

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213051Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

**NDA 213051 and 213182
Review 1**

Drug Name/Dosage Form	Rybelsus (semaglutide) tablets
Strength	3 mg, 7 mg, or 14 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Novo Nordisk
US agent, if applicable	-

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original and amendments (NDA 213051)	Original submission (3/20/2019) and amendments (5/23/19, 6/28/19, 7/02/29, 7/05/19, 7/29/19, 8/01/19, and 8/15/19).	Quality modules 3, 1.14 and 1.11
Original and amendments (NDA 213182)	Original submission (3/20/2019)	Quality modules 1.4 and 1.12.4

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Daniel Jansen	Branch II/New Drug API
Drug Product	Christopher Galliford	Branch VI/New Drug Products II
Process/Microbiology/Facility	Frank Wackes	Branch II/ Inspectional Assessment/OPF
Regulatory Business Process Manager	Leeza Rahimi	Branch I/Regulatory Business Process Management I
Application Technical Lead	Muthukumar Ramaswamy	Branch VI/New Drug Products II
Environmental Analysis (EA)	Christopher Galliford	Branch VI/New Drug Products II

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III	(b) (4)	(b) (4)	Adequate	12/14/2012 (Craig Bertha) and NDA 213051 review for drug product (8/8/19)	LOA 1/10/2019

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	114464	Semaglutide tablets

2. CONSULTS: None

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER

Executive Summary

I. Recommendations and Conclusion on Approvability

The recommendation from the Office of Pharmaceutical Quality (OPQ) for NDA 213051 and 213182 is approval. This recommendation includes acceptable recommendation for the facilities listed in the application.

II. Summary of Quality Assessments

A. Product Overview

Semaglutide is a long-acting analogue of GLP-1 molecule and is currently marketed as Ozempic (semaglutide) injection for improving glycemic control in adults with type 2 diabetes (NDA 209637). Novo Nordisk has submitted two new drug applications (NDA 213051 and NDA 213182) for the marketing approval of Rybelsus® (semaglutide) tablets. Rybelsus® tablets are intended for the following indications:

- Glycemic control in adults with type 2 diabetes (NDA 213051).
- To reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes and established CV (b) (4) (NDA 213182).

Rybelsus tablets will be available as 3, 7, and 14 mg tablets. Rybelsus tablets are for once daily oral administration. Each strength tablets will be available in cartons containing 3 child-resistant blister cards of 10 tablets. Rybelsus® tablets should to be stored at temperature between 68°F to 77°F (20°C to 25°C).

Semaglutide tablets are co-formulated with 300 mg of salcaprozate sodium (SNAC, a permeation enhancer). The isoelectric point of the semaglutide is 5.4. The peptide has a low solubility at pH range 2-6. Semaglutide is considered a BCS class 4 molecule (low permeability and low solubility). It is hypothesized that SNAC facilitates the oral absorption of semaglutide in stomach either by transiently increasing the transcellular permeability in gastric epithelium or through buffering action on the local environment near the site of action to provide a high pH and thereby protecting the semaglutide from degradation.

All CMC information necessary to support NDA 213182 was cross-referenced to Module 2 and 3 of NDA 213051. Therefore, the CMC review provided for NDA 213051 was used to make the OPQ recommendation for NDA 213182.

Proposed Indication(s) including Intended Patient Population	<i>Glycemic control and CV risk reduction; Refer to CTDL memo</i>
Duration of Treatment	<i>Refer to CTDL memo</i>
Maximum Daily Dose	<i>14 mg</i>

Alternative Methods of Administration

Not applicable

B. Quality Assessment Overview

Drug Substance

Semaglutide is a modified analogue of human GLP-1 [7-37] peptide. Compared to the amino acid sequence of GLP-1 [7-37] peptide, the semaglutide peptide sequence contains two amino acid substitutions (Ala8 to Aib8 (2-aminoisobutyric acid), Lys34 to Arg34) and a modification at lysine 26 side chain with fatty diacid moiety. The manufacturing process for semaglutide drug substance consists of (b) (4)

[REDACTED]

The drug substance batches produced from the proposed drug substance manufacturing process (process III) was used in Phase 1 and 3 clinical studies.

The CMC information for drug substance was reviewed by Dr. Daniel Jansen. Dr. Jansen's review concluded that the NDA contains adequate information on drug substance characterization and provides adequate manufacturing process description, process controls, and drug substance specification for manufacturing consistent quality drug substance. Based on stability data review, a shelf-life of (b) (4) months is granted for the semaglutide drug substance when stored (b) (4)

[REDACTED] For additional details, please refer to CMC review for drug substance in Panorama dated 5/28/2019.

Drug Product

Semaglutide tablets will be available in 3 strengths (3 mg, 7 mg, or 14 mg per tablet), as white to light yellow oval shaped tablets debossed with "novo" on one side and on the other side with 3 or 7 or 14. The tablets are packaged in blister cards (b) (4)

[REDACTED]

Each blister card will contain 10 tablets. Blister packs are further packaged in cartons (3 per carton).

Each strength tablet contains 300 mg of salcaprozate sodium. Besides salcaprozate sodium (SNAC), the tablets contain micro-crystalline cellulose (b) (4), Povidone (b) (4), and magnesium stearate (b) (4). Salcaprozate is a novel excipient. All other excipients present in the drug product are USP grade excipients.

Excipient related information including manufacturing and control information for salcaprozoate was reviewed by drug product reviewer. His review concluded that the manufacturing and control information for SNAC and other excipients are adequate. The proposed specifications for salcaprozate include (b) (4)

(b) (4). Salcaprazoate use in the product is supported non-clinical and clinical studies.

Rybelsus tablet manufacturing process uses (b) (4)

[Redacted]

The composition of the product, the process used for manufacturing the drug product batches and the packaging system used for the drug product in phase 3 clinical studies are the same as that proposed for commercial use. The manufacturing process flow information is aligned with the proposed master batch record. The batches used in clinical and non-clinical studies are identified in the application.

The applicant's control strategy for producing acceptable quality drug product is (b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

Dr. Frank Wackes reviewed the manufacturing process and control information and facility compliance information. OPF process review includes risk assessment for manufacturing process control and its relationship to drug product critical quality attributes. OPF review concluded that the process and facilities information provided in the NDA is adequate. Please refer to process/facilities review in Panorama dated 7/30/2019.

