CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208583Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation:
Approval
(including the Facility Review/Manufacturing Inspection Recommendation)

NDA 208583
Review #1
Review Date (see page 6)

Drug Name/Dosage Form	insulin degludec and liraglutide
Strength	100 Units and 3.6 mg per mL
Route of Administration	subcutaneous injection
Rx/OTC Dispensed	Rx
Applicant	Novo Nordisk

SUBMISSION(S) REVIEWED	DOCUMENT DATE
0000	9/14/15
0002	9/22/15
0004	10/28/15
0010	12/22/15
0019	1/29/16
0031	3/15/16
0032	3/18/16

Quality Review Team

DISCIPLINE	REVIEWER	DIVISION/OFFICE
Application Technical Lead	Suong Tran	New Drug Products I/ONDP
Regulatory Business Process Manager	Anika Lalmansingh	Regulatory Business Process Management I/OPRO
Drug Product	Xavier Ysern	New Drug API/ONDP
Process	Peter Krommenhoek	Process Assessment II/OPF
Microbiology	Peggy Kriger	Process Assessment II/OPF
Facility	Peter Krommenhoek	Inspectional Assessment/OPF
Facility	Christopher Brown	CDRH Compliance

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	V		(b) (4)	Adequate	5/3/2016	by P. Kriger
	V			Adequate	8/15/2011	by S. Langille
	III			Sufficient information provided in NDA (by X.Ysern/D.Christner)		

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	022341	liraglutide
NDA	203314	insulin degludec

2. CONSULTS: n/a

Executive Summary

I. Recommendation

The recommendation from the Office of Pharmaceutical Quality (including the manufacturing inspection recommendation) is for approval.

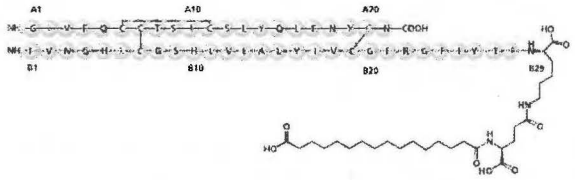
Labeling comments will be finalized during the multi-disciplinary review managed by OND.

II. Summary of Quality Assessment

This NDA is a 505(b)(1) application but not for an NME because the applicant has approved NDAs 22341 for liraglutide and 203314 for insulin degludec.

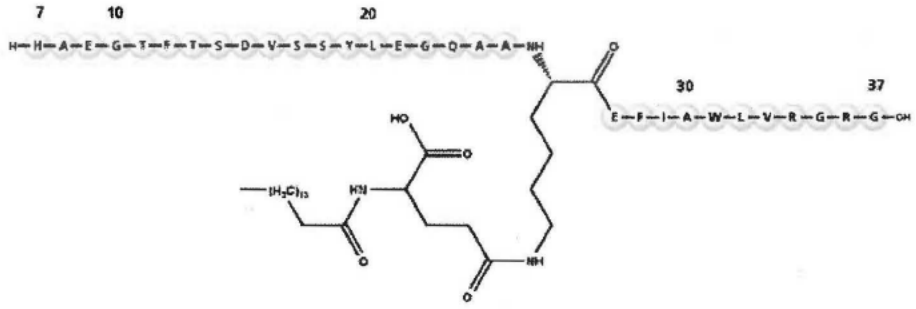
A. Drug Substance

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). Insulin degludec has a molecular formula of C274H411N65O81S6 and a molecular weight of 6103.97. It has the following structure:



NDA 203314 Tresiba (insulin degludec), by the same applicant, is referenced for all CMC information on the drug substance insulin degludec. The NDA is currently approved and the reference is adequate.

Liraglutide is an analog of human GLP-1 and acts as a GLP-1 receptor agonist. The peptide precursor of liraglutide, produced by a process that includes expression of recombinant DNA in Saccharomyces cerevisiae, has been engineered to be 97% homologous to native human GLP-1 by substituting arginine for lysine at position 34. Liraglutide is made by attaching a C-16 fatty acid (palmitic acid) with a glutamic acid spacer on the remaining lysine residue at position 26 of the peptide precursor. The molecular formula of liraglutide is C172H265N43O51 and the molecular weight is 3751.2 Daltons. The structural formula is:



NDA 22341Victoza (liraglutide), by the same applicant, is referenced for all CMC information on the drug substance liraglutide. The NDA is currently approved and the reference is adequate.

