMWP) in the drug product. As described in 3.2.P.5.5 Characterization of Impurities, the HMWP has been characterized to consist of (b) (4) insulin degludec/insulin degludec (b) (4). The insulin degludec (b) (4) will also be determined as part of the (b) (4) impurities in RP-HPLC method A6020a, as they will elute in the gradient part of the method. The acceptance criteria in the specifications have been set to ensure a total level (relative amount) of HMWP of ≤ (b) (4)% at release and ≤ (b) (4)% at end of shelf life.

Based on the above, the combined control strategy and the acceptance criteria in the proposed insulin degludec drug product specifications are considered justified.

Overall evaluation of the applicant's response: Adequate
The Applicant has proposed an acceptance criterion of (b) (4)% of the label claim for the (b) (4) content (quantitated as insulin degludec + related substances and impurities or as insulin aspart + related substances and impurities) during its shelf-life, which is acceptable. The Applicant has also committed to control the purity content of the product by RP-HPLC with an acceptance criteria of NMT (b) (4)% for insulin degludec related substances and impurities during its shelf-life. The available real-time stability data for primary batches indicated that purity of these batches was > (b) (4)% with respect to aspart related substances and impurities (See below, data reproduced from section 3.2.P.8) during a real-time storage period of 18-24 months. In light of the Applicant's limited stability experience with the product, the proposed acceptance criteria for individual and total insulin degludec related substances and impurities are acceptable.

Chemistry Assessment Section

Parameter	Proposed specification	Batch information	Batch no.	Storage time (Months) 0	3	6	9	12	18	24	30
Purity of insulin degludec (%)	Not applicable	Primary batches (study 1) C	XCQ0004	(b) (4)							NA
			XCQ0005								NA
			XCQ0006								NA
		Primary batches (study 2) C	XCQ0038								NA
			XCQ0039								NA
			XCQ0040								NA

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

/s/

MUTHUKUMAR RAMASWAMY
05/25/2012

ALI H AL HAKIM
05/25/2012

JOSEPH LEGINUS
05/25/2012

NDA 203314

Tresiba™
(Insulin Degludec [rDNA Origin] Injection)

Novo Nordisk Inc.

Joseph Leginus, PhD (Drug Substance Reviewer)
Muthukumar Ramaswamy, PhD (Drug Product Reviewer)

Division of Pre-Marketing Assessment III, Branch VII, ONDQA

For the Division of
Metabolism and Endocrinology Products

CHEMISTRY REVIEW #2

Table of Contents

Chemistry Review Data Sheet

1. NDA 203314

2. REVIEW #: 2

3. REVIEW DATE: May 25, 2012

4. REVIEWERS: Joseph Leginus, PhD and Muthukumar Ramaswamy, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA	29-Sept-2011
Amendment	22-Dec-2011

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	16-Mar-2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Novo Nordisk Inc.
Address:	100 College Road West, Princeton, NJ 08540
Representative:	Anne Phillips, MD, Corporate Vice President, CMR
Telephone:	609-786-4306

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Tresiba™
b) Non-Proprietary Name (USAN): Insulin Degludec
c) Code Name/# (ONDC only): NNC [redacted] (b) (4), Insulin 454
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: Standard

Chemistry Review Data Sheet

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

10. PHARMACOL. CATEGORY:
Glycemic control in adults with diabetes mellitus

11. DOSAGE FORM: Solution for injection

12. STRENGTH/POTENCY: a) 100 U/mL, and b) 200 U/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
_____ Not a SPOTS product

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

Chemical Name (WHO): $N^{6, B29}$-[N^{2}-(15-carboxypentadecanoyl)-L-γ-glutamyl]-des-B30-L-threonine-insulin human

USAN: Insulin degludec

Chemical Structure:

Molecular Formula: $C_{274}H_{411}N_{65}O_{81}S_{6}$

Molecular Weight: [redacted] (b) (4) Da – monoisotopic; 6,103.97 Da - average

17. RELATED/SUPPORTING DOCUMENTS:

Chemistry Review Data Sheet

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	V	Novo Nordisk, Inc.	(b) (4)	1	Adequate	Reviewed by B. Riley 3/13/2009	Letter of Authorization 5/11/2011
	III			1	Adequate	Reviewed by O. Stephens 9/6/2011	Letter of Authorization 11/23/2010
	III			1	Adequate	Reviewed by O. Stephens 8/24/2011	Letter of Authorization 11/23/2010

[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	76,496	Insulin degludec (rDNA origin) Injection
IND	73,198	Insulin degludec/Insulin aspart (rDNA origin) Injection
NDA	203313	Insulin degludec/Insulin aspart (rDNA origin) Injection

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending. EER was sent to Office of Compliance on 13-Oct-2011.	3/10/2012	OC recommendation is pending
Biopharm	May not be applicable. This is an injectable product, and the commercial formulation was used in Phase 3 studies.	N/A	

Chemistry Review Data Sheet

Methods Validation	Validation may be requested of FDA labs after test methods are finalized.	N/A	
CDRH	Review of the disposable multi-dose pen injector is pending.	TBD	Jackie Ryan/Quynhnhu Nguyen
EA	Completed	2/8/2012	Joseph Leginus
Microbiology	Review of 1) microbiology controls proposed for the drug substance and drug product, and 2) sterilization (b) (4) processing validation for the drug product is pending.	TBD	Vinayak Pawar

The Chemistry Review for NDA 203314

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a CMC perspective, the Applicant has resolved satisfactorily the deficiencies identified in Review #1. There is no pending issue specific to the CMC review. At this time, the CMC final recommendation is pending the recommendations from CDRH and microbiology reviewers for the acceptability of the (b) (4) injector for the proposed use and acceptability of microbiology information, respectively. In addition, OMPQ has not issued an overall recommendation for the commercial manufacturing and testing facilities listed in the NDA.

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

Not applicable

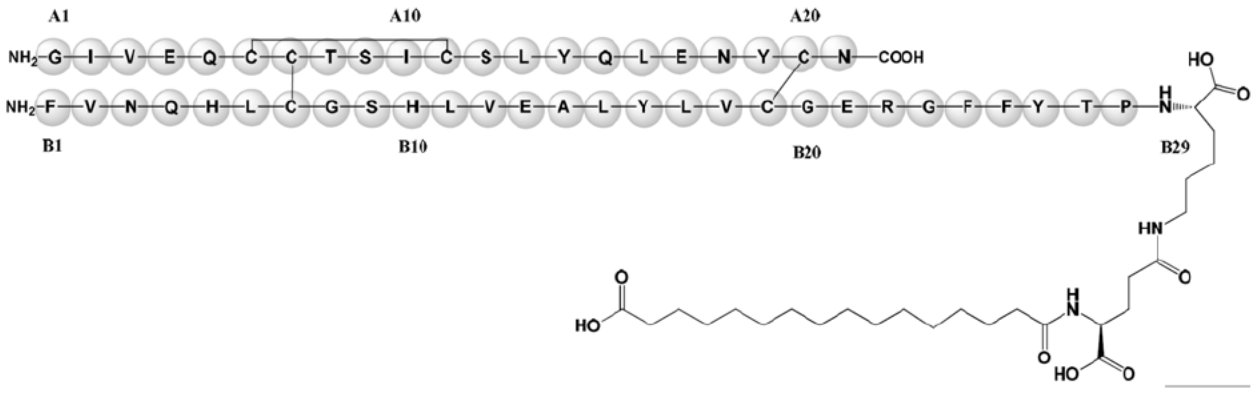
II. Summary of Chemistry Assessments

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

Note: Review of NDA 203314 was conducted as a Team Review with Joseph Leginus reviewing the Drug Substance and Muthukumar Ramaswamy reviewing the Drug Product.

DRUG SUBSTANCE

Tresiba™ (Insulin Degludec [rDNA Origin] Injection) contains a single drug substance, insulin degludec, an analog of human insulin. Insulin degludec is produced using recombinant DNA technology and chemical modification. The (b) (4) precursor of insulin degludec (desB30-insulin), produced by a process that includes expression of recombinant DNA in yeast (*Saccharomyces cerevisiae*) differs from human insulin by the omission of threonine in position B30. Insulin degludec is made by chemically attaching a C-16 fatty acid (hexadecanedioic acid) with a glutamic acid spacer on the lysine (b) (4) at position B29 of the insulin precursor. The chemical name of insulin degludec is $N^{6, 29B}$-[N-(15-carboxypentadecanoyl)-L-γ-glutamyl]-des-30B-L-threonine-human insulin, and its structure is presented below:



The molecular formula of insulin degludec is $C_{274}H_{411}N_{65}O_{81}S_6$ with a molecular weight of [redacted].

Insulin degludec is characterized as a [redacted]. It is freely soluble in water [redacted] Insulin degludec is slightly soluble in methanol [redacted]) and practically insoluble in ethanol [redacted]). The isoelectric point of insulin degludec is approximately [redacted] The pH of [redacted] aqueous solution of drug substance is approximately 7.4.

The structure of insulin degludec was elucidated by a variety of analytical and spectrophotometric techniques, including [redacted] analysis, mass spectrometry ([redacted] MS), [redacted], ultraviolet (UV) and [redacted]

Insulin degludec is produced by recombinant DNA technology from yeast (*Saccharomyces cerevisiae)* and chemical modification. The manufacturing process is a [redacted]

The proposed release specifications include appearance, identification [redacted] and HPLC), content (HPLC), bioactivity (cell-based assay), individual [redacted] related impurities (HPLC), loss on drying and bacterial endotoxin. The proposed regulatory methods have been validated. Reference standards for the API have been developed and characterized.

Product related impurities structurally related to insulin degludec generated during the [redacted] drug substance have classified based on their RP-HPLC elution position relative to the drug substance. These have been characterized as "[redacted] impurities", "[redacted] related substances", "[redacted] impurities" and "high molecular weight proteins." Process derived impurities originating from the insulin degludec manufacturing process were not detected in the drug substance.

A shelf life of [redacted] months will be granted for the drug substance when stored at [redacted]. This is based on acceptable long-term stability results from real-time studies obtained for the drug substance from Primary Stability batches at production scale.

DRUG PRODUCT

The drug product, Tresiba™ (Insulin Degludec [rDNA Origin] Injection) is a sterile, aqueous, clear, colorless solution that contains insulin degludec 100 Units/mL (U-100) or 200 Units/mL (U-200). The proposed product is a long-acting basal insulin formulation intended for once daily use by subcutaneous administration.

The 100 Units/mL presentation contains 600 nmol of insulin degludec, 19.6 mg glycerol [redacted], 1.50 mg phenol [redacted], 1.72 mg metacresol [redacted], 32.7 µg zinc [redacted] and water for injection. The 200 Units/mL presentation contains 1200 nmol of insulin degludec, 19.6 mg glycerol, 1.50 mg phenol, 1.72 mg metacresol, 71.9 µg zinc and water for injection. Hydrochloric acid or sodium hydroxide is added to adjust pH. The pH of the proposed product is approximately 7.6.

During Phase 1 and 2 studies, the Applicant has screened several insulin formulations containing 600-1200 nmol/mL of insulin degludec and excipients such as phenol/metacresol, glycerol, zinc, [redacted] for action profile and stability. Based on developmental data, the Applicant has chosen the proposed final formulation containing phenol/metacresol, glycerol, zinc for

Phase 3 clinical studies. The key difference between the two strength products is in their (b) (4) content. The NDA states that the formulation was optimized to ensure dihexameric form of insulin degludec in the proposed product. A concentration of (b) (4) were chosen with respect to (b) (4) of the insulin degludec 100 and 200 U/mL injection. The Applicant is proposing to use monograph grade excipients in the final formulation and is acceptable.

The Applicant is proposing to market the 100 U/mL strength product as (b) (4) pre-filled pen (cartridge pre-assembled in a PDS290 pen-injector). The 200 U/mL strength product will be available only as a prefilled pen (cartridge pre-assembled in a PDS290 pen-injector). The finished product will be marketed as 5 x 3 mL (b) (4) packaged in cartons or as 5 x 3 mL prefilled pens in cartons. The proposed product is light sensitive and therefore (b) (4) packaging is critical to assure the stability of the product.

The drug products, insulin degludec 100 and 200 U/mL are manufactured by (b) (4)

During development, the Applicant has defined Quality Target Product Profile (QTPP) and critical quality attributes (CQAs). The proposed CQAs for the drug product include content of each active, extractable volume, plunger friction (for measuring device performance), purity factors (individual impurities related to each active ingredients), high molecular weight proteins, product identity, (b) (4) content, closure integrity (sterility), (b) (4) efficacy, endotoxin levels, appearance (particulate load), and other physical tests such pH and isotonicity.

The Applicant has defined (b) (4) as a critical quality attribute (b) (4) in the product.

The Applicant also used design of experiments and risk assessment techniques to define critical process parameters. The Applicant's developmental work and process evaluation studies were targeted to ensuring the proposed process parameters are adequate to ensure complete dissolution of excipients and active ingredient. Developmental stability on in-process solutions and bulk formulation assured whether the proposed pH ranges for these solutions are adequate with respect chemical and physical attributes.

The NDA contains batch formula and a description of the proposed commercial process. Together with the information provided in the master batch record, the available information in the NDA is adequate to support the proposed commercial process. The NDA contains in-process control information for the manufacturing and filling of the proposed products (100 U/mL and 200 U/mL insulin degludec solution for injection). The proposed critical process parameters include (b) (4)

The Applicant has provided batch analysis data from development through commercial scale to support the manufacturability of the proposed products. The NDA contains adequate information on the release specification used for controlling for quality of the drug product. The Applicant has proposed general

tests typically expected for a parenteral product, and product-specific tests. The proposed general tests include pH, endotoxin limit, sterility, and particulate matter. The product-specific tests include identity, insulin content, zinc content, product related impurities (high molecular weight proteins, (b) (4) impurities, (b) (4) product related substances and (b) (4) impurities) (b) (4) content. In addition, the applicant is proposing to monitor the dose accuracy of the product filled in the delivery device. The Applicant is also performing in-process control tests such as closure integrity, the extractable volume test, and air content requirement (b) (4). The acceptance criteria, where applicable, are similar to those for approved insulin and other insulin analogs, and is consistent with parenteral regulatory requirements.

Due to method limitation, the Applicant has proposed collective limits for individual groups of product related substances and impurities (grouped as (b) (4) impurities, (b) (4) product related substances and (b) (4) impurities). Considering the complexity of the product and Firm's characterization data on impurities, the proposed approach is acceptable. The test methods proposed for the product are adequately described and are validated per applicable ICH guidelines.

The Applicant is proposing a separate release and shelf-life specification (i.e., wider than the release specification) for controlling and monitoring the quality of the drug product. *Per FDA request, the Applicant has tightened the shelf-life specification limits for* (b) (4) *related substances and* (b) (4) *impurities. Considering the manufacturer's limited experience with the product, the proposed shelf-life specifications for the product related substances and impurities are acceptable.*

The applicant has provided 24-30 month real time and 6 month accelerated stability data for several batches of the drug product (100 and 200 U/mL) manufactured at (b) (4) scale. This Application also contains limited stability information for product manufactured at commercial scale (b) (4) scale). In addition, this section also contains in-use stability and photo stability data for the proposed product packaged in (b) (4) packaging configurations. The stability studies were performed on the drug product packaged (b) (4). Since the drug product is only in contact with the (b) (4) the stability data of the drug product in the (b) (4) (in darkness) are considered to be representative for the stability of the drug product in the PDS290 pen-injector.

- *Based on the long term and accelerated stability data evaluated in this document, a shelf life of 30 months at* (b) (4) *is recommended for insulin degludec 100 and 200U/mL.*
- *Based on the in-use stability data evaluated in this document, an in-use period of 56 days at up to 30°C is recommended for insulin degludec 100 and 200 U/mL.*
- *Photo stability data show that the* (b) (4) *packaging (the PDS290 pen-injector* (b) (4) *and carton) provides adequate protection against light.*

The NDA contains post-approval stability protocol and commitment to place 3 full scale batches on stability and continue to update information on existing stability studies. The Applicant should update their stability protocol and post-approval stability protocol to include limits for individual product related substances and impurities.

The Applicant has adequately resolved issues identified during Chemistry Review #1.

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

Tresiba™ (Insulin Degludec [rDNA Origin] Injection) is indicated for the treatment of patients with diabetes mellitus (b) (4). It is intended for once-daily use at any time of day by

subcutaneous injection into the abdominal wall, thigh, or upper arm. The drug product should not be administered intravenously or intramuscularly or with insulin infusion pumps or mixed with any other insulin solutions. Tresiba should be inspected visually prior to administration and should only be used if the solution appears clear and colorless.

Drug product delivery system and appropriate storage are adequately described in both package insert and patient package insert. Drug product shelf-life is 30 months at 2°C - 8°C, protected from light. In-use shelf-life period is 56 days at temperatures not exceeding 30°C

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective the NDA is satisfactory. There is no pending issue specific to the CMC review. At this time, the CMC final recommendation is pending the recommendations from CDRH and microbiology reviewers for the acceptability of the (b) (4) injector for the proposed use and acceptability of microbiology information, respectively. In addition, OMPQ has not issued an overall recommendation for the commercial manufacturing and testing facilities listed in the NDA.

III. Administrative

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

Chemistry Assessment

Chemistry assessment was completed by team review. Dr. J. Leginus completed the review of the drug substance section and Dr. M. Ramaswamy completed the review of the drug product section.

On Mar 16, 2012, Novo Nordisk, Inc. submitted a complete response to the CMC request for information dated Feb 8, 2011 resulting from Chemistry Review #1. The deficiencies, Novo Nordisk's responses and review comments are provided as follows:

Drug Substance

Question 1

Provide the chemical structure, general physico-chemical properties and a certificate of analysis of the (b) (4)

Response to Question 1

The (b) (4)

(b) (4)

(b) (4)

[redacted]

A Certificate of Analysis has also been provided. See below.

Certificate of Analysis

novo nordisk®

Novo Nordisk A/S
Novo Allé
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Denmark

Tel. +45 4444 8888
Fax +45 4449 0555

(b) (4)

[redacted]

Question 2

Justify the parenthetical description of Content (' (b) (4) *in the Drug Substance specifications. This may be interpreted to mean inclusion of all* (b) (4) *variants in the sample, rather than only the main peak as defined by HPLC Method A7091a.*

Response to Question 2

The description 'Content ((b) (4) has been used throughout development to specify that the analytical method determines the total content of insulin degludec and molecular variants of insulin degludec (impurities and related substances), which elute together in the main peak. As documented in 3.2.S.3.2 Biological Activity of Insulin Degludec, (b) (4) insulin degludec drug substance (and drug products) has been shown, even for forced degraded samples. The RP-HPLC methods A7091a and A6021a, used for the determination of content in the insulin degludec drug substance and drug products respectively, are equivalent and based on the same analytical principle. In the validation of the analytical method A6021a (see 3.2.P.5.3 Validation of Analytical Procedure A6021a Identity and Quantification of Phenol and Metacresol, Identity and Content of Insulin Degludec and Content of Insulin Aspart), the method has been shown to be specific for insulin degludec compared to other relevant (b) (4) like insulin aspart, insulin detemir, insulin human and liraglutide.

Evaluation of Response to Question 2

The response is adequate. " (b) (4) includes insulin degludec and related substances and impurities that elute together using the validated RP-HPLC method for the determination of content in the drug substance. A correlation between the (b) (4) content and the bioactivity in insulin degludec drug substance has been shown in the NDA.

Question 3

The shelf life of insulin degludec (b) (4) batch 126.454.09.1 should be revised to reflect the available long-term, real-time stability evaluation.

Response to Question 3

In the document 3.2.S.5 Establishment of Novo Nordisk Insulin Degludec (b) (4) Batch no. 126.454.09.1, long-term stability data have been provided for the current (b) (4) batch 126.454.09.1 as well as the former (b) (4) batch 162.454.07.1. The reported stability data has been updated with the latest available real-time data, and the results are provided in Table 2 and Table 3. Both data sets are considered supportive for the stability evaluation of the current (b) (4) batch 126.454.09.1 as both batches are comparable, being insulin degludec drug substance weighed into separate containers, labelled and stored frozen.

Evaluation of Response to Question 3

The response is adequate. Acceptable updated stability data for insulin degludec (b) (4) batch 126.454.09.1 has been provided through (b) (4)

Question 4

The shelf life of the current insulin degludec (b) (4) batch 064.454.09.2 should be revised to reflect the available long-term, real-time stability evaluation of either the previous (b) (4) batch 179.454.07.2 (if appropriate) or the current (b) (4) batch.

Response to Question 4

All the stability data for the insulin degludec (b) (4) batch 179.454.07.2 are considered supportive for the stability evaluation of the current insulin

degludec (b) (4) batch 064.454.09.2 as both current and former (b) (4) are solutions of insulin degludec in a matrix corresponding to the drug product and both are stored frozen at temperatures (b) (4).