The applicant performed a risk assessment for elemental impurities per ICH Q3D and provided justification for not including routine elemental impurities testing in the product. In addition, Dr. Ramaswamy performed a risk assessment for the finished product critical quality attributes and his assessment concluded that the final quality risk is low for the proposed product (Refer to Appendix I).

The finished product specification was finalized by the drug product and biopharmaceutics reviewers. The drug product is tested for visual appearance, identity of semaglutide by RPHPLC and peptide mapping, assay, uniformity of dosage units, HMWP, impurities (b) (4), and sum of impurities), microbial purity, (b) (4) and dissolution. The quality attributes considered for inclusion in the drug product specification are in alignment with the attributes recommended for oral dosage forms under USP <2> Oral drug products – product quality tests. Please refer to Dr. Galliford's drug product review dated 8/9/19 for additional information.

A dissolution test is proposed for measuring the quality of semaglutide tablets. Dissolution acceptance criteria proposed for the product is based on data from primary stability batches. Dr. Vincent Li's reviewed the dissolution method and he proposed dissolution acceptance criteria. Per FDA recommendation, the applicant has agreed to use an interim dissolution specification of $Q = \frac{(b)}{(4)}\%$ semaglutide at 45 minutes for all strength tablets up to a period of one year and committed to provide additional dissolution data (b) (4) in the first annual report. Dr. Li's recommendation for this NDA is adequate. Please refer to biopharma review dated 8/9/19 in Panorama and NDA amendment dated 8/16/19 for additional information.

The applicant sought exemption from environmental impact analysis per 21CFR 25.31(a) as the action on this NDA does not increase the use of semaglutide. Dr. Galliford reviewed the request and granted categorical exclusion from submitting environment assessment. Please refer to drug product review dated 8/9/19 in panorama for additional information.

Expiration Date & Storage Conditions: Drug product is light sensitive. Therefore, storage of the product in blister packaging is warranted. The application contains 6 month accelerated stability (40°C/75% RH) and 24 months of intermediate/ long-term storage stability data (25°C/60% RH and 30°C/75% RH) for 3 primary stability batches manufactured at pilot scale. Stability information was reviewed by drug product reviewer and concluded that the product is stable in the proposed packaging. A shelf-life of 24 months is granted when stored at 68 -77°F ((20°-25°C) in original packaging. Excursions permitted to 59°-86°F (15°-30°C) [see USP Controlled Room Temperature]. Do not freeze. Please refer to drug product review dated 8/9/19 in Panorama for additional information.

Container and Carton Label Review: Drug product reviewer completed review of container and carton label. Dosage form, strength, established name, NDC #, Lot #/expiry, and storage conditions are adequately described in the carton and container label, which meets relevant regulatory requirements for labeling. Refer to drug product review for a copy of the label.

OVERALL ASSESSMENT AND SIGNATURES:

OPQ CMC review concludes that there are no outstanding deficiencies related to drug substance, drug product, process, facilities, biopharmaceutics, environmental analysis, container and carton label. *OPQ overall recommendation for NDA 213051 and 213182 is approval.*

Muthukumar Ramaswamy, Ph.D. 8/19/2019

Application Technical Lead Name and Date:

Attachment I: Final Risk Assessments

<i>From Initial Risk Identification</i>			<i>Review Assessment</i>		
<i>Attribute/ CQA</i>	<i>Factors that can impact the CQA</i>	<i>Initial Risk Ranking</i>	<i>Risk Mitigation Approach</i>	<i>Final Risk Ranking</i>	<i>Lifecycle Considerations/ Comments</i>
Drug content (potency)	Formulation, process (tablet weight), container/ stability/Method	H	(b) (4)	Acceptable	None
Dose Uniformity	Formulation, process (tablet weight), container/ stability/ Method	H		Acceptable	
Particle Size Distribution of API	Formulation, process	M		Acceptable	none
(b) (4)	Formulation, process	M		Acceptable	None
Hydrophobic and hydrophilic, Impurities/ HMWP	Formulation, stability, Process, Container closure	H		Acceptable	none
Appearance	Formulation, process, Container closure, stability	H		Acceptable	none
Microbial load	Container closure Process (b) (4)	H		Acceptable	none
Salcaprozate Content	Formulation, process and product performance	H		Acceptable	none
In vitro dissolution	Formulation, process, incoming materials	H		Acceptable	An-interim dissolution specification of Q= $\frac{(b)}{(4)}$ % at 45 min is proposed. The applicant committed to provide dissolution data for additional batches in the first annual report.
Salcaprozate (b) (4)	Formulation, process, product performance	H		Acceptable	none
Microbial contamination	Formulation, process, packaging	M		Acceptable	None



Muthukumar
Ramaswamy

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CHAPTER I: DRUG SUBSTANCE

Drug Substance Name	Semaglutide
NDA Number	213051
Assessment Cycle Number	1
DMF Number (If Applicable)	n/q
DMF Status	Adequate
Applicant Name	Novo-Nordisk
DMF Holder	n/a

Assessment Recommendation: Adequate



(b) (4)

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REGIONAL INFORMATION

Comparability Protocols

Assessment: N/A

Post-Approval Commitments

Assessment: N/A

Lifecycle Management Considerations

None

DRUG SUBSTANCE LIST OF DEFICIENCIES

None

Primary Drug Substance Assessor Name and Date:

Secondary Assessor Name and Date (and Secondary Summary, as needed):



Daniel
Jansen

Digitally signed by Daniel Jansen
Date: 5/28/2019 03:42:46PM
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Su (Suong)
Tran

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ASSESSMENT OF THE DRUG PRODUCT

2.3.P DRUG PRODUCT

This section of the review includes evaluation of data submitted in the original NDA (03/20/2019), and subsequent NDA amendments pertaining to drug product quality and labeling, submitted through 08/01/2019. From the perspective of drug product reviewer, the submitted materials are adequate to support the marketing of the drug product.