B. Drug Product

The drug product is a solution for SC injection and a fixed ratio combination drug consisting of 100 Units insulin degludec and 3.6 mg liraglutide per mL. It is packaged in a 3-mL cartridge, which is then assembled in a disposable single-user multiple-dose pen injector for commercial distribution. The total pen content is 300 Units insulin degludec and 10.8 mg liraglutide.

Inactive ingredients are (per mL): glycerol 19.7 mg, phenol 5.70 mg, zinc 55 mcg, and water for injection. Hydrochloric acid or sodium hydroxide may be added to adjust pH (to 8.15). There is an overage (b) (4) due to expected loss during manufacture (b) (4) efficacy testing data are provided in the NDA.

The drug product manufacturing process is standard for this type of dosage form and includes: (b) (4)

The manufacturing process was validated/qualified for three consecutive batches at commercial scale of (b) (4) L. The critical quality attributes of the drug product are listed in the table above and are addressed in the drug product review. The following steps during the manufacture of insulin degludec/liraglutide (100 U/3.6 mg/mL) are critical: (b) (4)

(See the separate review of the device manufacture by CDRH Compliance).

The drug product specification includes attributes standard for this type of drug substance (protein/peptide) and dosage form (injectable solution), and these attributes are the same as in NDAs 22341 and 203314 (actual test methods and acceptance criteria may vary to be product-specific). A study report on the

correlation between bioactivity and content of degradants is included. NDAs 22341 and 203314 are referenced for information on the correlation between bioactivity and drug content for the active ingredients.
Compared to the degradants in the products of NDAs 22341 and 203314, there is no new degradant in the new drug product. (b) (4) (b) (4)

(See the separate review of the device specification, including dose accuracy, by CDRH Device Evaluation).

Container closure system: The primary (product-contact) components consist of a USP type 1 glass cartridge (3-mL), with a (b) (4) rubber disc on one end and a (b) (4) rubber plunger on the other end. Extractable and leachable data are reported in the NDA with supporting safety information.
(See the separate review of the device components by CDRH Device Evaluation).

Expiration Date & Storage Conditions: 24 months at 2-8 °C, with an in-use storage for up to 21 days at room temperature or under refrigeration, based on real-time stability data for the primary batches with the commercial formulation.

There is a difference in the (b) (4) phase 3 formulation (b) (4) and the commercial formulation (b) (4). Comparability of the 2 formulations was confirmed via a BE study (See the review by Clinical Pharmacology), a comparison of degradation products, and stability profiles.

C. Summary of Drug Product Intended Use

Proprietary Name	[not finalized by GRMP goal; see CDTL's memo]
Non Proprietary Name of the Drug Product	insulin degludec and liraglutide
Non Proprietary Name of the Drug Substance	insulin degludec and liraglutide
Proposed Indication(s)	[not finalized by GRMP goal; see CDTL's memo]
Duration of Treatment	chronic
Maximum Daily Dose	[not finalized by GRMP goal; see CDTL's memo]
Alternative Methods of Administration	not applicable

D. Biopharmaceutics Considerations not applicable
E. Novel Approaches: not applicable
F. Any Special Product Quality Labeling Recommendations: not applicable
G. Life Cycle Knowledge Information (see Attachment)

OVERALL ASSESSMENT AND SIGNATURE:

Application Technical Lead Signature: I concur with the reviewers' conclusions.

Suong T. Tran -S

Digitally signed by Suong T. Tran -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Suong T. Tran -S, 0.9.2342.19200300.100.1.1=1300101629
Date: 2016.05.09 16:00:52 -04'00'

Su (Suong) Tran, PhD

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ENVIRONMENTAL ANALYSIS

Formula for calculation of EIC-Aquatic = A x B x C x D, where

- A = kg drug substance year
- B = 1 1.214 x 10^{11} (liters day entering Publicly Owned Wastewater Treatment Plants)
- C = 1 365 (days per year)
- D = 10^{9} µg kg (conversion factor)

The calculation of EIC-Aquatic is based on the following data and assumptions:

- Maximum amount of drug substances (API) for treatment of type 1 and 2 diabetes and weight management estimated for 2024:
  - Insulin degludec in Xultophy®: (b) (4) kg year
  - Liraglutide in Xultophy®: (b) (4) kg year
  - Insulin degludec in other products: (b) (4) kg API year
  - Liraglutide in other products: (b) (4) kg API year
- The drug product usage is evenly distributed over the year and throughout the United States
- No metabolism or depletion mechanism is included.