As seen in Table 4, Table 5, Table 6 and Table 7 (see submission for details) both batches of insulin degludec (b) (4) show no stability trend for the tested parameters when stored frozen at set-points of (b) (4)

Based on the updated long-term stability data covering up to (b) (4) months real-time stability and the documented absence of stability trends, Novo Nordisk proposes a shelf life of (b) (4) to be granted for the insulin degludec (b) (4) batch 064.454.09.2.

Evaluation of Response to Question 4
The response is adequate. Acceptable updated stability data for the previous (b) (4) batch 179.454.07.2 has been provided through (b) (4) months at (b) (4) Stability data for this batch of insulin degludec (b) (4) is supportive for the stability evaluation of the current insulin degludec (b) (4) batch 064.454.09.2. As a result a shelf life of (b) (4) months is granted for the insulin degludec (b) (4) batch 064.454.09.2., but not (b) (4) as suggested by the applicant. The applicant is reminded that according to ICH Q5C (Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products), "Primary data to support a requested storage period for either drug substance or drug product should be based on long-term, real-time, real-condition stability studies."

Question 5
Explain how insulin degludec (b) (4) batch 064.454.09.2, produced in March 2009, is traceable (for Content, Bioactivity) to the insulin degludec (b) (4) batch 126.454.09.1, which was produced two months later (May 2009).

Response to Question 5
Insulin degludec (b) (4) batch 064.454.09.2 was produced 05-March-2009 as part of a larger production campaign. As the insulin degludec (b) (4) batch 126.454.09.1 was not available before May 2009, all the analytical tests needed to characterise and calibrate the insulin degludec (b) (4) (listed in Table 2, Table 3 and Table 4 in 3.2.S.5 Establishment of Novo Nordisk Insulin Degludec (b) (4) Batch no. 064.454.09.2) were carried out in June 2009. By this, the identity of insulin degludec (b) (4) batch 064.454.09.2 was verified against insulin degludec (b) (4) batch 126.454.09.1, and the assigned content and bioactivity was based on calibration of insulin degludec (b) (4) batch 064.454.09.2 against insulin degludec (b) (4) batch 126.454.09.1.

Evaluation of Response to Question 5
The response is adequate. Insulin degludec (b) (4) ((b) (4) batch 126.454.09.1 was not available prior to May 2009. As a result, content and bioactivity of insulin degludec (b) (4) Batch 064.454.09.2 was not carried out until May 2009.

Question 6

A shelf life of 30 months will be granted for the drug substance when stored at (b) (4) *RH or lower temperatures. This is based on acceptable long term stability results from real-time studies obtained for the drug substance from the Primary Stability batches. The* (b) (4) *in the manufacture of insulin degludec drug substance has changed significantly from earlier campaigns, therefore, data from Supportive Stability batches were not considered for expiry dating.*

Response to Question 6

The primary stability studies were initiated on production scale batches of insulin degludec and the initial stability report presented long-term stability results after 30 months and 18 months of storage in study A and study B respectively. The stability studies document that insulin degludec drug substance is very stable, when stored under long term storage conditions at (b) (4) Stability data from additional sampling points are now available, confirming the conclusion that insulin degludec drug substance is very stable when stored at long-term storage conditions. In stability study A ((VK0SHP001, VK0SHP002, VK0SHP003) data after 36 and 38 months of storage is now available and for study B (XK0SHP014, XK0SHP015, XK0SHP016) data after 24 months of storage are now available. In order to ensure that all parameters are tested at the proposed shelf life of (b) (4) months, an additional timepoint at 38 months has been added to obtain results for Appearance and Bioactivity in study A. In study B, an additional sampling point for Appearance and Bioactivity has been included for the 36 months sampling point, and a new sampling time point at 30 months has also been added.

The stability results have been included in the attached updated document 3.2.S.7.3 Primary Stability Data for Insulin Degludec Drug Substance from Production Scale.

The stability results at (b) (4) documents no significant changes in the stability indicating parameters after storage for up to 38 months, and thus, the data supports the proposed shelf life of (b) (4) months.

Evaluation of Response to Question 6

The response is adequate. The stability study includes the first three consecutive production scale batches of insulin degludec drug substance from campaign 10 (study A). These batches are released for phase 3 clinical trials and are representative for the drug substance batches intended for the market. Acceptable updated stability data for insulin degludec primary stability batches VK0SHP001, VK0SHP002, VK0SHP003 have been provided through 38 months at (b) (4) . As a result, a shelf life of 30 months will be granted for the drug substance when stored at (b) (4) RH or lower temperatures.

Question 7

Provide data showing photostability of the insulin degludec drug substance.

Response to Question 7

In agreement with the ICH Q1B guideline, a forced degradation study has been conducted to evaluate the photo-sensitivity of the insulin degludec drug substance. The study was included in the comprehensive forced degradation study carried out to evaluate the degradation of insulin degludec under extreme conditions and the ability of the analytical methods used in drug

substance and drug product release and stability testing to detect such degradation, see 3.2.S.3.2 Forced Degradation Study of Insulin Degludec. From the study, it was concluded that insulin degludec drug substance is susceptible to degradation if subjected to a combined light intensity of (b) (4) hours. Such degradation would result in changed impurity profiles by the two specification test methods: RPHPLC method A7091a as well as GPC method A7092a. As insulin degludec drug substance is stored frozen at long-term storage conditions (b) (4) and therefore always kept in the dark, it was not considered necessary to perform a confirmatory photo-stability study.

Evaluation of Response to Question 7

The response is adequate. Photostability studies conducted on the drug substance in agreement with ICH Q1B indicate that insulin degludec is susceptible to degradation due to light. However, since the drug substance is stored under long term conditions in the dark, no additional formal confirmatory photo-stability studies need be conducted.

Drug Product

FDA Question 1

Provide information on the following:

a. Levels of soluble di-hexameric forms of insulin degludec present in your drug product.

Response to FDA Question 1a

During formulation development, the association pattern of insulin degludec has been investigated by (b) (4) High Performance Liquid Chromatography ((b) (4) -HPLC) and Analytical (b) (4)). The drug product formulation has been characterized to primarily consist of soluble, non-covalently bound di-hexamers to a level above 95%. In the chromatogram more than 95% of insulin degludec (b) (4) corresponding to the molecular mass of an insulin degludec di-hexamer.

b. The stoichiometry of (b) (4)

(b) (4)

(b) (4)

FDA Question 1c

Data to support the proposed levels of zinc and phenol for the proposed drug products.

Response:

(b) (4)

FDA Question 2

Your CMC section does not contain information on the levels of individual insulin degludec related substances and impurities present in the drug product. ICH Q6B guidance states that if

impurities are known to be introduced or formed during the production and/or storage of the drug product, the levels of these impurities should be determined and acceptance criteria established. Therefore, provide the following:

a. Information on the levels of individual insulin degludec related substances and impurities present in batches used in phase 3 clinical studies and stability studies.

Response to FDA Question 2a

In accordance with the ICH Q6B guideline, the development of the RP-HPLC method A6020a to determine insulin degludec related substances and impurities has focused on the separation of the desired product (insulin degludec) from the different degradation products. The established analytical procedure A6020a has been shown to provide satisfactory selectivity and ability to detect the degradation of insulin degludec even for drug products subjected to extreme conditions (reference is made to 3.2.P.5.5 Biological Activity of Degradation Products in Insulin Degludec/Insulin Aspart Drug Product, where characterization by mass spectrometry of the main peak in method A6020a from the degraded samples showed more than (b) (4)% of the mass signals to comply with the theoretical monoisotopic mass for insulin degludec). A number of molecular variants of insulin degludec are formed during storage of the drug product at accelerated conditions (see 3.2.P.5.5 Characterization of Impurities). They elute well separated from the insulin degludec main peak, but not individually separated from each other, and collective acceptance criteria have therefore been established in accordance with ICH Q6B.

The separation of individual impurities may vary between analytical runs due to column-to-column variations, and integration of the product related substances and impurities in the three groups ((b) (4) impurities, (b) (4) related substances and (b) (4) impurities) therefore ensures the most robust method. At the same time, this approach ensures the most sensitive detection of all degradation products since all area segments eluting within the (b) (4) would be less than the quantification limit. In addition, isomers and isolated degradation products of insulin degludec, representing all the major components of the three groups of insulin degludec related substances and impurities in degraded drug product, have been characterized with regard to biological activity. (b) (4) (see 3.2.S.3.1 Biological Activity of Insulin Degludec).

Based on the above, the use of collective acceptance criteria for insulin degludec related substances and impurities have been justified. Levels of insulin degludec related substances and impurities in drug product batches used in phase 3 clinical studies and stability studies, reported

as [redacted] impurities, [redacted] related substances and [redacted] impurities, have been provided in 3.2.P.5.4 Insulin Degludec/Insulin Aspart 100 U/mL, Batch Analysis and 3.2.P.8.1 Insulin Degludec/Insulin Aspart 100 U/mL, Stability Summary and Conclusion.

b. Explain which impurities are increasing during manufacturing, during long-term, accelerated and in-use stability studies.

Response to FDA Question 2b

For the insulin degludec/insulin aspart drug product and the insulin degludec drug substance used for drug product manufacturing, comparable impurity profiles and levels of insulin degludec related substances and impurities have been documented in 3.2.P.5.5 Characterization of Impurities (see Figure 3 and Table 1 below, for convenience copied from the report).

Table 1 Content of insulin degludec related substances and impurities by RP-HPLC (A6020a) for insulin degludec drug substance and insulin degludec/insulin aspart drug product

Sample	Batch	[redacted] impurities (%)	[redacted] related substances (%)	[redacted] impurities (%)
Insulin degludec/insulin aspart drug product	YQ50522	[redacted]		
Insulin degludec drug substance	YK0SHP006			

It is therefore concluded that no new impurities of insulin degludec were found due to the manufacturing of the insulin degludec/insulin aspart drug product, and the drug product manufacturing process has only a very limited effect on the levels of insulin degludec related substances and impurities.

In the 3.2.P.5.5 Characterization of Impurities report, the impurity profile of insulin degludec/insulin aspart drug product, stored at accelerated conditions (25°C ± 2°C) for 6 months, was compared to the drug product kept at long term conditions (5°C ± 3°C), and the impurity profiles are provided in Figure 4 of the quality amendment dated 03/15/12. From the figure, it is seen that all the related substances and impurities separated by RP-HPLC method A6020a are increasing upon accelerated storage, except the two peaks eluting just after the main peak of insulin degludec. These two peaks are due to the [redacted] insulin degludec, originating from the manufacturing of insulin degludec drug substance as described in 3.2.S.3.2 Overview of Potential Impurities in Drug Substance. Similarly, the potential [redacted] insulin degludec (eluting in the group of [redacted] impurities), the potential [redacted] insulin degludec (eluting in the group of [redacted] related substances), and the potential [redacted] insulin degludec (eluting in the group of [redacted] impurities) would not increase in level during storage as they also originate from the insulin degludec drug substance manufacturing.

All the other insulin degludec related substances and impurities separated from the main peak by RP-HPLC method A6020a are degradation products of insulin degludec and increase in level upon storage at long-term, accelerated, and in-use stability conditions.

c. Based on available data, propose a limit for each of the individual product related substances and impurities present in the product including limits for (b) (4) *insulin degludec) and* (b) (4) *insulin degludec) in the drug product.*

Response to FDA Question 2c

As described in our response to FDA Question 2a above, collective acceptance criteria have been established for insulin degludec related substances and impurities in accordance with ICH Q6B. The (b) (4) insulin degludec have been characterized as insulin degludec related substances, and acceptance criteria for these compounds are covered by the acceptance criteria for (b) (4) related substances.

d. Update your post-approval stability protocol to include limits for individual product related substances and impurities.

Response to FDA Question 2d

As described in our response to FDA Question 2a and 2c above, collective acceptance criteria have been established for insulin degludec related substances and impurities rather than individual limits. Thus, the post-approval stability protocol would remain unchanged from what was submitted in the original NDA.

e. Clarify whether glycerol used in the formulation (b) (4) *of the insulin degludec in your product.*

Response to FDA Question 2e

The insulin degludec drug product formulation includes glycerol as an excipient. Glycerol is an alcohol containing (b) (4) functional groups. The insulin degludec molecule includes (b) (4)

(b) (4)

(b) (4)

This is supported by the experimental data of the degradation products of insulin degludec. None of the observed impurities possess relative molecular mass (M_r) values which could be assigned to the (b) (4) products between glycerol and insulin degludec (b) (4)

(b) (4)

f. Provide intact and reduced mass data for each of the individual impurities separated by the analytical method, A6020a.

Response to FDA Question 2f

The insulin degludec related substances and impurities were comprehensively characterized using a combination of analytical methods including different mass spectrometric procedures. The impurities and related substances in the insulin degludec drug substance originating from the manufacturing process have been characterized as described in 3.2.S.3.2 Overview of Potential Impurities in Drug Substance, and all the major degradation products of insulin degludec have been characterized as described in 3.2.P.5.5 Characterization of Impurities.

Table 2 Potential product related substances and impurities in insulin degludec determined by RP-HPLC

Classification	Identity/Content	Monoisotopic mass M_r		Experimental reduced	
		Theoretical	Experimental	A-chain	B-chain
(b) (4) impurities determined by RP-HPLC	(b) (4)				
(b) (4) related substances determined by RP-HPLC					
(b) (4) impurities determined by RP-HPLC					

* Mass data repor

(b) (4) Not determined

A list of all the potential product related substances and impurities in insulin degludec, separated by the RP-HPLC method A6020a (and the equivalent drug substance specification method A7090a), is provided in Table 2, including the theoretical and experimental determined intact monoisotopic mass of each of the identified components determined using high-resolution MS. The analytical method A6020a uses mobile phases, which are not compatible with on-line MS detection, and therefore, the identification of the different components was primarily based on characterization of fractions isolated by the RP-HPLC method.

Determination of reduced masses for the isolated components in the insulin degludec product related substances and impurities was also included in the characterization for the majority of the components, and the experimentally determined reduced average mass using conventional (b) (4)- MS have been provided in Table 2 for the (b) (4) insulin degludec. The theoretical average mass of insulin degludec (b) (4), respectively.

g. Clarify whether your proposed test method is capable of quantitating individual product-related substances and impurities with adequate specificity, accuracy and precision in the proposed product.

Response to FDA Question 2g

As described in the response to question 2a) above, the drug product specification test method A6020a, which has been established and optimized to determine all insulin degludec related substances and impurities, is not considered capable of providing quantitative information for all components on an individual basis because of a number of (b) (4). By dividing the insulin degludec related substances and impurities into the three groups ((b) (4) impurities, (b) (4) related substances and (b) (4) impurities), a selective, accurate, and precise method has been obtained.

h. Explain your choice of RP HPLC over other applicable methods (e.g., ion exchange chromatography) for the quantitation of charged variants.

Response to FDA Question 2h

The RP-HPLC method A6020a developed to determine the insulin degludec related substances and impurities has focused on separating all changed molecular variants from the main peak of insulin degludec. By general experience with insulin products, RP-HPLC is a more selective principle in liquid chromatography when compared to ion exchange chromatography. By proper

selection of the chromatographic conditions, charged variants of the parent substance may also be separated by RP-HPLC. This is the case for RP-HPLC method A6020a, where all the charged variants of insulin degludec are well separated from insulin degludec. The superiority of the selected RP-HPLC method over ion exchange chromatography in detecting product related impurities has been demonstrated in the comparability studies for different campaigns of insulin degludec drug substance (see 3.2.S.2.6 Demonstration of Comparability of Drug Substance Manufactured from Campaign 1 to Campaign 12).

Overall evaluation of the Applicant's response to questions 2a-h: Adequate.

a. *The Applicant's response indicated that some of the peaks corresponding to insulin degludec related substances and impurities elute closely or co-elute partly in the chromatogram. The Applicant has explained that the proposed analytical method (A6020a) is not capable of providing quantitative information on individual insulin degludec related substances and impurities. Therefore, the requested information on the levels of individual drug substance related substances and impurities in batches used in phase 3 clinical studies and stability studies was not available for review.*
b. *For the above reason, the Applicant has grouped the impurities that elute in the RP-HPLC chromatogram into three groups ((b) (4) impurities, (b) (4) related substances and (b) (4) impurities) and established collective acceptance criteria for each group. Considering the complexity of the product, the proposed approach is acceptable and ensures the detection of all degradation products below the proposed limit. This is further supported by the 18-24 months stability data available for primary stability batches. The stability data indicated that the product maintained a purity > (b) (4)% with respect to insulin degludec related substances and impurities during 18-24 months of real-time storage conditions.*
c. *The Applicant has characterized the identity of insulin degludec related substances and impurities formed during storage at long-term, accelerated, and in-use stability conditions (see Table 2, above). Due to method limitation, quantitative information on individual impurities is not available for review. Information provided within the CMC section indicated that (b) (4) insulin degludec) and (b) (4) insulin degludec) are the major impurities among them. The Applicant has also indicated that the levels of the following drug substance related substances do not increase during drug product storage:*
    a) *(b) (4) of insulin degludec (eluting in the group of (b) (4) impurities),*
    b) *(b) (4) insulin degludec (eluting in the group of (b) (4) related substances),*
    c) *(b) (4) insulin degludec (eluting in the group of (b) (4) impurities).*
d. *The Applicant's explanation that formation of (b) (4) (b) (4) insulin degludec under*

neutral pH conditions is acceptable. If formed, this impurity could be identified during characterization studies by its unique mass.

e. *The Applicant has provided satisfactory mass spec data information (intact and reduced mass data) for each of the individual impurities separated by the analytical method, A6020a (Table 2). In addition, the applicant has characterized the biological activity of isomers and isolated degradation products of insulin degludec.*

f. *The Applicant's explanation for the choice of RP-HPLC over other applicable methods (e.g., ion exchange chromatography) to analyze charged variants is acceptable. In addition, the Applicant has used the same RP-HPLC method to demonstrate the comparability of various batches of drug substance manufactured during campaign runs.*

FDA Question 3

Considering the expected purity of your drug product is ≥ (b) (4)%, the combined limits for (b) (4) related substances, (b) (4) impurities and % HMWP would exceed the (b) (4)% total impurity level. Therefore, revise your proposed limit for (b) (4) related substances, (b) (4) impurities and % HMWP to meet the purity expectations.

Novo Nordisk Response:

In the proposed specifications for the insulin degludec drug products, the acceptance criteria for content of insulin degludec are (b) (4)% of label claim. The acceptance criteria for content of insulin degludec cannot be directly compared to the acceptance criteria for insulin degludec related substances and impurities and for HMWP, since quality attributes related to quantity and purity are controlled by three different methods:

- Determination of the insulin degludec related substances and impurities by RP-HPLC method A6020a
- Determination of the identity and content of insulin degludec by RP-HPLC method A6021a
- Determination of HMWP by GPC method A6022a

The methods and the acceptance criteria in the specifications are further explained below:

RP-HPLC method A6020a: This method determines the relative distribution of the insulin degludec and the insulin degludec related substances and impurities (divided into three groups: (b) (4) impurities, (b) (4) related substances and (b) (4) impurities). From the acceptance criteria proposed in the specifications for each of the three groups, a total level (relative amount) of insulin degludec related substances and impurities of ≤ (b) (4)% at release and ≤ (b) (4)% at end of shelf life may be calculated. The major part of the molecular variants of insulin degludec separated by RP-HPLC method A6020a and included in the limits described above have been characterized to possess full or high relative bioactivity compared to insulin degludec (reference is made to 3.2.S.3.1 Biological Activity of Insulin Degludec).

RP-HPLC method A6021a: The analytical method determines the combined content ([(b) (4)] of insulin degludec and molecular variants of insulin degludec (impurities and related substances), which elute together in one main peak of insulin degludec. As documented in 3.2.S.3.1 Biological Activity of Insulin Degludec, [(b) (4)] degraded samples. It has therefore been concluded that the RP- HPLC method for the determination of the [(b) (4)] content offers a reliable indication of the biological activity of insulin degludec in the drug product. The acceptance criteria in the specifications ensure that the content of insulin degludec in the drug product is consistently within [(b) (4)]% of label claim throughout the shelf-life of the product.

GPC method A6022a: This method determines the total relative amount of high molecular weight proteins (HMWP) in the drug product. As described in 3.2.P.5.5 Characterization of Impurities, the HMWP has been characterized to consist of [(b) (4)] insulin degludec/insulin degludec [(b) (4)]. The insulin degludec [(b) (4)] will also be determined as part of the [(b) (4)] impurities in RP-HPLC method A6020a, as they will elute in the gradient part of the method. The acceptance criteria in the specifications have been set to ensure a total level (relative amount) of HMWP of ≤[(b) (4)]% at release and ≤ [(b) (4)]% at end of shelf life.