2.3.P.1 Description and Composition of the Drug Product

Semaglutide is a glucagon like peptide-1 (GLP-1) analog for the treatment of type 2 diabetes. The semaglutide drug product presentations are white to light yellow oval shaped tablets (7.5 mm x 13.5 mm). The tablets are debossed with a unique identification depending on the strength:

- 3 mg tablets: “3” is debossed on one side of the tablet and “novo” on the other side.
- 7 mg tablets: “7” is debossed on one side of the tablet and “novo” on the other side.
- 14 mg tablets: “14” is debossed on one side of the tablet and “novo” on the other side.

The tablet weight is around 0.4 g and depends on the strength. The quantitative composition of the drug product in each strength is as follows:

Table 1 Compositions of the semaglutide drug products

Component	Quantity per tablet (mg/tablet)			Function	Reference to standards
	Semaglutide 3 mg tablet	Semaglutide 7 mg tablet	Semaglutide 14 mg tablet		
Active pharmaceutical ingredient					
Semaglutide	3	7	14	Active ingredient	Novo Nordisk A/S
Excipients					
Salcaprozate sodium	300	300	300	Absorption enhancer	Novo Nordisk A/S
Cellulose, microcrystalline	(b) (4)				Ph. Eur., USP, JP
Povidone					Ph. Eur., USP, JP
Magnesium stearate					Ph. Eur., USP, JP
Gross weight^a	400.7	404.7	411.7	-	-

The proposed proprietary name is Rybelsus. When approved, the full name of the drug product will be: Rybelsus™ (semaglutide) tablets 3 mg, 7 mg or 14 mg.

Reviewer’s Assessment: Adequate.

Adequate information and data are provided in support of drug product composition. The API, semaglutide, is manufactured Novo Nordisk A/S, Hallas Allé 1, Kalundborg, Sjælland 4400, Denmark.

2.3.P.2 Pharmaceutical Development

The semaglutide drug product is a tablet formulation containing 3, 7 or 14 mg of the active pharmaceutical ingredient semaglutide. The corresponding injection formulation, Ozempic® (NDA 209637), was approved by the agency on Dec 5, 2017. Therefore, this application is a new formulation of the same API. The tablets are uncoated immediate release tablets intended for oral administration. The drug product compositions for each strength are reproduced from the application below:

Table 1 Compositions of the semaglutide drug products

Component	Quantity per tablet (mg/tablet)			Function	Reference to standards
	Semaglutide 3 mg tablet	Semaglutide 7 mg tablet	Semaglutide 14 mg tablet		
Active pharmaceutical ingredient					
Semaglutide	3	7	14	Active ingredient	Novo Nordisk A/S
Excipients					
Salcaprozate sodium	300	300	300	Absorption enhancer	Novo Nordisk A/S
Cellulose, microcrystalline	(b) (4)				Ph. Eur., USP, JP
Povidone					Ph. Eur., USP, JP
Magnesium stearate					Ph. Eur., USP, JP
Gross weight ^a	400.7	404.7	411.7	-	-

(b) (4)



I. Review of Common Technical Document-Quality (Ctd-Q) Module 1 Labeling & Package Insert

1. Package Insert

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **TRADENAME** safely and effectively. See full prescribing information for **TRADENAME**.

TRADENAME (semaglutide) tablets, for oral use
Initial U.S. Approval: 2017

WARNING: RISK OF THYROID C-CELL TUMORS *See full prescribing information for complete boxed warning.*

- In rodents, semaglutide causes thyroid C-cell tumors. It is unknown whether **TRADENAME** causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as the human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined (5.1, 13.1).
- **TRADENAME** is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and symptoms of thyroid tumors (4, 5.1).

INDICATIONS AND USAGE

TRADENAME is a glucagon-like peptide 1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (1).

Limitations of Use

- Not recommended as first-line therapy for patients inadequately controlled on diet and exercise (1, 5.1).
- Has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies (1, 5.2).
- Not indicated for use in patients with type 1 diabetes mellitus or for the treatment of patients with diabetic ketoacidosis (1).

DOSAGE AND ADMINISTRATION

(b) (4)

DOSAGE FORMS AND STRENGTHS

Tablets: 3 mg, 7 mg and 14 mg (3).

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: RISK OF THYROID C-CELL TUMORS

1	INDICATIONS AND USAGE	8.5 Geriatric Use
2	DOSAGE AND ADMINISTRATION	8.6 Renal Impairment
3	DOSAGE FORMS AND STRENGTHS	8.7 Hepatic Impairment
4	CONTRAINDICATIONS	10 OVERDOSAGE
5	WARNINGS AND PRECAUTIONS	11 DESCRIPTION
5.1	Risk of Thyroid C-Cell Tumors	12 CLINICAL PHARMACOLOGY
5.2	Pancreatitis	12.1 Mechanism of Action
5.3	Diabetic Retinopathy	12.2 Pharmacodynamics
5.4	Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin	12.3 Pharmacokinetics
5.5	Acute Kidney Injury	13 NONCLINICAL TOXICOLOGY
5.6	Hypersensitivity	13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
6	ADVERSE REACTIONS	14 CLINICAL STUDIES
6.1	Clinical Trials Experience	14.1 Overview of Clinical Studies
6.2	Immunogenicity	14.2 Monotherapy Use of TRADENAME in Patients with Type 2 Diabetes Mellitus
7	DRUG INTERACTIONS	14.3 Combination Therapy Use of TRADENAME in Patients with Type 2 Diabetes Mellitus
7.1	Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin	14.4 Cardiovascular Outcomes Trial of TRADENAME in Patients with Type 2 Diabetes Mellitus
7.2	Oral Medications	16 HOW SUPPLIED/STORAGE AND HANDLING
8	USE IN SPECIFIC POPULATIONS	17 PATIENT COUNSELING INFORMATION
8.1	Pregnancy	
8.2	Lactation	
8.3	Females and Males of Reproductive Potential	
8.4	Pediatric Use	

CONTRAINDICATIONS

- Personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (4).
- Known hypersensitivity to **TRADENAME** or any of the product components (4).

WARNINGS AND PRECAUTIONS

- **Pancreatitis:** Has been reported in clinical trials. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed (5.2).
- **Diabetic Retinopathy:** Has been reported in a cardiovascular outcomes trial with semaglutide injection. Patients with a history of diabetic retinopathy should be monitored (5.3).
- **Hypoglycemia:** When **TRADENAME** is used with an insulin secretagogue or insulin, consider lowering the dose of the secretagogue or insulin to reduce the risk of hypoglycemia (5.4).
- **Acute Kidney Injury:** Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions (5.5).
- **Hypersensitivity Reactions:** Discontinue **TRADENAME** if suspected and promptly seek medical advice (5.6).