Calculation of EIC-Aquatic for insulin degludec:

- EIC (degludec, Xultophy®) = (b) (4) *10^{9} / (1.214*10^{11}*365) = (b) (4) µg litre.
- EIC (degludec, other) = (b) (4) *10^{9} / (1.214*10^{11}*365) = (b) (4) µg litre.
- EIC (degludec, total) = (b) (4) *10^{9} / (1.214*10^{11}*365) = (b) (4) µg litre.

The calculated EIC for insulin degludec is thus (b) (4) µg litre for Xultophy® and (b) (4) µg litre for all Novo Nordisk products containing insulin degludec. This is significantly below the threshold value (b) (4) µg litre.

Calculation of EIC-Aquatic for liraglutide:

- EIC (liraglutide, Xultophy®) = (b) (4) *10^{9} / (1.214*10^{11}*365) = (b) (4) µg litre.
- EIC (liraglutide, other) = (b) (4) *10^{9} / (1.214*10^{11}*365) = (b) (4) µg litre.
- EIC (liraglutide, total) = (b) (4) *10^{9} / (1.214*10^{11}*365) = (b) (4) µg litre.

The calculated EIC for liraglutide is thus (b) (4) µg litre for Xultophy® and (b) (4) µg litre for all Novo Nordisk products containing liraglutide. This is significantly below the threshold value (b) (4) µg litre.

<u>Reviewer's Assessment</u>: The applicant's claim of categorical exclusion is acceptable; the estimated concentration of each drug at the point of entry into the aquatic environment will be below 1 ppb and there is no extraordinary circumstance.

Suong (Su) Tran, Application Technical Lead

Labeling

Labeling comments regarding the Prescribing Information and container/carton labels will be finalized during the multi-disciplinary review managed by OND.

"Highlights" Section

XULTOPHY® (insulin degludec and liraglutide (b) (4) injection) solution for subcutaneous (b) (4)

(b) (4)

"Full Prescribing Information" Section

Section 3 Dosage Forms and Strengths

(b) (4)

Section 11 Description

(b) (4)

Insulin degludec

Insulin degludec is an (b) (4) long-acting basal human insulin analog (b) (4) 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). Insulin degludec has a molecular formula of $C_{274}H_{411}N_{65}O_{81}S_6$ and a molecular weight of 6103.97. It has the following structure:

Figure 1: Structural Formula of Insulin degludec

Liraglutide

Liraglutide is an analog of human GLP-1 and acts as a GLP-1 receptor agonist. The peptide precursor of liraglutide, produced by a process that includes expression of recombinant DNA in *Saccharomyces cerevisiae*, has been engineered to be 97% homologous to native human GLP-1 by substituting arginine for lysine at position 34. Liraglutide is made by attaching a C-16 fatty acid (palmitic acid) with a glutamic acid spacer on the remaining lysine residue at position 26 of the peptide precursor. The molecular formula of liraglutide is $C_{172}H_{265}N_{43}O_{51}$ and the molecular weight is 3751.2 Daltons. The structural formula (Figure 2) is:

Figure 2: Structural formula of liraglutide

XULTOPHY is a sterile, aqueous, clear, and colorless solution. Each pre-filled pen contains 3 mL equivalent to 300 units insulin degludec and 10.8 mg liraglutide. (b) (4)

(b) (4)

XULTOPHY contains the following inactive ingredients per mL: glycerol 19.7 mg, phenol 5.70 mg, zinc 55 mcg, and water for injection. XULTOPHY has a pH of approximately 8.15. Hydrochloric acid or sodium hydroxide may be added to adjust pH.