Based on the above, the combined control strategy and the acceptance criteria in the proposed insulin degludec drug product specifications are considered justified.

Overall evaluation of the applicant's response: Adequate.
The Applicant has proposed an acceptance criterion of [(b) (4)]% of the label claim for the [(b) (4)] content (quantitated as insulin degludec + related substances and impurities or as insulin aspart + related substances and impurities) during its shelf-life, which is acceptable. The Applicant has also committed to control the purity content of the product by RP-HPLC with an acceptance criteria of NMT [(b) (4)]% for insulin degludec related substances and impurities during its shelf-life. The available real-time stability data for primary batches indicated that purity of these batches was > [(b) (4)]% with respect to aspart related substances and impurities (See below, data reproduced from section 3.2.P.8) during a real-time storage period of 18-24 months. In light of the Applicant's limited stability experience with the product, the proposed acceptance criteria for individual and total insulin degludec related substances and impurities are acceptable.

Parameter	Proposed specification	Batch information	Batch no.	Storage time (Months) 0	3	6	9	12	18	24	30
Purity of insulin degludec (%)	Not applicable	Primary batches (study 1)C	XCQ0004	[(b) (4)]							NA
			XCQ0005								NA

			XCQ0006	(b) (4)	N A
		Primary batches (study 2) C	XCQ0038		N A
			XCQ0039		N A
			XCQ0040		N A

FDA Question 4

Your proposal to have wider shelf-life specification for insulin degludec related substances and impurities is not supported by the observed stability profile of your primary stability batches (i.e., very little degradation is seen under real-time storage conditions). Revise your shelf-life specification to current release specification level or justify the same.

Novo Nordisk Response:

Summary of approach for shelf-life specification limits for insulin degludec related substances and impurities

Novo Nordisk would like to clarify that the proposed shelf-life limits for HMWP, insulin degludec related substances and impurities have been based, not only on the stability profile of the primary stability batches, but on all available stability data, from pilot to full production scale batches (i.e. (b) (4) batch scale for insulin degludec 100 U/ml and 100, (b) (4) batch scale for insulin degludec 200 U/ml). By including all available stability results for the different batch scales into the calculation of the specification limits, the calculation of the limits becomes more robust. With this comprehensive approach, more reliable information on batch to batch variation, uncertainty of the expected stability trend, and the intermediate precision are built into the specification limits for the insulin degludec related substances and impurities.

The calculation of shelf-life specification limits based only on primary stability batches will differ from what has currently been presented in 3.2.P.5.6 Insulin Degludec 100 U/ml, Justification of Specifications and 3.2.P.5.6 Insulin Degludec 200 U/ml, Justification of Specifications due to the following factors:

The drug substance batches used for the production of the primary stability batches contained impurity levels below their specification limit. While the impurity level observed for these batches are representative for most drug substances batches, the drug product production must allow for use of drug substance batches released at the upper limit for individual impurities. Handling, which consists of activities related to inspection, assembly in pen-injector, packaging, labeling, storage, and transport of the product from production site to users, has been at a minimum in the stability programs. Stability samples are transferred directly from the production facilities into the relevant stability chambers, therefore minimizing the handling time and the

temporary exposure to temperatures outside the recommended storage conditions. The degradation which is typically expected during handling is therefore not reflected in the observed stability results.

Therefore, since the starting level for impurities in the drug product will sometimes be higher than has been the case in the reported stability programs, the contribution for release limit for drug substance should be set at the upper limit for individual impurities. Similarly, in order to compensate for the degradation related to handling, a handling contribution must be included in the specification limits.

The calculations of the specification limits as reported in 3.2.P.5.6 are based on the above described contributions.

Revision of shelf life specification limits

Following the FDA request of revision of the shelf life limits, the calculation of the shelf life specification has been updated based on the above described principles and on currently available stability data. An overview of the batches included in the calculation of the updated specification and the latest available time point for insulin degludec 100 U/ml and insulin degludec 200 U/ml is given in Table 10 and Table 11.

Table 10 Batches used for calculation of the specification limits – Insulin degludec 100 U/ml

Drug product batch no.	Drug substance batch used	Batch size	Use of batch	Latest time point available for calculation of specification limits
ACQ0020	YK0SHP007	(b) (4)	Process challenge	6 months at 5°C
ACQ0019	YK0SHP006		Process challenge	6 months at 5°C
YQ50518	YK0SHP008		Process validation	12 months at 5°C
YQ50517	YK0SHP007		Process validation	12 months at 5°C
YQ50516	YK0SHP006		Process validation	12 months at 5°C
YCQ0012	VK0SHP004		Process challenge	18 months at 5°C
XCQ0049	XK0SHP003		Phase 3 clinical trials	18 months at 5°C
XCQ0044	XK0SHP015		Phase 3 clinical trials	24 months at 5°C
XCQ0037	XK0SHP014		Phase 3 clinical trials	24 months at 5°C
XCQ0036	XK0SHP020		Phase 3 clinical trials	24 months at 5°C
XCQ0010	XK0SHP003		Phase 3 clinical trials	24 months at 5°C
XCQ0009	VK0SHP007		Phase 3 clinical trials	12 months at 5°C
XCQ0008	VK0SHP007		Phase 3 clinical trials	12 months at 5°C
XCQ0003	VK0SHP003		Phase 3 clinical trials	12 months at 5°C
XCQ0002	VK0SHP003		Phase 3 clinical trials	12 months at 5°C
XCQ0001	VK0SHP001		Phase 3 clinical trials	30 months at 5°C
VCQ0015	VK0SHP003		Phase 3 clinical trials	30 months at 5°C
VCQ0014	VK0SHP002		Phase 3 clinical trials	30 months at 5°C
VCQ0013	VK0SHP001		Phase 3 clinical trials	15 months at 5°C
TQ50434	LP454K4S07		Phase 2 clinical trials	30 months at 5°C

Table 11 Batches used for calculation of the specification limits – Insulin degludec 200 U/ml

Drug product batch no.	Drug substance batch used	Batch size	Use of batch	Latest time point available for calculation of specification limits
AW50398	XK0SHP009 XK0SHP012	(b) (4)	Process challenge	3 months at 5°C
AW50395	XK0SHP006 XK0SHP013		Process challenge	3 months at 5°C
ACQ0021	YK0SHP009		Stability	6 months at 5°C
YQ50521	YK0SHP008		Process validation	12 months at 5°C
YQ50520	YK0SHP007		Process validation	12 months at 5°C
YQ50519	YK0SHP006		Process validation	9 months at 5°C
YCQ0014	XK0SHP004		Process challenge	18 months 5°C
YCQ0007	XK0SHP002		Phase 3 clinical trials	18 months at 5°C
XCQ0043	XK0SHP015		Phase 3 clinical trials	18 months at 5°C
XCQ0042	XK0SHP014		Phase 3 clinical trials	24 months at 5°C
XCQ0041	XK0SHP020		Phase 3 clinical trials	24 months at 5°C
XCQ0019	VK0SHP007		Phase 3 clinical trials	12 months at 5°C
XCQ0018	VK0SHP002		Phase 3 clinical trials	24 months at 5°C
XCQ0017	VK0SHP003		Phase 3 clinical trials	24 months at 5°C
XCQ0016	VK0SHP001		Phase 3 clinical trials	24 months at 5°C
XCQ0014	VK0SHP007		Phase 3 clinical trials	12 months at 5°C

Based on the recalculations, the impurity contribution during storage at 5°C has been decreased for (b) (4) related substances and (b) (4) impurities, while HMWP and (b) (4) impurities remains unchanged.

Therefore, Novo Nordisk proposes a minor revision of the shelf life limits for insulin degludec impurities and related substances as given in Table 12. The revised proposed shelf life specification are present in the updated 3.2.5.P.1 Insulin Degludec 100 U/ml Specifications and 3.2.P.5.1 Insulin Degludec 200 U/ml Specifications and justified in 3.2.P.5.6 Insulin Degludec 100 U/ml, Justification of Specification and 3.2.P.5.6 Insulin Degludec 200 U/ml, Justification of Specification.

Table 12 Previously proposed limits and revised proposed limits for impurities and related substances for insulin degludec 100 U/ml and insulin degludec 200 U/ml

Parameter	Proposed limits in the NDA	Revised proposed limits
HMWP, (%)	Release limit: (b) (4) Shelf life limi	Release limit: (b) (4) Shelf life limi
(b) (4) mpurities, (%)	Release limit: Shelf life limi	Release limit: Shelf life limi
(b) (4) related substances, (%)	Release limit: Shelf life limi	Release limit: Shelf life limi
(b) (4) impurities, (%)	Release limit: Shelf life limi	Release limit: Shelf life limi

A detailed description of the revision of the specification is given below:

Principle for calculation of the specification limits

The proposed shelf life limits for HMWP and insulin degludec impurities and related substances include the following contributions:

- Release limit for insulin degludec drug substance
- Contribution from drug product manufacturing process

- Contribution from handling (inspection, assembling, packaging, and distribution)
- Predicted change during 30 months at 5°C

For an illustration of the different contributions, a representative example using (b) (4) related substances is displayed in Figure 6.

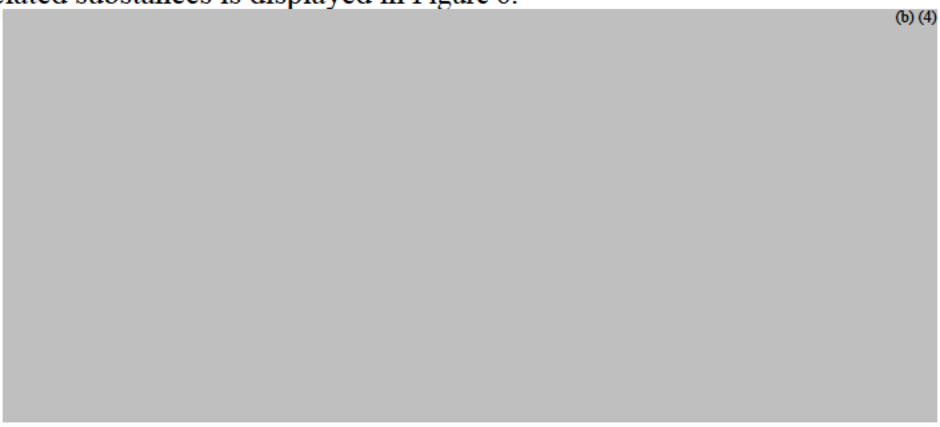


Figure 6 Contribution for calculation of the drug product specification limits – (b) (4) related substances

A detailed evaluation of each contribution is reported in the following.

Specification limit for drug substance

The limits proposed in the NDA are given in Table 13.

Table 13 Proposed limits for insulin degludec drug substance

Parameter	Proposed limits in the NDA
HMWP, (%)	(b) (4)
(b) (4) impurities, (%)	
related substances, (%)	
impurities, (%)	

Contribution from drug product manufacturing process

Release data for all batches produced from pilot to commercial scale ((b) (4) for insulin degludec 100 U/ml and 100 to (b) (4) for insulin degludec 200 U/ml) have been used for recalculation of the contribution from the manufacturing process. The contribution from the manufacturing process for HMWP, insulin degludec impurities and related substances is given in Table 14.

Table 14 Contribution from the manufacturing process

Parameter	Contribution from the manufacturing process
HMWP, (%)	(b) (4)
(b) (4) impurities, (%)	
related substances, (%)	
impurities, (%)	

Recalculation has confirmed the previously proposed manufacturing contribution for HMWP and insulin degludec impurities and related substances.

Contribution from handling

Some excursions outside the recommended storage conditions must be allowed for the finished product. Before reaching the patient, the drug product is exposed to the following handling activities:

- Inspection of the finished product
- Assembly in pen-injector, labeling and packaging of the product
- Transport of the product from the production site to the users

As a consequence of these activities, the level of HMWP and insulin degludec impurities and related substances will increase. Any batch that has been exposed to these activities should be able to meet the release specification limits due to the following reasons:

- Patients will receive product exposed to handling
- Reanalysis for local release of product after shipment

In order to compensate for degradation related to the handling activities, the handling contribution has been estimated and included in the calculation of the release limits. The handling contribution is not reflected in the stability trend of the primary stability batches since all stability batches are placed in stability chambers immediately after inspection without having been through the full time/temperature exposure due to handling.

The handling contribution calculated by the Arrhenius equation is given in Table 15. Recalculation has confirmed the previously proposed handling contribution for impurities and related substances.

Contribution for 30 months storage at 5°C

The recalculation of the expected change during 30 months at 5°C has been based on the current available stability data (see Table 10 and Table 11). The following elements are consideration when estimating the change during shelf life storage:

- The expected degradation during 30 months storage at 5°C
- The uncertainty of the expected change
- The intermediate precision, which allow for random variation in the determination of the release value.

The updated calculation of the change during 30 months storage at 5°C is given in Table 16

Table 16 Calculated contribution during 30 months storage at 5°C

Parameter	Contribution in the NDA	Revised contribution
HMWP, (%)		(b) (4)
(b) (4) impurities, (%)		
(b) (4) related substances, (%)		
(b) (4) impurities, (%)		

Recalculation based on updated stability data has confirmed the previously proposed storage contribution for HMWP and (b) (4) impurities.

For (b) (4) related substances, an additional contribution of (b) (4)% was added to the estimated change at the time of NDA submission. As more stability data from upscale batches have become available, the additional contribution of (b) (4)% can be omitted from the recalculation of the shelf life limits. The contribution for (b) (4) impurities has been lowered by (b) (4)%.

New proposed shelf life specification limits for insulin degludec impurities and related substances

Based on the recalculation and considerations for each step, revised shelf life specification limits are proposed for insulin degludec impurities and related substances in Table 17. The shelf life limits have been narrowed for (b) (4) related substances and (b) (4) impurities.

Table 17 New proposed release and shelf life limits for insulin degludec 100 U/ml and insulin degludec 200 U/ml

Parameter	Specification limit of DS	Contribution from drug product	Contribution from handling	Release limit	Predicted degradation during 30	Proposed shelf life limits
HMWP, (%)	(b) (4)					
(b) (4) impurities, (%)						
(b) (4) related						
(b) (4) impurities, (%)						

Evaluation: Acceptable.

The Firm's proposal to tighten the shelf-life limits for (b) (4) related substances and (b) (4) impurities is acceptable, which is consistent with FDA request.

Table 12 Previously proposed limits and revised proposed limits for impurities and related substances for insulin degludec 100 U/ml and insulin degludec 200 U/ml

Parameter	Proposed limits in the NDA	Revised proposed limits
HMWP, (%)	Release limit: (b) (4) Shelf life limi	Release limit: (b) (4) Shelf life limi
(b) (4) mpurities, (%)	Release limit: Shelf life limi	Release limit: Shelf life limi
related substances, (%)	Release limit: Shelf life limi	Release limit: Shelf life lim
mpurities, (%)	Release limit: Shelf life limi	Release limit: Shelf life limi

In addition, the Applicant has updated the above information for insulin degludec 100 U/mL and 200 U/mL drug products under Section 3.2.P.5.1.

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
05/25/2012

ALI H AL HAKIM
05/25/2012

MUTHUKUMAR RAMASWAMY
05/25/2012

NDA 203314

Tresiba™
(Insulin Degludec [rDNA Origin] Injection)

Novo Nordisk Inc.

Joseph Leginus, PhD (Drug Substance Reviewer)
Muthukumar Ramaswamy, PhD (Drug Product Reviewer)

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 203314

2. REVIEW #: 1

3. REVIEW DATE: 8-Feb-2012

4. REVIEWERS: Joseph Leginus, PhD and Muthukumar Ramaswamy, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA	29-Sept-2011
Amendment	22-Dec-2011

7. NAME & ADDRESS OF APPLICANT:

Name:	Novo Nordisk Inc.
Address:	100 College Road West, Princeton, NJ 08540
Representative:	Anne Phillips, MD, Corporate Vice President, CMR
Telephone:	609-786-4306

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Tresiba™
b) Non-Proprietary Name (USAN): Insulin Degludec
c) Code Name/# (ONDC only): NNC (b) (4), Insulin 454
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: Standard

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

Chemistry Review Data Sheet

10. PHARMACOL. CATEGORY:
Glycemic control in adults with diabetes mellitus

11. DOSAGE FORM: Solution for injection

12. STRENGTH/POTENCY: a) 100 U/mL, and b) 200 U/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
_____ Not a SPOTS product

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

Chemical Name (WHO): $N^{6, B29}$-[N^{2}-(15-carboxypentadecanoyl)-L-γ-glutamyl]-des-B30-L-threonine-insulin human
USAN: Insulin degludec
Chemical Structure:

Molecular Formula: $C_{274}H_{411}N_{65}O_{81}S_6$
Molecular Weight: (b) (4) Da – monoisotopic; 6,103.97 Da - average

17. RELATED/SUPPORTING DOCUMENTS:

Chemistry Review Data Sheet

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	V	Novo Nordisk, Inc.	(b) (4)	1	Adequate	Reviewed by B. Riley 3/13/2009	Letter of Authorization 5/11/2011
	III		(b) (4)	1	Adequate	Reviewed by O. Stephens 9/6/2011	Letter of Authorization 11/23/2010
	III			1	Adequate	Reviewed by O. Stephens 8/24/2011	Letter of Authorization 11/23/2010

[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	76,496	Insulin degludec (rDNA origin) Injection
IND	73,198	Insulin degludec/Insulin aspart (rDNA origin) Injection
NDA	203313	Insulin degludec/Insulin aspart (rDNA origin) Injection

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending. EER was sent to Office of Compliance on 13-Oct-2011.		
Biopharm	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 is pending.	TBD	Jackie Ryan/Quynhnhu Nguyen
EA	Completed	8-Feb-2012	Joseph Leginus
Microbiology	Review of 1) microbiology controls proposed for the drug substance and drug product, and 2) sterilization (b) (4) processing validation for the drug product is pending.	TBD	Vinayak Pawar

The Chemistry Review for NDA 203314

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The recommendation from a CMC perspective is pending satisfactory responses to the deficiencies identified in Review #1. At this time, the Office of Compliance has not issued acceptable cGMP recommendations for the three manufacturing and testing facilities. An Overall Compliance recommendation is pending as of 8-Feb-2012.

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

Not applicable

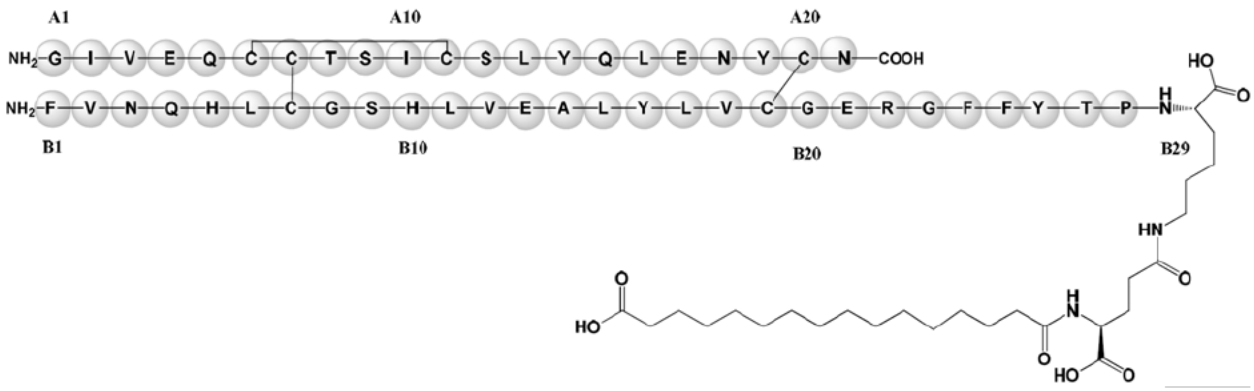
II. Summary of Chemistry Assessments

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

Note: Review of NDA 203314 was conducted as a Team Review with Joseph Leginus reviewing the Drug Substance and Muthukumar Ramaswamy reviewing the Drug Product.

DRUG SUBSTANCE

Tresiba™ (Insulin Degludec [rDNA Origin] Injection) contains a single drug substance, insulin degludec, an analog of human insulin. Insulin degludec is produced using recombinant DNA technology and chemical modification. The (b) (4) of insulin degludec (desB30-insulin), produced by a process that includes expression of recombinant DNA in yeast (*Saccharomyces cerevisiae*) differs from human insulin by the omission of threonine in position B30. Insulin degludec is made by chemically attaching a C-16 fatty acid (hexadecanedioic acid) with a glutamic acid spacer on the lysine (b) (4) at position B29 of the insulin precursor. The chemical name of insulin degludec is (b) (4) -human insulin, and its structure is presented below:



The molecular formula of insulin degludec is $C_{274}H_{411}N_{65}O_{81}S_6$ with a molecular weight of (b) (4).

