CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209637Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation:
APPROVAL
(including the Facility Review/Overall Manufacturing Inspection Recommendation)

NDA 209637
Review #1
Review Date (see last page)

Drug Name/Dosage Form	semaglutide injection
Strength	1.34 mg/mL (as 2 mg/1.5 mL per pen injector)
Route of Administration	subcutaneous injection
Rx/OTC Dispensed	Rx
Applicant	Novo Nordisk

SUBMISSION(S) REVIEWED	DOCUMENT DATE
0001	12/5/16
0007	3/1/17
0014	5/1/17
0017	5/8/17
0027	6/23/17

Quality Review Team

DISCIPLINE	REVIEWER	DIVISION/OFFICE
Regulatory Business Process Manager	Anika Lalmansingh	Regulatory Business Process Management I/OPRO
Application Technical Lead	Suong (Su) Tran	New Drug Products II/ONDP
API	Joe Leginus/Donna Christner	New Drug API/ONDP
Drug Product	Muthu Ramaswamy/Danae Christodoulou	New Drug Products II/ONDP
Process	Chaoying Ma/Yong Hu	Process Assessment II/OPF
Facility	Vidya Pai/Juandria Williams	Inspectional Assessment/OPF
	Christopher Brown	CDRH Compliance
Microbiology	Elizabeth Bearr/ Erika Pfeiler	Microbiology Assesment/OPF

Quality Review Data Sheet

1. **RELATED/SUPPORTING DOCUMENTS:**
   A. **DMFs:** Adequate
   B. **Other Documents:** not applicable
2. **CONSULTS:** CDRH Compliance (recommendation is included in the OPQ Facility review; see separate review in DARRTS)

Executive Summary

I. Recommendation and Conclusion on Approvability

The final OPQ recommendation is for Approval, including the overall manufacturing inspection recommendation.

II. Summary of Quality Assessment

A. Product Overview

This is a 505(b)(1) NDA for semaglutide, a New Molecular Entity.
Semaglutide is an analog of the 7-37 peptide fragment of the human glucagon-like peptide-1 (GLP-1).
The drug product is a clear solution for subcutaneous injection, 1.34 mg/mL, packaged in a 1.5 mL (or 2 mg semaglutide) cartridge pre-assembled in a multi-dose single-patient pen injector.

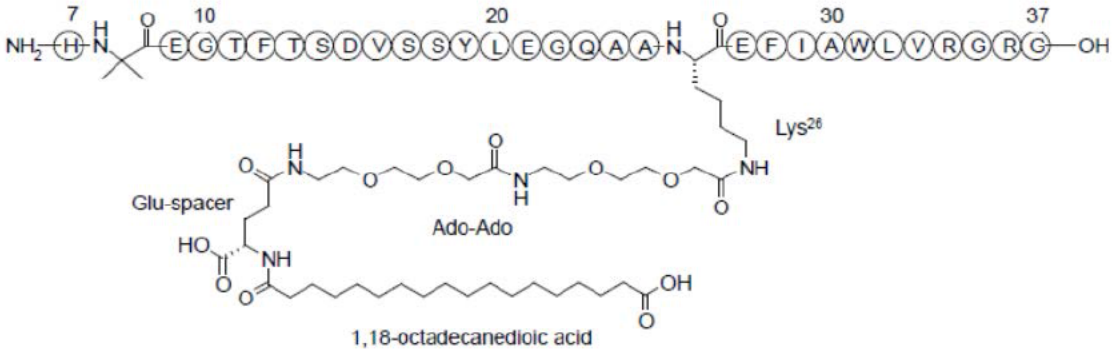
Proposed Indication(s)	[not finalized by GRMP goal; see CDTL's memo]
Duration of Treatment	[not finalized by GRMP goal; see CDTL's memo]
Maximum Daily Dose	[not finalized by GRMP goal; see CDTL's memo]
Alternative Methods of Administration	n/a

B. Quality Assessment Overview

Drug Substance

Semaglutide is an analog of human GLP-1(residues 7-37) and acts as a GLP-1 receptor agonist. The drug substance is (b) (4) chemical modifications (attachment of octadecanedioic acid via linkers to Lysine 26, and change in position 8 from Alanine to 2-aminoisobutyric acid).