ADVERSE REACTIONS

The most common adverse reactions, reported in $\geq 5\%$ of patients treated with **TRADENAME** are: nausea, abdominal pain, diarrhea, decreased appetite, vomiting and constipation (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk Inc., at 1-888-XXX-XXXX or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

(b) (4)

USE IN SPECIFIC POPULATIONS

Females and Males of Reproductive Potential: Discontinue **TRADENAME** in women at least 2 months before a planned pregnancy due to the long washout period for semaglutide (8.3).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: XXXXXX

(a) “Highlights” Section (21CFR 201.57(a))

Item	Information Provided in NDA	Reviewer’s Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Rybelsus™ (semaglutide tablets), 3, 7 or 14 mg.	Adequate accepted by DMEPA
Dosage form, route of administration	Tablets for oral administration.	Adequate
Controlled drug substance symbol (if applicable)	Not required	Adequate
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Tablets for oral administration in 3, 7 or 14 mg strengths.	Adequate

Conclusion: Adequate

(b) “Full Prescribing Information” Section

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

Rybelsus™ (semaglutide tablets), 3, 7 or 14 mg.

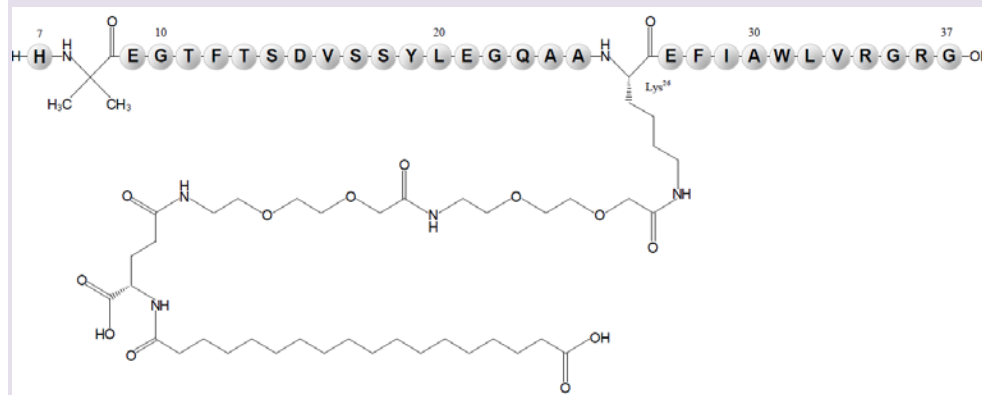
Item	Information Provided in NDA	Reviewer’s Assessment
Available dosage forms	Rybelsus tablets are available as: • 3 mg, white to light yellow, oval shaped debossed with “3” on one side and “novo” on the other side. • 7 mg, white to light yellow, oval shaped debossed with “7” on one side and “novo” on the other side. • 14 mg, white to light yellow, oval shaped debossed with “14” on one side and “novo” on the other side.	Adequate
Strengths: in metric system	3, 7 or 14 mg.	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Rybelsus tablets, for oral use, contains semaglutide, a GLP-1 receptor agonist. The peptide backbone is produced by yeast fermentation. The main protraction mechanism of semaglutide is albumin binding, facilitated by modification of position 26 lysine with a hydrophilic spacer and a C18 fatty di-acid. Furthermore, semaglutide is modified in position 8 to provide stabilization against degradation by the enzyme dipeptidyl-peptidase 4 (DPP-4). A minor modification was made in position 34 to ensure the attachment of only one fatty di-acid. The molecular formula is C ₁₈₇ H ₂₉₁ N ₄₅ O ₅₉ and the molecular weight is 4113.58 g/mol. Semaglutide is a white to almost white hygroscopic powder. Each tablet of Rybelsus contains 3 mg, 7 mg or 14 mg of semaglutide	Adequate

	and the following inactive ingredients: salcaprozate sodium, microcrystalline cellulose, povidone and magnesium stearate.	

Conclusion: Adequate

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

Rybelsus tablets, for oral use, contains semaglutide, a GLP-1 receptor agonist. The peptide backbone is produced by yeast fermentation. The main protraction mechanism of semaglutide is albumin binding, facilitated by modification of position 26 lysine with a hydrophilic spacer and a C18 fatty di-acid.



Furthermore, semaglutide is modified in position 8 to provide stabilization against degradation by the enzyme dipeptidyl-peptidase 4 (DPP-4). A minor modification was made in position 34 to ensure the attachment of only one fatty di-acid. The molecular formula is C₁₈₇H₂₂₉N₄₅O₅₉ and the molecular weight is 4113.58 g/mol.

Semaglutide is a white to almost white hygroscopic powder. Each tablet of Rybelsus contains 3 mg, 7 mg or 14 mg of semaglutide and the following inactive ingredients: salcaprozate sodium, microcrystalline cellulose, povidone and magnesium stearate.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Provided	Adequate
Dosage form and route of administration	Provided	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	Provided	Adequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Provided	Adequate
Statement of being sterile (if applicable)	Not required	Adequate
Pharmacological/ therapeutic class	Provided	Adequate
Chemical name, structural formula, molecular weight	Provided	Adequate
If radioactive, statement of important nuclear characteristics.	Not required	Adequate
Other important chemical or	Provided	

physical properties (such as pKa, solubility, or pH)		Adequate

Conclusion: Adequate

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

Store in the original package to protect from light and moisture. Store at 68°-77°F (20°-25°C); excursions permitted to 59°-86°F (15°-30°C) [see USP Controlled Room Temperature]. DO NOT FREEZE.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	3, 7 or 14 mg tablets	Adequate
Available units (e.g., bottles of 100 tablets)	Rybelsus® is available in blister packs of 10 tablets of 3, 7 and 14 mg strengths.	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Provided	Adequate
Special handling (e.g., protect from light, do not freeze)	Provided	Adequate
Storage conditions	Provided	Adequate