Insulin degludec is characterized as a [redacted]. It is freely soluble in water [redacted] Insulin degludec is slightly soluble in methanol [redacted]) and practically insoluble in ethanol ([redacted] mg/mL). The isoelectric point of insulin degludec is approximately [redacted]. The pH of [redacted] aqueous solution of drug substance is approximately 7.4.

The structure of insulin degludec was elucidated by a variety of analytical and spectrophotometric techniques, including [redacted], mass spectrometry ([redacted] MS), [redacted], ultraviolet (UV) and [redacted]

Insulin degludec is produced by recombinant DNA technology from yeast (*Saccharomyces cerevisiae)* and chemical modification. The manufacturing process is a [redacted]

The proposed release specifications include appearance, identification ([redacted] and HPLC), content (HPLC), bioactivity (cell-based assay), individual [redacted] related impurities (HPLC), loss on drying and bacterial endotoxin. The proposed regulatory methods have been validated. Reference standards for the API have been developed and characterized.

Product related impurities structurally related to insulin degludec generated during the [redacted] drug substance have classified based on their RP-HPLC elution position relative to the drug substance. These have been characterized as "[redacted] impurities", "[redacted] related substances", "[redacted] impurities" and "high molecular weight proteins." Process derived impurities originating from the insulin degludec manufacturing process were not detected in the drug substance.

A shelf life of 30 months will be granted for the drug substance when stored at [redacted]. This is based on acceptable long-term stability results from real-time studies obtained for the drug substance from Primary Stability batches at production scale.

DRUG PRODUCT:

The drug product, Tresiba™ (Insulin Degludec [rDNA Origin] Injection) is a sterile, aqueous, clear, colorless solution that contains insulin degludec 100 Units/mL (U-100) or 200 Units/mL (U-200). The proposed product is a long-acting basal insulin formulation intended for once daily use by subcutaneous administration.

The 100 Units/mL presentation contains 600 nmol of insulin degludec, 19.6 mg glycerol [redacted], 1.50 mg phenol [redacted] 1.72 mg metacresol [redacted], 32.7 µg zinc [redacted] and water for injection. The 200 Units/mL presentation contains 1200 nmol of insulin degludec, 19.6 mg glycerol, 1.50 mg phenol, 1.72 mg metacresol, 71.9 µg zinc and water for injection. Hydrochloric acid or sodium hydroxide is added to adjust pH. The pH of the proposed product is approximately 7.6.

During Phase 1 and 2 studies, the Applicant has screened several insulin formulations containing 600-1200 nmol/mL of insulin degludec and excipients such as phenol/metacresol, glycerol, zinc, [redacted] for action profile and stability. Based on developmental data, the Applicant has chosen the proposed final formulation containing phenol/metacresol, glycerol, zinc for Phase 3 clinical studies. The key difference between the two strength products is in their [redacted] content. The NDA states that the formulation was optimized to ensure dihexameric form of insulin degludec in the

proposed product. A concentration of [redacted] were chosen with respect to [redacted] of the insulin degludec 100 and 200 U/mL injection. The Applicant is proposing to use monograph grade excipients in the final formulation and is acceptable.

The Applicant is proposing to market the 100 U/mL strength product as [redacted] pre-filled pen (cartridge pre-assembled in a PDS290 pen-injector). The 200 U/mL strength product will be available only as a prefilled pen (cartridge pre-assembled in a PDS290 pen-injector). The finished product will be marketed as 5 x 3 mL [redacted] packaged in cartons or as 5 x 3 mL prefilled pens in cartons. The proposed product is light sensitive and therefore [redacted] packaging is critical to assure the stability of the product.

The drug products, insulin degludec 100 and 200 U/mL are manufactured by [redacted]

During development, the Applicant has defined Quality Target Product Profile (QTPP) and critical quality attributes. The proposed critical quality attributes (CQAs) for the drug product include content of each active, extractable volume, plunger friction (for measuring device performance), purity factors (individual impurities related to each active ingredients), high molecular weight proteins, product identity, [redacted] content, closure integrity (sterility), [redacted] efficacy, endotoxin levels, appearance (particulate load), and other physical tests such pH and isotonicity.

The Applicant has defined [redacted] as the critical quality attribute that [redacted] in the proposed product.

The Applicant also used design of experiments and risk assessment techniques to define critical process parameters. The Applicant's developmental work and process evaluation studies were targeted to ensuring the proposed process parameters are adequate to ensure complete dissolution of excipients and active ingredient. Developmental stability on in-process solutions and bulk formulation assured whether the proposed pH ranges for these solutions are adequate with respect chemical and physical attributes.

The NDA contains batch formula and a description of the proposed commercial process. Together with the information provided in the master batch record, the available information in the NDA is adequate to support the proposed commercial process. The NDA contains in-process control information for the manufacturing and filling of the proposed products (100 U/mL and 200 U/mL insulin degludec solution for injection). The proposed critical process parameters include [redacted]

The Applicant has provided batch analysis data from development through commercial scale to support the manufacturability of the proposed products. *With the exception of limits on individual product related substances and impurities*, the NDA contains adequate information on the release specification used for controlling for quality of the drug product. The Applicant has proposed general tests typically expected

for a parenteral product, and product-specific tests. The proposed general tests include pH, endotoxin limit, sterility, and particulate matter. The product-specific tests include identity, insulin content, zinc content, product related impurities (high molecular weight proteins, (b) (4) impurities, (b) (4) product related substances and (b) (4) impurities) (b) (4) content. In addition, the applicant is proposing to monitor the dose accuracy of the product filled in the delivery device. The Applicant is also performing in-process control tests such as closure integrity, the extractable volume test, and air content requirement (b) (4). The acceptance criteria, where applicable, are similar to those for approved insulin and other insulin analogs, and is consistent with parenteral regulatory requirements.

With the exception of reporting limits for individual product related substances and impurities, the test methods proposed for the product are adequately described and are validated per applicable ICH guidelines. The Applicant should explain the validity of the method to quantitate insulin degludec related substances and impurities.

The Applicant is proposing a separate release and shelf-life specification (i.e., wider than the release specification) for controlling and monitoring the quality of the drug product. *The request for wider shelf-life specifications for the product related substances and impurities is not appropriately supported by the observed degradation profile for product related substances and impurities in primary stability batches. We recommend that the Applicant propose a common release and shelf-life specification for the drug product.*

The applicant has provided 24-30 month real time and 6 month accelerated stability data for several batches of the drug product (100 and 200 U/mL) manufactured at (b) (4) scale. This Application also contains limited stability information for product manufactured at commercial scale ((b) (4) scale). In addition, this section also contains in-use stability and photo stability data for the proposed product packaged in (b) (4) packaging configuration. The stability studies were performed on the drug product packaged (b) (4). Since the drug product is only in contact with the (b) (4) cartridge, the stability data of the drug product in the cartridge (in darkness) are considered to be representative for the stability of the drug product in the PDS290 pen-injector.

- *Based on the long term and accelerated stability data evaluated in this document, a shelf life of 30 months at (b) (4) is recommended for insulin degludec 100 and 200U/mL.*
- *Based on the in-use stability data evaluated in this document, an in-use period of 56 days at up to 30°C is recommended for insulin degludec 100 and 200U/mL.*
- *Photo stability data show that the (b) (4) packaging (the PDS290 pen-injector (b) (4) and carton) provides adequate protection against light.*

The NDA contains post-approval stability protocol and commitment to place 3 full scale batches on stability and continue to update information on existing stability studies. The Applicant should update their stability protocol and post-approval stability protocol to include limits for individual product related substances and impurities.

Deficiencies identified during the review of the drug product section are summarized at the end of the Chemistry Review.

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

Tresiba™ (Insulin Degludec [rDNA Origin] Injection) is indicated for the treatment of patients with diabetes mellitus (b) (4) It is intended for once-daily use at any time of day by

subcutaneous injection into the abdominal wall, thigh, or upper arm. The drug product should not be administered intravenously or intramuscularly or with insulin infusion pumps or mixed with any other insulin solutions. Tresiba should be inspected visually prior to administration and should only be used if the solution appears clear and colorless.

Drug product delivery system and appropriate storage are adequately described in both package insert and patient package insert. Drug product shelf-life is 30 months at 2°C - 8°C, protected from light. In-use shelf-life period is 56 days at temperatures not exceeding 30°C

C. Basis for Approvability or Not-Approval Recommendation

The recommendation from a CMC perspective is pending satisfactory responses to the deficiencies identified in Review #1 and acceptable recommendation for manufacturing facilities associated with this application. At this time, Office of Compliance has not issued acceptable cGMP recommendations for the three manufacturing and testing facilities. An Overall Compliance recommendation is pending as of 8-Feb-2012.

This is a 505(b)(1) application where the drug substance, insulin degludec, is a New Molecular Entity (NME). The IND for insulin degludec (76,496) was received on 9/5/2007. An EOP2 meeting was held on 2/24/2009. A pre-NDA meeting was held on 6/17/2011.

The drug substance (insulin degludec) will be manufactured for commercial use by Novo Nordisk A/S located in Bagsvaerd Denmark (b) (4)) and Kalundborg Denmark (b) (4)).

The finished product is manufactured in their sterile product manufacturing facility (building (b) (4)) located at Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd.

The finished product is at Brennum Park, DC3400, Hille Roed, Denmark.

III. Administrative

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

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

A APPENDICES

A.1 Facilities and Equipment

The applicant has submitted full and adequate floor diagrams, descriptions of the areas and procedures used in the a) (b) (4) drug product. Descriptions of the area classifications, segregation of operations and intermediate products and equipment design were also provided. Relevant information pertaining to finished product manufacturing is reproduced below:

The finished product is manufactured in their sterile product manufacturing facility (building (b) (4)) located at Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd. A description of the manufacturing areas of building (b) (4) and lists the equipment with direct product-contact. The document also describes the contamination precautions taken in the classified areas of the facility.

Description of the manufacturing flow: The drug substances are (b) (4)

(b) (4)

EES Report

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 203314/000	**Sponsor:**	NOVO NORDISK INC
Org. Code:	510		100 COLLEGE RD WEST
Priority:	1		PRINCETON, NJ 08540
Stamp Date:	29-SEP-2011	**Brand Name:**	insulin degludec (rDNA origin) Injection
PDUFA Date:	29-JUL-2012	**Estab. Name:**	insulin degludec (rDNA origin) Injection
Action Goal:		**Generic Name:**	
District Goal:	30-MAY-2012	**Product Number; Dosage Form; Ingredient; Strengths**	001; SOLUTION, INJECTION; INSULIN DEGLUDEC; 100UNT 002; SOLUTION, INJECTION; INSULIN DEGLUDEC; 200UNT

FDA Contacts:	K. SHARMA	Project Manager	
	M. RAMASWAMY	Review Chemist	301-796-2430
	S. TRAN	Team Leader	301-796-1764

Overall Recommendation:	PENDING	on 24-JAN-2012	by EES_PROD
	PENDING	on 13-OCT-2011	by EES_PROD
	PENDING	on 13-OCT-2011	by EES_PROD

Establishment:	**CFN:** 9610699	**FEI:** 3002807751			
	NOVO NORDISK A/S HALLAS ALLE KALUNDBORG, , DENMARK				
DMF No:			**AADA:**		
Responsibilities:	DRUG SUBSTANCE MANUFACTURER FINISHED DOSAGE LABELER FINISHED DOSAGE PACKAGER				
Profile:	(b) (4)		**OAI Status:**	NONE	
Last Milestone:	OC RECOMMENDATION				
Milestone Date:	24-JAN-2012				
Decision:	ACCEPTABLE				
Reason:	BASED ON PROFILE				
Profile:	(b) (4)		**OAI Status:**	NONE	
Last Milestone:	ASSIGNED INSPECTION TO IB				
Milestone Date:	14-OCT-2011				

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	CFN: 9613244 FEI: 3002807752 NOVO NORDISK A/S BERNNUM PARK, DK-3400 HILLEROED, , DENMARK		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE LABELER FINISHED DOSAGE PACKAGER FINISHED DOSAGE STABILITY TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	ASSIGNED INSPECTION TO IB		
Milestone Date:	23-OCT-2011		
Profile:	(b) (4)	**OAI Status:**	NONE
Last Milestone:	ASSIGNED INSPECTION TO IB		
Milestone Date:	23-OCT-2011		

Establishment:	CFN: 9616213 FEI: 3000151819 NOVO NORDISK A/S NOVO ALLE BAGSVAERD, , DENMARK		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER FINISHED DOSAGE MANUFACTURER		
Profile:	(b) (4)	**OAI Status:**	NONE
Last Milestone:	SUBMITTED TO OC		
Milestone Date:	24-JAN-2012		
Profile:	(b) (4)	**OAI Status:**	NONE
Last Milestone:	ASSIGNED INSPECTION TO IB		
Milestone Date:	14-OCT-2011		

A.2 Adventitious Agents Safety Evaluation

The Applicant has evaluated the Virus and (b) (4) safety evaluation for drug substances insulin degludec and the manufacturing process and formulation of insulin degludec 100 or 200 U/mL drug products, which does not include any (b) (4). The overall conclusion of this safety evaluation is therefore that insulin degludec drug product is safe with regard to both virus and (b) (4) agents.

R REGIONAL INFORMATION

R1 Executed Batch Records

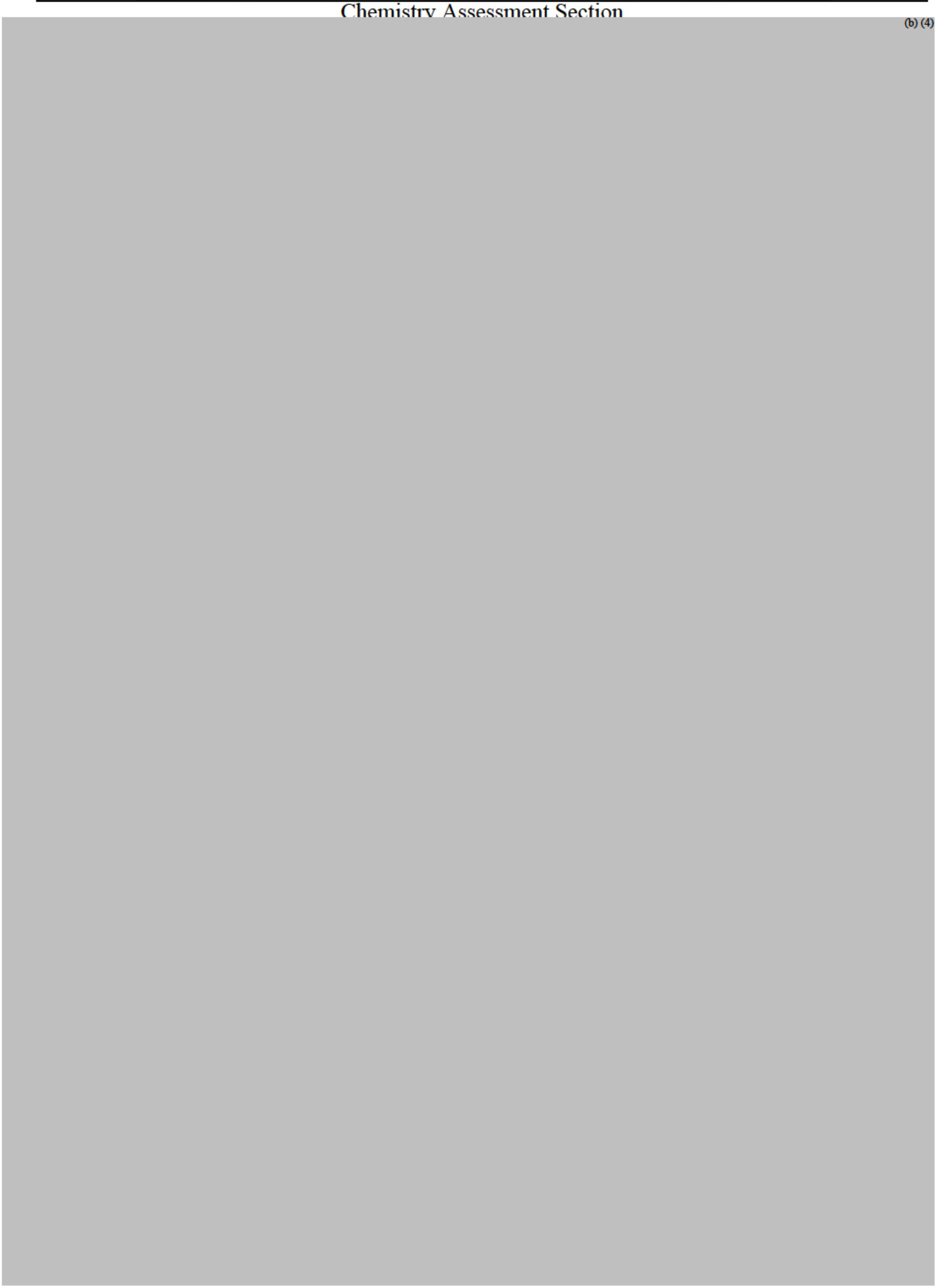
Drug Substance: The applicant has submitted copies of executed batch records for (b) (4) Also included were executed batch records the formulation and filling of insulin degludec drug product. These are acceptable.

Drug Product: The Applicant has provided master batch record (English) and executed batch record drug products batch YQ50518 (100 U/mL) and YQ50521 (200 U/mL). These product batches were manufactured at (b) (4) scale, respectively. The Firm uses a (b) (4) for formulation and filling stages. The drug products insulin degludec, 100 and 200 U/mL are identified by item no. 5-1810-00 and 5-1812-00, respectively.

R2 Comparability Protocols

The Applicant is proposing to add an additional manufacturing site (a cGMP compliant site) for the (b) (4)

(b) (4)



(b) (4)

[redacted]

R3 Methods Validation Package

The applicant has made available to the FDA four identical samples for methods validation upon request. Descriptions of the drug substance, drug product and reference material samples reserved to be submitted to an FDA laboratory are provided below.

Samples Available to FDA Upon Request – 100 U/mL

Sample Description	Packaging Type	Quantity per Sample	Batch Number	Date of Manufacture
Insulin Degludec Drug Substance	(b) (4) [redacted]	(b) (4) [redacted]	YK0SHP006	23-Sep-2010
			YK0SHP007	25-Sep-2010
			YK0SHP008	27-Sep-2010
Drug Product	Glass cartridges 3 mL		YQ50516	12-Oct-2010
			YQ50517	18-Oct-2010
			YQ50518	25-Oct-2010

(b) (4) [redacted]

Samples Available to FDA upon Request – 200 U/mL

Sample Description	Packaging Type	Quantity per Sample	Batch Number	Date of Manufacture
Insulin Degludec Drug Substance	(b) (4) [redacted]	(b) (4) [redacted]	YK0SHP006	23-Sep-2010
			YK0SHP007	25-Sep-2010
			YK0SHP008	27-Sep-2010
Drug Product	Glass cartridges 3 mL		YQ50519	2-Nov-2010
			YQ50520	5-Nov-2010
			YQ50521	12-Nov-2010

(b) (4) [redacted]

Certificates of Analysis for the (b) (4) and the insulin degludec drug substance and drug product batches listed have been provided. Method validations of the non-pharmacopeial analytical procedures for both the drug substance (S.4.3) and drug product (P.5.3) have been provided and reviewed.

(b) (4)

A.2 Adventitious Agents Safety Evaluation

Insulin degludec drug substance is produced (b) (4)

(b) (4)

(b) (4)

The manufacturing process and formulation of insulin degludec drug product does not include any (b) (4)

A.3 Novel Excipients

Not Applicable

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

1. Labeling

Section 1.14 contains information on carton and container labels proposed for the 100 and 200 U/mL Insulin degludec (rDNA) injection product filled in (b) (4) assembled in pre-assembled pen injector.

Representative label for Flextouch product carton and Flextouch container labels are shown below:
Packaging Configuration: The Applicant is proposing to package 5 x 3 mL 100 U/mL pre-filled pens per carton or 5 x 3 mL (b) (4) 100 U/mL cartridges per carton.
For the 200 U/mL strength product, the Applicant is proposing to package 5 x 3 mL 200 U/mL pre-filled pens per carton.

Flextouch container Label **Flextouch carton Label**

(b) (4)

(b) (4)

(b) (4)

[redacted]

B. Environmental Assessment Or Claim Of Categorical Exclusion

Novo Nordisk is requesting a categorical exclusion from submitting an environmental assessment for the drug product insulin degludec based on the regulations in 21 CFR, part 25, section 25.31(b). Section 25.31(b) provides for categorical exclusion if the concentration of the drug substance at the point of entry into the aquatic environment is below 1 part per billion (1 ppb = 1 mcg/liter). Using the Expected Introduction Concentration (EIC) calculation described below, Novo estimates that the EIC of liraglutide drug substance is [redacted] (b) (4) ppb).