The molecular formula for semaglutide is $C_{187}H_{291}N_{45}O_{59}$ and the molecular mass is 4113.6 Da.



The drug substance differs from human GLP-1 by a substitution of lysine at position 34 by arginine and the two chemical modifications described above, which are designed to slow the plasma degradation of the molecule and decrease its renal clearance, prolonging its half-life. Semaglutide also differs from liraglutide (an approved product by the same applicant) in that liraglutide has a different fatty acid and linkers attached to Lysine 26 and is not modified at position 8.

The drug substance manufacturing process consists (b) (4) Manufacturing Process 6R produced drug substance batches used in product batches for the phase 3 clinical studies and primary stability studies, and the same process has been validated as the commercial process. Adequate information on the manufacturing process, including cell banking and comparability of earlier manufacturing processes, is provided in the NDA. The manufacturing process (b) (4)

Characterization of the drug substance is standard for a (b) (4) peptide, including the following testing: peptide mapping, circular dichroism, mass spectrometry, potency by a cell-based bioassay (cAMP-sensitive luciferase reporter gene assay and BHK cells), isoelectric focusing, solubility, pH, UV spectroscopy, dynamic water sorption, RP- and SE- HPLC, visual appearance, and a potency-content by HPLC correlation.Characterization of peptide-related impurities and degradants is provided, including the relative bioactivities (b) (4) .

The drug substance specification includes attributes standard for this type of drug substance ((b) (4)). The same bioassay used for characterization is included in the drug substance specification. Impurities are grouped by their hydrophilic and hydrophobic properties, with limits based on nonclinical and clinical batches. The specification includes high molecular weight proteins and host cell proteins; (b) (4) . The drug substance is (b) (4) .

The long term storage is at (b) (4) °C, in a (b) (4) , with a shelf life (not retest) of (b) (4) months. The drug substance is sensitive to (b) (4) (b) (4)

Drug Product

The drug product is a clear solution for subcutaneous injection, 1.34 mg/mL, packaged in a 1.5 mL (or 2 mg semaglutide) cartridge pre-assembled in a multi-dose single-patient pen injector. The commercial formulation is the same as that used in the pivotal phase 3 studies and primary stability studies.

Excipients: disoldium phosphate dihydrate (1.42 mg/mL), propylene glycol (14.0 mg/mL), phenol (5.5 mg/mL), water for injection, and hydrochloric acid and sodium hydroxide for pH adjustment (pH 7.4). All excipients are compendial. There is no novel excipient, and there is no human/animal-derived excipient. The formulation has an (b) (4)

The drug product manufacturing process consists (b) (4) the same process has been validated as the commercial process. Sufficient information is provided to demonstrate sterility assurance. Reference is made to DMF (b) (4) for information on the (b) (4) information; this DMF is currently adequate. The phase 3 product batches were manufactured at the commercial site, using the commercial process with minor differences. Reference is made to the CDRH review of the pen injector-cartridge assembly and other device-related manufacturing information.

The regulatory drug product specification is adequate based on the supporting release and stability data and ICH guidelines for this type of dosage form. It does not include testing for biological activity because the assay method by HPLC is found to be adequately correlated with potency (by the cell-based bioassay of the drug substance). Same as for the drug substance impurities, degradants are grouped by their hydrophilic and hydrophobic properties, with limits based on nonclinical and clinical batches. The specification includes high molecular weight proteins and (b) (4) content. (b) (4) meets the compendial criteria for antimicrobial effectiveness. (b) (4) and is not part of the drug product specification. Reference is made to the CDRH review of dose accuracy, which is part of the pen injector design and performance.