Section 16 How Supplied/Storage and Handling

How Supplied

(b) (4)

Recommended Storage

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

After (b) (4) use, the XULTOPHY (b) (4) can be stored for 21 days at controlled room temperature (59°F to 86°F; 15°C to 30°C) or in a refrigerator (36°F to 46°F; 2°C to 8°C). Keep all XULTOPHY away from direct heat and light. **Always remove the needle after each injection and store the XULTOPHY (b) (4) without a needle attached. This prevents contamination and/or infection, or leakage of XULTOPHY, and will ensure accurate dosing. Always use a new needle for each injection to prevent contamination.**

(b) (4)

The storage conditions are summarized in Table 9:

Table 9: Storage Conditions for XULTOPHY (b) (4)

Prior to first use	After first use	
Refrigerated 36°F to 46°F (2°C to 8°C)	Room Temperature 59°F to 86°F (15°C to 30°C)	Refrigerated 36°F to 46°F (2°C to 8°C)
Until expiration date	21 Days	

End of the PI/After Section 17

Manufactured by:
Novo Nordisk A/S
DK-2880 Bagsvaerd, Denmark

Reviewer's Assessment:
See revisions made in the text above. With the revisions, the PI language is consistent with approved labeling for Tresiba and Victoza.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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Product Quality Microbiology Review

May 5, 2016

NDA: 208583

Drug Product Name
Proprietary: Xultophy
Non-proprietary: Insulin degludec/liraglutide

Review Number: #1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
9/12/2015	9/14/2015	N/A	9/24/2015
10/28/2015	10/28/2015	N/A	N/A
12/22/2015	12/22/2015	N/A	N/A
3/15/2016	3/15/2016	N/A	3/16/2016

Applicant/Sponsor
Name: Novo Nordisk Inc.
Address: P.O. Box 846, Plainsboro, NJ 08536
Representative: Rick Spring, Associate Director, Regulatory Affairs
Telephone: 609-987-5046
Fax: 609-580-2355

Name of Reviewer: Peggy Kriger, Ph.D.

Conclusion: The submission is **recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUBMISSION:** Original NDA

2. **SUBMISSION PROVIDES FOR:** Initial marketing of sterile drug product

3. **MANUFACTURING SITE:**
Novo Nordisk A/S
Novo Alle, Bagsvaerd, Denmark DK-2880

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile injection; SC; 100 U insulin degludec /3.6 mg/mL liraglutide, packaged as 1 mL in a 3 mL sealed cartridge assembled in a multi-dose pen-injector

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

6. **PHARMACOLOGICAL CATEGORY:** An adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

B. **SUPPORTING/RELATED DOCUMENTS:**
DMF 21494 (Type V, Novo Nordisk Inc.) is referenced for (b) (4) validation information at the Bagsvaerd, Denmark manufacturing site. An LOA, dated May 22, 2015, is provided. Relevant information in DMF 21494 was reviewed by P. Kriger (21494mic4.doc, dated May 3, 2016, adequate), K. Paul (021494mic3.doc, dated April 13, 2016, adequate), V. Pawar (DMF-21494R1.doc, dated May 30, 2012, adequate) and B. Riley (D21494_2008_05_01_A1.doc, dated March 13, 2009, adequate).

(b) (4)

Microbiology review by B. Riley (N022341R1.doc, dated March 10, 2009, recommended for approval) is referenced for review of liraglutide (Victoza), including approval of a comparability protocol (b) (4) .

Microbiology supplement reviews by S. Langille (N022341 (b) (4) and N022341 (b) (4)) are referenced for

a comparability protocol [redacted] (b) (4) and the comparability protocol report, respectively, and both recommended approval.

Microbiology review by V. Pawar (N203314R1.doc, dated June 13, 2012, recommended for approval) is referenced for review of insulin degludec (Tresiba).

C. **REMARKS:** This is an eCTD submission. Some tables were copied from the submission. A comparability protocol was submitted [redacted] (b) (4)

The 10/28/2015 amendment is referenced for the partial response to the Product Quality Microbiology 74-day comments and an updated Form 356h. The 12/22/2015 amendment is referenced for a response to the Product Quality Microbiology 74-day comments and updated comparability protocols. The 3/15/2016 amendment is referenced for the response to the Product Quality Microbiology Information Request sent to the sponsor on 2/18/2016.

Filename: 208583.doc
Template version: OGD modified_AP_2014v6.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability -
The submission is **recommended** for approval on the basis of sterility assurance.