Assumptions for calculation of EIC:
1. Amount of drug substance = [redacted] (b) (4) kg/year (estimate for 2018)
2. The drug product usage is evenly distribution over the year and throughout the United States
3. No metabolism or depletion mechanism is included.

Formula for calculation of EIC: EIC = A x B x C x D, where
A = kg drug substance/year
B = [redacted] (b) (4) (liters/day entering publicly owned wastewater treatment plants)
C = 1/365 (days per year)
D = [redacted] (b) (4) ug/kg (conversion factor)
EIC = [redacted] (b) (4) µg/liter.

Evaluation: The concentration of insulin degludec drug substance at the point of entry into the aquatic environment is below the threshold value of 1 ppb. As a result, the applicant's request for a categorical exclusion from submitting an environmental assessment is granted.

List of Deficiencies To Be Communicated

Drug Substance

1. Provide the chemical structure, general physico-chemical properties and a certificate of analysis of the [redacted]
2. Justify the parenthetical description of Content ("[redacted] in the Drug Substance specifications. This may be interpreted to mean inclusion of all [redacted] variants in the sample, rather than only the main peak as defined by [redacted] Method [redacted]
3. The shelf life of insulin degludec [redacted] batch 126.454.09.1 should be revised to reflect the available long-term, real-time stability evaluation.
4. The shelf life of the current insulin degludec [redacted] batch 064.454.09.2 should be revised to reflect the available long-term, real-time stability evaluation of either the previous [redacted] batch 179.454.07.2 (if appropriate) or the current [redacted] batch.
5. Explain how insulin degludec [redacted] batch 064.454.09.2, produced in March 2009, is traceable (for Content, Bioactivity) to the insulin degludec [redacted] batch 126.454.09.1, which was produced two months later (May 2009).
6. A shelf life of 30 months will be granted for the drug substance when stored at [redacted] or lower temperatures. This is based on acceptable long term stability results from real-time studies obtained for the drug substance from the Primary Stability batches. The [redacted] insulin degludec drug substance has changed significantly from earlier campaigns, therefore, data from Supportive Stability batches were not considered for expiry dating.
7. Provide data showing photostability of the insulin degludec drug substance.

Drug Product

1. Provide information on the following:
    a. Levels of soluble di-hexameric forms of insulin degludec present in your drug product.
    b. The stoichiometry of [redacted]
    c. Data to support the proposed levels of zinc and phenol for the proposed drug products.
2. Your CMC section does not contain information on the levels of individual insulin degludec related substances and impurities present in the drug product. ICH Q6B guidance states that if impurities are known to be introduced or formed during the production and/or storage of the drug product, the levels of these impurities should be determined and acceptance criteria established. Therefore, provide the following:
    a. Information on the levels of individual insulin degludec related substances and impurities present in batches used in phase 3 clinical studies and stability studies.
    b. Explain which impurities are increasing during manufacturing, during long-term, accelerated and in-use stability studies.
    c. Based on available data, propose a limit for each of the individual product related substances and impurities present in the product including limits for [redacted] insulin degludec) and [redacted] insulin degludec) in the drug product.
    d. Update your post-approval stability protocol to include limits for individual product related substances and impurities.
    e. Clarify whether glycerol used in the formulation can [redacted] of the insulin degludec in your product.
    f. Provide intact and reduced mass data for each of the individual impurities separated by the analytical method, A6020a.
    g. Clarify whether your proposed test method is capable of quantitating individual product-related substances and impurities with adequate specificity, accuracy and precision in the proposed product.

h. Explain your choice of RP HPLC over other applicable methods (e.g., ion exchange chromatography) for the quantitation of charged variants.

3. Considering the expected purity of your drug product is ≥ (b) (4)%, the combined limits for (b) (4) related substances, (b) (4) impurities and % HMWP would exceed the (b) (4)% total impurity level. Therefore, revise your proposed limit for (b) (4) related substances, (b) (4) impurities and % HMWP to meet the purity expectations.

4. Your proposal to have wider shelf-life specification for insulin degludec related substances and impurities is not supported by the observed stability profile of your primary stability batches (i.e., very little degradation is seen under real-time storage conditions). Revise your shelf-life specification to current release specification level or justify the same.

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/s/

JOSEPH LEGINUS
02/08/2012

ALI H AL HAKIM
02/08/2012

NDA 20-3313

Ryzodeg™
(70% Insulin Degludec and 30% Insulin Aspart [rDNA origin] Injection)

Novo Nordisk Inc.

Joseph Leginus, PhD (Drug Substance Reviewer)
Muthukumar Ramaswamy, PhD (Drug Product Reviewer)

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 203313

2. REVIEW #: 1

3. REVIEW DATE: Feb. 7, 2012

4. REVIEWER: Joseph Leginus, PhD and Muthukumar Ramaswamy, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	Sep 29, 2011
Amendment	Dec 22, 2011

7. NAME & ADDRESS OF APPLICANT:

Name:	Novo Nordisk Inc.
Address:	100 College Road West, Princeton, NJ 08540
Representative:	Eddie Li, PhD, Vice President, Regulatory Affairs
Telephone:	609-786-4593

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Ryzodeg™
Non-Proprietary Name (USAN): Insulin Degludec/Insulin Aspart
b) Code Name/# (ONDC only): Insulin degludec: NNC [redacted] (b) (4), Insulin 454
c) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Treatment of diabetes mellitus

11. DOSAGE FORM: Solution for Injection

12. STRENGTH/POTENCY: 100 U/mL

13. ROUTE OF ADMINISTRATION: Subcutaneous Administration

14. Rx/OTC DISPENSED: __X_Rx ___OTC

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

_____Not a SPOTS product

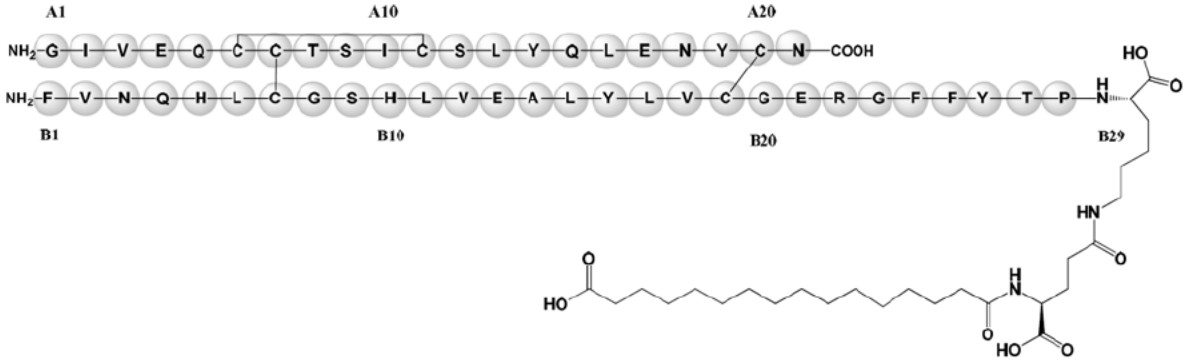
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Insulin Degludec

Chemical Name (WHO): $N^{6,B29}$-[N^{2}-(15-carboxypentadecanoyl)-L-γ-glutamyl]-des-B30-L-threonine-insulin human

USAN: Insulin degludec

Chemical Structure:



Molecular Formula: $C_{274}H_{411}N_{65}O_{81}S_6$

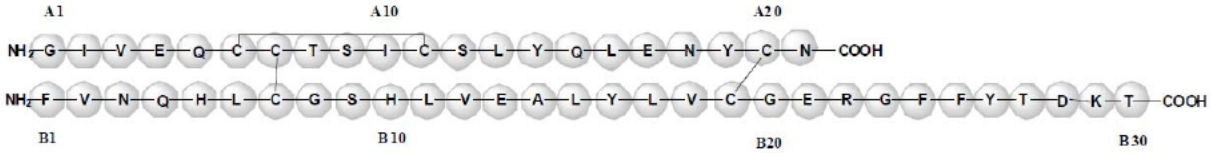
Molecular Weight: [redacted] (b) (4) Da – monoisotopic; 6,103.97 Da - average

Insulin Aspart

Chemical Name (WHO): B28 insulin aspart

USAN: Insulin aspart

Chemical Structure:



Molecular Formula: $C_{256}H_{381}N_{65}O_{79}S_6$
Molecular Weight: 5825.8 Da

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED (b) (4)	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	V	Novo Nordisk, Inc.		1	Adequate	Reviewed by B. Riley 3/13/2009	Letter of Authorization 5/11/2011

[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	73198	[Insulin degludec/Insulin aspart] (rDNA origin) Injection
NDA	203314	Insulin degludec (rDNA origin) Injection
NDA	20986	Insulin aspart (rDNA origin) Injection

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending. EER was sent to Office of Compliance on 13-Oct-2011.	2/7/12	OC recommendation is pending
Biopharm	May not be applicable. This is an injectable product, and the commercial formulation was used in Phase 3 studies.	N/A	
Methods Validation	Validation may be requested of FDA labs after test methods are finalized.	N/A	
CDRH	Review of the disposable multi-dose pen	TBD	CDRH review is pending

	injector.		
EA	Acceptable	2/7/12	Joseph Leginus
Microbiology	Review of 1) microbiology controls proposed for the drug substance and drug product, and 2) sterilization (b) (4) processing validation for the drug product.	TBD	Review pending/ Reviewer Dr. V. Pawar

The Chemistry Review for NDA 203313

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The recommendation from a CMC perspective is pending resolution of satisfactory responses to the deficiencies identified in Review #1. At this time, the Office of Compliance has not issued acceptable cGMP recommendations for the three manufacturing and testing facilities associated with this application. An overall compliance recommendation is pending as of 7-Feb-2012.

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

Not Applicable

II. Summary of Chemistry Assessments

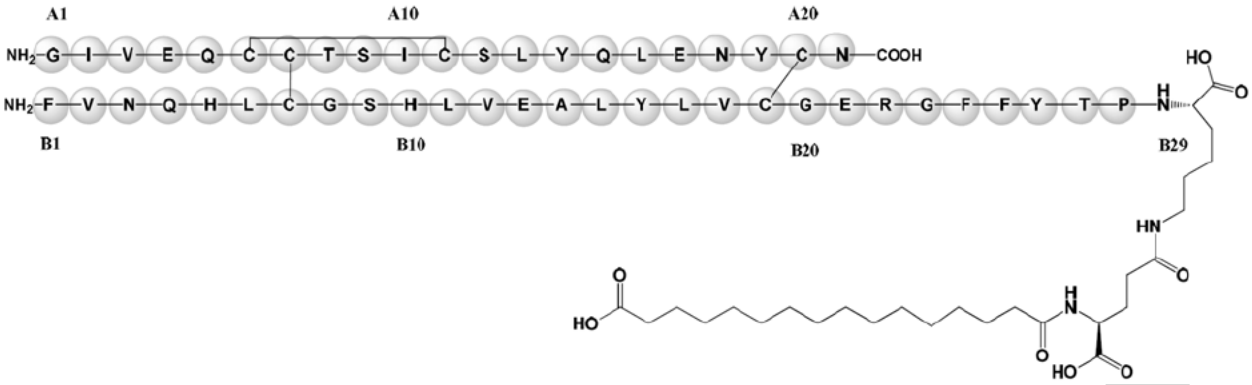
A. Description of the Drug Product(s) and Drug Substance(s)

Note: Review of NDA 203313 was conducted as a Team Review with Joseph Leginus reviewing the Drug Substance and Muthukumar Ramaswamy reviewing the Drug Product.

DRUG SUBSTANCE

Ryzodeg™ (70% Insulin Degludec and 30% Insulin Aspart [rDNA Origin] Injection) 100 U/mL solution for subcutaneous injection contains 420 nmol of insulin degludec and 180 nmol of insulin aspart per mL. Insulin aspart was approved previously for human use under NDA 20986.

One of the two drug substances, insulin degludec, is a new molecular entity and is an analog of human insulin. The chemical name of insulin degludec is $N^{6, 29B}$-[N-(15-carboxypentadecanoyl)-L-γ-glutamyl]-des-30B-L-threonine-human insulin, and its structure is presented below:



Insulin degludec is produced using recombinant DNA technology and chemical modification. The (b) (4) precursor of insulin degludec (desB30-insulin), produced by a process that includes expression of recombinant DNA in yeast (*Saccharomyces cerevisiae*) differs from human insulin by the omission of threonine in position B30. Insulin degludec is made by chemically attaching a C-16 fatty acid (hexadecanedioic acid) with a glutamic acid spacer on the lysine (b) (4) at position B29 of the insulin precursor.

Executive Summary Section

The molecular formula of insulin degludec is $C_{274}H_{411}N_{65}O_{81}S_6$ with a molecular weight of [redacted].

Insulin degludec is a [redacted] It is freely soluble in water [redacted] The isoelectric point of insulin degludec is approximately [redacted]. The pH of a [redacted] aqueous solution of drug substance is approximately 7.4.

The structure of insulin degludec was elucidated by a variety of analytical and spectrophotometric techniques, including [redacted] analysis, mass spectrometry [redacted] F MS). [redacted] ultraviolet (UV) and [redacted]

Insulin degludec is produced by recombinant DNA technology from yeast (*Saccharomyces cerevisiae)* and chemical modification. The manufacturing process [redacted].

The proposed release specifications include appearance, identification ([redacted] and HPLC), content (HPLC), bioactivity (cell-based assay), individual [redacted] related impurities (HPLC), loss on drying and bacterial endotoxin. The proposed regulatory methods have been validated. Reference standards for the API have been developed and characterized.

Product related impurities structurally related to insulin degludec generated during the [redacted] of the drug substance have classified based on their RP-HPLC elution position relative to the drug substance. These have been characterized as "[redacted] impurities", "[redacted] related substances", "[redacted] impurities" and "high molecular weight proteins." Process derived impurities originating from the insulin degludec manufacturing process were not detected in the drug substance.

A shelf life of 30 months will be granted for the drug substance when stored at [redacted]. This is based on acceptable long-term stability results from real-time studies obtained for the drug substance from Primary Stability batches at production scale.

DRUG PRODUCT:

The proposed drug product (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. Each mL of the proposed contains 480 nmol of insulin degludec and 180 nmol of insulin aspart, 19.0 mg glycerol [redacted], 1.50 mg phenol [redacted], 1.72 mg metacresol [redacted]), sodium chloride (0.58 mg, [redacted], and 27.4 µg zinc [redacted] and water for injection. Hydrochloric acid or sodium hydroxide is added to adjust pH to approximately 7.4. The potency of the proposed formulation is 100 Units/mL (U-100). The proposed product is intended for once or twice daily use as meal time insulin by subcutaneous administration.

During Phase 1 and 2 studies, the Applicant has screened formulations containing different ratios of insulin degludec/insulin aspart and different levels of excipients (e.g., phenol/metacresol, glycerol, zinc, sodium chloride, and [redacted]) for action profile and stability. Based on developmental data, the Applicant has chosen a formulation containing insulin degludec/insulin aspart at a ratio of 70:30 and phenol/metacresol, glycerol, sodium chloride, and zinc as excipients for use in Phase 2/3 studies. The proposed final formulation is the same as the one used in Phase 3 clincial studies.

Insulin degludec and insulin aspart together with [redacted] promote self-association into di-hexamer and hexamer, respectively. The NDA states that drug product formulation has been optimized to ensure di-hexamer and hexamer forms. A concentration in total of [redacted] and a pH of 7.4 have been identified as

optimal to confer [redacted] of the formulation. The Applicant is proposing to use monograph grade excipients in the final formulation and is acceptable.

The Applicant is proposing to market the proposed product as [redacted] pre-filled pen (cartridge pre-assembled in a PDS290 pen-injector). The finished product will be marketed as 5 x 3 mL [redacted] packaged in cartons or as 5 x 3 mL prefilled pens in cartons. The proposed product is light sensitive and therefore [redacted] packaging is critical to assure the stability of the product.

The drug product, insulin degludec/insulin aspart 100 U/mL is manufactured by [redacted].

The drug product is [redacted]

During development, the Applicant has defined Quality Target Product Profile (QTPP) and critical quality attributes. The proposed critical quality attributes (CQAs) for the drug products include insulin content of each active ingredient, extractable volume, plunger friction (for measuring device performance), *purity factors (individual impurities related to each active ingredients, high molecular weight proteins, product identity,* [redacted] *content)*, closure integrity (sterility), [redacted] efficacy, endotoxin levels, appearance (particulate load), and other physical test such pH and isotonicity.

Although the Applicant has defined the [redacted] form of insulin degludec as a critical quality attribute, the Application does not contain information on the stoichiometry of the [redacted] insulin degludec complex and targeted levels of [redacted] content of insulin degludec in the proposed product.

The Applicant also used design of experiments and risk assessment techniques to define critical process parameters. The Applicant's developmental work and process evaluation studies were targeted to ensuring the proposed process parameters are adequate to ensure complete dissolution of excipients and active ingredients. Developmental stability on in-process solutions and bulk formulation assured whether the proposed pH ranges for these solutions are adequate with respect chemical and physical attributes.

The NDA contains batch formula and a description of the proposed commercial process. Together with the information provided in the master batch record, the available information in the NDA is adequate to support the proposed commercial process. The NDA contains process control information for manufacturing the proposed product. The proposed critical process parameters (in-process tests) include [redacted]

The NDA contains batch analysis data from development through commercial scale to support the manufacturability of the proposed product. With the exception of limits on individual product related substances and impurities of insulin degludec, the NDA contains adequate information on the release specification used for controlling for quality of the drug product. The Applicant has proposed general tests typically expected for a parenteral product, and product-specific tests. The proposed general tests include pH, endotoxin limit, and sterility, and particulate matter. The product-specific tests include identity, insulin content, zinc content, product

related impurities (high molecular weight proteins, (b) (4) impurities, (b) (4) product related substances and (b) (4) impurities) and (b) (4) content. In addition, the applicant is proposing to monitor the dose accuracy of the product filled in the delivery device. The proposed limits for monitoring the individual insulin aspart related substances and impurities are acceptable.

With the exception of reporting limits for individual product related substances and impurities of insulin degludec, the test methods proposed for the product are adequately described and are validated per applicable ICH guidelines. The Applicant needs to explain the validity of the proposed method (A6020a) to quantitate individual insulin degludec related substances and impurities.

The Applicant is proposing a separate release and shelf-life specification (i.e., wider than the release specification) for controlling and monitoring the quality of the drug product. The proposed (b) (4) shelf-life specification for the product related substances and impurities is not supported by the *degradation profile for product related substances and impurities in primary stability batches. We recommend that the Applicant propose a common release and shelf-life specification for the drug product.*

The applicant has provided 18-24 month real time and 6 month accelerated stability data for several batches of the drug product manufactured at (b) (4) scale. This Application also contains limited stability information for product manufactured at commercial scale (b) (4)). In addition, the NDA contains in-use stability and photo stability data for the proposed product packaged in (b) (4) packaging configuration. The stability studies were performed on the drug product packaged in (b) (4). *Photo stability data show that the* (b) (4) *packaging (the PDS290 pen-injector* (b) (4) *carton) provides adequate protection against light.* Since the drug product is only in contact with the (b) (4) cartridge, the stability data of the drug product in the cartridge (in darkness) in the PDS290 pen-injector is not needed.

- *Based on the long term and accelerated stability data evaluated in this document, a shelf life of 24 months at 5°C ± 3°C is recommended for Insulin degludec/Insulin aspart 100 U/mL.*
- *Based on the in-use stability data evaluated in this document, an in-use period of 28 days at up to 30°C is recommended for Insulin degludec/Insulin aspart 100 U/mL.*

The NDA contains a post-approval stability protocol and commitment to place 3 full scale batches on stability and continue to update information on existing stability studies. The Applicant should update their stability protocol and post-approval stability protocol to include limits for individual product related substances and impurities.

Deficiencies identified during the review of the drug product section are summarized at the end of the Chemistry Review.

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

Ryzodeg™ (70% Insulin Degludec and 30% Insulin Aspart [rDNA Origin] Injection) solution is intended for once or twice daily administration with any main meals in diabetic patients. When needed, the patient can change the time of administration as long as Ryzodeg is dosed with a main meal. The Ryzodeg drug can be administered either alone or in combination with oral anti-diabetic drugs (OADs).

The dosage of Ryzodeg™ should be individualized under the supervision of a health care provider in accordance with the needs of the patient with appropriate glucose monitoring. For patients with type 2 diabetes mellitus, the recommended total daily starting dose of IDegAsp is 10 Units with meal(s) followed by individual

dosage adjustments. For patients with type 1 diabetes mellitus, IDegAsp is to be used once-daily at meal-time and with short-/rapid-acting insulin at the remaining meals followed by individual dosage adjustments.