Manufacturer/distributor name listed at the end of PI, following Section #17

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	Adequate

Conclusion: Adequate

2. Container and Carton Labeling

1) Immediate Container Label

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Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Rybelsus® 3, 7, 14 mg tablets.	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	3, 7 or 14 mg tablets	Adequate
Route of administration (21.CFR 201.100(b)(3))	oral	Adequate
Net contents* (21 CFR 201.51(a))	3, 7 or 14 mg tablets	Adequate
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Provided	Adequate
Lot number per 21 CFR 201.18	Space is provided	Adequate
Expiration date per 21 CFR 201.17	Space is provided	Adequate
“Rx only” statement per 21 CFR 201.100(b)(1)	Provided	Adequate
Storage (not required)	Provided	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	Adequate
Bar Code per 21 CFR 201.25(c)(2)***	Provided	Adequate
Name of manufacturer/distributor (21 CFR 201.1)	Provided	Adequate
Warnings	Store in the original package to protect from light and moisture. Store at 68°-77°F (20°-25°C); excursions permitted to 59°-86°F (15°-30°C) [see USP Controlled Room Temperature]. DO NOT FREEZE.	Adequate

*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.
 **For solid oral dosage forms, CDER policy provides for exclusion of “oral” from the container label

**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

2) Carton Labeling

(b) (4)

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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))	Rybelsus® 3, 7, 14 mg tablets.	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	3, 7 or 14 mg tablets	Adequate
Net contents (21 CFR 201.51(a))	3, 7 or 14 mg tablets	Adequate
Lot number per 21 CFR 201.18	Space is provided	Adequate
Expiration date per 21 CFR 201.17	Space is provided	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables][201.10(a), 21CFR201.100(d)(2)]	Provided	Adequate
Sterility Information (if applicable)	Space is provided	Adequate
“Rx only” statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Provided	Adequate
Storage Conditions	Provided	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	Provided	Adequate
Name of manufacturer/distributor	Provided	Adequate
“See package insert for dosage information” (21 CFR 201.55)	Provided	Adequate
“Keep out of reach of children” (optional for Rx, required for OTC)	Keep out of reach of children	Adequate
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))	Not required	Adequate

Conclusion: Adequate.

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:

ADEQUATE

Secondary Review Comments and Concurrence:

I concur with the reviewer's assessment.



Christopher
Galliford

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Date: 8/21/2019 12:42:41PM
GUID: 56324afd003b6374e3a936887dea798c



Muthukumar
Ramaswamy

Digitally signed by Muthukumar Ramaswamy
Date: 8/21/2019 12:43:45PM
GUID: 508da7210002a0c0870017f6c83398f4

MANUFACTURING INTEGRATED ASSESSMENT

Application ID	NDA 213051 & NDA 213182 Priority Review based on Tropical Disease Voucher
Drug Product Name	semaglutide
Strengths	3 mg, 7 mg, 14 mg
Dosage Form	tablet
Administration Route	oral
Indication	[Same product and strengths, but, 2 different indications] NDA 213051: As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus NDA 213182: To reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction or non-fatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease (b) (4)
Applicant Name	Novo Nordisk Inc.

I. Manufacturing Summary

Facility Assessment Recommendation: Adequate
Process Assessment Recommendation: Adequate

(b) (4)





2. *Pre-Approval Inspection Summary*
Not Applicable

(over)

IV. Testing Facilities / Primary Packaging Facilities

1. List of Testing Facilities

The following commercial DS/DP Control Testing Laboratories have been proposed by the applicant to support external testing function of the pending drug product. The facilities proposed below, unless noted otherwise, are within compliance standards and have the ability to perform the function and responsibilities outline in the application following assessment:

Facility Name/FEI	Responsibilities	Previous OPF evaluation (Link)
Novo Nordisk A/S – FEI 3003131673	1. Quality control (b) (4) [REDACTED] [REDACTED] chemical/physical testing 2. Quality control of raw materials 3. Storage of raw materials, [REDACTED] (b) (4) and drug substance 4. Quality control of DP excipients: Chemical testing 5. Quality control of primary packaging materials: Chemical testing 6. Storage of DP excipients	Relevant and acceptable.

2. Facility Level Evaluation of Commercial DS/DP Testing Facility
Not Applicable

3. Facility Level Evaluation of Primary Packaging Facility
Not Applicable

4. Pre-Approval Inspection Summary
Not Applicable

V. List of Outstanding Information Request/Deficiencies:
 Not Applicable

VI. Signature Block

Round#	Primary Name	Secondary & Other Names	Date of Completion	Assessment Outcome	Facility OMIR
1a	Frank Wackes	Ying Zhang	5/28/2019	IR	Approve
1b	Frank Wackes	Christina Capacci-Daniel (only follow-up IR language)	7/1/2019	IR	Approve
1c	Frank Wackes	Ying Zhang	7/19/2019	IR	Approve
1d	Frank Wackes	Ying Zhang	7/30/2019	Adequate	Approve



Frank
Wackes

Digitally signed by Frank Wackes

Date: 7/30/2019 12:00:58PM

GUID: 53b5aba70000559b0ef1af4e030aa45a

Comments:

(b) (4)



Ying
Zhang

Digitally signed by Ying Zhang

Date: 8/01/2019 01:28:32PM

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CHAPTER VI: BIOPHARMACEUTICS
[IQA NDA Assessment Guide Reference](#)

Product Information	RYBELSUS (Semaglutide Immediate release Tablet)
NDA Number	213051
Assessment Cycle Number	1a
Drug Product Name/ Strength	RYBELSUS (Semaglutide Immediate release Tablet)/ 3 mg, 7 mg or 14 mg
Route of Administration	Oral
Applicant Name	NOVO NORDISK INC
Therapeutic Classification/ OND Division	ODEII/DMEP
RLD/RS Number	NDA - 209637
Proposed Indication	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Assessment Recommendation: Adequate

Assessment Summary:

The applicant has developed Semaglutide tablets, 3 mg/7 mg/14 mg as an immediate release eroding tablets to release the enhancer, Salcaprozate Sodium and the drug, Semaglutide, at a similar rate to promote the absorption of the drug. The manufacturing processes involves (b) (4)

(b) (4) The applicant stated that the drug is primarily absorbed in the stomach. The major challenges for the bioavailability of the drug is GI stability of the drug, poor permeability of the drug and the gastric emptying of the eroding tablet. An enhancer is included to promote the absorption of the drug. The administration to the onset of gastric emptying of the tablet dictates the bioavailability of the drug. (b) (4)

(b) (4) . The dissolution data was not submitted for the clinical batches with the final dissolution method since the method was changed after phase 3 studies (b) (4)

An interim specification of Q= (b) (4)% in 45 minutes is

recommended based on the data. The proposed specification is considered liberal based on risk assessment as stated above and the applicant will be asked to submit additional dissolution data for batches up to an year so that the data can be reevaluated to provide a final acceptance criterion.