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

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology - (b) (4)

B. Brief Description of Microbiology Deficiencies – none identified

C. Contains Potential Precedent Decision(s) - ☐ **Yes** ☒ **No**

III. Product Quality Microbiology Risk Assessment

A. Initial Product Quality Microbiology Risk Assessment

CQA	Risk Factor	Prob. of Occ. (O)	Severity of Effect (S)	Detect. (D)	Risk Priority Number[6] (RPN)	Additional Review Emphasis based on Risk (in addition to normal review process)
(b) (4)		10	5	5	250	Simulations and interventions conducted (b) (4), Environmental monitoring
Endo		4	4	4	64	

2 = (b) (4)

6 = RPN = O (after modification when applicable)×S×D
RPN <50 = Low Risk; RPN 50-120 = Moderate Risk; RPN >120 = High Risk

B. Final Risk Assessment - None, sufficient sterility assurance information is provided.

IV. Administrative

A. Reviewer's Signature _____

B. Endorsement Block
Microbiologist/Peggy Kriger, Ph.D.
Microbiology Quality Assessment Lead (acting)/Erika Pfeiler, Ph.D.

C. CC Block
cc: Field Copy

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Overall Manufacturing Inspection Recommendation

Task Summary | Task Details | Documents | Approvals | Updates | Application Life Cycle

Inspection Management Form

As of Aug 24, 2016 8:23 am GMT

Inspection Management Form

NDA-208583-ORIG-1

NOVO NORDISK A/S | 3000151819 | SVS STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS | Approve Facility

NOVO NORDISK A/S | 3002807751 | CSS STERILE API BY CHEMICAL SYNTHESIS | Approve Facility

NOVO NORDISK A/S | 3003131673 | SVS STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS | Approve Facility

Overall Manufacturing Inspection Recommendation

- Approve
- Withhold

Save Cancel

Assigned To

Peter Krommenhoek

IM - OPF Reviewer

Edit Assignment

This was done on
May 4, 2016
(112 days ago)

Status
Complete

Requested by

DARRTS Integration

This task is waiting on
Facilities

Last Update
May 4, 2016

Submitted On
Sep 15, 2015

Reference Number
5623533

Submission Manufacturing Facilities

Facility Status	Completion Date	Project Name	FEI	DUNS	Global ID	Facility Name	Profile Code
Approve Facility	5/3/2016	NDA-208583-ORIG-1	3002807751	305156788	69449	NOVO NORDISK A/S	CSS STERILE API BY C
Approve Facility	4/18/2016	NDA-208583-ORIG-1	3003131673	309477891	98248	NOVO NORDISK A/S	SVS STERILE-FILLED S
Approve Facility	2/3/2016	NDA-208583-ORIG-1	3000151819	305914798	67372	NOVO NORDISK A/S	SVS STERILE-FILLED S

Facilities Pending Profile Entry

Facility Status	Project Name	FEI	DUNS	Global ID	Facility Name	Association (per 356h)	Alert
Not Applicable	NDA-208583-ORIG-1	3003131673	309477891	98248	NOVO NORDISK A/S	PENDING	None

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Manufacturing & Quality
Respiratory, ENT, General Hospital, & Ophthalmic Devices Branch

DATE: November 30, 2015

TO: Suong Tran , OMPT/CDER/OPQ/ONDP/DNDPI/NDPBII
WO21 RM2518
Suong.Tran@fda.hhs.gov

Anika Lalmansingh, OMPT/CDER/OPQ/OPRO/DRBPMI/RBPMBI
WO75, RM4631
anika.lalmansingh@fda.hhs.gov

Office of combination products at combination@fda.gov

Through: LT Viky Verna, Combination Product Branch Lead, REGO/DMQ/ OC/CDRH, WO-66, Room 3435

Viky Verna -A
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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Viky Verna -A, 0.9.2342.19200300.100.1.1=2000495623
Date: 2015.12.08 14:40:29 -05'00'

From: Christopher J Brown, P.E., REGO/DMQ/ OC/CDRH
WO-66, Room 3428

Applicant: Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark
FEI# 3000151819

Application # NDA 208583

Consult # ICC1500522

Product Name: IDegLira pen-injector for use with Insulin degludec and liraglutide

Inspection Needed: No **Recommendation Date:** 11/30/2015

Documentation Review: Under Review/ Additional Information Required

Final Recommendation: **DELAY APPROVAL**

The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of NDA 208583.