Ryzodeg™ should be administered by subcutaneous injection into the abdominal wall, thigh, or upper arm. Ryzodeg™ should not be administered intravenously or intramuscularly or with insulin infusion pumps or mixed with any other insulin solutions. Ryzodeg should be inspected visually prior to administration and should only be used if the solution appears clear and colorless.

Drug product delivery system and appropriate storage are adequately described in both package insert and patient package insert. Drug product shelf-life is 24 months at (b) (4) protected from light. In-use shelf-life period is 28 days at temperatures not exceeding 30°C

C. Basis for Approvability or Not-Approval Recommendation

The recommendation from a CMC perspective is pending satisfactory responses to the deficiencies identified in Review #1 and acceptable recommendation for manufacturing facilities associated with this application. At this time, Office of Compliance has not issued acceptable cGMP recommendations for the three manufacturing and testing facilities. An Overall Compliance recommendation is pending as of 7-Feb-2012.

This is a 505(b)(1) application where one of the two drug substances, insulin degludec, is a New Molecular Entity (NME). The IND for insulin degludec/insulin aspart (73198) was received on 3/20/2008 and the IND for insulin degludec (76496) was received on 9/5/2007. An EOP2 meeting was held on 2/24/2009. A pre-NDA meeting was held on 6/17/2011. The other drug substance, insulin aspart was approved previously for human use under NDA 20986.

The drug substance (insulin degludec) will be manufactured for commercial use by Novo Nordisk A/S located in Bagsvaerd Denmark (b) (4) and Kalundborg Denmark (b) (4)

The finished product is manufactured in their sterile product manufacturing facility (building (b) (4)) located at Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd.

III. Administrative

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

(b) (4)

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A APPENDICES

A.1 Facilities and Equipment (biotech only)

This section gives an overview of the production facilities used for the production of insulin degludec drug substance and drug product. The Applicant has referenced the following facility documents in this section. Descriptions of the area classifications, segregation of operations and intermediate products and equipment design were also provided. Relevant information pertaining to finished product manufacturing is reproduced below:

The finished product is manufactured in their sterile product manufacturing facility (building (b) (4)) located at Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd.

Description of the manufacturing flow: (b) (4)

(b) (4)

(b) (4)

Establishment Evaluation Report – OC recommendation is pending (See Enclosed)

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 203313/000	**Sponsor:**	NOVO NORDISK INC
Org. Code:	510		100 COLLEGE RD WEST
Priority:	14		PRINCETON, NJ 08540
Stamp Date:	29-SEP-2011	**Brand Name:**	Ryzodeg
PDUFA Date:	29-JUL-2012	**Estab. Name:**	[Insulin degludec/Insulin aspart] (rDNA origin) Injection
Action Goal:		**Generic Name:**	
District Goal:	30-MAY-2012	**Product Number; Dosage Form; Ingredient; Strengths**	001; SOLUTION, INJECTION; INSULIN DEGLUDEC; 100UNT

FDA Contacts:	K. SHARMA	Project Manager		
	J. LEGINUS	Review Chemist	(HFD-810)	301-796-4102
	S. TRAN	Team Leader		301-796-1764

Overall Recommendation:	PENDING	on 24-JAN-2012	by EES_PROD
	PENDING	on 13-OCT-2011	by EES_PROD

Establishment:	**CFN:** 9610699	**FEI:** 3002807751		
	NOVO NORDISK A/S HALLAS ALLE KALUNDBORG, , DENMARK			
DMF No:			**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER FINISHED DOSAGE LABELER FINISHED DOSAGE PACKAGER			
Profile:	(b) (4)		**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION			
Milestone Date:	24-JAN-2012			
Decision:	ACCEPTABLE			
Reason:	BASED ON PROFILE			
Profile:	(b) (4)		**OAI Status:**	NONE
Last Milestone:	ASSIGNED INSPECTION TO IB			
Milestone Date:	14-OCT-2011			

Establishment:	**CFN:** 9613244 **FEI:** 3002807752		
	NOVO NORDISK A/S BERNNUM PARK, DK-3400 HILLEROED, , DENMARK		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE LABELER FINISHED DOSAGE PACKAGER FINISHED DOSAGE STABILITY TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	ASSIGNED INSPECTION TO IB		
Milestone Date:	23-OCT-2011		

Profile:	(b) (4)	**OAI Status:**	NONE
Last Milestone:	ASSIGNED INSPECTION TO IB		
Milestone Date:	23-OCT-2011		

Establishment:	**CFN:** 9616213 **FEI:** 3000151819		
	NOVO NORDISK A/S NOVO ALLE BAGSVAERD, , DENMARK		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER FINISHED DOSAGE MANUFACTURER		
Profile:	(b) (4))	**OAI Status:**	NONE
Last Milestone:	SUBMITTED TO OC		
Milestone Date:	24-JAN-2012		

Profile:	(b) (4)	**OAI Status:**	NONE
Last Milestone:	ASSIGNED INSPECTION TO IB		
Milestone Date:	14-OCT-2011		

A.2 Adventitious Agents Safety Evaluation

The Applicant has evaluated the Virus and [redacted] safety evaluation for drug substances insulin degludec and insulin aspart (part of marketed product) and the manufacturing process and formulation of insulin degludec/insulin aspart 100 U/mL drug product, [redacted] The overall conclusion of this safety evaluation is therefore that insulin degludec/insulin aspart drug product is safe with regard to both virus and [redacted] agents.

A.3 Novel Excipients: Not applicable

R REGIONAL INFORMATION

R1 Executed Batch Records

The Applicant has provided master batch record (English) and an executed batch record for drug product batch YQ50524 (in Danish) manufactured at [redacted] scale. The production of insulin degludec/insulin aspart 100 U/mL [redacted] for formulation and filling. The drug product insulin degludec/insulin aspart, 100 U/mL (strength 420 nmol insulin degludec/mL and 180 nmol insulin aspart/mL) is identified by item no. 5-1814-00.

R2 Comparability Protocols – Acceptable

Comparability Protocol for Insulin Degludec/Insulin Aspart 100 U/mL Additional Drug Product Manufacturing Site

Novo Nordisk proposed to add an additional manufacturing site for [redacted]

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(b) (4)

R3 Methods Validation Package

Filter Validation Report: **Adequate**

The information section contains validation report for the (b) (4) used for sterile filtration of insulin degludec/insulin aspart 100 U/mL. The (b) (4)

(b) (4)

(b) (4)

Evaluation: Adequate information on (b) (4) validation for the proposed (b) (4) is provided in this document.

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling Review will be completed in collaboration with other Team members. Labeling review will evaluate conformance to relevant sections of Subpart A and B of CFR 201.

A. Labeling & Package Insert

Section 1.14 contains information on carton and container labels proposed for the 100 U/mL insulin degludec/insulin aspart (rDNA) injection product filled in (b) (4) assembled in pre-assembled pen injector. *Representative label for FlexTouch product carton and Flextouch container labels are shown below:*

Flextouch container Label **Flextouch carton Label**

(b) (4)

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(b) (4)

[redacted]

B. Environmental Assessment Or Claim Of Categorical Exclusion **Adequate**

It has been concluded that the concentration of insulin degludec drug substance at the point of entry into the aquatic environment is below the threshold value of 1 ppb. As a result, the applicant's request for a categorical exclusion from submitting an environmental assessment is granted. For details, please refer to CMC review for NDA 203314.

III. List Of Deficiencies To Be Communicated

Drug Product

1. Provide information on the following:
    a. Levels of soluble di-hexameric forms of insulin degludec present in your drug product.
    b. The stoichiometry of [redacted]
    c. Data to support the proposed levels of zinc and phenol for the proposed drug products.
2. Your CMC section does not contain information on the levels of individual insulin degludec related substances and impurities present in the drug product. ICH Q6B guidance states that if impurities are known to be introduced or formed during the production and/or storage of the drug product, the levels of these impurities should be determined and acceptance criteria established. Therefore, provide the following:
    a. Information on the levels of individual insulin degludec related substances and impurities present in batches used in phase 3 clinical studies and stability studies.
    b. Explain which impurities are increasing during manufacturing, during long-term, accelerated and in-use stability studies.
    c. Based on available data, propose a limit for each of the individual product related substances and impurities present in the product including limits for [redacted] of insulin degludec) and [redacted] insulin degludec) in the drug product.
    d. Update your post-approval stability protocol to include limits for individual product related substances and impurities.
    e. Clarify whether glycerol used in the formulation can [redacted] of the insulin degludec in your product.
    f. Provide intact and reduced mass data for each of the individual impurities separated by the analytical method, A6020a.
    g. Clarify whether your proposed test method is capable of quantitating individual product-related substances and impurities with adequate specificity, accuracy and precision in the proposed product.
    h. Explain your choice of RP HPLC over other applicable methods (e.g., ion exchange chromatography) for the quantitaion of charged variants.
3. Considering the expected insulin aspart content specification [redacted]% of label claim at the end of shelf-life, your proposed combined limit for total Insulin aspart related substances and impurities (~[redacted]% level) does not meet the purity expectations of drug product at the end of shelf-life. Therefore, revise your proposed limit for Insulin aspart related substances and impurities to meet the purity expectations or justify your proposed specifications.

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

/s/

MUTHUKUMAR RAMASWAMY
02/08/2012

ALI H AL HAKIM
02/08/2012

Division of Metabolism and Endocrinology Products

NDA:	**203313**
Applicant:	Novo Nordisk Inc.
Stamp Date:	**29-SEP-2011**
PDUFA Date:	**29-JUL-2012**
Proposed Proprietary Name:	Ryzodeg
Established Name:	Insulin degludec/insulin aspart
Dosage form and strength:	Injectable solution, 100 U/mL
Route of Administration:	Subcutaneous injection
Indications:	Treatment of diabetes.
CMC Lead:	Su (Suong) Tran, ONDQA
ONDQA Fileability:	**Yes**

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

- Clarify what the reference is for the units of the dosage strength (b) (4). In the proposed drug product specification, the content of insulin degludec and insulin aspart in the formulation is measured as "nmol". Provide a reference for the units of the dosage strength (b) (4), comparable to that submitted for your insulin detemir product (i.e., one unit (24 nmol) of insulin detemir corresponds to one IU of human insulin (6 nmol) based on clinical data).
- Clarify how your proposed dosage strength of 100 (b) (4) for the combined content of insulin degludec and insulin aspart complies with 21 CFR 201.100, which requires the labeling to state "the quantity or proportion of each active ingredient in the drug product".

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharmaceutics	*May not be applicable. This is an injectable product, and the commercial formulation was used in Phase 3 studies.*
CDRH	Review of the multi-dose pen injector.
EA	Categorical exclusion request will be assessed by Primary Reviewer.
EES	EER was sent to Office of Compliance on 13-OCT-2011.
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 (b) (4) 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.*

This is an electronic NDA, filed as a 505(b)(1) application. The associated IND is IND 76496.

The drug substance insulin degludec is a New Molecular Entity (NME) for the CMC review purpose. It is produced by recombinant DNA (rDNA) technology in *Saccharomyces cerevisiae*. Insulin degludec is a human insulin mutant where Thr B30 is deleted and the ε-amino group of Lys B29 is coupled with hexadecanedioic acid via a γ-Glu spacer. Insulin degludec is designed to be an ultra-long-acting basal insulin with a duration of action beyond 42 hours. Similarly to the approved insulin detemir (same applicant), after subcutaneous injection, the di-hexameric form self-assembles into soluble multi-hexamers and binds to albumin, creating a depot in the subcutaneous tissue. Monomers slowly and continuously enter circulation, resulting in a long half-life.

Reference is made to the approved NDA 20986 (same applicant) for all information on insulin aspart. Insulin aspart is a human insulin mutant where Pro is replaced by Asp at position B28. It is produced by recombinant DNA (rDNA) technology in *Saccharomyces cerevisiae*.

The 100 U/mL drug product is a sterile solution for subcutaneous injection, packaged in a (b) (4) disposable 3-mL pen injector (PDS290 or FlexTouch). The pen injector includes (b) (4) 3-mL cartridge; the device and cartridge are assembled (b) (4)

The product has an approximate pH of 7.4. The inactive ingredients are glycerol 19.6 mg/mL, phenol 1.50 mg/mL, metacresol 1.72 mg/mL, sodium chloride 0.58 mg/mL, zinc 27.4 mcg/mL, and water for injection. Hydrochloric acid or sodium hydroxide may be added to adjust the pH.

Has all information requested during the IND phases and at the pre-NDA meetings been included?

See the discussion in the review.

Drug substances

Insulin degludec differs from human insulin in that the threonine in position B30 has been omitted and a side-chain consisting of glutamic acid and a C16 fatty acid has been attached (chemical name: LysB29(Nε-hexadecandioyl-γ-Glu) des(B30) human insulin) and is produced by recombinant DNA technology utilizing *Saccharomyces cerevisiae*. Insulin degludec has a molecular formula of $C_{274}H_{411}N_{65}O_{81}S_6$ and a molecular weight of 6103.97.

Insulin degludec has a molecular formula of $C_{274}H_{411}N_{65}O_{81}S_6$ and a molecular weight of 6103.97.

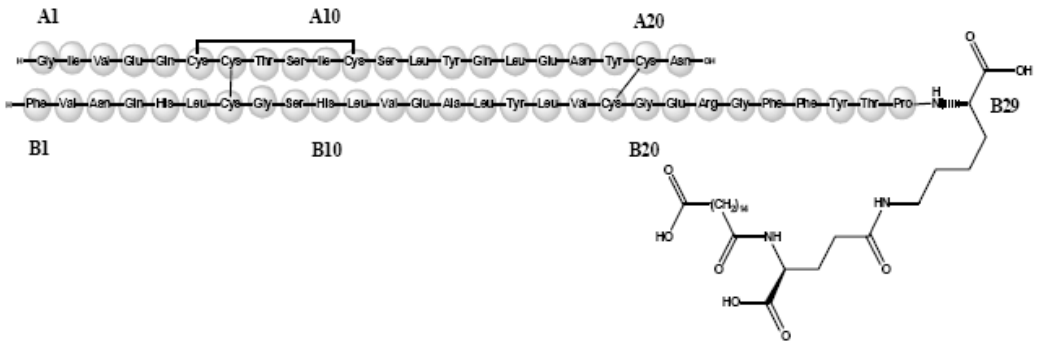


Figure 1: Structural formula of insulin degludec

Insulin aspart is homologous with regular human insulin with the exception of a single substitution of the amino acid proline by aspartic acid in position B28, and is produced by recombinant DNA technology utilizing *Saccharomyces cerevisiae*. Insulin aspart has a molecular formula of $C_{256}H_{381}N_{65}O_{79}S_6$ and a molecular weight of 5825.8.

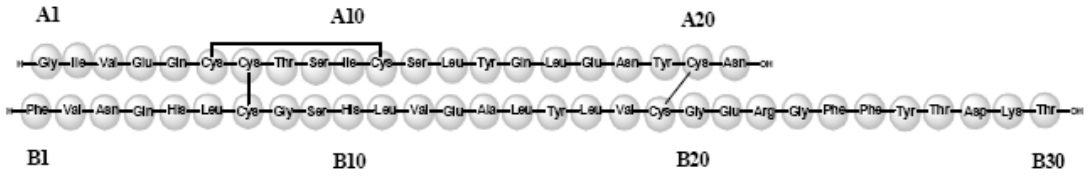


Figure 2: Structural formula of insulin aspart

See the IQA/filing review of the pending NDA 203314 for the information on insulin degludec.

The applicant refers to the approved NDA 20986 for all CMC information on insulin aspart.

Drug product:

Insulin degludec/insulin aspart 100 U/ml is a clear, colourless solution. The solution is filled in a [redacted] (b) (4)

The composition of insulin degludec/insulin aspart 100 U/ml is listed in Table 1.

Table 1 Composition of insulin degludec/insulin aspart 100 U/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	[redacted] (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]	q.s.	pH adjustment	Ph Eur, USP, JP
Sodium hydroxide[3]	q.s.	pH adjustment	Ph Eur, USP, JP
Water for injections	to make 1.00 ml	[redacted] (b) (4)	Ph Eur, USP, JP

[1] An overage up to [redacted] (b) (4) of the [redacted] (b) (4) is added to compensate for loss during manufacturing

[2] Zinc is added [redacted] (b) (4) according to Ph Eur, USP, JPE

[3] To reach pH 7.4

- **Formulations**. The applicant confirms that the primary stability batches and the Phase 3 clinical formulation IDegAsp(F) is the same as the commercial formulation, manufactured at the commercial site.
- **Dosage strength**.
  - It is unclear what the reference is for the units of the dosage strength [redacted] (b) (4) In the proposed drug product specification, the content of insulin degludec and insulin aspart in the formulation is measured as "nmol". An explanation comparable to that submitted for insulin detemir should be provided by the applicant (see the 74-day letter comment). The ClinPharm team mentioned at the filing meeting that 1 unit of insulin degludec is equivalent to 1 unit of insulin glargine based on clinical data. This information should be confirmed by the applicant in the CMC section.
  - Another issue is that there are two different drug substances in the drug product, each with a different in vivo profile, but the applicant has only one combined dosage strength

of 100 (b) (4) for both. Per 21 CFR 201.100, the labeling is required to state "the quantity or proportion of each active ingredient in the drug product" (see the 74-day letter comment). This issue will be discussed with the Clinical team and OSE at the filing meeting.

- **Overage of** (b) (4). Based on the Microbiology input and stability data, the reviewer will determine whether the (b) (4) overage of (b) (4) will be sufficient to assure (b) (4).

Drug product manufacture.

(b) (4)

- (b) (4)

the optimization of the (b) (4) addition step (b) (4)).Process validation data are included in the NDA.

Drug product specification. (copied on the next page)

- **Insulin degludec and insulin aspart content**. The drug product specification does not include testing for biological activity. Data are provided in the referenced NDA 203314 for the correlation between potency (bioactivity) of insulin degludec and (b) (4) content by RP-HPLC; the information will be evaluated by the reviewer. The reviewer will also confirm the same correlation in the referenced NDA 20986 for insulin aspart.
- **Filling volume of the drug product**. The drug product specification does not have Filling Volume because this testing is performed (b) (4).
- **Metacresol content, phenol content, bacterial endotoxins, and sterility**. These attributes will be evaluated as part of the Microbiology review.
- **Dose accuracy.** Dose accuracy in the drug product specification only applies to the pen injector assembly and will be evaluated as part of the CDRH review.
- **Limits on degradation products.** The drug product specifications (release and stability) include the same groups of product-related substances, process-related and product-related impurities as in the drug substance specification, although with higher limits. The reviewer will determine whether the higher limits are adequately justified by batch release and stability data of the primary stability batches and whether they are supported by all available data (as per ICH Q6B, acceptance criteria or limits for these impurities should be based on data from nonclinical, clinical, and stability batches). Stability data to be considered should include the in-use data.

Table 1 Release and shelf life limits for insulin degludec/insulin aspart 100 U/ml

Test	Analytical procedure	Acceptance criteria
Characters: Macroscopy	Visual inspection No. A3196b	Complies[1]
Identity of insulin aspart	RP-HPLC No. A6023a	Complies[2]
Identity of insulin degludec	RP-HPLC No. A6021a	Complies[3]
Content of insulin aspart	RP-HPLC No. A6021a	(b) (4) nmol/ml [(b) (4) %]
Content of insulin degludec	RP-HPLC No. A6021a	(b) (4) nmol/ml (b) (4) %]
pH	Potentiometry (Ph Eur, USP)	(b) (4)
High Molecular Weight Proteins	GPC No. A6022a	Release: ≤ (b) (4) Shelf life: ≤ (b) (4) %
Insulin degludec:		
(b) (4) impurities	RP-HPLC No. A6020a	Release: ≤ (b) (4) Shelf life: %
(b) (4) related substances	RP-HPLC No. A6020a	Release: ≤ (b) (4) Shelf life: %
(b) (4) impurities	RP-HPLC No. A6020a	Release: (b) (4) Shelf life %
Insulin aspart:		
(b) (4) insulin aspart	RP-HPLC No. A6023a	Release: ≤ (b) (4) Shelf life: %
(b) (4) insulin aspart	RP-HPLC No. A6023a	Release: ≤ (b) (4) Shelf life: %
Insulin aspart related impurities	RP-HPLC No. A6023a	Release: ≤ (b) (4) Shelf life: %

Test	Analytical procedure	Acceptance criteria
Zinc total	AAS (Ph Eur[4], USP)	(b) (4) µg/ml
Bacterial endotoxins	Chromogenic kinetic method (Ph Eur Method D, USP)	(b) (4) IU/ml[5+6]
Sterility	Membrane filtration method (Ph Eur, USP)	Complies
Identity of metacresol	RP-HPLC No. A6021a	Complies[7]
Identity of phenol Metacresol	RP-HPLC No. A6021a RP-HPLC No. A6021a	Complies[8] (b) (4) mg/ml
Phenol	RP-HPLC No. A6021a	(b) (4) mg/ml
Particulate matter ≥ 10 µm ≥ 25 µm	Light obscuration (Ph Eur, USP)	(b) (4) container (b) (4) container
Dose accuracy[9]	Weighing A29001a	Complies[10]

[1] Complies means a colourless liquid free from turbidity and essentially free from particulate matter

[2] Complies means verified as insulin aspart

[3] Complies means verified as insulin degludec

[4] This method complies with the requirements in the monograph for Insulin preparations injectable, Ph Eur

[5] One International Unit (IU) of endotoxin is equal to one Endotoxin Unit (EU)

[6] This limit corresponds to (b) (4) IU of endotoxin/100 U of insulin degludec/insulin aspart

[7] Complies means verified as metacresol

[8] Complies means verified as phenol

[9] Only performed when the (b) (4), PDS 290 pen-injector, item no. 5-9564-xx

[10] Complies means that the specification limit ±(b) ( ) units is fulfilled using ISO 3951 part 1 or 2 (the limit is in accordance with ISO 11608-1)

Container closure system of the drug product.