Primary container closure system: The drug product is packaged in a 1.5-mL clear type I glass cartridge sealed with a (b) (4) plunger on one end and a (b) (4) cap on the other end. Primary stability batches were stored in this primary container closure system. Packaging components meet requirements of USP<660> Glass and USP<381> and <87> Elastomeric Closures. The leachable (b) (4) has a limit of (b) (4) mcg/mL, which is found by the Pharmacology Toxicology team to be pose no safety risk. The same primary container closure system is approved for the liraglutide drug product (an approved product by the same applicant).
Reference is made to the CDRH review of the pen injector, including any bridging information on different devices, if applicable.

Expiration Date & Storage Conditions: The shelf life of the drug product is 36 months at 5°C, and the in-use shelf life is 56 days at 5°C to 30°C after initial use.

The long-term expiry is based on 18- to 36-month long-term data for six primary stability batches ((b) (4) scale), with three batches assembled in pen injectors. In addition, 3-month data are provided for three full-scale validation batches ((b) (4) scale). The in-use expiry is based on 56-day data at 5°C and 30°C for three primary stability batches. All batches were manufactured at the commercial site, using the commercial process with minor differences.

C. Special Product Quality Labeling Recommendation: not applicable

D. Life Cycle Knowledge Information/ Final Risk Assessment:

API	none
Drug product	none
Process	none
Facilities	page 10 of Chapter VI
Microbiology	page 22 of Chapter VIII

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

Suong T. Tran -S

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MICROBIOLOGY

Product Background: -

NDA: 209637

Drug Product Name / Strength: Ozempic® (semaglutide), 1.34 mg/mL

Route of Administration: subcutaneous injection

Applicant Name: Novo Nordisk Inc.

Manufacturing Site: Novo Nordisk A/S, Novo Allé 1, Bagsværd, Hovedstaden 2880, Denmark

Method of Sterilization: (b) (4) processing

Review Recommendation: The submission is recommended for approval on the basis of sterility assurance.

Review Summary: (b) (4)

List Submissions being reviewed: 12/05/2016; 03/01/2017; 05/01/2017; 06/23/2017

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: None

Supporting/Related Documents:

- **DMF # (b) (4), Type V, for Novo Nordisk A/S, Novo Allé, 2880 Bagsværd, Denmark, for (b) (4) processing of the subject drug product.**
- **DMF # (b) (4) review (b) (4).doc, dated 07/24/2017, by E. Bearr. (Adequate)**

Remarks Section: Tables and container closure system figure are adapted from the submission. The most updated packaging instructions are provided in the applicant's submission dated 03/01/2017. The applicant's submission dated 05/01/2017 is in response to the Agency's

Information Request dated 03/30/2017. The applicant's submission dated 06/23/2017 is in response to the Agency's Information Request dated 05/24/2017.

S Drug Substance – Not applicable, (b) (4)

P.1 Description of the Composition of the Drug Product

- Description of drug product – Clear, colorless, sterile solution, 1.34 mg/mL, pH (b) (4), filled in a 1.5 mL cartridge and assembled in a PDS290 pen-injector for subcutaneous injection. The active drug substance is a peptide analogue for improvement of glycemic control.
- Drug product composition –

Ingredient	Reference Standard	Content per mL	Function
Semaglutide	Applicant's	1.34 mg	Active drug substance
Disodium phosphate, dehydrate	USP/Ph. Eur.	1.42 mg	(b) (4)
Propylene glycol	USP/JP/Ph. Eur.	14.0 mg	
Phenol[a]	USP/JP/Ph. Eur.	5.50 mg	
Hydrochloric acid	USP/JP/Ph. Eur.	q.s. to pH 7.4	pH adjustment
Sodium hydroxide	USP/JP/Ph. Eur.	q.s. to pH 7.4	pH adjustment
Water for Injection	USP/JP/Ph. Eur.	(b) (4) mL	(b) (4)