PRODUCT DESCRIPTION

PDS290 IDegLira pen-injector is a pen-shaped, prefilled device containing a 3 ml cartridge with drug, see Figure 1. According to the firm the drug is not in contact with the device. The device is intended to function with a standard needle thread 1 or a needle with a bayonet coupling. The intended use is as a pen-injection delivery system for use with Insulin degludec and liraglutide. The drug is intended to improve glycemic control in adults with type 2 diabetes mellitus.
Physical characteristics:

- Length and thickness: Approximately 138 mm without cap and 156 mm with cap. Thickness is approximately Ø19 mm
- Dose button displacement: Approximately 2 mm, non-rotating dial during injection
- (b) (4)
- Components: (b) (4) 1 cartridge
- (b) (4)
- End-of-dose click

According to the firm, the PDS290 IDegLira pen-injector was developed to fulfil the international standard for drug injectors, ISO 11608-1 (Needle-based injection systems for medical use - requirements and test methods – Part 1: Needle-based injection systems).

Figure 1. Image PDS290 IDegLira pen-injector

The pen mechanism can be considered as two interacting systems:

- Dose system
- Dial system

During dose setting, the dial mechanism consisting of dial (b) (4) rotates sequentially (b) (4)

To deliver a set dose, the dose button (b) (4) is pushed by the user. (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