The pen injector device will be evaluated by CDRH.

The NDA includes information on compatibility, extractables, and leachables for the primary container closure system (i.e., cartridge). The applicant follows ICH Q3 guidelines in evaluating the safety of the extractable and leachables. The information will be assessed by the reviewer, with input from the PharmTox team if necessary.

Stability.

- The unopened product is stored under refrigeration, 2-8 °C.
- An expiry of (b) (4) months is proposed by the applicant based on up to 24-month stability data at 5 °C and 6-month at 25 °C for three primary stability batches manufactured at the commercial site. These batches were used in phase 3 clinical studies. Supportive data include validation and production batches. The reviewer will consider all available data, including data for the (b) (4) and accounting for the same/different container closure systems, and determine whether the proposed expiry is appropriate (per ICH Q5C guidelines).
- An in-use shelf life of the opened product is proposed to be 28 days at (b) (4), based on 4-week stability data at 30 °C. The in-use testing was performed on fresh and aged samples, which were subjected to movement and needle penetration to simulate patient use. A photostability report is provided.

Comparability protocols. The NDA includes two comparability protocols for post-approval changes: additional assembly facility for packaging the drug cartridges into the pen injectors and additional drug product manufacturing facility. The reviewer will evaluate the adequacy of the testing programs proposed

to demonstrate comparability of the products before and after the change in manufacturing sites. It is noted that a comparability protocol for a new manufacturing facility may not appropriate for downgrading a post-approval submission because such a change requires a GMP inspection request. Input from the Post-Marketing Branch may be obtained.

GMP facilities: **EER was sent** to the Office of Compliance on 13-OCT-2011

Table 1 Drug Substance Establishment Information

Manufacturing Location	Contact Information	Activity
Novo Nordisk A/S Hallas Allé DK-4400 Kalundborg Denmark **FEI Number: 3002807751** **CFN Number: FCDA069** **DUNS Number: 305156788**	Torben Enstrøm Corporate Vice President Global Quality Audits Telephone. +011 45 4443 3172 Direct. +011 45 3075 3172 e-mail: toe@novonordisk.com	(b) (4)
Novo Nordisk A/S Novo Allé DK-2880 Bagsværd Denmark **FEI Number: 3000151819** **(Changed from 3001392218 per FDA as of 6-16-10)** **CFN Number: FCDA039** **DUNS Number: 312296002**	Torben Enstrøm Corporate Vice President Global Quality Audits Telephone. +011 45 4443 3172 Direct. +011 45 3075 3172 e-mail: toe@novonordisk.com	
All sites ready for inspection		

Table 2 Drug Product Establishment Information

Manufacturing Location	Contact Information	Activity
Novo Nordisk A/S Novo Allé DK 2880 Bagsværd Denmark **FEI Number: 3000151819 (Changed from 3001392218 per FDA as of 6-16-10)** **CFN Number: FCDA039** **DUNS Number: 312296002** **DMF number associated with the process(es) conducted at the facility: 21494**	Torben Enstrøm Corporate Vice President Global Quality Audits Telephone. +011 45 4443 3172 Direct. +011 45 3075 3172 e-mail: toe@novonordisk.com	(b) (4) [redacted]
Novo Nordisk A/S Brennum Park DK-3400 Hillerød Denmark **FEI Number: 3003131673** **CFN Number: FCDA070** **DUNS Number: 309477891**	Torben Enstrøm Corporate Vice President Global Quality Audits Telephone. +011 45 4443 3172 Direct. +011 45 3075 3172 e-mail: toe@novonordisk.com	
Novo Nordisk A/S Hallas Allé DK-4400 Kalundborg Denmark **FEI Number: 3002807751** **CFN Number: FCDA069** **DUNS Number: 305156788**	Torben Enstrøm Corporate Vice President Global Quality Audits Telephone. +011 45 4443 3172 Direct. +011 45 3075 3172 e-mail: toe@novonordisk.com	
All sites ready for inspection		

PRODUCT QUALITY
FILING REVIEW FOR NDA (ONDQA)

NDA Number: 203313

Established/Proper Name: Insulin degludec/insulin aspart

Applicant: Novo Nordisk **Letter Date: 29-SEP-2011** **Stamp Date: 29-SEP-2011**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		
B. facilities*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			
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		

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		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
D. drug substance/active pharmaceutical ingredient (DS/api)				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	x		
12.	Does the section contain a description of the DS manufacturing process?	X		
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.	Have any biowaivers 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		Review issue: whether data and analysis are adequate to support expiry
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		x	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	
F. methods validation (Mv)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	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		
I. Labeling				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	x		
33.	Have the immediate container and carton labels been provided?	x		
J. filing conclusion				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	x		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	x		See page 1 of the IQA/filing review.

{See appended electronic signature page}
Su (Suong) Tran
CMC Lead, Office of New Drug Quality Assessment
Date *{see appended electronic signature page}*

{See appended electronic signature page}
Ali Al Hakim
Branch Chief, Office of New Drug Quality Assessment
Date *{see appended electronic signature page}*

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

/s/

SUONG T TRAN
11/22/2011

ALI H AL HAKIM
11/22/2011

Division of Metabolism and Endocrinology Products

NDA:	**203314**
Applicant:	Novo Nordisk Inc.
Stamp Date:	**29-SEP-2011**
PDUFA Date:	**29-JUL-2012**
Proposed Proprietary Name:	Tresiba
Established Name:	Insulin degludec
Dosage form and strength:	Injectable solution, 100 U/mL and 200 U/mL
Route of Administration:	Subcutaneous injection
Indications:	Treatment of diabetes.
CMC Lead:	Su (Suong) Tran, ONDQA
ONDQA Fileability:	**Yes**

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

Clarify what the reference is for the units of the dosage strength (b) (4). In the proposed drug product specification, the content of insulin degludec in the formulation is measured as "nmol", and you state that 100 (b) (4) corresponds to 600 nmol/ml. Provide a reference for the units of the dosage strength (b) (4), comparable to that submitted for your insulin detemir product (i.e., one unit (24 nmol) of insulin detemir corresponds to one IU of human insulin (6 nmol) based on clinical data).

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharmaceutics	*May not be applicable. This is an injectable product, and the commercial formulation was used in Phase 3 studies.*
CDRH	Review of the multi-dose pen injector.
EA	Categorical exclusion request will be assessed by Primary Reviewer.
EES	EER was sent to Office of Compliance on 13-OCT-2011.
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 (b) (4) 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.*

This is an electronic NDA, filed as a 505(b)(1) application. The associated IND is IND 73198.

The drug substance insulin degludec is a New Molecular Entity (NME) for the CMC review purpose. It is produced by recombinant DNA (rDNA) technology in *Saccharomyces cerevisiae*. Insulin degludec is a human insulin mutant where Thr B30 is deleted and the ε-amino group of Lys B29 is coupled with hexadecanedioic acid via a γ-Glu spacer. Insulin degludec is designed to be an ultra-long-acting basal insulin with a duration of action beyond 42 hours. Similarly to the approved insulin detemir (same applicant), after subcutaneous injection, the di-hexameric form self-assembles into soluble multi-hexamers and binds to albumin, creating a depot in the subcutaneous tissue. Monomers slowly and continuously enter circulation, resulting in a long half-life.

The 100 U/mL drug product is a sterile solution for subcutaneous injection, packaged (b) (4) in a disposable 3-mL pen injector (PDS290 or FlexTouch). The pen injector includes the same 3-mL cartridge; the device and cartridge are assembled at the manufacturing site.

The 200 U/mL drug product is a sterile solution for subcutaneous injection, packaged **only** in a disposable 3-mL pen injector (PDS290 or FlexTouch). The pen injector includes a 3-mL product cartridge; the device and cartridge are assembled at the manufacturing site.

The product has an approximate pH of 7.6. The inactive ingredients are glycerol 19.6 mg/mL, phenol 1.50 mg/mL, metacresol 1.72 mg/mL, zinc (32.7 mcg/mL in the 100 U/mL and 71.9 mcg/mL in the 200 U/mL), and water for injection. Hydrochloric acid or sodium hydroxide may be added to adjust the pH.

Has all information requested during the IND phases and at the pre-NDA meetings been included?

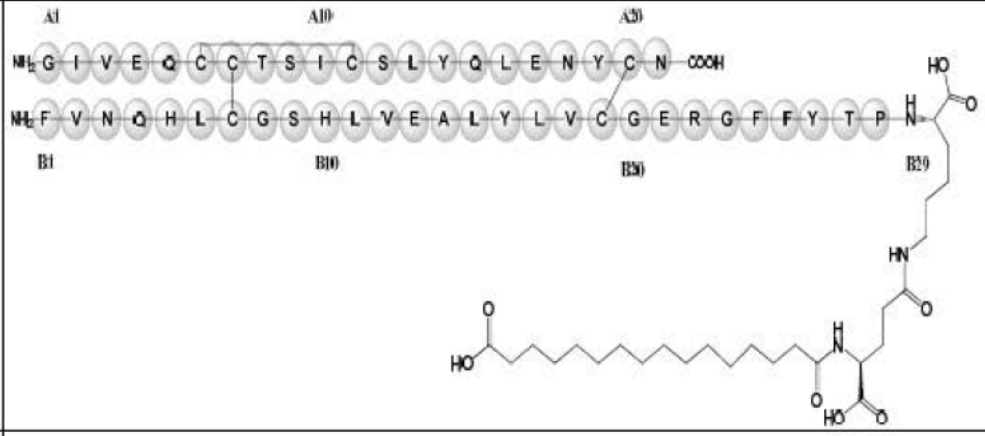
See the discussion in the review.

Drug substance

Insulin degludec is an analogue of human insulin where threonine in position B30 has been omitted and where the ε-amino group of lysine B29 has been coupled with hexadecanedioic acid via a γ-glutamic acid spacer. Insulin degludec is produced using recombinant DNA technology in yeast (*Saccharomyces cerevisiae*) and chemical modification.

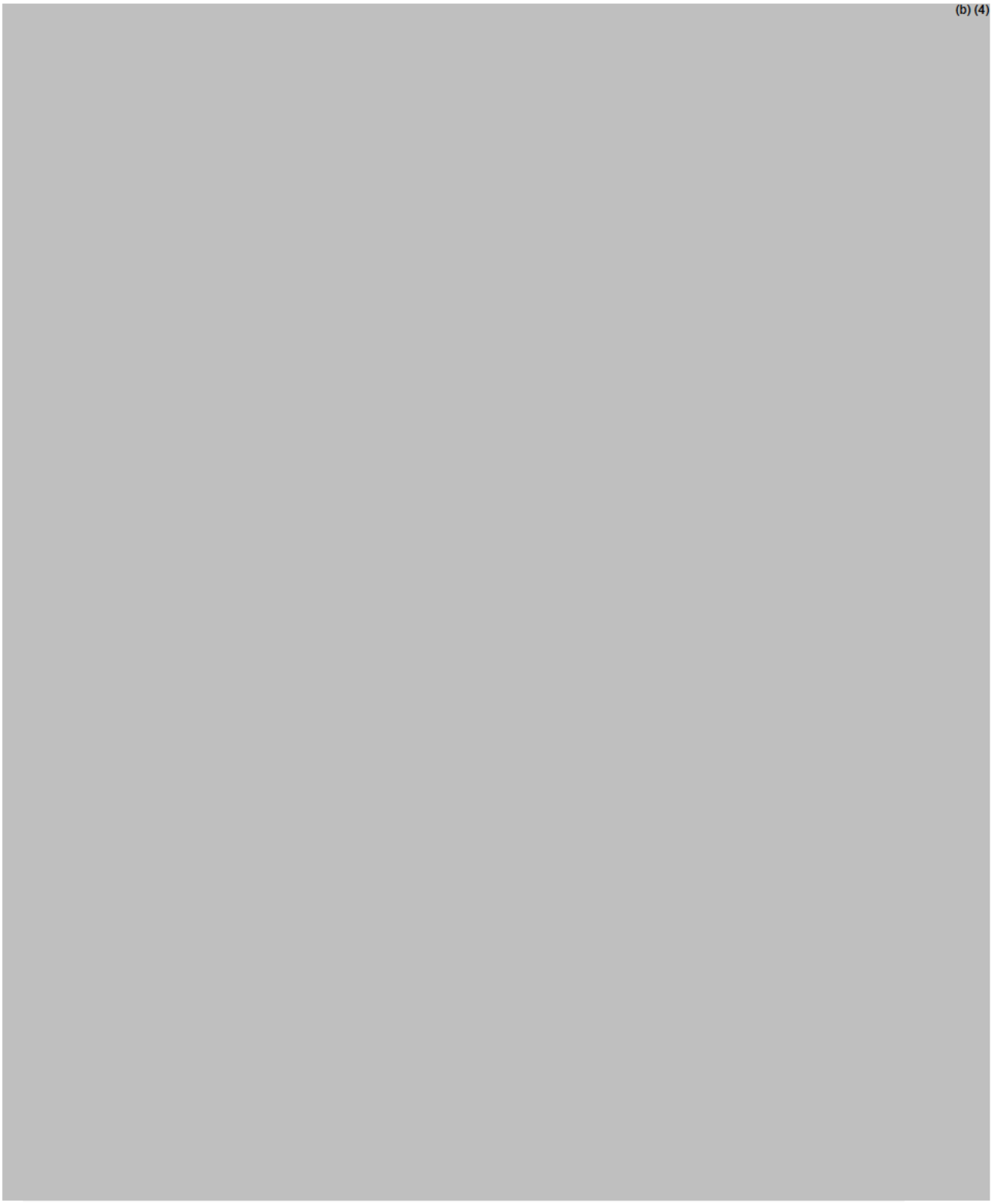
The structural characteristics of insulin degludec are provided in Table 2.

Table 2 Structural characteristics

Characteristic	Result
Structural formula	
Molecular formula	$C_{274}H_{411}N_{65}O_{81}S_6$
Theoretical monoisotopic weight	(b) (4) Da
Theoretical average molecular weight	6103.97 Da

Manufacture of the drug substance:

(b) (4)



Review comments:

- Insulin degludec is a recombinant human insulin mutant. (b) (4)
- Insulin degludec is produced (b) (4) Saccharomyces cerevisiae strain (b) (4)). (b) (4) . The cell bank characterization will include information on adventitious agents.
- The applicant states that (b) (4)
- (b) (4)

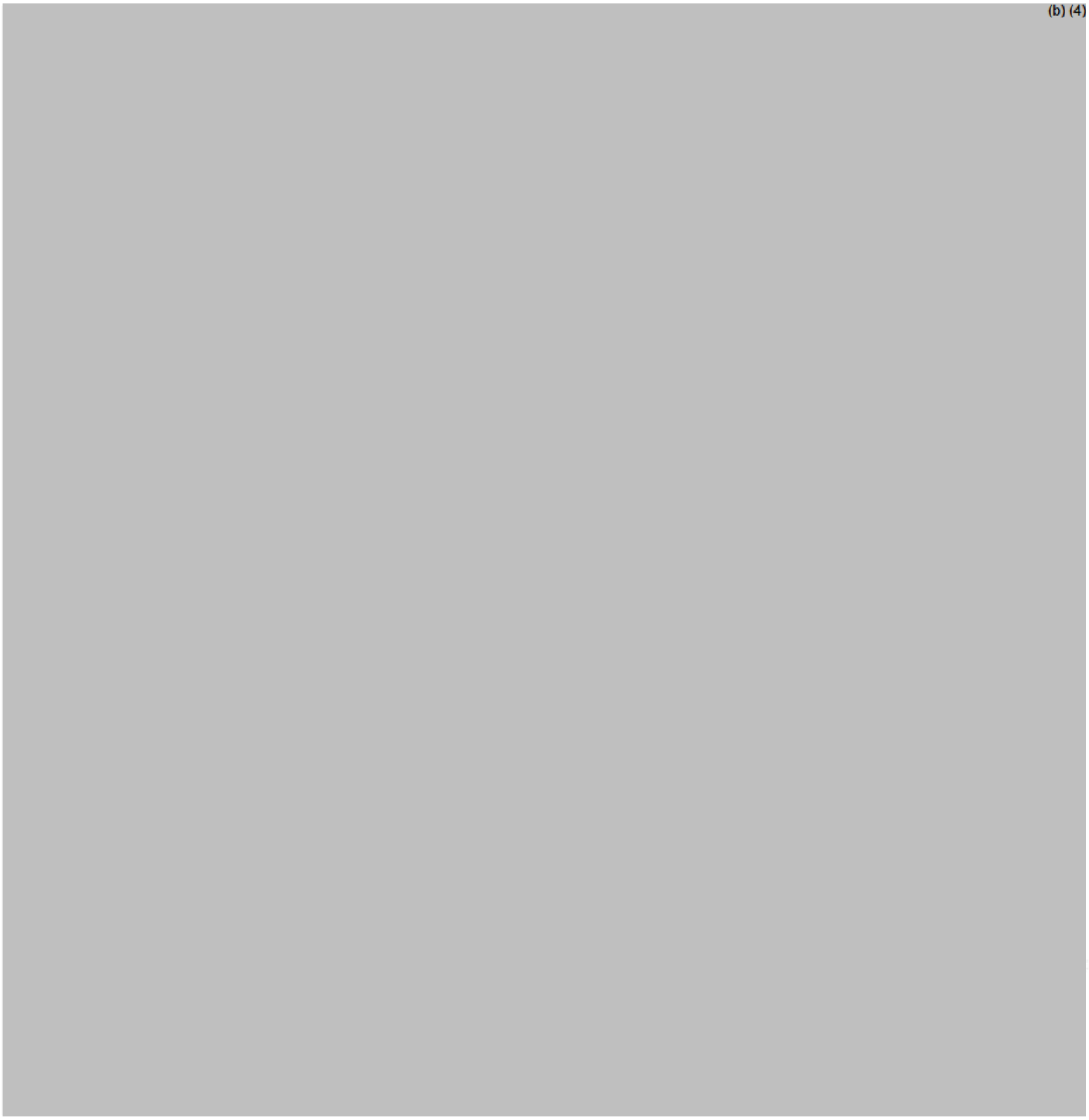

(b) (4)

Table 21 Batches of insulin degludec included in comparability studies

Comparability study	Batch	Campaign	Process	Use of batch
1	O454-05-E003	1	(b) (4)	Phase 1 clinical trials, Non-clinical trials (4 weeks and 6 months toxicity)
1	LP454K4S02	4		Stability, Primary Reference Material, Released for clinical trials (phase 1 and 2)
1 and 2	LP454K4T01	5		Non-clinical trials (12 months toxicity)
1 and 2	VK0SHP001	10		Stability. Primary and Secondary Reference Material. Released for phase 3 clinical trials
2	XK0SHP002	11		Released for phase 3 clinical trials
2 and 3	XK0SHP014	12		Stability. Released for phase 3 clinical trials
2 and 3	XK0SHP015	12		Stability. Released for phase 3 clinical trials
3	XK0SHP016	12		Stability. Released for phase 3 clinical trials
3	YK0SHP006	PV		Stability. Released to be used for marketed products
3	YK0SHP007	PV		Stability. Released to be used for marketed products
3	YK0SHP008	PV		Stability. Released to be used for marketed products
3	AK0SHP007	PV		Stability. Released to be used for marketed products
3	AK0SHP008	PV		Stability. Released to be used for marketed products
3	AK0SHP010	PV		Stability. Released to be used for marketed products

* Except that the (b) (4) f insulin degludec was not implemented

Characterization of the drug substance:

(b) (4)

Table 1 Methods and results for elucidation of structural and physico-chemical properties of insulin degludec