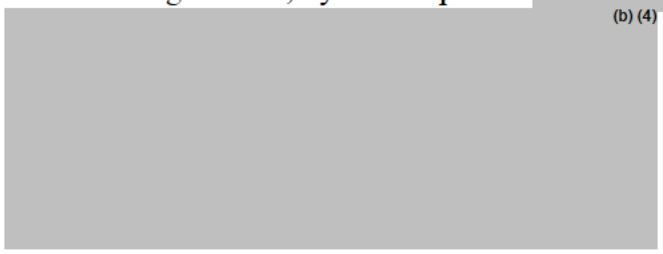
[a] (b) (4)

- Description of container closure system – The primary packaging is a 1.5 mL cartridge with a plunger and (b) (4) rubber disc. The rubber disc is inserted into an aluminum cap (secondary packaging).

Component	Description	Manufacturer
Cartridge	1.5 mL colorless Type I glass. (b) (4)	(b) (4)
Cap	8 mm aluminum cap (b) (4)	
Plunger (b) (4)	9.66 mm (b) (4) I rubber plunger. (b) (4)	

The schematic of the closed cartridge provided below is adapted from Section 3.2.P.7, Cartridge 1.5 ml, System Report for (b) (4), p. 4.

(b) (4)



The applicant states that there is no direct contact between the PDS290 pen-injector and the product. Two pen-injector variants are proposed:

- PDS290 pen-injector for semaglutide 1.34 mg/mL (0.25 mg / 0.5 mg / 1.0 mg), which can deliver doses of 0.25 mg, 0.5 mg, or 1.0 mg.
- PDS290 pen-injector for semaglutide 1.34 mg/mL (1.0 mg), which can only deliver doses of 1.0 mg.

The submission indicates that the difference between the 2 pen-injector variants is limited to the imprint on the scale drum. The device is intended to function with a standard needle (b) (4)

Reviewer's Assessment: The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

Acceptable

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity

(Section 2.3.P.2, Pharmaceutical Development; Section 3.2.P.2.5, Microbiological Attributes)

The submission indicates that container closure integrity of the proposed cartridge sealed with the rubber disc is correlated with Residual Seal Force (RSF). (b) (4)

The RSF test is performed by measuring the force as a function of movement of the testing-fixture. (b) (4)

he correlation between RSF and CCI was determined by performing microbial ingress tests on cartridges filled with media and sealed with different RSF values. The cartridges were incubated according to the conditions used for media fill simulations (not provided) and then inspected for bacterial growth. The microbial ingress test is performed at time 0 and repeated at the end of shelf life. The lowest acceptable limit for the RSF value is determined based on the lowest RSF value tested where the filled cartridges show no sign of growth in the CCI test at the end of shelf life. The applicant indicates that CCIT is on-going to confirm the integrity at the end of shelf life and will be finalized in 2017. The RSF and microbial ingress test data are not provided. Additional information regarding CCIT was provided in DMF (b) (4)

Note to Reviewer: The container-closure integrity validation provided in DMF # (b) (4) was reviewed and found not adequate on 03/14/2017 in microbiology review D (b) (4) M05R01.doc, by E. Bearr.

The following deficiency was issued by the Agency in the Information Request dated 03/30/2017.

DMF # (b) (4) has been reviewed and found inadequate.

In their response dated 05/01/2017, the applicant refers the Agency to the response submitted to DMF # (b) (4) on 05/01/2017.

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Reviewer's Assessment: The (b) (4) validation of the cartridges is adequate. The (b) (4) validation of equipment and the (b) (4) validation of caps and plungers are also adequate.

Acceptable

Media Fill Procedures and Specification and Actions Concerning Product When Media Fills Fail

The subject NDA does not provide information concerning media fill procedures and specification and actions concerning product when media fills fail.