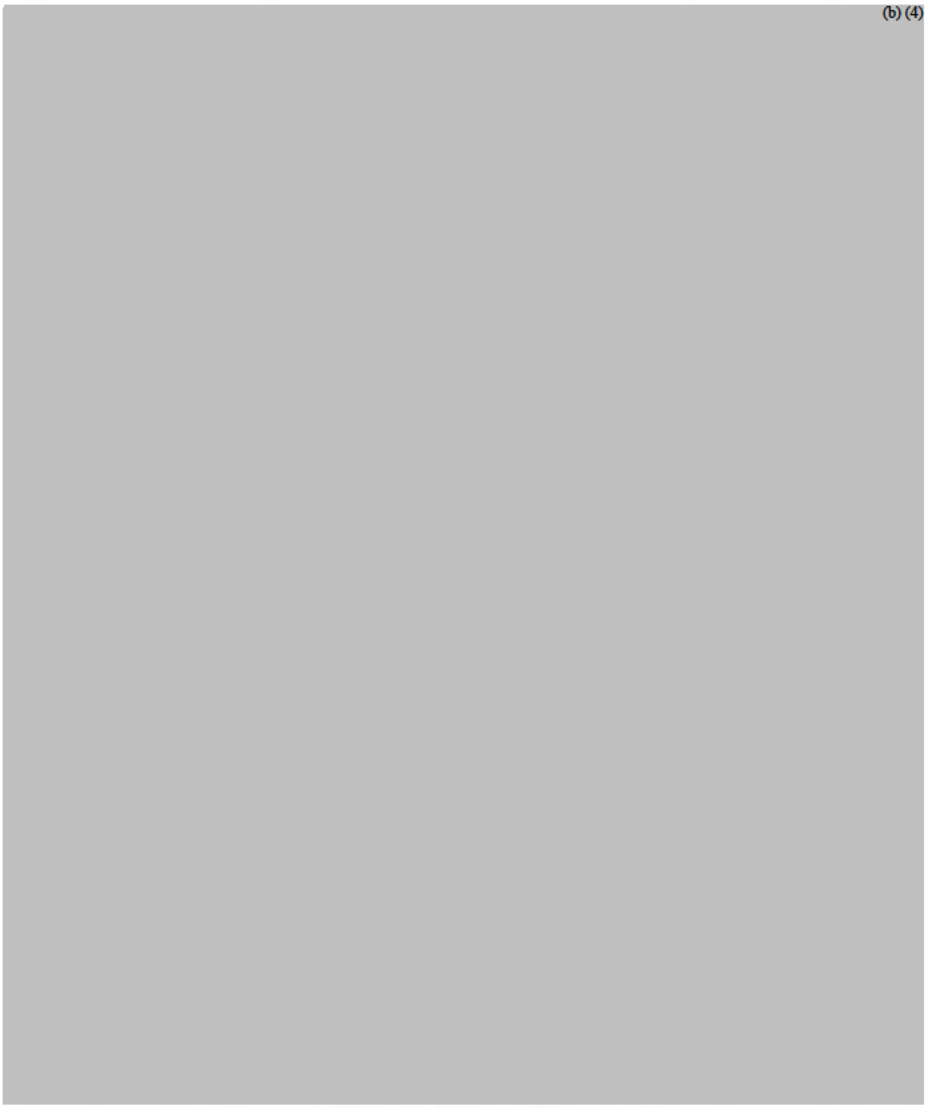

Figure 2. Exploded View of Injector Pen

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Documentation Review Recommendation
This application was deficient overall. Additional information is required for an adequate documentation review.

Deficiencies to be conveyed to the applicant
The following deficiencies have been identified while doing the documentation review of application Product Name, Application NDA 208583, in reference to applicable 21 CFR 820 regulations and (or) manufacturing of the finished combination product:

1. Your firm has inadequately addressed the requirement for 21 CFR 820.30, Design controls. Your firm provided "Design reviews in medical device development projects" (029116). However, you did not appear to provide a copy or a summary of the specific plan used to design the combination product or explain how the plan was implemented for the combination product project. Please provide a copy or a summary of the specific design plan for the final combination product that includes the drug and the pen-injector device.

2. Please provide a summary of the procedure(s) for environmental and contamination controls, and a detailed description of the manufacturing assembly process for the combination product to include the pen-injector.

3. Please provide receiving, in-process and finished device acceptance procedures (e.g.

SOPs, Work Instruction), quality criteria and detailed packaging information that includes any sterilization of the combination product.

You may find useful information regarding the types of documents to provide in the document called 'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003). This document may be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm

RECOMMENDATION

The Office of Compliance at CDRH has completed the evaluation of NDA 208583 and has the following recommendations:

The approvability of application for IDegLira pen-injector – NDA 208583 should be delayed for the following reasons:

(1) Deficiencies were identified during the documentation review. Additional information from the firm is needed to complete the documentation review.

Christopher J. Brown -S
2015.12.09 08:03:25 -05'00'

Christopher J Brown, P.E.

Prepared: CJBrown: 11/30/2015
Reviewed: VVerna 12/3/2015; 12/7/15

CTS No.: ICC1500522
NDA 208583

Review Cycle Meeting Attendance:
November 02, 2015

Inspectional Guidance

Firm to be inspected:
Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark
FEI Number: 3000151819

CDRH recommends the inspection under the applicable Medical Device Regulations of Novo Nordisk, located in Bagsværd, Denmark (FEI # 3000151819).

A limited inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), and Design Controls (21 CFR 820.30) for the for IDegLira pen-injector – (NDA 208583). Additionally, evaluate the manufacturing activities associated with the manufacturing/assembly of the finished combination product, including in process and final acceptance activities. Detailed inspection guidance will be provided upon request.

REGULATORY STRATEGY

The establishment inspection report (EIR) for the firm should be shared with CDRH (The EIR should be assigned to CDER and then sent to CDRH as a consult for review). If the inspection is being classified Official Action Indicated (OAI), the District should consider recommending appropriate regulatory action with consultation from CDER and CDRH and whether the violation is drug or device related.

Questions regarding this consult should be referred to one of the following individuals:

Primary Contact

Christopher J Brown, P.E.
Mechanical Engineer,
Respiratory, ENT, General Hospital and Ophthalmic (REGO)
Division of Manufacturing Quality (DMQ)
Office of Compliance, WO66 RM 3428
Phone: 301-796-0380

Secondary Contacts (if Primary is unavailable and a timely answer is required)

Francisco Vicenty
Branch Chief, REGO, DMQ
Office of Compliance, WO66 RM 3430
Phone: 301-796- 5577

THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM OR SHOWN TO THEM DURING THE INSPECTION. THIS ATTACHMENT CONTAINS PREDECISIONAL INFORMATION

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

/s/

ANIKA A LALMANSINGH
02/08/2016
Uploading on behalf of Christopher J Brown.