This Biopharmaceutics review evaluated:

- Choice of dissolution method and dissolution acceptance criterion
- Appropriateness of bridging of different phases of formulations
- Biowavier evaluation

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Application 213051 - Sequence 0001 - 0001 (1) 03/20/2019 ORIG-1 /Multiple Categories/Subcategories	3/20/2019
Application 213051 - Sequence 0013 - 0013 (13) 06/28/2019 ORIG-1 /Quality/Response To Information Request	6/28/2019
Application 213051 - Sequence 0020 - 0020 () /	8/1/2019

Highlight Key Issues from Last Cycle and Their Resolution:

Issue #1

- Missing dissolution data used to calculate the discriminatory power of the dissolution method

Resolution

The applicant provided the missing information in SD#3 [Application 213051 - Sequence 0013 - Response to FDA IR dated June 14, 2019 - CMC Information](#)

The information provided is adequate. The f2 values were confirmed by the Reviewer.

Issue #2

- Missing individual quantitative data for the all the Phase 3a clinical batches.

Resolution

The applicant provided their response in [Application 213051 - Sequence 0013 - Response to FDA IR dated June 14, 2019 - CMC Information. The applicant](#) did not use the clinical phase 3a batches to set the proposed dissolution acceptance criteria. (b) (4)

. The modified analytical procedure with paddle

speed of (b) (4) rpm was implemented for the primary stability batches, supportive stability batches and process performance qualification (PPQ) batches. A comparability study was performed comparing the dissolution data for clinical phase 3a batches and PPQ batches to ensure that the *in-vitro* drug product dissolution performance was comparable for the phase 3a clinical batches and the intended commercial product. Since clinical batch data was not used, the applicant will be asked to provide additional data for up to an year to reevaluate the acceptance criterion. The applicant's method and acceptance criterion are tentatively acceptable.

Concise Description of Outstanding Issues (List bullet points with key information and update as needed):

An interim specification of Q= (b) (4) % in 45 minutes is recommended based on the data. The proposed specification is considered liberal based on risk assessment and the applicant will be asked to submit additional dissolution data for batches up to an year so that the data can be reevaluated to provide a final acceptance criterion.

B.1 BCS DESIGNATION

The applicant stated in 3.2.S.1.1 that Semaglutide is freely soluble above pH 6 and the solubility decreases significantly below pH 6.



Based on the low solubility and low bioavailability, Semaglutide was classified as a BCS Class IV compound by the applicant.

Assessment: Adequate

The applicant claimed that the drug belongs to BCS Class IV.

Solubility:

The pH-solubility data showed that the drug is of low solubility below pH 6 considering the maximum daily dose of 14 mg/day.

Permeability:

No permeability data was submitted. However, the absolute bioavailability is about 1% (See Appendix 4.1 P.33, 2.7.1 Summary of biopharmaceutics studies and associated analytical methods)

Dissolution:

The applicant provided the dissolution method development information in [Module 3.2.P.5.2](#).

The dissolution method used USP Apparatus II in a dissolution media of pH of 6.8 phosphate buffer with surfactant, Brij 35. (b) (4)

[Redacted text]

Dissolution Method:

The Applicant proposed the following dissolution method in the original submission SD #1:

Dissolution apparatus	Rotational speed	Dissolution media	Volume	Acceptance criterion
II	70 rpm	50 mM phosphate buffer (pH 6.8) with 0.05% Brij 35	500 mL	Q (b) (4) % in 45 (b) (4) minutes

Dissolution method development included the evaluation of the followings:

[Redacted text]

- Discriminatory Ability

The discriminating ability of the 70-rpm dissolution method was demonstrated by comparison of dissolution profiles of Semaglutide drug product that were intentionally manufactured varying manufacturing variables. The product attributes ((b) (4)) varied, are presented in Table 3 of [Response to FDA IR dated June 14, 2019 -CMC Information](#). ([Application 213051 - Sequence 0013 - Response to FDA IR dated June 14, 2019 - CMC Information](#)). During Type C meeting for IND 114464, the applicant enquired about changing of RPM from (b) (4) rpm to 70 rpm. The applicant was asked to provide comparable or better discriminating ability for 70 rpm in comparison to (b) (4) rpm, photographic evidence for cone formation to be reduced or improved of 70 rpm when compared to (b) (4) rpm and dissolution data for bio-batches, stability and registration batches using dissolution method both at (b) (4) rpm and 70 rpm. The applicant provided comparative dissolution data to show that paddle speed of 70 rpm reduced the RSD at earlier timepoints prior to 45 minutes and photographic evidence in support of 70 rpm. The applicant has not provided discriminatory ability of the method using the (b) (4) rpm in comparison to 70 rpm as requested.

Table 3 Extent of changes for 7 mg semaglutide drug product development batches manufactured with variations in manufacturing variables

Reference batch	Test batch	Extent of changes
1613_180262, all parameters at target	1613_180262,	(b) (4)
1613_180262, all parameters at target	1613_180263,	
1613_180264, all parameters at target	1613_180264,	
1613_180264, all parameters at target	1613_180265,	(b) (4)
1613_180264, all parameters at target	1613_180276,	

The individual data can be found in Table 15 – 19 in the Appendix E of the aforementioned [Analytical Development report](#).

Table 14 Evaluation by f_2 of 7 mg semaglutide drug product development batches manufactured with variations in manufacturing variables

Reference batch	Test batch	f_2
1613_180262, all parameters at target	1613_180262,	(b) (4) 45
1613_180262, all parameters at target	1613_180263,	40
1613_180264, all parameters at target	1613_180264,	43
1613_180264, all parameters at target	1613_180265,	32
1613_180264, all parameters at target	1613_180276,	41

Dissolution Acceptance Criterion

- Dissolution single value 45-minute data for all three primary registration stability batches using the final dissolution method are shown below.