Note to Reviewer: Media fill simulation validation and actions concerning product when media fills fail are provided in DMF # (b) (4). The 2015 – 2017 media fill simulations of the (b) (4) used for the 1.5 mL cartridge have been reviewed and found adequate in microbiology review D (b) (4) M05R01.doc, dated 07/24/2017, by E. Bearr.

Reviewer's Assessment: The media fill simulation provided in DMF # (b) (4) validates the (b) (4) process for the subject drug product.

Acceptable

P.5 Control of Drug Product

P. 5.1 Specification

The product release specification includes the following microbiological tests:

Test	Test Method	Acceptance Criteria
Bacterial Endotoxins	USP <85>, kinetic chromogenic method	(b) (4) IU/mL
Sterility	USP <71>, membrane filtration method	Complies
(b) (4) content	RP-HPLC	(b) (4) mg/mL

Reviewer's Assessment: The release specification contains adequate tests and acceptance criteria to ensure the microbiological quality of the subject drug product.

Acceptable

P.5.2 Analytical Procedures – see P.5.1 and P.5.3

P.5.3 Validation of Analytical Procedures

Endotoxins

(Section 3.2.R, Bacterial Endotoxins Test, Suitability Test Report)

The bacterial endotoxins level of the drug product is tested by USP <85>, kinetic chromogenic method. The endotoxins specification is (b) (4) IU/mL. (b) (4)

Monograph limit. The lysate sensitivity is (b) (4) IU/mL ((b) (4) . The drug potency is 1.34 mg/mL.

The submission indicates that for liquid samples, the concentration of sample solution equals 1 and is therefore omitted from the general formula for MVD (MVD = Endotoxin limit/λ). Using the applicant's general formula, the MVD = (b) (4)

The test for interfering factors was performed in quadruplicate on batch #FW5L607, #FW5L608, and #FW5L609 using a test dilution of (b) (4)

Acceptance criteria:

- The endotoxin % recovery for the positive product control must be between (b) (4) %.
- The pH of the lysate / product mixture is within the range of (b) (4)

Results: All acceptance criteria were met. The endotoxins % recovery ranged from (b) (4) % for the three test batches. The pH was (b) (4) for each batch.

Validation of the test shows no inhibition or enhancement using a dilution of (b) (4). A dilution of (b) (4) will be used for routine testing.

Finished lot # FW5M022, #FW5L981, and #FW5L887 contain (b) (4) EU/mL (Section 3.2.P.5.4 Batch Analyses).

Maximum dose for a 70 kg adult in 1 hour according to the package insert: 1 mg
Calculated endotoxin dose at the proposed endotoxins specification and maximum dose: (b) (4)

Reviewer's Assessment: The bacterial endotoxins method is suitable for the drug product. The endotoxin dose at the proposed endotoxins specification and maximum dose as calculated by this reviewer is within the USP <85> recommendation of (b) (4) EU/kg/hr.

Acceptable

Sterility

The sterility of the drug product is tested according to USP <71>, (b) (4) . The sterility test method validation was not provided. Finished lot # FW5M022, #FW5L981, and #FW5L887 met the release specification of sterility (complies) (Section 3.2.P.5.4 Batch Analyses).

The following deficiency was issued by the Agency in the Information Request dated 03/30/2017.

Please provide data supporting the suitability of the sterility test method for the subject drug product.

In their response dated 05/01/2017, the applicant provided the results of sterility test method suitability for the subject drug product. Suitability testing was performed using 3 batches of the drug product: FW5L887, FW5L981, and FW5M022. (b) (4) [redacted]. The suitability and routine test methods are the same.

Reviewer's Assessment: The sterility test method was shown to be suitable for the subject drug product.

Acceptable

(b) (4) [redacted]

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Erika Pfeiler

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ATTACHMENT I: Final Risk Assessments

See Executive Summary

Su (Suong) Tran

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