Test	Function	Conclusion for insulin degludec
Test methods used in structural characterisation		
[redacted]		(b) (4)
Mass spectrometry (MS)	Molecular weight of intact drug substance	The structural formula of insulin degludec has been confirmed by mass spectrometry, showing experimentally determined monoisotopic masses in accordance with the theoretical value, see Table 3
(b) (4) spectroscopy	(b) (4) structure	(b) (4)

Test	Function	Conclusion for insulin degludec
Bioactivity	(b) (4) structure	The bioactivity of insulin degludec drug substance has been tested during drug substance batch release, (b) (4) drug substance specification test method (b) (4) . A further discussion of the biological activity of insulin degludec, including isomers and isolated degradation products of insulin degludec, is provided in section 2
Test methods used in elucidation of physico-chemical properties		
Visual appearance	Description	By visual inspection, all batches of insulin degludec drug substance appear as (b) (4).
Solubility	Solubility	The solubility in water is more than (b) (4) mg/ml at pH 7.4. Between pH 3.0 to pH 5.5, the solubility decreases dramatically. In this pH range, the solubility is below (b) (4) ug/ml. At pH below 2.0 and at pH above 6.5, the solubility is greater than (b) (4) mg/ml. The solubility in methanol is (b) (4) mg/ml and the solubility in ethanol is (b) (4) mg/ml
pII in water	pII	The pII of an aqueous solution of insulin degludec drug substance is approximately 7.4
Isoelectric focusing	Charge heterogeneity, pI	The isoelectric point has been experimentally determined by isoelectric focusing to be (b) (4) (see Figure 4). All batches showed an identical focusing pattern. A minor band more acidic than the main band from insulin degludec is observed in the IEF gel, however this is an analytical artefact. (b) (4)
UV absorption	UV absorbance	In the absorbance spectrum (210 – 350 nm) of insulin degludec, no absorbance at wavelengths higher than (b) (4) nm was observed as is to be expected for a pure protein (see Figure 5). The molar extinction coefficient at (b) (4) nm is approximately (b) (4) $M^{-1}cm^{-1}$
Water absorption	Water absorption behaviour	The dynamic vapour sorption/desorption behaviour of insulin degludec has been measured, showing that insulin degludec is hygroscopic. At 24.9 °C and a relative humidity of 40%, the equilibrium moisture content is close to (b) (4) %, see Figure 6. At this temperature the water absorption increases linearly from (b) (4) % RH, whereas water absorption is slightly increased from linearity in the area above 60% RH.
RP-HPLC (Reversed Phase High Pressure Liquid Chromatography)	(b) (4) properties	The (b) (4) properties of insulin degludec have been evaluated using two different RP-HPLC methods (method A and method B). The different batches tested showed the expected and identical chromatographic behaviour, see Figure 7 and Figure 8
GPC (Gel Permeation Chromatography)	Hydrodynamic properties	The hydrodynamic properties of insulin degludec have been evaluated by GPC. The different batches showed the expected and identical chromatographic behaviour, see Figure 9

- **Characterization of the drug substance**. The reviewer will confirm that the proposed structure of the drug substance is adequately supported by analytical data. The characterization results will determine what attributes should be included in the specifications.
- **Drug substance specification** (copied on the next page).
  - The specification includes a bioassay test. The KIRA-TRIFMA cell-based bioactivity assay measures the activation of the human insulin receptor upon binding to insulin degludec, using Chinese hamster ovary cells transfected with human insulin receptor. Data are provided for the correlation between potency (bioactivity) and the total (b) (4) content by RP-HPLC (see summary copied below); the information will be evaluated by the reviewer.

Table 1 Summary of correlation between bioactivity and (b) (4) content

Material	Mean value for correlation	RSD for correlation (%)	Number of data points
Insulin degludec drug substance at release	(b) (4)		
Insulin degludec drug substance in stability			
Insulin degludec drug products in stability			

  - In addition to the cell-based bioassay, the drug substance specification includes content testing by RP-HPLC. It is unclear whether this test is specific to insulin degludec because it is described as "(b) (4) which can mean to include all (b) (4) variants in the sample. The actual calculation in the test method seems to be specific for insulin degludec content.
  - The drug substance specification does not include testing for contaminants such as host cell proteins, residual DNA, residual solvents and reagents, and for certain minor product related impurities such as the (b) (4). The reviewer will determine whether the applicant's justification for the omission is acceptable.

Table 1 Drug substance specification for insulin degludec

Test	Analytical procedure	Acceptance criteria
Appearance	Visual inspection No. A3105a	Complies [note 1]
Identity	(b) (4) No. A7093a	Complies [note 2]
Identity	RP-HPLC No. A7091a	Complies [note 3]
Content ((b) (4)	RP-HPLC No. A7091a	(b) (4) nmol/mg as is
(b) (4) impurities	RP-HPLC No. A7090a	≤ (b) (4)%
(b) (4) related substances	RP-HPLC No. A7090a	≤ %
(b) (4) impurities	RP-HPLC No. A7090a	≤ %
High Molecular Weight Proteins	GPC No. A7092a	≤ %
Bioactivity [note 4]	KIRA-TRIFMA No. B2003a	(b) (4) nmol/mg as is
Loss on Drying	Drying Ph Eur, USP, JP	≤ (b) (4)
Bacterial Endotoxins	Kinetic chromogenic method Ph Eur Method D, USP, JP	≤ (b) (4) IU/mg [note 5]
Total Aerobic Microbial Count	Plate count Ph Eur, USP, JP	≤ (b) (4) CFU per g

Notes:
[1] Complies means verified to be a (b) (4).
[2] Complies means verified to be insulin degludec by (b) (4)
[3] Complies means verified to be insulin degludec.
[4] Tested on one out of 100 batches or one batch a quarter, whichever comes first.
[5] One International Unit for Endotoxin (IU), used in Ph Eur is equal to one Endotoxin Unit (EU), used in USP and JP

- **Information on the product-related substances and impurities** is included in the NDA (see copied summary below). As per ICH Q6B, acceptance criteria or limits should be based on data from nonclinical, clinical, and stability batches. The reviewer will document the biological activity of the related substances. In addition, the reviewer will evaluate the

characterization of process-related and product-related impurities and assess the capability of the purification process to remove/reduce them. In the proposed drug substance specification, the product-related impurities and substances are grouped according to their physical property of being (b) (4) or (b) (4) The reviewer will determine whether each grouping is adequately justified.

Table 6 Potential product related substances and impurities in insulin degludec

Type of related substances and impurities	Classification	Identity/Content
Related substances and impurities analysed with RP-HPLC	(b) (4) impurities determined by RP-HPLC	(b) (4)
	(b) (4) related substances determined by RP-HPLC	
	(b) (4) impurities determined by RP-HPLC	
Impurities analysed with GPC	HMWP determined by GPC	(b) (4)

- **Container closure and shelf life of the drug substance**. The reviewer will evaluate the safety and compatibility of the container closure system used to store the drug substance. Primary stability data include 6 primary drug substance batches at production scale (up to 30 months at the long-term – 20 °C) and 6 process validation batches (6 months at the long-term -20 °C). Based on all available stability data and with no extrapolation to extend the dating period beyond the long term data, the reviewer will determine a shelf life (i.e., not a retest period) for the protein drug substance.

Drug product:

Insulin degludec 100 U/ml and insulin degludec 200 U/ml is a clear, colourless solution. The solution is filled in a [redacted]

The composition of insulin degludec 100 U/ml and insulin degludec 200 U/ml is listed in Table 1.

Table 1 Composition of insulin degludec 100 U/ml

Name of components	Quantity per ml		Function	Reference to standards
	Insulin degludec 100 U/ml	Insulin degludec 200 U/ml		
Active substance				
Insulin degludec	600 nmol	1200 nmol	Drug substance	Novo Nordisk
Excipients				
Phenol[1]	[redacted]	[redacted]	[redacted]	Ph Eur ,USP, JP
Metacresol[1]				Ph Eur, USP
Glycerol				Ph Eur ,USP, JP
Zinc				Ph Eur ,USP, JPE[2]
Hydrochloric acid[3]	q.s.	q.s.	pH adjustment	Ph Eur ,USP, JP
Sodium hydroxide[3]	q.s.	q.s.	pH adjustment	Ph Eur ,USP, JP
Water for injections	[redacted]		[redacted]	Ph Eur ,USP, JP

[1] An overage up to [redacted] of the [redacted] is added [redacted]

[2] Zinc is added [redacted] according to Ph Eur, USP, JPE

[3] To reach pH [redacted]

- **Formulations**. The applicant confirms that the primary stability batches and Phase 3 clinical formulations [IDeg(M) for the 100 U/mL and IDeg (P) for the 200 U/mL] are the same as the commercial formulations, manufactured at the commercial site. The 2 dosage strengths differ in [redacted].
- **Dosage strength**. It is unclear what the reference is for the units of the dosage strength [redacted]. In the proposed drug product specification, content of insulin degludec in the formulation is measured as "nmol". The applicant states that the [redacted] corresponds to 600 nmol/ml without any rationale. An explanation comparable to that submitted for insulin detemir should be provided by the applicant (see the 74-day letter comment). The ClinPharm team mentioned at the filing meeting that [redacted] based on clinical data. This information should be confirmed by the applicant in the CMC section.

- **Overage of** [redacted]. Based on the Microbiology input and stability data, the reviewer will determine whether the [redacted] overage of [redacted] will be sufficient to assure [redacted].

Drug product manufacture.

Insulin degludec 100 U/ml is prepared [redacted]

- [redacted]

Drug product specification. (copied on the next page)

- **Insulin degludec content**. The drug product specification does not include testing for biological activity. Data are provided for the correlation between potency (bioactivity) and [redacted] content by RP-HPLC; the information will be evaluated by the reviewer.
- **Filling volume of the drug product**. The drug product specification does not have Filling Volume because this testing is performed as an [redacted].
- **Metacresol content, phenol content, bacterial endotoxins, and sterility**. These attributes will be evaluated as part of the Microbiology review.
- **Dose accuracy.** Dose accuracy in the drug product specification only applies to the pen injector assembly and will be evaluated as part of the CDRH review.

- **Limits on degradation products.** The drug product specifications (release and stability) include the same groups of product-related substances, process-related and product-related impurities as in the drug substance specification, although with higher limits. The reviewer will determine whether the higher limits are adequately justified by batch release and stability data of the primary stability batches and whether they are supported by all available data (as per ICH Q6B, acceptance criteria or limits for these impurities should be based on data from nonclinical, clinical, and stability batches). Stability data to be considered should include the in-use data.

Table 1 Release and shelf life limits for insulin degludec 100 U/ml

Test	Analytical procedure	Acceptance criteria
Characters: Macroscopy	Visual inspection No. A3196b	Complies[1]
Identity of insulin degludec	RP-HPLC No. A6021a	Complies[2]
Content of insulin degludec	RP-HPLC No. A6021a	(b) (4) mol/ml
pH	Potentiometry (Ph Eur, USP)	(b) (4)
High Molecular Weight Proteins	GPC No. A6022a	Release: (b) (4) Shelf life: %
Insulin degludec: (b) (4) mpurities	RP-HPLC No. A6020a	Release: (b) (4) Shelf life %
(b) (4) related substances	RP-HPLC No. A6020a	Release: (b) (4) Shelf life: %
(b) (4) mpurities	RP-HPLC No. A6020a	Release: (b) (4) Shelf life: %
Zinc total	AAS (Ph Eur[3], USP)	(b) (4) µg/ml
Bacterial endotoxins	Chromogenic Kinetic method (Ph Eur Method D, USP)	(b) (4) IU/ml[4,5]
Sterility	(b) (4) method (Ph Eur, USP)	Complies
Identity of metacresol	RP-HPLC No. A6021a	Complies[6]
Identity of phenol	RP-HPLC No. A6021a	Complies[7]
Metacresol	RP-HPLC No. A6021a	(b) (4) mg/ml
Phenol	RP-HPLC No. A6021a	mg/ml

Test	Analytical procedure	Acceptance criteria
Particulate matter ≥ 10 µm ≥ 25 µm	Light obscuration (Ph Eur, USP)	(b) (4) /container ontainer
Dose accuracy[8]	Weighing A29001a	Complies[9]

[1] Complies means a (b) (4) free from particulate matter

[2] Complies means verified as insulin degludec

[3] This method complies with the requirements in the monograph for Insulin preparations injectable, Ph Eur

[4] One International Unit (IU) of endotoxin is equal to one Endotoxin Unit (EU)

[5] This limit corresponds to (b) (4) IU of endotoxin/100 U of insulin degludec

[6] Complies means verified as metacresol

[7] Complies means verified as phenol

[8] Only performed when the (b) (4) cartridge is assembled into PDS290 pen-injector, item no. 5-9560-xx

[9] Complies means that the specification limit (b) (4) units is fulfilled using ISO 3951 part 1 or 2 (the limit is in accordance with ISO 11608-1)

Table 2 Release and shelf life limits for insulin degludec 200 U/ml

Test	Analytical procedure	Acceptance criteria
Characters: Macroscopy	Visual inspection No. A3196b	Complies[1]
Identity of insulin degludec	RP-HPLC No. A6021a	Complies[2]
Content of insulin degludec	RP-HPLC No. A6021a	(b) (4) nmol/ml (b) (4) %]
pH	Potentiometry (Ph Eur, USP)	(b) (4)
High Molecular Weight Proteins	GPC No. A6022a	Release: (b) (4) Shelf lif %]
Insulin degludec: (b) (4) impurities	RP-HPLC No. A6020a	Release: (b) (4) Shelf life %]
(b) (4) related substances	RP-HPLC No. A6020a	Release: ≤ (b) (4) Shelf life: %]
(b) (4) impurities	RP-HPLC No. A6020a	Release: ≤ (b) (4) Shelf life: %]

Test	Analytical procedure	Acceptance criteria
Zinc total	AAS (Ph Eur[3], USP)	(b) (4) µg/ml
Bacterial endotoxins	Chromogenic kinetic method (Ph Eur Method D, USP)	(b) (4) IU/ml[4+5]
Sterility	Membrane filtration method (Ph Eur, USP)	Complies
Identity of metacresol	RP-HPLC No. A6021a	Complies[6]
Identity of phenol	RP-HPLC No. A6021a	Complies[7]
Metacresol	RP-HPLC No. A6021a	(b) (4) mg/ml
Phenol	RP-HPLC No. A6021a	(b) (4) ng/ml
Particulate matter ≥ 10 µm ≥ 25 µm	Light obscuration (Ph Eur, USP)	≤ (b) (4) container ≤ ontainer
Dose accuracy	Weighing A29001a	Complies[8]

[1] Complies means a (b) (4) free from particulate matter

[2] Complies means verified as insulin degludec

[3] This method complies with the requirements in the monograph for Insulin preparations injectable, Ph Eur

[4] One International Unit (IU) of endotoxin is equal to one Endotoxin Unit (EU)

[5] This limit corresponds to (b) (4) IU of endotoxin/100 U of insulin degludec

[6] Complies means verified as metacresol

[7] Complies means verified as phenol

[8] Complies means that the specification limit (b) (4) nits is fulfilled using ISO 3951 part 1 or 2 (the limit is in accordance with ISO 11608-1)

Container closure system of the drug product.

The primary packaging is a (b) (4) The cartridge is made of clear, colourless type I (b) (4) glass. The closure at one end of the (b) (4) cartridge is a (b) (4) rubber disc with the (b) (4) rubber (Type 1, Ph Eur) in contact with the drug product. At the opposite end there is a red (b) (4) rubber (Type 1, Ph Eur) plunger.

The (b) (4) cartridge (b) (4) assembled into a pre-filled disposable device, a PDS290 pen-injector. For insulin degludec 100 U/ml the (b) (4)

The pen injector device will be evaluated by CDRH.

The NDA includes information on compatibility, extractables, and leachables for the primary container closure system (i.e., cartridge). The applicant follows ICH Q3 guidelines in evaluating the safety of the

extractable and leachables. The information will be assessed by the reviewer, with input from the PharmTox team if necessary.

Stability.

The unopened product is stored under refrigeration, 2-8 °C.

- For the 100 U/ml strength: an expiry of 30 months is proposed by the applicant based on 30-month stability data at 5 °C and 6-month at 25 °C for three primary stability batches. These batches were used in phase 3 clinical studies. Supportive data include validation and production batches.
- For the 200 U/ml strength: an expiry of 30 months is proposed by the applicant based on 18-month stability data at 5 °C and 6-month at 25 °C for three primary stability batches. These batches were used in phase 3 clinical studies. Supportive data include validation and production batches. Of note is a supportive batch with 30-month long term data. The reviewer will consider all available data, including data for the lower strength and accounting for the same/different container closure systems, and determine whether the proposed expiry is appropriate (per ICH Q5C guidelines).

For both strengths, an in-use shelf life of the opened product is proposed to be 56 days at room temperature, based on 8-week stability data at 30 °C. The in-use testing was performed on fresh and aged samples, which were subjected to movement and needle penetration to simulate patient use. A photostability report is provided.

Comparability protocols. The NDA includes two comparability protocols for post-approval changes: additional assembly facility for packaging the drug cartridges into the pen injectors and additional drug product manufacturing facility. The reviewer will evaluate the adequacy of the testing programs proposed to demonstrate comparability of the products before and after the change in manufacturing sites. It is noted that a comparability protocol for a new manufacturing facility may not appropriate for downgrading a post-approval submission because such a change requires a GMP inspection request. Input from the Post-Marketing Branch may be obtained.

GMP facilities: **EER was sent** to the Office of Compliance on 13-OCT-2011

Table 1 Drug Substance Establishment Information

Manufacturing Location	Contact Information	Activity
Novo Nordisk A/S Hallas Allé DK-4400 Kalundborg Denmark **FEI Number: 3002807751** **CFN Number: FCDA069** **DUNS Number: 305156788**	Torben Enstrøm Corporate Vice President Global Quality Audits Telephone. +011 45 4443 3172 Direct. +011 45 3075 3172 e-mail: toe@novonordisk.com	(b) (4)
Novo Nordisk A/S Novo Allé DK-2880 Bagsværd Denmark **FEI Number: 3000151819** **(Changed from 3001392218 per FDA as of 6-16-10)** **CFN Number: FCDA039** **DUNS Number: 312296002**	Torben Enstrøm Corporate Vice President Global Quality Audits Telephone. +011 45 4443 3172 Direct. +011 45 3075 3172 e-mail: toe@novonordisk.com	
All sites ready for inspection		

Table 2 Drug Product Establishment Information

Manufacturing Location	Contact Information	Activity
Novo Nordisk A/S Novo Allé DK 2880 Bagsværd Denmark **FEI Number: 3000151819 (Changed from 3001392218 per FDA as of 6-16-10)** **CFN Number: FCDA039** **DUNS Number: 312296002** **DMF number associated with the process(es) conducted at the facility: 21494**	Torben Enstrøm Corporate Vice President Global Quality Audits Telephone. +011 45 4443 3172 Direct. +011 45 3075 3172 e-mail: toe@novonordisk.com	(b) (4)
Novo Nordisk A/S Brennum Park DK-3400 Hillerød Denmark **FEI Number: 3003131673** **CFN Number: FCDA070** **DUNS Number: 309477891**	Torben Enstrøm Corporate Vice President Global Quality Audits Telephone. +011 45 4443 3172 Direct. +011 45 3075 3172 e-mail: toe@novonordisk.com	(b) (4)
Novo Nordisk A/S Hallas Allé DK-4400 Kalundborg Denmark **FEI Number: 3002807751** **CFN Number: FCDA069** **DUNS Number: 305156788**	Torben Enstrøm Corporate Vice President Global Quality Audits Telephone. +011 45 4443 3172 Direct. +011 45 3075 3172 e-mail: toe@novonordisk.com	(b) (4)
All sites ready for inspection		

PRODUCT QUALITY
FILING REVIEW FOR NDA (ONDQA)

NDA Number: 203314

Established/Proper Name: Insulin degludec

Applicant: Novo Nordisk **Letter Date: 29-SEP-2011** **Stamp Date: 29-SEP-2011**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		
B. facilities*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			
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		

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		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
D. drug substance/active pharmaceutical ingredient (DS/api)				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	x		
12.	Does the section contain a description of the DS manufacturing process?	X		
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.	Have any biowaivers 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		Review issue: whether data and analysis are adequate to support expiry
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		x	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	
F. methods validation (Mv)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	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		
I. Labeling				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	x		
33.	Have the immediate container and carton labels been provided?	x		
J. filing conclusion				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	x		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	x		See page 1 of the IQA/filing review.

{See appended electronic signature page}
Su (Suong) Tran
CMC Lead, Office of New Drug Quality Assessment
Date *{see appended electronic signature page}*

{See appended electronic signature page}
Ali Al Hakim
Branch Chief, Office of New Drug Quality Assessment
Date *{see appended electronic signature page}*

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

/s/

SUONG T TRAN
11/22/2011

ALI H AL HAKIM
11/22/2011