Table 2 Batch information for semaglutide tablets

Tablet strength	Drug product batch no	Batch size	Site of manufacture	Date of manufacture	Drug substance batch number	Start of study		
3 mg	F2RC034	Pilot scale (b) (4) tablets	Pilot facility Novo Nordisk A/S, Novo Nordisk Park, DK-2760, Måløv, Denmark	19 Oct 2016	B000108668	03 Nov 2016		
	F2RC035			20 Oct 2016	B000111202			
	F2RC036			25 Oct 2016	B000111203			
7 mg	F2RC037			Pilot scale (b) (4) tablets	Pilot facility Novo Nordisk A/S, Novo Nordisk Park, DK-2760, Måløv, Denmark	27 Oct 2016	B000108668	16 Nov 2016
	F2RC038					31 Oct 2016	B000111202	
	F2RC039					31 Oct 2016	B000111203	
14 mg	F2RC040			Pilot scale (b) (4) tablets	Pilot facility Novo Nordisk A/S, Novo Nordisk Park, DK-2760, Måløv, Denmark	03 Nov 2016	B000108668	28 Nov 2016
	F2RC041					03 Nov 2016	B000111202	
	F2RC042					04 Nov 2016	B000111203	

Dissolution, semaglutide single values (%), 25°C/60%RH

Batch / time point (months)	F2RC034	F2RC035	F2RC036	F2RC037	F2RC038	F2RC039	F2RC040	F2RC041	F2RC042
0	(b) (4)								
0	(b) (4)								
0	(b) (4)								
0	(b) (4)								
0	(b) (4)								
0	(b) (4)								
3	(b) (4)								
3	(b) (4)								
3	(b) (4)								
3	(b) (4)								
3	(b) (4)								
3	(b) (4)								
6	(b) (4)								
6	(b) (4)								
6	(b) (4)								
6	(b) (4)								
6	(b) (4)								
6	(b) (4)								
9	(b) (4)								
9	(b) (4)								
9	(b) (4)								
9	(b) (4)								
9	(b) (4)								
9	(b) (4)								
12	(b) (4)								
12	(b) (4)								
12	(b) (4)								
12	(b) (4)								
12	(b) (4)								
12	(b) (4)								
18	(b) (4)								
18	(b) (4)								
18	(b) (4)								
18	(b) (4)								
18	(b) (4)								
18	(b) (4)								

Dissolution, semaglutide single values (%), 25°C/60%RH

Batch / time point (months)	F2RC034	F2RC035	F2RC036	F2RC037	F2RC038	F2RC039	F2RC040	F2RC041	F2RC042
24									(b) (4)
24									
24									
24									
24									
24									

Dissolution, semaglutide single values (%), 30°C/75%RH

Batch / time point (months)	F2RC034	F2RC035	F2RC036	F2RC037	F2RC038	F2RC039	F2RC040	F2RC041	F2RC042
0									(b) (4)
0									
0									
0									
0									
0									
3									
3									
3									
3									
3									
3									
6									
6									
6									
6									
6									
9									
9									
9									
9									
9									

Dissolution, semaglutide single values (%), 30°C/75%RH

Batch / time point (months)	F2RC034	F2RC035	F2RC036	F2RC037	F2RC038	F2RC039	F2RC040	F2RC041	F2RC042
12									(b) (4)
12									
12									
12									
12									
12									
12									
12									
12									
12									
12									
12									
12									
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24									
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24									
24									

Based on the above data (b) (4)

the Applicant proposed the following dissolution acceptance criteria in SD #1:

The acceptance criteria were revised in SD #20 per the Agency's request to

Q = (b) (4)% for Semaglutide at 45 minutes for 3 mg, 7 mg and 14 mg strength

Comparison of Representative Clinical Phase 3 Batches to PPQ Batches

A comparability study has been performed on representative clinical phase 3 and Process Performance Qualification (PPQ) Semaglutide drug product batches to document comparability after change of the manufacturing facility for PPQ batches and commercial product. The batches included in the comparability study are listed in [Table 1](#).

Table 1 Test materials

Use of batch	Site of manufacture	Date of manufacture	Batch no.	Drug product		
Phase 3 clinical batches	Pilot facility	23 Feb 2016	F2RC015	3 mg semaglutide tablet		
		17 Aug 2016	F2RC026			
		01 Dec 2016	F2RC045			
				26 Feb 2016	F2RC016	7 mg semaglutide tablet
				25 Aug 2016	F2RC028	
				05 Dec 2016	F2RC046	
				29 Aug 2016	F2RC030	14 mg semaglutide tablet
				07 Dec 2016	F2RC047	
				07 Dec 2016	F2RC048	
PPQ batches	Commercial facility	05 Nov 2018	H081033	3 mg semaglutide tablet		
		21 Nov 2018	H081048			
		07 Dec 2018	H081028			
				07 Nov 2018	H081035	7 mg semaglutide tablet
				26 Nov 2018	H081049	
				10 Dec 2018	H081030	14 mg semaglutide tablet
				09 Nov 2018	H081042	
		28 Nov 2018	H081050			
				11 Dec 2018	H081052	

¹ Stored at 25°C/75%RH until analysis

The comparability study included in this document covers the following elements:

- Comparison of impurity profiles
- Comparison of dissolution profiles by similarity factor f_2
- Comparison of specification test results of quality parameters

Dissolution profiles

Individual dissolution results, average, %RSD and range are given for clinical phase 3 batches and PPQ batches in [Appendix C](#) and [Appendix D](#), respectively in [Module 3.2.P.2.3. Comparability Report Phase 3 to Process Performance Qualification Report. \(Application 213051 - Sequence 0001 - 3.2.P.2.3 Comparability of Drug Product Manufactured in Pilot Facility and Commercial Facility Site Maaloev\)](#)

Table 5 Similarity factor f_2 between clinical phase 3 and PPQ batches

3 mg semaglutide tablet		7 mg semaglutide tablet		14 mg semaglutide tablet	
PPQ batch	Clinical phase 3 batches	PPQ batch	Clinical phase 3 batches	PPQ batch	Clinical phase 3 batches
H081033	92	H081035	82	H081042	98
H081048	86	H081049	86	H081050	93
H081028	98	H081030	89	H081052	87

The results of the comparability study comparing drug products batches manufactured in the clinical phase 3 and PPQ facilities have confirmed:

- Comparison of dissolution profiles of PPQ semaglutide drug products to the clinical phase 3 semaglutide drug products demonstrated comparable dissolution characteristic for the batches.
- Specification test results including impurities are comparable for semaglutide drug product batches manufactured during PPQ and clinical phase 3. The clinical phase 3 and the PPQ batches are within the respective specification limits at release.

