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
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Application Technical Lead	Suong (Su) Tran	New Drug Products II/ONDP
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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.

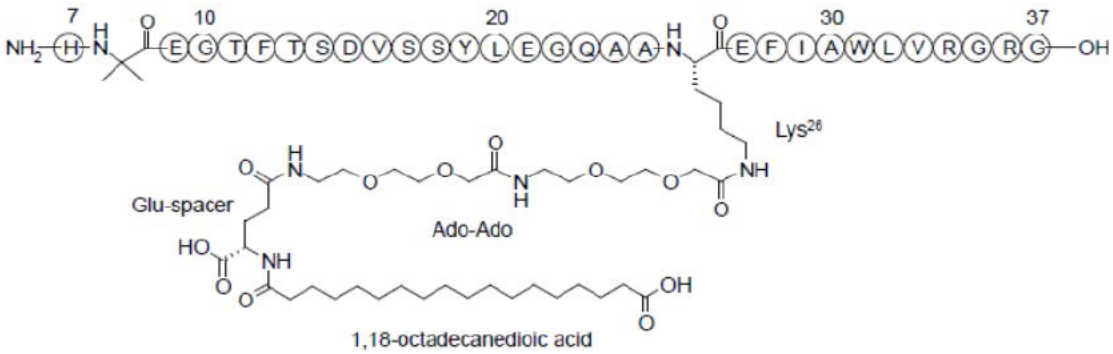
Proposed Indication(s)	[not finalized by GRMP goal; see CDTL's memo]
Duration of Treatment	[not finalized by GRMP goal; see CDTL's memo]
Maximum Daily Dose	[not finalized by GRMP goal; see CDTL's memo]
Alternative Methods of Administration	n/a

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 [redacted] 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 [redacted]

Characterization of the drug substance is standard for a [redacted] 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 [redacted].

The drug substance specification includes attributes standard for this type of drug substance ([redacted]). 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; [redacted]. The drug substance is [redacted].

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

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.

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