Additional Dissolution Data of Phase 3a Clinical Batches

Additional individual dissolution data of the Phase 3a batches are in submission SD#13. [Application 213051 - Sequence 0013 - Response to FDA IR dated June 14, 2019 - CMC Information.](#)

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment:

Dissolution Assay Method

The assay method for the dissolution test is the same as the Assay method. The adequacy of the assay method will be reviewed by DP reviewer.

Dissolution Method: Adequate

1. The development data showed that the method has been optimized for pH, paddle speed and surfactant concentration to achieve low RSD and discriminatory power for particle size, excipient and manufacturing variations based on the f2 values provided by the applicant. The manufacturing and formulation variations are what we could be expected if there are content non-uniformity and manufacturing deviations. The developed dissolution method is discriminatory to critical manufacturing and process variables, however it is not sensitive to changes within ± 10 -20% changes.
2. The increase in paddle speed from (b) (4) rpm and 70 rpm paddle speed from Primary Stability batches onwards minimized the coning artefact; The increase in paddle speed decreased the variability and the applicant provided additional photographic evidence as requested.
3. The f2 values of all these formulation and manufacturing attributes were <50% provided in the Table 14 above by the applicant, supporting the discriminatory power of the dissolution method. Timepoints used in f2 calculation are 10,15, 20, 30 with one timepoint with dissolution (b) (4)%. The f2 values were confirmed by the Reviewer.

4. (b) (4)
(b) (4)
(b) (4)
(b) (4) The acceptance criterion for Particle size distribution (PSD) is set to (b) (4) (b) (4) μm based on the PSD range which is evaluated suitable for the drug product manufacturing process. (b) (4) (b) (4) the test method will generate a particle size distribution. The consistency is ensured by the established manufacturing process which is optimized via design of experiment with established design space. Per the applicant's report, the particle size of semaglutide drug substance encountered throughout the development resulted in acceptable (b) (4) of drug product. (b) (4) (b) (4) the risk associated with dissolution is considered high.

Dissolution Acceptance Criteria: An interim specification of Q (b) (4) % in 45 minutes is found to be acceptable.

1. Semaglutide is largely restricted to absorption in the stomach (See Sci Transl Med 10, eaar7047.; DOI: 10.1126/scitranslmed.aa7047).

Absolute bioavailability of oral Semaglutide is about 1%. The absorption of Semaglutide is promoted by the presence of the absorption enhancer, Salcaprozate sodium. (b) (4)

(b) (4) The major challenges for bioavailability of the drug are GI stability of the drug, GI permeability of the drug and gastric emptying of the (b) (4) tablet. Note that the developed dissolution method is not biorelevant.

2. The applicant stated that they did not use the clinical phase 3a batches to set the proposed dissolution acceptance criteria due to the fact that Novo Nordisk has changed the analytical procedure for dissolution testing between clinical phase 3a and manufacturing for commercial use. The analytical procedure was changed with regards to paddle speed from (b) (4) rpm to 70 rpm. The modified analytical procedure with paddle speed of 70 rpm was implemented for the primary stability batches, supportive stability batches and process performance qualification (PPQ) batches and this analytical procedure (OFP1001a) will be used for release and stability testing of the commercial batches. All comparative dissolution profile data between the clinical batches manufactured at the pilot facilities and the PPQ batches manufactured at the commercial facility are comparable. The applicant has not provided discriminatory ability of the method using (b) (4) RPM in comparison to 70 rpm as requested.
3. The applicant stated that the proposed acceptance criteria for the dissolution test are based on stability data generated on the primary stability batches. Per Biopharmaceutics Division's current policy, dissolution specifications are based on clinical lots and not stored lots. Since the method has been modified clinical lots data is not available. Dissolution data for the production lots should be considered and not stability data. The applicant will be asked to provide additional dissolution data for up to an year post approval and the dissolution acceptance criterion will be re-evaluated.

Overall Assessment:

The risk evaluation based on dissolution is high due to the following reasons:

- Low solubility and low permeability (BCS Class IV)
- Dissolution method is not discriminatory to meaningful variations in critical material and process attributes.
- Controls on particle size of drug substance (b) (4).
- Clinical data was not used in setting of dissolution specification due change in method for stability and registration batches.
- Discriminatory ability of the method using (b) (4) rpm in comparison to 70 rpm was not provided.

The [proposed acceptance criteria](#) of Q = (b) (4) % for Semaglutide at 45 minutes for 3 mg 7 mg and 14 mg strength in SD#20 are acceptable on an interim basis. The applicant will be asked to submit additional dissolution data for batches up to an year so that the data can be reevaluated to provide a final acceptance criterion.

B.12 BRIDGING OF FORMULATIONS

Assessment: N/A

There was no change in formulations from late Phase I. No bridging of formulations is needed.

B. 13 BIOWAIVER REQUEST

Assessment: N/A

There is no biowavier request as clinical trials covered all proposed marketed strengths. (b) (4)

R. REGIONAL INFORMATION

Comparability Protocols

Assessment: N/A

Post-Approval Commitments

The applicant will be asked to provide dissolution data for additional batches for up to an year post approval for re-evaluation.

Lifecycle Management Considerations

None

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

Primary Biopharmaceutics Assessor's Name and Date:

Vincent Li, Ph.D., 8/1/2019

*Secondary Assessor Name and Date (and Secondary Summary, as needed):
Haritha Mandula, Ph.D.*



Vincent
Li

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Haritha
Mandula

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Muthukumar
Ramaswamy

Digitally signed by Muthukumar Ramaswamy
Date: 8/21/2019 02:21:55PM
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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MUTHUKUMAR RAMASWAMY
08/21/2019 02:40:08 PM